Chemoradiotherapy in locally advanced head and neck cancer patients:

efficacy, toxicity and impact on quality of life

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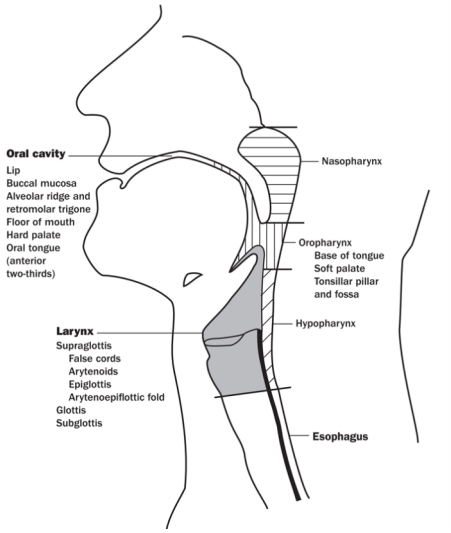
Head and neck cancer

Head and neck cancers encompass a rare group of malignancies, localized in the lip, oral cavity, nasal cavity, paranasal sinuses, pharynx (oropharynx, hypopharynx and nasopharynx), larynx and salivary glands (Figure 1). Apart from the latter, almost all these tumors are squamous cell carcinomas. In 2016 3192 new cases of head and neck squamous cell carcinoma were diagnosed in the Netherlands, which account for 3% of the total number of newly diagnosed cancer patients in that year. [1] Two-thirds of the patients with head and neck cancer are male.

Figure 1. Anatomy of the head and neck region where squamous cell carcinoma can develop



Risk factors for developing head and neck squamous cell carcinomas are the use/abuse of tobacco and alcohol, and, especially in oropharyngeal cancer, infection with the human papillomavirus (HPV).[2]

The five-years overall survival of patients with head and neck squamous cell carcinoma is largely dependent on disease stage. Thirty to forty percent of the patients present with early disease (stage I and II), their 5-years overall survival ranges from 60 to 98% and varies between tumor sites. These patients are mainly treated with surgery and/or radiotherapy. Locally advanced head and neck cancer (LAHNC) (stage III and IV) is present in more than 50% of the patients. LAHNC patients are treated with combined modalities, comprising (1) primary surgery with or without postoperative radiotherapy or chemoradiotherapy or (2)

primary concomitant chemoradiotherapy or radiotherapy in combination with cetuximab (bioradiotherapy) or radiotherapy as single treatment. Primary surgery is the treatment of choice in patients with locally advanced oral cavity cancers and hypopharyngeal and laryngeal cancer without a functional larynx. Despite these intensive treatments, the prognosis of these patients is in general poor, with 5-years overall survival rates ranging from 30-50%. Locally advanced HPV-associated oropharyngeal cancer patients have a distinct behaviour and have overall a better prognosis. This HPV positive group can be divided in three risk groups based on smoking habits and the T or N stage: a good-risk, an intermediate risk and a poor risk group with a 3-year overall survival of 94%, 67% and 42%, respectively. [3]

Treatment of locally advanced squamous cell cancer of the head and neck

Chemoradiotherapy

In locally advanced oropharyngeal, hypopharyngeal and laryngeal cancers chemoradiotherapy is the standard treatment in patients with a good performance score. Primary chemoradiotherapy can be given for two reasons: 1. organ preservation or 2. unresectable disease. In case of locally advanced laryngeal cancer chemoradiotherapy is most frequently given for organ preservation. The primary goal is to retain the organ, i.e. the voice. In one of the first landmark studies of the Radiation Therapy Oncology Group (RTOG) three treatment options were studied: induction chemotherapy followed by radiation, concurrent chemoradiotherapy and radiotherapy alone. Concomitant chemoradiotherapy was most effective for larynx preservation and locoregional control.[4]

In patients with unresectable LAHNC treated with concomitant chemoradiotherapy the primary goal is to improve survival. Chemoradiotherapy in this setting is also proven to be more effective compared to radiotherapy alone. [5,6]

In a large meta-analysis containing 93 trials with 17,346 patients, the effect of chemotherapy in head and neck cancer has been evaluated.[7] An absolute survival benefit of 4.5% at 5 years has been found when chemotherapy was added to locoregional treatment (radiotherapy or surgery). The most effective modality was concomitant chemoradiotherapy with a hazard ratio of death of 0.81 (95% confidence interval 0.78 -0.86) and an absolute survival benefit of 6.5% at 5 years. Single agent chemotherapy is equally effective as polychemotherapy and amongst the different cytostatic treatments, platin-based chemotherapy is the most effective, with most trials using cisplatin. In this meta-analysis locoregional treatment followed by chemotherapy and induction chemotherapy followed by locoregional treatment did not show to be significantly better than loco-regional treatment alone.

Chemoradiotherapy is not only used as primary treatment, but also in the adjuvant setting, after surgery, especially in oral cavity cancers. Postoperative chemoradiotherapy has

proven to be more effective than radiotherapy alone in patients with high risk pathological features, i.e. irradical resection or extracapsular extension of lymph nodes. [8,9]

Different schedules of primary chemoradiotherapy
The most commonly applied treatment schedule (RTOG schedule) in locally advanced head and neck cancer patients consists of cisplatin 100 mg/m^2 on days 1, 22 and 43 combined with conventional radiotherapy (70 Gy in 35 fractions in 7 weeks).[4,5]

In an attempt to improve local-regional control and survival, accelerated radiotherapy has been studied. It is hypothesized that acceleration of radiation treatment reduces the repopulation of tumor cells and thus could lead to improvement of locoregional control.[10,11] Accelerated radiotherapy has shown a higher local control rate (hazard ratio 0.74 CI 0.67-0.83) and a slightly better locoregional control rate (hazard ratio 0.79 CI 0.72 – 0.87) compared to conventional radiotherapy.[10] This results in a benefit of 7.3% in locoregional control at 5 years, but only a small benefit of 2% in 5-years survival compared to conventional radiotherapy.

Patients treated with accelerated radiotherapy cannot be treated with cisplatin 100 mg/m^2 on days 1, 22 and 43 because the shortening of the overall treatment time (around 35 days). Therefore, alternative cisplatin schedules have been studied. One of the most frequently used alternative schedules is weekly cisplatin 40 mg/mg^2 concomitant with accelerated radiotherapy.[12-14] A direct comparison in a prospective randomized trial in LAHNC between cisplatin 100 mg/m^2 with conventional radiotherapy and weekly cisplatin 40mg/m^2 with accelerated radiotherapy as primary chemoradiotherapy has not been performed yet.

Bioradiotherapy
In 90% of the squamous cell carcinomas of the head and neck the expression of the epidermal growth factor receptor (EGFR) is high. EGFR mutations are very rare. Cetuximab is an IgG1 monoclonal antibody against the ligand-binding domain of EGFR and has synergistic activity when given combined with radiotherapy in mice models. Therefore, in a phase III study the combination of cetuximab and radiotherapy was compared to radiotherapy alone.[15] Cetuximab was given in a loading dose of 400 mg/m^2 one week before start of radiotherapy and then weekly in a dose of 250 mg/m^2 during radiotherapy. The combination of cetuximab and radiotherapy resulted in a significant prolonged locoregional control rate, progression-free survival and overall survival compared with radiotherapy alone. Compared to radiotherapy alone, in the combination arm with cetuximab more grade 3 toxicity and more acneiform rash and infusion reactions were observed. Otherwise toxicities were not different between the two treatment arms.

Unfortunately, no phase III studies have been performed comparing concomitant chemoradiotherapy with concomitant bioradiotherapy. Although a comparison between the phase III studies is not allowed, three years overall survival rates are in favor of cisplatin-based chemoradiotherapy, making the latter still standard of care. [16] Alternatively, cetuximab in combination with radiotherapy can be given in patients who cannot tolerate chemoradiotherapy with cisplatin, e.g., patients with hearing problems or decreased renal function. A phase III study in which the addition of cetuximab to cisplatin-based chemoradiotherapy was evaluated, did not show any survival benefit for the combination, but it led to increased toxicity, and did not change the standard of care.[17]

Induction (or neo-adjuvant) chemotherapy

Adding induction chemotherapy prior to radiotherapy is another attempt to improve survival of LAHNC patients. The main objectives of induction chemotherapy are reduction of tumor volume and eradication of systemic micrometastases.[18] Furthermore, in some studies, induction chemotherapy was used as a measure for radiosensitivity, i.e., response to chemoradiotherapy, especially in organ-preserving studies in larynx cancer.[18-20]

In the seventies and eighties the first studies on induction chemotherapy in head and neck cancer were published, most often using a combination of cisplatin and bleomycin.[21-23] Later, three pilot studies were performed at the Wayne State University, to test feasibility of three different treatment schemes:[24] (1) two cycles of bleomycin, cisplatin and vincristine were compared to (2) two cycles of cisplatin with 96-hour infusion of 5-fluorouracil or (3) to three cycles of cisplatin with 120-hour infusion of 5-fluorouracil. The latter schedule showed the highest complete response (54%) and overall-response (93%), making this the standard treatment scheme for induction chemotherapy for many years.

Two phase III trials compared this Wayne State University scheme (cisplatin/5-flourouracil, i.e. PF) to the combination of docetaxel, cisplatin, 5-fluorouracil (TPF) to evaluate efficacy. The TAX 323 compared 4 cycles TPF (docetaxel 75 mg/m^{2,} cisplatin 75 mg/m^2 and 5-fluorouracil 750 mg/m^2) versus PF followed by radiotherapy in patients with locally advanced head and neck cancer.[25] TPF significantly improved progression-free (11.0 versus 8.2 months) and median overall survival (18.8 versus 15.5 months), respectively). The TAX 324 study compared 3 cycles of TPF (docetaxel 75 mg/m^{2,} cisplatin 100 mg/m^2 and 5-fluorouracil 1000 mg/m^2) with PF, both followed by chemoradiotherapy with weekly carboplatin AUC 1.5. The median overall survival in this study was also significantly in favor of the TPF arm (71 versus 30 months). [26] As described earlier, in a meta-analysis no survival benefit has been found for induction chemotherapy, however, TPF based schedules were not included in this analysis[7].

Neo-adjuvant chemotherapy prior to standard cisplatin-based concomitant chemoradiotherapy has not been studied, yet. When TPF would be combined with cisplatin-based chemoradiotherapy, patients receive up to 600 mg/m^2 cisplatin in total, which can lead to profound toxicity. This raises the question if TPF followed by cisplatin-based chemoradiotherapy is feasible. Moreover, TPF has not been administered prior to accelerated chemoradiotherapy.

Treatment induced toxicities and quality of life

Patients with head and neck cancer, who are treated with radiotherapy or concomitant chemoradiotherapy experience a lot acute and late toxicities. Most local toxicities, such as impaired speech and decreased adequate oral intake due to swallowing problems, have a large impact on quality of life.

Acute toxicity induced by chemoradiotherapy consists of mucositis, dermatitis, swallowing problems, dysgeusia, ototoxicity and fatigue. Oral and pharyngeal mucositis, grade 3-4, is reported in approximately 25% of the patients treated with conventional radiotherapy.[27] However, in schedules with accelerated or hyperfractionated radiotherapy grade 3-4 mucositis is observed in 60-70% of the patients.[27,28] Dermatitis can vary from hyperpigmentation until moist desquamation. Dysphagia leads to feeding tube dependency in approximately 80% of the patients, and 4 - 30% of patients will remain dependent on tube feeding after end of treatment. [14,29]. Since the introduction of intensity modulated radiotherapy (IMRT), significantly less xerostomia and dermatitis are reported.[30]

Table 1. Overview of acute and late toxicities of treatment with chemoradiation in head and neck cancer [31]

Acute toxicities	Late toxicites
Mucositis	Xerostomia
Dermatitis	Aspiration
Dysphagia	Dysphagia
Xerostomia	Osteoradionecrosis
Dysgeusia	Caries
Fatigue	Trismus
Nausea and vomiting	Thyroid dysfunction
Nephrotoxicity	Ototoxicity
Ototoxicity	Myelitis
Polyneuropathy	Fibrosis
	Nephrotoxicity

Common and potentially permanent side effects encountered in patients treated with cisplatin-based chemoradiotherapy are ototoxicity and nephrotoxicity. Cisplatin-induced nephrotoxicity can be manifested as an impaired glomerular infiltration rate, or as a tubulopathy, causing reduced serum magnesium and potassium levels.[32,33] Nephrotoxicity is cisplatin dose-dependent and can be dose-limiting.[12,32]

Ototoxicity can be induced by radiotherapy and by the use of cisplatin. Radiotherapy-induced ototoxicity is less commonly observed but has become more clinically relevant since radiotherapy is combined with cisplatin. Radiotherapy-induced ototoxicity has different manifestations. It can present as conductive hearing loss as a result of edema and/or fibrosis of the middle ear, or secondly, as sensorineural hearing loss, which is most likely caused by lesions in the cochlea, which can be irreversible.[34] As a result of the radiotherapy fields radiation-induced ototoxicity is especially seen in patients with tumors at the skull base or nasopharyngeal tumors, and less frequently in other head and neck tumors. Ototoxicity caused by cisplatin is dose- and schedule dependent.[35,36] The incidence of sensorineural hearing loss after chemoradiotherapy with cisplatin schedules in head and neck cancer patients is 17-88%.[34]

Late toxicity presents months to years after end of treatment and can be permanent. Xerostomia is the most common long-term complication of chemoradiation, as a result of damage of the salivary glands. Moreover, patients with head and neck cancer are at risk for development of second malignancies in head and neck and elsewhere in the body. Most of this risk is due to smoking and alcohol abuses, but they can also be caused by radiation treatment itself.

The toxicity of treatment, in combination with the disease itself, has a major impact on quality of life of head and neck cancer patients. During radiotherapy and chemoradiotherapy the global health score of the quality of life decreases, but this recovers to baseline levels one year after end of treatment.[37] [38,39]

Aim of the thesis

As described above, prognosis of patients with locally advanced head and neck cancer is poor and treatment is associated with a high frequency of severe toxicities and a negative impact on quality of life. The main aim of the research described in this thesis is to evaluate options to improve the efficacy and decrease toxicity of concomitant chemoradiotherapy in patients with LAHNC.

In **Chapter 2** a retrospective analysis is performed to evaluate the toxicity, efficacy and feasibility of weekly cisplatin 40 mg/m^2 combined with accelerated radiotherapy in 104 LAHNC cancer patients.

In **Chapter 3** we compare the effects on nephrotoxicity of patients treated with chemoradiotherapy with high dose cisplatin (100 mg/m^2 on days 1, 22 and 43) or intermediate dose cisplatin (40 mg/m^2 weekly). Furthermore, we describe different grading systems for nephrotoxicity.

As described above, no data are available on cisplatin-based chemoradiotherapy after TPF induction chemotherapy. To evaluate feasibility of induction chemotherapy with TPF followed by two different schedules of cisplatin-based chemoradiotherapy, a phase II study in LAHNC, the CONDOR study, was designed. In this study we particularly focused on the feasibility of the total dose of up to a maximum of 600 mg/m^2 cisplatin. Patients were treated with 2-4 cycles TPF (with a maximum of 300 mg/m2 of cisplatin) and, thereafter, were randomized to either conventional radiotherapy with cisplatin 100 mg/m^2 on days 1, 22 and 43 or accelerated radiotherapy with weekly cisplatin 40 mg/m^2. The results of this study are described in **Chapter 4**. The effect of both treatment regimens on quality of life, a secondary endpoint, is described in **Chapter 5**. The patients in our study underwent audiological testing. The effects on hearing of the high dosages cisplatin in combination with radiotherapy in both arms of the study were studied and reported in **Chapter 6**. The use of genetic variants to predict cisplatin-induced ototoxicity and nephrotoxicity in LAHNC patients is described in **Chapter 7**.

This thesis ends with a summary of the studies and future perspectives in **Chapter 8**.

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Toxicity and efficacy of accelerated radiotherapy with concurrent weekly cisplatin for locally advanced head and neck carcinoma

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Abstract

Background: The purpose of this report was to present the results of accelerated radiotherapy with concomitant weekly cisplatin in head and neck cancer.

Methods: One hundred six patients received concomitant cisplatin 40 mg/m^2 weekly with accelerated radiotherapy up to a dose of 68 Gy over 5.5 weeks.

Results: Ninety-nine percent of the patients received planned radiotherapy and 90% received ≥ 5 cycles of cisplatin. Moist desquamation of skin developed in 45% and confluent mucositis in 82%. Feeding tubes were required in 79% of the patients, and after 12 months in 4%. One patient developed nephrotoxicity. Three-year locoregional control, disease-free survival and overall survival (OS) were 72%, 54% and 61%, respectively. Human papillomavirus (HPV) status was positive on polymerase chain reaction (PCR) and p16 in 11 of 50 tested oropharyngeal carcinoma patients. Three-years OS was 81% and 66% in HPV-positive versus HPV-negative patients with oropharyngeal carcinoma.

Conclusion: Concomitant weekly cisplatin 40 mg/m^2 with accelerated radiotherapy was well tolerated and treatment compliance was high.

Introduction

In locally advanced head and neck cancer (LAHNC), concomitant chemoradiotherapy is standard treatment in patients with a good performance score because of a better overall survival (OS) compared to radiotherapy (RT) alone or neoadjuvant chemotherapy followed by RT[1]. The most widely used schedule is concomitant cisplatin 100 mg/m2 on days 1, 22 and 43 with conventional RT (Radiation Therapy Oncology Group [RTOG] schedule)[2]. Acute toxicity, such as mucositis, dermatitis, dysphagia, nausea, vomiting, polyneuropathy, ototoxicity, nephrotoxicity, and bone marrow suppression with neutropenic fever, is significant and approximately 25% of the patients cannot tolerate all 3 cisplatin courses[2,3]. About 80% to 90% of the patients treated with this schedule will receive ≥ 200 mg/m^2 cisplatin[2,4]. Late toxicity, pharyngeal dysfunction or laryngeal dysfunction, was observed in 39% to 51% of the patients[5,6].

Several attempts have been made to improve outcome of LAHNC patients. One of the advantages of accelerated RT is a higher local control rate and a slightly higher OS compared to conventional RT[7,8]. The normally used high-dose cisplatin schedule of once per 3 weeks 100 mg/m^2 on day 1,22, 43 cannot be combined with accelerated RT because of the shortened period of RT (around 35 days). In our institution patients with LAHNC are treated with accelerated RT combined with weekly cisplatin 40 mg/m^2. This weekly intermediate-dose cisplatin schedule in combination with RT has been described for nasopharyngeal cancer and cervical cancer with an increase in local control, OS, and a good feasibility[9,10]. However, in LAHNC data on chemoradiotherapy with weekly cisplatin are limited[4,11-13].

With this retrospective analysis we aim to add new data on acute toxicity, efficacy and feasibility to the current literature, describing our series of LAHNC patients treated with concomitant weekly cisplatin 40 mg/m^2 and accelerated RT. Data on late toxicity were reported earlier[14].

Patients and methods

Patients

Between 2003 and 2010, patients with a histologically proven LAHNC (oral cavity, oropharynx, hypopharynx or larynx), aged between 18 and 70, and Karnofsky performance status ≥70 received concomitant weekly cisplatin 40 mg/m^2 with accelerated RT and were analyzed retrospectively. These patients had their diagnostic workup and were all treated at the Radboud University Medical Center. All patients were seen by the multidisciplinary head and neck oncology team. Routine pretreatment evaluation consisted of a complete medical history, physical examination, endoscopic evaluation, CT or MRI, ultrasonography of the neck nodes and chest X-ray or CT. All cases were discussed in the multidisciplinary head and neck oncology tumor board for tumor classification and treatment recommendations.

Treatment

Cisplatin 40 mg/m^2 in 1 L NaCl 0.9% was administered weekly as a 1-hour intravenous infusion, with a maximum of 6 cycles at the outpatient clinic. Patients received standard antiemetics, such as dexamethasone and ondansetron. Prehydration consisted of 1L NaCl 0.9% in 1.5 hours and posthydration consisted of 1.5 L NaCl 0.9% in 2 hours respectively with addition of potassium chloride and magnesium chloride. The scheduled time between the end of chemotherapy and start of radiotherapy was at least 1 hour. On days of twice daily RT, the cisplatin administration was in between 2 fractions. Cisplatin was delayed or discontinued in case the Karnofsky Score fell below 70, neutrophils < 1.5 x 10^9/l, or thrombocytes < 75 x 10^9/l. In case the creatinine clearance was below 60 ml/min due to dehydration, cisplatin was only administered if the creatinine clearance recovered to ≥ 60 ml/min after rehydration.

From 2003 until 2006, a 3D-conformal RT was used. Thereafter, intensity-modulated radiation therapy (IMRT) with simultaneous integrated boost was gradually introduced for all tumor sites. Radiation dose was 68 Gy in 34 fractions for the primary tumor and macroscopic involved lymph nodes, the elective area received 44 Gy in 22 fractions with 3D-conformal RT or 50.3 Gy in 34 fractions with IMRT with a simultaneous integrated boost. An accelerated fractionation schedule delivering 2 fractions per day during the last 1.5 weeks was used with both modalities. The overall treatment time was 5.5 weeks. Although this schedule could be administered on an outpatient clinical base, a number of the patients was admitted to the hospital during the twice daily RT mainly for logistic reasons, in particular travel distance.

Evaluation of toxicity and efficacy

During treatment, the patients consulted a medical oncologist, radiation oncologist, nurse, dietician and oral hygienist at least weekly. According to international guidelines, patients who already had more > 10% weight loss before start of therapy were given nasogastric tube feeding. All other patients were closely monitored during treatment and were given a feeding tube if they had > 10% weight loss during the course of therapy or had clearly inadequate oral intake for several consecutive days.

Blood samples were drawn weekly for hematology and chemistry. The medical oncologist used the 'Common Toxicity Criteria version 3.0 (CTC version 3.0)[15], the radiation oncologist used a validated list of criteria for the acute radiation toxicity[16].

After completion of treatment, patients were seen on a weekly basis until acute toxicity resolved and thereafter every 2, 3, 4 and 6 months for the first, second, third, fourth and fifth years, respectively. The response during and after treatment was assessed by physical examination complemented with endoscopic evaluation, when indicated. When tumor recurrence was suspected, imaging was performed to document the extent of the disease and biopsies were taken for pathological confirmation. The toxicity data as well as data on loco-regional tumor control, distant metastasis and survival were retrieved from the patients' records and from the general practitioners.

Human papillomavirus analysis

Human papillomavirus (HPV) status was determined in all patients with oropharyngeal carcinomas.

p16 Immunohistochemistry

Paraffine-embedded specimens were used for immunohistochemical (IHC) analysis. They were immunostained using an anti-p16 monoclonal antibody (clone G 175-405; BD Pharmingen, San Diego, CA) at a dilution of 1:10. As positive control, a cervical carcinoma tissue specimen with high p16 expression was used. p16 IHC was scored positive if a strong nuclear and cytoplasmic staining was present in > 70% of the malignant cells[17,18]. All other staining patterns were scored as negative.

Polymerase chain reaction

Polymerase chain reaction (PCR) analysis was performed as described by Melchers et al[19].

Statistical analysis

The endpoints for efficacy were locoregional control (LRC), distant metastasis-free survival, disease-free survival (DFS) and OS. Locoregional failure was defined as recurrent or residual disease in the head and neck region, biopsy proven, at least 6-8 weeks after ending chemoradiotherapy. DFS was measured from the date of diagnosis to the date of recurrent/residual disease or death and OS was measured from the date of diagnosis to the date of death. Patients who received a salvage cervical lymph node dissection were considered to have a recurrence. All survival data were measured from time of diagnosis of the primary tumor. The closeout date for survival was January 1, 2012. Cumulative survival data and toxicity data were calculated using the Kaplan-Meier method. For comparison of categorical variables, the chi-square test was used. All analyses were performed using SPSS for Windows version 20.0.

Results

Patient characteristics and achievement of planned therapy

Patient characteristics of the 106 analyzed patients are summarized in Table 1. For 2 patients, despite having a Karnofsky Score of 60 this treatment was deemed as their best option and they were included in this analysis.

Table 1. Patient and tumour characteristics (*n* =106)

Variable	No. of patients (%)
Sex	
Male	81 (76.4)
Female	25 (23.6)
Age, median (range)	56 (32-72)
Karnofsky score	
100	6 (5.7)
90	62 (58.5)
80	26 (24.5)
70	9 (8.5)
60	2 (1.9)
Primary tumor site	
Oral cavity	12 (11.3)
Oropharynx	53 (50.0)
Hypopharynx	34 (32.1)
Larynx	7 (6.6)
T classification	
T1	4 (3.8)
T2	13 (12.3)
T3	46 (43.4)
T4	43 (40.6)
N classification	
N0	15 (14.2)
N1	14 (13.2)
N2a	3 (2.8)
N2b	29 (27.4)
N2c	37 (34.9)
N3	8 (7.5)
Stage	
III	19 (17.9)
IV	87 (82.1)

Sixty-four patients received all 6 planned cisplatin cycles and 31 patients received 5 cycles; thus, 89.6% of the patients received at least 200 mg/m^2 cisplatin. Reasons to skip a dose of cisplatin were: hematological toxicity (50%), clinical deterioration for non-infectious reasons (21%), infection (10%) or ototoxicity (2%). In 7 patients the sixth cisplatin dose was not administered due to other reasons, such as severe moist desquamation.

RT was given as planned without any delay in all but 1 patient, who discontinued RT after a dose of 54 Gy, due to clinical deterioration. In 28% of the patients, IMRT was used, in the other 72%, conventional RT was used.

Acute toxicity

The acute cisplatin-related toxicity is presented in Table 2. Overall, the tolerability of this schedule was relatively good, with a low frequency of grade 3 or 4 adverse events. Twelve patients (11%) developed neutropenic fever.

Table 2. The main acute toxicities according to Common Toxicity Criteria version 3.0

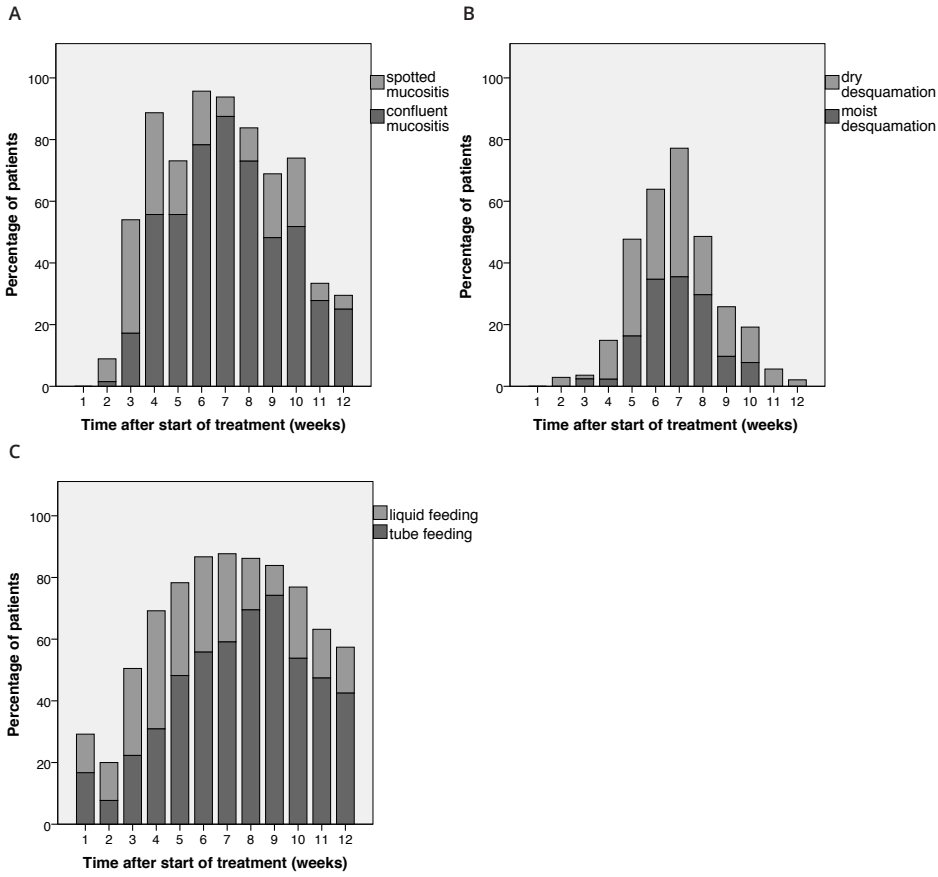
	No. of patients (%)				
Adverse event	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**All grade**
Nausea	44 (41.5)	10 (9.4)	4 (3.8)		58 (54.7)
Vomiting	26 (24.5)	9 (8.5)	4 (3.8)		39 (36.7)
Anemia	81 (76.4)	13 (12.3)			94 (88.7)
Neutropenia	14 (13.2)	18 (17.0)	30 (28.3)	6 (5.6)	68 (64.2)
Thrombocytopenia	30 (28.3)	14 (13.2)	5 (4.7)		49 (46.2)
Nephrotoxity	1 (0.9)				1 (0.9)

Local toxicity within the irradiated area was high with confluent mucositis in 77% and moist dermatitis in 27% of patients treated with IMRT and in 87% and 54% patients treated with 3D conformal RT, respectively. Moist desquamation was significantly less in patients treated with IMRT (p <0.05). Incidence over time of mucositis, dermatitis and dysphagia during the first 12 weeks after start of chemoradiotherapy is presented in Figure 1.

In total, 78% of the patients needed tube feeding, and 39% of the patients had an elective placement of a percutaneous radiologic gastrostomy before start of treatment. The median duration of tube feeding was 8.0 weeks (range 1 to 108 weeks). Four patients (4%) needed tube feeding for more than 1 year. Fifty-eight patients (55%) were admitted to the hospital during or within 2 weeks after the end of the chemoradiotherapy. In 21% the admission was for logistic reasons (ie, a long travelling distance to the hospital). Other reasons for admission were fever (24%), pneumonia (12%), dehydration (12%),

nausea or vomiting (7%), or problems with taking care for dermatitis or mucositis (7%). Very often a combination of adverse events (often grade 1 or 2) determined the necessity of admission.

Figure 1. Scores for mucositis (A), dermatitis (B), and dysphagia (C) percentage of patients reaching a certain score versus the time after the start of chemoradiotherapy

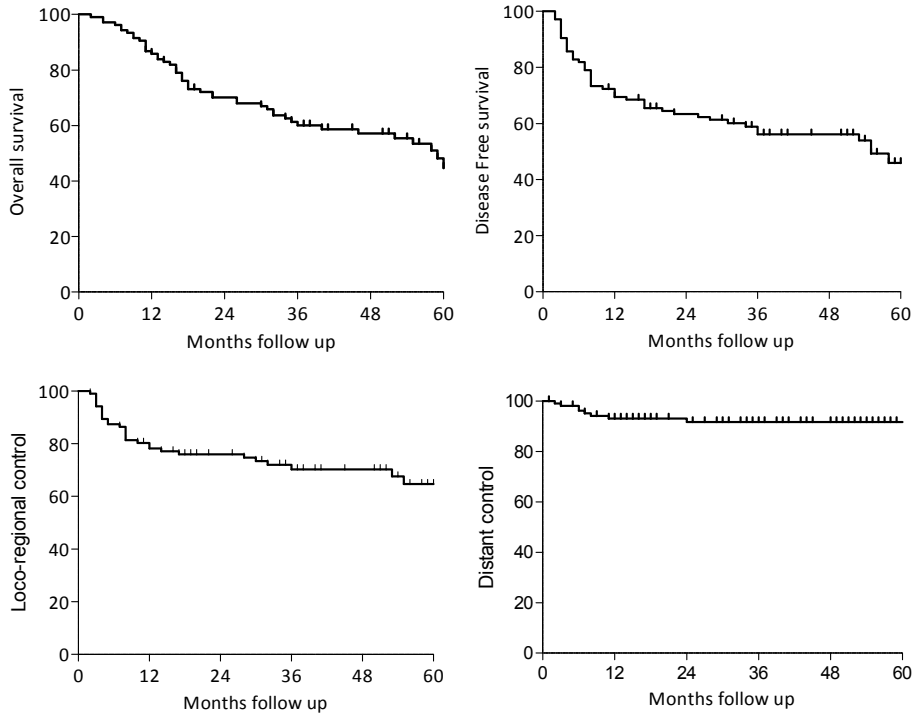


Tumor response and survival

After a median follow-up of 34 months (range 2-92 months), 28% of the patients developed a local or loco-regional recurrence and 8% developed distant metastasis, of which 1 had concurrent local failure. Eight patients (8%) had a cervical lymph node dissection because of a residual lymph node after treatment. The actuarial estimate of loco-regional control at 3 and 5 years was 72% and 65%, respectively (Figure 2). The distant control rate at 3 and 5 years was 92%. A loco-regional failure rate at 3 years of 15% versus 52% (p =0.054) was observed with IMRT versus 3D conformal RT, respectively.

At the end of the evaluation period, 51 (48%) patients had died: disease progression (*n* = 30); myocardial infarction during neutropenia and pneumonia 4 days after end of treatment (*n* =1); second primary malignancy (*n* = 6; 2 of whom died with a second head and neck tumor); other causes (*n* =7); unknown cause of death (*n* =7). Three-year DFS and OS were 54% and 61% respectively, the 5-year DFS and OS 39% and 48%, respectively (Figure 2).

Figure 2. Kaplan–Meier estimate of disease-free survival (DFS), overall survival (OS), and locoregional and distant control



Survival and HPV status

In 50 of 53 patients with oropharyngeal carcinoma, the HPV status was determined. In 11 patients (22%) both PCR on HPV 16, 18 or 33 and p16 IHC were positive, and in 28 patients (56%) both were negative. Discrepancy between IHC and PCR was seen in 22% of the patients (Table 3) . DFS and OS at 3 years were 85% and 85% in p16 positive OPC, respectively, versus 51% and 63% in the p16 negative OPC (p =0.09 and p =0.18). DFS and OS at 3 years for the patients with HPV PCR positive were 79% and 84%, respectively, versus 46% and 58% in the patients with HPV PCR negative oropharyngeal carcinoma (p =0.10 and p =0.11).

Table 3. HPV status of patients with oropharyngeal cancer

HPV status	PCR					No. of patients (%)
	negative	HPV 16	HPV 18	HPV 33	unknown	total
p16 positive	2	11	0	1	1	15 (30)
p16 negative	28	4	1	0	2	35 (70)

Discussion

We retrospectively evaluated the feasibility, efficacy and toxicity of concomitant weekly cisplatin 40 mg/m^2 with accelerated RT in a large cohort of LAHNC patients. The feasibility of the schedule was excellent, with RT given as planned without delay to all but 1 patient. Sixty percent of the patients received all 6 planned cycles of cisplatin, whereas 90% of the patients received a cumulative dose of at least 200 mg/m^2 cisplatin. It is assumed that a cumulative dose of 200 mg/m^2 cisplatin is sufficient for antitumor effects, because this dose has probably no diminishing effect on locoregional and distant control rates[6,13,20].

Compared with other studies, we were able to administer this dose in a higher number of patients than reported before. Only 41%, 65%, 68% and 71% of the patients in four other retrospective studies using concomitant weekly cisplatin 40mg/m2 with radiotherapy received a cumulative dose of at least 200 mg/m2 cisplatin[4,12,13,21]. In a prospective study in 37 patients with weekly cisplatin 40 mg/m^2 combined with hyperfractionated radiotherapy, only 7 patients (19%) received a cumulative dose of at least 200 mg/m^2 cisplatin[11]. These observations led to question why we could administer a much higher cumulative dosage of cisplatin. Taking into consideration the known risk factors, such as age and performance score, we had a relatively young population of patients, median 56 versus 55-65 years of age in the other retrospective studies[4,11,13]. Unfortunately, performance score was not mentioned in the studies mentioned above. Other reasons may be the way of administration of cisplatin and other supportive care measures. In contrast to the description in other studies, we administer a larger volume of NaCl 0.9% during prehydration and posthydration (ie, 3,5L of NaCl 0.9% in 5.5 hours), which may have impact on the tolerance and toxicity of cisplatin[11,12]. With regard to acute cisplatin-induced nephrotoxicity, the incidence of 0.9% in our study is much less then described previously, which may be due to our larger volume pre- and posthydration[4,11-13].

Until now no randomized studies comparing cisplatin weekly 40 mg/m^2 and cisplatin 100 mg/m^2 on days 1,22 and 43, have been performed. Acknowledging the limitations of retrospective comparisons, treatment-related grade 3-5 toxicity of the 100 mg/m^2 schedule with conventional RT was higher for hematological toxicity 45% versus 39%,and renal toxicity 7-8% versus 1% in our population, but less for mucositis, 42% versus 77% in our population; the latter is probably caused by the accelerated RT [2,22].

In a study using the same accelerated radiotherapy schedule we observed a similar incidence of confluent mucositis of 79%, which indicates that concomitant weekly cisplatin does not further enhance mucosal toxicity[23]. Studies using conventional RT combined with weekly cisplatin showed 31-75% mucositis ≥ grade 3, but similar rates of

hematological and renal toxicity as we found.[21,24-26] Hospital admissions were required in 55% of our patients, 40% for acute reasons and 15% for logistical reasons. In a study using conventional RT with weekly cisplatin the number of admissions was comparable to our results (40%) and thus, the accelerated radiotherapy does not seem to contribute much to the admissions.[27]

Seventy-eight percent of our patients were temporarily feeding tube dependent, of whom only 4 patients were still feeding tube dependent after one year. In the RTOG 0129 study feeding tube rates at the end of treatment were 67% and 69% for accelerated and standard fractionation and after one year 26 and 29%, respectively. [28] In other chemoradiation trials approximately 80% of the patients received tube feeding during treatment and 4-39% after one year of treatment, which is in the same range as in our series.[6,11,12,29]

Comparing our efficacy data with previous studies is prone to bias, but nevertheless provides a rough indication of the effectiveness of our schedule. In this study we found 3-years DFS and OS of 54% and 61% and 3-years LRC of 72%. These results are consistent with those described in other studies using weekly cisplatin 40 mg/m^2 which report 2-years DFS and OS in a range of 46-78% and 51-67%, respectively and LRC of 69-79%[4,11,12]. Phase III studies with chemoradiotherapy with cisplatin 100mg/m^2 reported 5-years OS in a range of 30-54%, which is in concordance with our 5-year OS of 48%[2,22].

We found a significant difference between LRC rates in patients treated with or without IMRT. However, patient and tumor characteristics between the 3D-conformal RT (*n* =76) and IMRT (*n* =30) differed greatly. For example, our IMRT-treated patients were significantly younger and had a significantly higher p16 positive rate. This makes that these results are hard to interpret. The RTOG 0129 trial compared accelerated versus standard fractionation in combination with cisplatin 100mg/m^2 in a phase III study.[28] They did not show a difference in overall survival. However, there were no differences in grade 3-5 toxicity. Furthermore, the GORTEC 99-02 study showed no gain in efficacy of accelerated chemoradiotherapy compared to conventional RT.[29] Although these studies showed no benefit of accelerated RT with chemotherapy in the general population of head and neck cancer patients, there might be subgroups that an profit from this strategy. Two studies have shown that patients with tumors with a high EGFR-expression benefit from accelerated RT whereas low EGFR-expressing tumors do not.[30,31] Selection of patients based on their EGFR-expression in the tumor, or possible other key-molecules of downstream signaling pathways, will possibly show significant differences between conventional and accelerated (chemo)radiotherapy.

The difference in OS between HPV-positive and HPV-negative oropharyngeal carcinoma in our study was not significant, as has been described in other series[17]. This might be caused by the low number of HPV-positive oropharyngeal carcinoma . It is known that patients with HPV-negative oropharyngeal carcinoma have a worse prognosis, with a 3-years OS of 32%-57%[17,32]. However, in our study, we found a 3- years OS in p16-negative and p16-positive oropharyngeal carcinoma of 63% and 85%, respectively. Since smoking status of our patients was not known, we were not able to determine if the p16-negative oropharyngeal carcinoma cases were at intermediate or high risk, as described by Ang et al[17].

In conclusion, our schedule of concomitant cisplatin 40mg/m^2 weekly combined with accelerated radiotherapy in LAHNC patients is feasible, and compliance is excellent and compares well to previously described combined chemoradiation schedules with weekly cisplatin. Although there seems to be more local toxicity because of the accelerated radiotherapy, we observed less hematological and much less renal toxicity compared to the conventional chemotherapy schedule, whereas the OS of our schedule is in the upper range of previous studies. Selection based on biological tumor features and not only on clinical characteristics will likely improve identification of patients who are most likely to benefit from this treatment strategy. We therefore plea to further investigate the value of this weekly cisplatin 40 mg/m^2 concomitant schedule head-to-head with the still standard 3 weekly schedule of 100 mg/m^2 in a prospective randomized multicenter trial.

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Degree of nephrotoxicity after intermediate or high dose cisplatin-based chemoradiotherapy in patients with locally advanced head and neck cancer

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Abstract

Background: The purpose of this study was to compare the occurrence of cisplatin-induced nephrotoxicity between concomitant chemoradiotherapy with high versus intermediate-dose cisplatin.

Methods: One hundred forty-four patients with locally advanced head and neck (LAHNC) or nasopharyngeal cancer (NPC) were included; 40 patients received cisplatin 100 mg/m^2 (high dose) on days 1, 22 and 43, and 104 patients received cisplatin 40 mg/m^2 weekly (intermediate dose) during 6 weeks in combination with radiotherapy.

Results: During treatment with intermediate- dose cisplatin, 6.7% developed an increase of ≥50% serum creatinine versus 60.0% treated with high-dose cisplatin (p<0.05). Nephrotoxicity (all grades) scored by Common Toxicity Criteria for Adverse Events (CTCAE) version 3.0 or CTCAE version 4.03 was 53% and 100% in the high-dose group and 4.8% and 68% in the intermediate- dose group, respectively.

Conclusion: Significantly less nephrotoxicity occurs during chemoradiotherapy with intermediate-dose cisplatin compared with high-dose cisplatin. The CTCAE version 4.03 seems to be more appropriate in scoring nephrotoxicity than the CTCAE version 3.0.

Introduction

Concomitant chemoradiotherapy is the standard treatment for patients with locally advanced head and neck cancer (LAHNC) based on the results of 2 meta-analyses.[1,2] Concomitant chemoradiotherapy showed a survival benefit of 8% compared to radiotherapy alone. Radiotherapy with concurrent cisplatin 100 mg/m^2 on days 1, 22 and 43 is worldwide the most often used schedule for treatment of patients with LAHNC in primary and post-operative settings. [3-6] For patients with nasopharyngeal cancer (NPC), chemoradiotherapy with cisplatin 100 mg/m^2 is proven superior to radiotherapy alone.[7] Although very effective, this treatment is associated with high rates of acute toxicity. An alternative treatment schedule is radiotherapy with weekly cisplatin 40 m/m^2 with good feasibility and efficacy.[8,9]

The main adverse events associated with cisplatin-based treatment are nephrotoxicity, ototoxicity and neuropathy. The clinical manifestations of nephrotoxicity are an impaired glomerular filtration rate (GFR) leading to a higher serum creatinine, and reduced serum magnesium and potassium levels as common symptoms of cisplatin-induced tubulopathy. [10-12] The onset of renal failure is gradual, occurring approximately 3 to 5 days after administration and is dose-dependent. [10] Because of this acute nephrotoxicity, a number of patients do not receive the optimal cisplatin dose.[8] A suboptimal cisplatin dose can lead to decreased survival rates.[13] In addition, life-threatening and even fatal renal damage has been reported in patients with head and neck cancer receiving definitive chemoradiotherapy, often due to reduced oral intake because of mucositis.[14,15]

In literature nephrotoxicity is reported using several scoring systems, such as: (1) a predefined absolute or relative increase in serum creatinine; (2) the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0; (3) the updated CTCAE version 4.0; or (4) the Risk, Injury, Failure, Loss, End-stage (RIFLE) kidney disease criteria.[3,8,16-19] The RIFLE have been published by the Acute Dialysis Quality Initiative Group as a consensus definition and classification system with the purpose to create a uniform definition of acute kidney injury [20,21]. In other fields than oncology, these criteria are widely accepted. Classification in the CTCAE version 3.0 and earlier was based on subcategories defined on serum creatinine relative to the local upper limit of normal value, whereas the RIFLE criteria classify renal function relative to baseline serum creatinine, or decrease of estimated glomerular filtration rate (Table 1). The CTCAE version 4.03 takes into account both upper limit of normal and baseline creatinine. This broad variation in scoring systems is the reason why studies are not always comparable. In addition, this could presumably lead to an underestimation of nephrotoxicity.

The purpose of this retrospective analysis was to compare nephrotoxicity in patients with LAHNC or NPC treated with high-dose cisplatin 100 mg/m^2 administered once per 3 weeks or intermediate-dose cisplatin 40 mg/m2 administered weekly with concurrent radiotherapy. Furthermore, we compared nephrotoxicity, as scored by CTCAE version 3.0, with the updated CTCAE version 4.03 and the RIFLE criteria.

Table 1. CTCAE and RIFLE criteria for 'creatinine increase - nephrotoxicity' and acute kidney injury

	Grade				
	1	2	3	4	
CTCAE v 3.0[22]	>ULN – 1.5 x ULN	> 1.5-3.0 x ULN	>3.0-6.0 x ULN	>6.0 x ULN	
CTCAE v 4.03[19]	>1-1.5 x baseline; ULN-1.5x ULN	>1.5-3.0 x baseline; >1.5-3.0 x ULN	>3.0 x baseline; >3.0-6.0 x ULN	>6.0 x ULN	
	Stage				
	Risk	**I**njury	**F**ailure	**L**oss	**E**SRD
RIFLE	≥ 1.5-2.0 x baseline Decrease eGFR ≥ 25%	≥ 2.0-3.0 x baseline Decrease eGFR ≥ 50%	≥ 3.0 x baseline Decrease eGFR ≥ 75% S-creatinine ≥ 354 mM with acute rise of ≥ 44 mM	Complete loss of renal function > 4 weeks	End stage renal disease

Abbreviation: ULN = upper limit of normal

Patients and methods

Patients

We reviewed the medical records of LAHNC or NPC patients treated with cisplatin-containing concomitant chemoradiotherapy at the Radboud university medical center from 2003 to 2011. Inclusion criteria for this retrospective study were LAHNC patients for whom treatment with concurrent chemoradiotherapy was chosen as primary curative treatment or as adjuvant postoperative treatment. In addition, patients with NPC treated with concurrent chemoradiotherapy were included. Patients, of whom data on baseline serum creatinine and one or more repeated serum creatinine during treatment were not available, were excluded from this study.

Before the patients started with concomitant chemoradiotherapy, the Multidisciplinary Head- and-Neck Oncology Team discussed all patients, as part of the diagnostic workup.

Treatment

Post-operative LAHNC patients and NPC patients received cisplatin 100 mg/m^2 every 3 weeks in combination with conventional radiotherapy. Patients who were primarily treated with concomitant chemoradiotherapy received weekly cisplatin 40 mg/m^2 in combination with accelerated radiotherapy.[9] From 2003 until 2006, a 3D-conformal radiotherapy technique was used. Since 2006, intensity-modulated radiation therapy with simultaneous integrated boost (IMRT-SIB) was gradually introduced for all tumor sites and both schedules.

Cisplatin 100 mg/m^2 was administered in 1 L of saline as a 3-hours infusion on days 1, 22 and 43 in a clinical setting. Prehydration consisted of 1 L saline and posthydration of 3 L of saline in 18 hours with potassium and magnesium chloride, 30 mmol and 15 mmol in total, respectively. Patients received antiemetics, including dexamethasone, ondansetron and aprepitant.

Cisplatin 40 mg/m^2 was administered intravenously in 1 L of saline as 1-hour infusion weekly, with a maximum of 6 cycles in the outpatient clinic. Prehydration and posthydration existed of 1 L and 1.5 L of saline with addition of potassium and magnesium chloride, 25 mmol, and 25 mmol in total, respectively. Patients received standard antiemetics, such as dexamethasone and ondansetron. Dose modifications for cisplatin were done in case the neutrophils were below 1.5 x 10^9/L or the platelets were below 75 x 10^9/L. In case the estimated glomerular filtration rate was below 60 mL/min, cisplatin was only administered if the estimated glomerular filtration rate recovered to ≥ 60 mL/min after rehydration. Patients treated with high-dose cisplatin dose received a dose reduction in case of the

neutrophils or the platelets did not recover after a week's delay and cisplatin was delayed or discontinued in case Karnofsky Score fell below 70. Applying similar toxicity rules to patients treated with intermediate-dose cisplatin, courses were skipped or discontinued, without dose reductions.

Nephrotoxicity evaluation

Baseline creatinine was obtained within 4 weeks prior to the start of the chemoradiotherapy. During treatment, the highest creatinine level measured between the administration of the first dose of cisplatin and 4 weeks after the last dose was recorded. During treatment, creatinine was measured weekly until 1 week after end of treatment. Thereafter, it was measured only when indicated (eg, when renal function was not restored to normal). During follow up, the highest creatinine level was retrieved from four weeks after the last dose until one year after the end of treatment to determine late nephrotoxicity. There were no standardized follow-up measurements in our patients. In some patients, no measurements were performed in this period, whereas, in other patients, multiple measurements were performed.

The RIFLE classification uses an increase of 50% in serum creatinine or a decrease in estimated glomerular filtration rate of 25% as the main criteria for acute kidney injury .[21] That is why our main analysis was performed with an increase of creatinine of 50% as primary outcome measure. The estimated glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.[23] This formula takes age, race and sex into account calculating the glomerular filtration rate, and is better suited to estimate glomerular filtration rate in individuals with normal renal function than other algorithms.

The secondary aim was to compare the CTCAE version 3.0, on which most of the current literature on the evaluation of cisplatin-induced nephrotoxicity is based, with the newer version 4.03.[18,19] Because the adverse event "acute renal toxicity" is only defined in the CTCAE version 4.03 and not in CTCAE version 3.0, we used the adverse event "serum creatinine increase" to compare renal function according to the both versions. As is stated in Table 1, the main difference between these 2 versions in grading nephrotoxicity is the comparison of current serum creatinine with the upper limit of normal in version 3.0, while in version 4.03 also the difference between the current serum creatinine with baseline serum creatinine is defined. Hospitalization because of nephrotoxicity and outpatient rehydration were also taken into account when evaluating nephrotoxicity.

Other factors of interest

As baseline laboratory parameters creatinine, albumin and magnesium, were considered in our analysis. Furthermore, concurrent medications were evaluated for an association with nephrotoxicity, in particular loop diuretics, angiotensin-converting-enzyme (ACE) inhibitors, and angiotensin II receptor antagonists.[16] In addition, comorbidity, such as diabetes mellitus and hypertension, were considered in the analysis.

Statistical analysis

Data on treatment, hospitalizations, and follow-up were assessed through the patient information system of the Radboud University Medical Center and individual patient charts. All statistical analyses were performed using SPSS version 20, and a *p*-value <0.05 was considered significant.

For all nominal independent data, number and percentage was calculated, as was the mean and SD for continuous independent variables. Differences in mean values between the two regimes were analyzed using the independent-samples *t* test, if shown to have a normal distribution.

We performed a logistic regression analysis with serum creatinine increase of 50% over baseline level as the dependent variable and as independent variables age, treatment group, sex, hypertension, diabetes mellitus, treatment with loop diuretics, ACE inhibitors or angiotensin receptor antagonists and baseline albumin and magnesium levels.

Results

In total 144 patients were included, of whom 40 patients received cisplatin 100 mg/m2 on days 1, 22, and 43, and 104 patients received cisplatin 40 m/m2 weekly, with a maximum of 6 weeks. Patient baseline characteristics are listed in Table 2.

Table 2. Patient characteristics

	Cisplatin 40 mg/m² (***n*** **=104)**	**Cisplatin 100 mg/m²** (***n*** **= 40)**
Sex		
Male	80 (76.9)	28 (70.0)
Female	24 (23.1)	12 (30.0)
Age, mean (SD)	55.83 (7.607)	49.25 (10.337)
Tobacco use		
Yes	54 (51.9)	6 (15.0)
Quit	40 (38.5)	19 (47.5)
No	9 (8.7)	15 (37.5)
Unkown	1 (1.0)	0 (0.0)
Alcohol use		
Moderate or Heavy drinker	48 (46.2)	7 (17.5)
Social drinker	25 (24.0)	9 (22.5)
Quit	22 (21.2)	8 (20.0)
No	6 (5.8)	16 (40.0)
Unkown	3 (2.9)	0 (0.0)
Karnofsky score		
100	6 (5.8)	2 (5.0)
90	61 (58.7)	25 (62.5)
80	26 (25.0)	11 (27.5)
70	9 (8.7)	2 (5.0)
60	2 (1.9)	0 (0.0)
Primary tumour site		
Oral cavity	12 (11.5)	11 (27.5)
Oropharynx	52 (50.0)	0 (0.0)
Hypopharynx	33 (31.7)	1 (2.5)
Larynx	7 (6.7)	2 (5.0)
Nasopharynx	0 (0.0)	22 (55.0)
Vestibulum nasi	0 (0.0)	1 (2.5)
Unknown primary	0 (0.0)	1 (2.5)
Regional recurrence	0 (0.0)	2 (5.0)

Table 2. Continued

	Cisplatin 40 mg/m^2 (*n* =104)	Cisplatin 100 mg/m^2 (*n* = 40)
T classification		
T1	4 (3.8)	7 (18.9)
T2	13 (12.5)	9 (24.3)
T3	44 (42.3)	6 (16.2)
T4	43 (41.3)	15 (40.5)
N classification		
N0	15 (14.4)	7 (18.9)
N1	14 (13.5)	12 (32.4)
N2a	3 (2.9)	0 (0.0)
N2b	28 (26.9)	5 (13.5)
N2c	37 (35.6)	2 (5.4)
N2 (NPC)	0 (0.0)	6 (16.2)
N3	7 (6.7)	5 (13.5)
Treatment intention		
Primary	104 (100)	22 (55.0)
Postoperative	0 (0.0)	18 (45.0)
Baseline serum creatinine, mean (range)	69 µmol/l (41 – 105)	68 µmol/l (32 - 102)
Baseline CKD-EPI, mean (range)	97.8 (60.4 – 123.3)	103.4 (76.7 - 125)

Abbreviations: NPV, nasopharyngeal cancer; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration

Treatment compliance

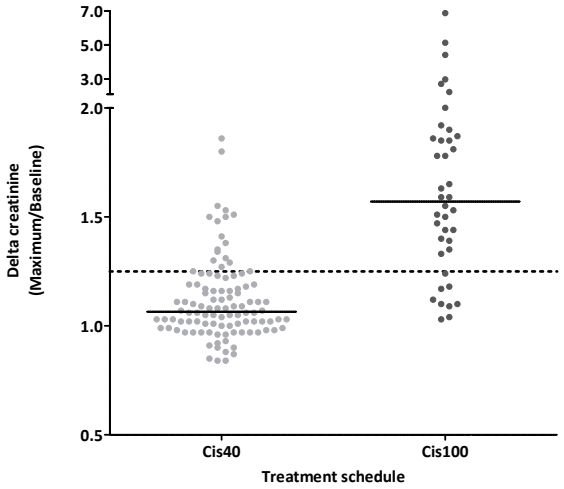
Sixty-eight percent of the patients treated with high-dose cisplatin received all planned 3 cycles, 20% received 2 cycles, and 13% received only 1 cycle of cisplatin 100 mg/m^2. Of all patients treated with high-dose cisplatin, 53% received the planned 300 mg/m^2, and 88% of the patients received ≥200 mg/m^2 cisplatin. Of the patients treated with intermediate-dose cisplatin, 62% received all planned 6 cycles and, thus, the planned 240 mg/m^2, whereas 28% received 5 cycles (ie, 200 mg/m2), 9% received 4 cycles (ie, 160 mg/m2) and 2% received only 3 cycles (ie, 120 mg/m2). Thus, a total of 90% of the intermediate-dose cisplatin patients received ≥200 mg/m^2 cisplatin.

Nephrotoxicity was the reason for delayed administration or terminating cisplatin in 18% of the patients treated with high-dose versus 0% of the patients with intermediate-dose cisplatin (p<0.05). Other reasons for modifying cisplatin were ototoxicity (8% vs 1%, p =0.07), hematological toxicity (20% vs 15%, p =0.33), infection (0% vs 4%, p =0.27), clinical deterioration (0% vs 9%, p <0.05) and other (0% vs 10%, p <0.05) in the high-dose versus intermediate-dose groups, respectively.

Nephrotoxicity

At baseline, there was no statically significant difference (p =0.78) in serum creatinine levels between the 2 patient groups (Table 2). At baseline, all patients had an estimated glomerular filtration rate using the CKD-EPI formula of 60 or more, and there was no statistical difference in estimated glomerular filtration rate between the two groups (p <0.001; Figure 1). An increase of ≥50% in serum creatinine relative to baseline (RIFLE criteria) was found in 60% of patients in the high-dose versus 6.7% in the intermediate-dose group (p <0.001). The median rise in serum creatinine was 57% versus 6%, respectively.

Figure 1. Delta creatinine in the 2 treatment groups. The black line in each group represents the median value in that group. The dotted line on the graph represents 50% increase of creatinine



In patients treated with the high-dose cisplatin, who developed an increase of ≥50% in serum creatinine, the maximum increase in serum creatinine was reached most often after 1 or 2 cycles of cisplatin, whereas patients treated with intermediate dose cisplatin, reached the maximum increase in serum creatinine mostly after 6 cycles (Table 3). In the high-dose schedule 32.5% developed a decrease of ≥25% in CKD-EPI during treatment relative to baseline compared to 2.9% in the intermediate-dose regime.

Table 4 provides the distribution of cisplatin-induced nephrotoxicity during treatment graded by the CTCAE version 3.0 and version 4.03 and the RIFLE criteria in the 2 treatment regimes. Fifty-three percent of the patients in the high-dose group experienced at least grade 1 nephrotoxicity according to CTCAE version 3.0, compared to 100% of the patients when CTCAE version 4.03 was used. For the intermediate-dose group these numbers were 5% and 75%, respectively. Scoring with the CTCAE version 4.03 showed that nephrotoxicity

grade 2 and 3 occurred in 60% versus 6.7% in the high-dose versus the intermediate-dose, whereas scoring with the CTCAE version 3.0 showed nephrotoxicity grade 2 and 3 only in 10% versus 0%, respectively. Using the RIFLE criteria, only 6.7% of patients in the intermediate-dose group were classified in the Risk category, and no Injury or Failure, whereas the high-dose group scored 17% of patients in the Risk catergory, 10% in Injury and 7.5% in Failure.

Table 3. The table shows all patients that developed an increase of ≥50% in serum creatinine and illustrates after which dose the highest serum creatinine was reached

	Dose after which the highest creatinine was reached	No. of patients (%)
Cisplatin 100 mg/m^2 total (*n* = 24/40)	100 mg/m^2	8 (33.3)
	200 mg/m^2	8 (33.3)
	280 mg/m^2	1 (4.2)
	300 mg/m^2	7 (29.2)
Cisplatin 40 mg/m^2 total (*n* = 7/104)	160 mg/m^2	2 (28.6)
	200 mg/m^2	2 (28.6)
	240 mg/m^2	3 (42.9)

Table 4. Nephroxoticity according to the Common Terminology Criteria for Adverse Events version 3.0 and 4.03 (using elevation above baseline with version 4.03) and the Risk, Injury, Failure, Loss, Endstage criteria

	Cisplatin 100 mg/m^2 No. of patients (%)	Cisplatin 40 mg/m^2 No. of patients (%)
CTCAE 3.0		
0	19 (47.5)	99 (95.2)
1	17 (42.5)	5 (4.8)
2	3 (7.5)	0 (0.0)
3	1 (2.5)	0 (0.0)
4	0 (0.0)	0 (0.0)
CTCAE 4.03		
0	0 (0.0)	26 (25.0)
1	16 (40.0)	71 (68.3)
2	21 (52.5)	7 (6.7)
3	3 (7.5)	0 (0.0)
4	0 (0.0)	0 (0.0)
RIFLE criteria		
Risk	17 (42.5)	7 (6.7)
Injury	4 (10.0)	0 (0.0)
Failure	3 (7.5)	0 (0.0)
Loss	0 (0.0)	0 (0.0)
End stage renal disease	0 (0.0)	0 (0.0)

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; RIFLE, Risk, Injury, Failure, Loss, End-stage renal disease

Data of renal function during follow-up were not always available, because serum creatinine was not routinely evaluated after treatment. Serum creatinine after treatment could be retrieved in 30 of 40 patients from the high-dose regime and in 51 of 104 patients from the intermediate- dose regime. Of these patients, 37% and 4% (p <0.05) had an increase of ≥50% in serum creatinine in comparison to baseline in the high-dose versus intermediate-cisplatin group, respectively. Ninety percent of these patients acquired the impaired renal function during treatment, whereas 10% developed it after the end of treatment.

In the high-dose regime, 3 of 40 patients (8%) are currently being treated by a nephrologist because of renal impairment, whereas none of the patients in the intermediate-dose group are attending. Two of these patients received a cumulative dose of only 100 mg/m^2 cisplatin and 1 of 200 mg/m^2. Their baseline creatinine levels were 60, 66 and 74 µmol/L and, after only 1 cycle their serum creatinine increased to 308 and 291. The patient who received 2 cycles of cisplatin had a creatinine of 508 µmol/L after these two cycles. None of these patients needed renal replacement therapy.

Hospitalization and rehydration

Overall, patients treated with high-dose cisplatin needed significantly (p < 0.05) more unplanned hospitalizations. Thirty of the 40 patients (75%) in the high-dose group were admitted, of whom 15 were admitted twice. Sixty of the 104 patients (58%) in the intermediate-group were admitted, of whom 16 needed 2 hospitalizations and 2 needed 3.

Nephrotoxicity in combination with dehydration was the main reason for hospitalization in 44% of patients in the high-dose cisplatin versus none in the intermediate-dose cisplatin group. Other reasons for hospitalization in both regimes were: dehydration without nephrotoxicity, nausea and vomiting, fever, leucopenia and rarely pneumonia, pain, delirium, mucositis, hyponatremia or complications of percutanous endoscopic gastronomy tube. Additionally, in 9% of patients in the high-dose group who had alternative main reasons for hospitalization, nephrotoxicity was diagnosed during the hospitalization, which prolonged the hospital stay.

In case of a minor increase of creatinine or urea, extra fluids were given in an outpatient setting. Twent- five percent of the patients treated with high-dose cisplatin needed extra fluid versus 12% in the intermediate-dose group (p =0.08). Of the patients treated with high-dose cisplatin 58% needed a percutanous endoscopic gastronomy tube versus 79% of the patients treated with intermediate-dose cisplatin (p =0.01).

Other factors of interest

The logistic regression analysis showed that the main determinant of nephrotoxicity is the cisplatin dose (Table 5). A low magnesium was the only baseline laboratory parameter that was correlated with an increase in serum creatinine > 50% that was proven to be statistically significant. At baseline, there was no statically significant difference (p=0.54) in serum magnesium levels between the 2 patient groups. The use of ACE inhibitors was also significantly correlated with renal function (ie, the use of ACE inhibitors was associated with an increase in serum creatinine of > 50%). However, as only 12 of the 144 patients had a hypomagnesaemia at baseline and only 11 of the patients used ACE inhibitors, it is hard to draw firm conclusions. Clinical parameters, other medication, or co-morbidities were not correlated with the development of nephrotoxicity.

Table 5. Association between nephrotoxicity and various clinical and treatment parameters

Variable	Significance	Exp(B)	Confidence interval
Sex	0.405	0.54	[0.13-2.28]
Treatment group	**0.000**	140.58	[21.66-912.20]
Age	0.193	1.05	[0.98-1.12]
Hypertension	0.196	0.15	[0.01-2.64]
Diabetes mellitus	0.695	0.47	[0.01-21.32]
Loop diuretics	1.000	0.00	[0.00]
ACE inhibitors	**0.014**	57.82	[2.29-1460.96]
Angiotensin receptor antagonists	0.213	18.72	[0.9-1890.18]
Baseline albumin	0.719	1.03	[0.87-1.23]
Baseline magnesium	**0.036**	0.00	[0.00-0.51]

Abbreviation: ACE, angiotensin-converting enzyme

Discussion

In this retrospective study we evaluated nephrotoxicity of 2 cisplatin-based chemoradiotherapy schedules in patients with LAHNC. Our study showed that 100 mg/m^2 cisplatin on days 1, 22, and 43 led to more acute and chronic kidney injury, compared to weekly cisplatin 40 mg/m^2 during six weeks. Patients treated with high-dose cisplatin needed significantly more hospitalizations, with nephrotoxicity being one of the main causes. Moreover, we showed that within the same dataset, using CTCAE version 4.03 significantly more cases of nephrotoxicity and higher nephrotoxicity scores were reported than using the CTCAE version 3.0. The CTCAE version 4.03 correlated better with the nephrotoxicity defined as ≥ 50% increase of creatinine than the CTCAE version 3.0. The combined grade 2 to 4 nephrotoxicity scored with the CTCAE version 4.03, expectedly, correlates well with classification using the RIFLE criteria.

Although a former retrospective study already showed a trend toward higher incidence of acute renal failure in high-dose cisplatin when defining acute renal failure as a ≥25% increase in serum creatinine, our study found a significant difference between high-dose and intermediate-dose cisplatin treatment using several scoring systems and definitions of acute renal failure.[8] Both Espeli et al and our group showed that there was a higher incidence of chronic kidney injury in the high-dose cisplatin schedule. In a retrospective study comparing 4 different chemoradiotherapy regimes in patients with LAHNC, renal function was evaluated using the CTCAE version 2.0 (similar to CTCAE version 3.0 in creatinine increase).[24] They found a significant difference in grade 3 nephrotoxicity between patients treated with cisplatin 100 mg/m^2 on days 1, 22, and 43 and cisplatin 20 mg/m^2 on days 1-5 and 29-33 of 8% versus 1% (p =0.02).

In the landmark studies of chemoradiotherapy with cisplatin 100 mg/m^2, nephrotoxocitiy is reported using the CTCAE version 3.0 or older.[3-5] They report an incidence of grade 3 to 4 nephrotoxicity of 4% to 8%. In our study, we found a grade 3 to 4 according to CTCAE version 3.0 with an even lower incidence (2.5%). Importantly, we demonstrated a 3 times higher incidence of grade 3 to 4 nephrotoxicity (7.5%) according to CTCAE version 4.03 than using the CTCAE version 3.0. Moreover, grade 2 nephrotoxicity according to the CTCAE version 4.03 means an increase in serum creatinine of 50 to 300%, which is clinical relevant nephrotoxicity. This suggests that nephrotoxicity as defined by CTCAE version 3.0 in the landmark studies is substantially underestimated. Of note, the RIFLE criteria are internationally adopted criteria for acute kidney injury (Table 1).

Acute nephrotoxicity was found in a high number of patients, especially those treated with high-dose cisplatin. None of these patients though, became dialysis dependent. However, it is important to realize that acute renal failure, with or without the need for temporary dialysis, is associated with increased long-term mortality risk, independent of the residual kidney function.[25] Moreover, an episode of acute kidney injury in patients with normal baseline creatinine, despite complete recovery, is associated with increased risk of later developing CKD-EPI estimated glomerular filtration rate of < 60 mL/min/1.73m^2.[26] This indicates that cisplatin-induced nephrotoxicity, even with normalization of renal function at the end of treatment, can still have impact on long-term morbidity and mortality. The long-term results of the Radiation Therapy Oncology Group 91-11 in which radiotherapy alone was compared to chemoradiotherapy and induction chemotherapy followed by radiotherapy in patients with advanced laryngeal cancer, showed that overall survival differences between the 2 treatment arms.[27] However, more deaths unrelated to laryngeal cancer or treatment were found in patients treated with concomitant chemoradiotherapy, especially after a prolonged follow-up. Hypothetically, nephrotoxicity could have played a role in these unexpected deaths. The long-term results of the Radiation Therapy Oncology Group 95-01 trial, in which radiotherapy alone was compared to chemoradiotherapy in the postoperative setting, also did not show any survival differences between the 2 treatment arms despite better tumor control rates in the chemotherapy arm, also suggesting that (cisplatin-induced) nephrotoxicity could have played a role in late morbidity or mortality.[28]

One of the major limitations, besides the fact that this was a retrospective study, was the lack of systematical assessments of serum creatinine during follow-up. Reviewing patients of whom we had data on serum creatinine after treatment holds the risk of confounding. The available creatinine measurements could have been performed for other reasons than follow-up of treatment, for example, an intercurrent illness. Despite this, we cannot ignore the fact that a high number of patients treated with high-dose cisplatin had an increase of ≥50% in serum creatinine at follow-up in relation to baseline. The best way of analyzing the difference in incidence and severity of nephrotoxicity would be a prospectively designed nephrotoxicity substudy linked to a clinical trial containing both cisplatin schedules.

We found a significantly lower baseline magnesium in the patients who developed nephrotoxicity in both groups, compared to those who did not. Other serum parameters were not correlated to development of nephrotoxicity. This in contrast to a study on cisplatin-induced nephrotoxicity, that found associations with higher baseline calcium and platelet counts and lower serum chloride, but not lower magnesium levels. Earlier, studies in magnesium-deficient rats showed that cisplatin-induced renal dysfunction was

significantly increased compared to rats fed a standard magnesium diet.[29,30] Moreover, several retrospective and prospective studies in humans showed that magnesium supplementation has a protective effect on developing cisplatin-induced nephrotoxicity.[31-33] Our patients treated with intermediate-dose cisplatin received more magnesiumchloride during pre- and posthydration of the cisplatin infusion, which may have protected them from developing nephrotoxicity. We also found that the use of ACE inhibitors was significantly correlated with an increase in creatinine, which is not in line with a putative protective effect of ACE inhibition suggested previously. [34]

In conclusion, using the CTCAE version 4.03, nephrotoxicity is a common side effect in LAHNC and NPC patients treated with concomitant chemoradiotherapy with high-dose cisplatin. Renal function does not fully recover to baseline in most patients. The CTCAE version 3.0 criteria have important limitations when used as a measure of nephrotoxicity in clinical trials. Reported nephrotoxicity using CTCAE version 4.03 gave results that were more in line with the internationally adopted RIFLE criteria. Therefore we suggest using CTCAE version 4.03 criteria in reporting nephrotoxicity in cancer clinical trials.

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Induction chemotherapy with docetaxel/cisplatin/5-fluorouracil followed by randomization to two cisplatin-based concomitant chemoradiotherapy schedules in patients with locally advanced head and neck cancer (CONDOR study) (Dutch Head and Neck Society 08-01): a randomized phase II study

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Abstract

Purpose: To study the feasibility of induction chemotherapy added to concomitant cisplatin-based chemoradiotherapy (CRT) in patients with locally advanced head and neck cancer (LAHNC).

Patients and methods: LAHNC patients were treated with 4 courses of docetaxel/cisplatin/5-fluorouracil (TPF) followed by randomization to either cisplatin 100 mg/m^2 with conventional radiotherapy (cis100+RT) or cisplatin 40 mg/m^2 weekly with accelerated radiotherapy (cis40+ART). Primary endpoint was feasibility, defined as receiving ≥ 90% of the scheduled total radiation dose. Based on power analysis 70 patients were needed.

Results: 65 patients were enrolled. The data safety monitoring board advised to prematurely terminate the study, because only 22 % and 41% (32% in total) of the patients treated with cis100 (*n* =27) and cis40+ART (*n* =29) could receive the planned dose cisplatin during CRT, respectively, even though the primary endpoint was reached. Most common grade 3-4 toxicity was febrile neutropenia (18%) during TPF and dehydration (26% vs 14%), dysphagia (26% vs 24%) and mucositis (22% vs 57%) during cis100+RT and cis40+ART, respectively. For the patients treated with cis100+RT and cis40+ART, two years progression free survival and overall survival were 70% and 78% versus 72% and 79%, respectively.

Conclusion: After TPF induction chemotherapy, cisplatin-containing CRT is not feasible in LAHNC patients, because the total planned cisplatin dose could only be administered in 32% of the patients due to toxicity. However, all but 2 patients received more than 90% of the planned radiotherapy.

Introduction

Most locally advanced head and neck cancer (LAHNC) patients are treated with concomitant chemoradiotherapy, since it has been shown that 5-years survival increased with 6-8% as compared to radiotherapy alone.[1] The most common used schedule is the RTOG schedule with cisplatin 100 mg/m^2 on days 1, 22 and 43 combined with conventional radiotherapy. [2] Alternatively cisplatin 40 mg/m^2 combined with conventional or accelerated radiotherapy is applied.[3-5] A direct comparison of these two schedules with respect to toxicity, feasibility, or efficacy has not been performed yet.

Induction chemotherapy (IC) may improve the prognosis of LAHNC. Docetaxel, cisplatin and fluorouracil (TPF) has been proven superior to cisplatin and fluorouracil (PF) as induction chemotherapy in LAHNC with regard to efficacy and toxicity in two phase III studies, followed by radiotherapy alone, or by radiotherapy and concurrent carboplatin.[6,7] The main criticism on these phase III studies is their omission to use standard concomitant cisplatin-based chemoradiotherapy after TPF. Before the start of our study, no data were available on the feasibility of cisplatin containing TPF followed by cisplatin-based concomitant chemoradiotherapy. We conducted a randomized phase II study in which all LAHNC patients received TPF followed by randomization to either concomitant chemoradiotherapy with cisplatin 100 mg/m^2 once every 3 weeks with conventional radiotherapy (cis100+RT) or chemoradiotherapy with weekly cisplatin 40 mg/m^2 and accelerated radiotherapy (cis40+ART). The aim of this CONDOR study was to evaluate the feasibility of these schedules.

Patients and Methods

Patients eligibility

Patients with pathologically proven non-metastatic, previously untreated, locally advanced squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx or larynx, stage III or IV, were eligible. Patients were between 18 and 65 years of age, had a WHO performance status of 0-1, adequate bone marrow, hepatic and renal function. Exclusion criteria were active alcohol addiction, admission for chronic obstructive pulmonary disease during the last 12 months, weight loss of more than 10% during the last 3 months prior to study entry.

The ethics committee of the participating centers approved the protocol and the study was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent.

Treatment

The TPF regimen was the same regimen as used in the EORTC 24971/TAX 323 study. [7] TPF was administered via a central venous catheter on an inpatient basis for the first two days. Thereafter the patients received the last 3 days of 5-FU using a medication cassette reservoir at home. After two cycles radiological evaluation according to RECIST version 1.0 was performed. In case of complete response (CR), partial response (PR) or SD with minor response, patients were randomized and received another two cycles of TPF. Otherwise they were randomized and started concomitant CRT.

All patients started concomitant chemoradiotherapy between 3 and 6 weeks after the last cycle of TPF. Intensity-modulated radiation therapy (IMRT) technique was mandatory. Dose to gross tumor volume was 70 Gy/35 fractions, dose to elective nodal areas 46 Gy/23 fractions. Patients randomized to cis100+RT received cisplatin 100 mg/m^2 on days 1, 22 and 43 combined with conventional radiotherapy 5 fractions per week with a total treatment time of 7 weeks. Patients randomized to cis40+ART received weekly cisplatin 40 mg/m^2 for 6 cycles and accelerated radiotherapy of 6 fractions per week, with a total treatment time of 6 weeks. On one day of each week two fractions were delivered with an interval of at least 6 h.

Carboplatin AUC 1.5 weekly was given instead of cisplatin in case of MDRD <60 ml/min or ototoxicity grade 3 or 4. In case of neutrophils <1.5 x 10^9/l or platelets <100 x 10^9/l cisplatin was interrupted for one week or skipped in case of weekly cisplatin. Neck dissection was considered for patients with residual tumor.

Assessments

Adverse events were scored according to the NCIC-CTG Common Toxicity Criteria version 3.0. Late radiation toxicity in the follow up was scored according to RTOG/EORTC criteria. Weight was assessed before the start of each cycle. In case of more than 10% weight loss or aspiration a feeding tube was placed.

Tumor evaluation was performed after 2 cycles of TPF, at the end of induction chemotherapy and 12 weeks after the end of chemoradiotherapy. HPV status was determined with p16 immunohistochemistry and PCR.[8] Quality of life questionnaires (EORTC QLQ-C30 and EORTC H&N53) were assessed and audiometry was performed at different time points (will be published separately). Interim analysis by a data safety monitoring board (DSMB) was planned after treatment of 30 patients. Except for the primary endpoint, no stopping rules were defined.

Statistical analysis

Primary endpoint was feasibility of the treatment schedules. All patients were classified according to whether or not they completed the treatment based on receiving at least 90% of the scheduled total radiation dose. The secondary end points were toxicity, tumor response, progression free survival (PFS), overall survival (OS) and quality of life.

Based on a previous study in which 80% of the patients received 100% of the total radiation dose, we expected that 90% of the patients in our trial would receive at least 90% of the radiation dose. If 32 of the 35 patients in each arm completed treatment , we could conclude with 95% certainty that treatment was feasible in at least 80% of the patients. Therefore, a total of 70 patients were needed.

Time to progression was calculated from the date of treatment start to the date of the first tumor progression. Overall survival was determined by measuring the time from the start of treatment to the date of death. Cumulative survival data were calculated using the Kaplan-Meier method. Feasibility was assessed by intention-to treat as defined as the population of all randomized patients analyzed in the arm they were assigned by randomization.

Results

Patients and Treatment

Between December 2008 and February 2012 65 patients from three centers in the Netherlands were included. Of the 65 registered patients, 62 were assessable; two patients were excluded due to ineligibility and one patient withdrew consent (Figure 1). Baseline demographic and clinical characteristics are shown in Table 1. HPV status was positive in 13 patients, negative in 15 and unknown in 11 oropharyngeal cancer patients.

Figure 1. CONSORT diagram

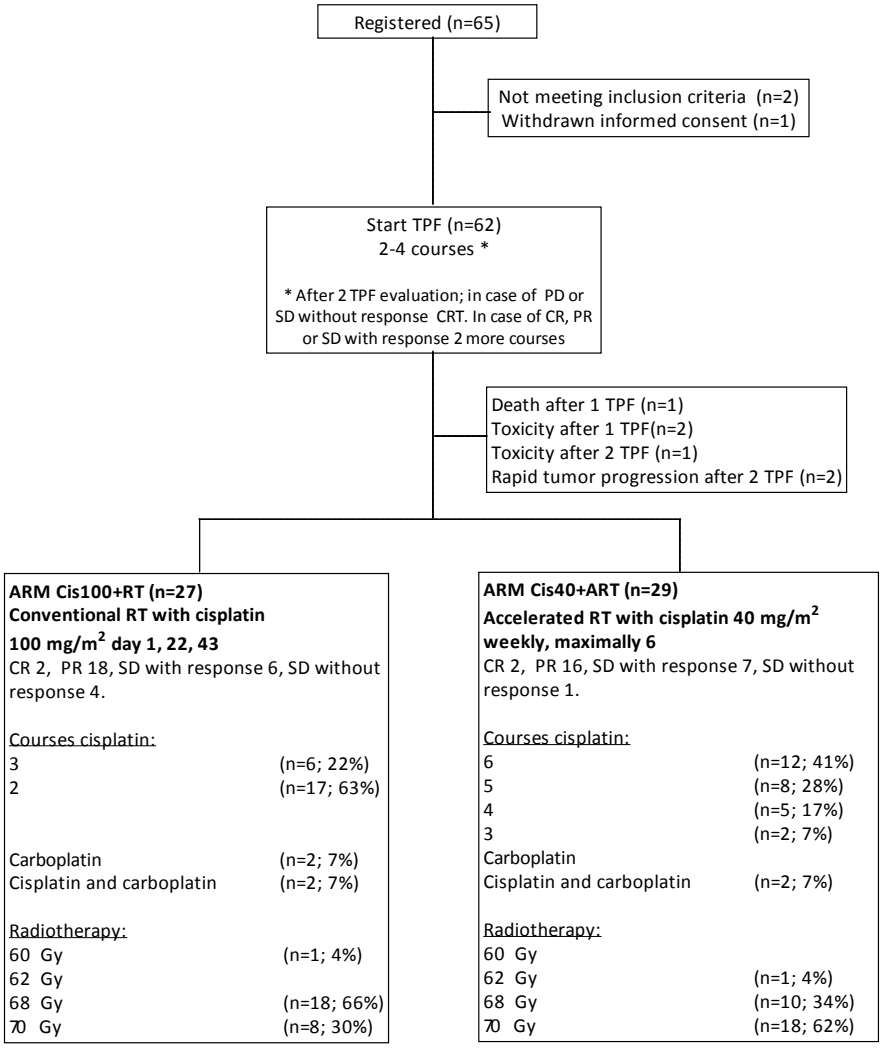


Table 1. Patient characteristics

	Total = 62 pts N (%)	Cis100+RT = 27 pts N (%)	Cis40+ART = 29 pts N (%)
Sex			
Male	50 (80.6)	17 (63)	27 (93.1)
Female	12 (19.4)	10 (37)	2 (6.9)
Age, years			
Mean	53,4	54.0	53.2
Range	27 – 65	32 - 65	27 - 64
WHO performance status			
0	49 (79)	23 (85.2)	23 (79.3)
1	13 (21)	4 (14.8)	6 (20.7)
Tumor site			
Oral Cavity	12 (19.4)	4 (14.8)	6 (20.7)
Oropharynx	37 (59.7)	18 (66.7)	16 (55.2)
Hypopharynx	8 (12.9)	3 (11.1)	5 (17.2)
Larynx	5 (8.1)	2 (7.4)	2 (6.9)
T stage			
T1	4 (6.5)	0 (0)	3 (10.3)
T2	7 (11.3)	5 (18.5)	2 (6.9)
T3	22 (35.5)	8 (29.6)	12 (41.4)
T4	29 (46.8)	14 (51.9)	12 (41.4)
N stage			
N0	14 (22.6)	5 (18.5)	8 (27.6)
N1	3 (4.8)	2 (7.4)	1 (3.4)
N2a	8 (12.9)	3 (11.1)	4 (13.8)
N2b	22 (35.5)	9 (33.3)	10 (34.5)
N2c	15 (24.2)	8 (29.6)	6 (20.6)
Disease stage			
III	5 (8.1)	2 (7.4)	3 (10.3)
IV	57 (91.9)	25 (92.6)	26 (89.7)
HPV status OPC			
Negative	15 (40.5)	5 (27.8)	9 (56.3)
Positive	13 (35.1)	7 (38.9)	5 (31.3)
Unknown	9 (24.3)	6 (33.3)	2 (12.5)

Abbreviations: pts: patients; Cis100+RT: cisplatinum 100mg/m^2 with conventional radiotherapy; Cis40+ART: cisplatinum 40 mg/m^2 with accelerated radiotherapy. OPC: oropharyngeal cancer

Sixty-two patients started with induction chemotherapy, 47 patients (75.8%) received four cycles of TPF. Four patients (6.5%) received only 3 cycles because of toxicity. Eight patients (12.9%) received only two cycles of TPF, of whom five patients because they did not show any response and three patients were treated off protocol due to rapid PD (*n*=2) and poor clinical condition due to toxicity (*n*=1). Three patients only received one TPF; one patient died after 1 TPF, one patient had an infective arthritis and was treated off protocol and one patient developed renal insufficiency.

Therefore, 56 patients were randomized to concomitant chemoradiotherapy, 27 patients to cis100+RT and 29 patients to cis40+RT. The mean RT dose in arm cis100+RT was 68.3 Gy (SD 1,9) and in arm cis40+ART 69.0 Gy (SD 1.7). In arm cis100+RT, 6 (22.2%) and 17 (63.0%) patients received three and two cycles of cisplatin 100 mg/m^2, respectively. Two patients completed protocol with carboplatin instead of cisplatin and two patients received one course cisplatin and two courses carboplatin. In arm cis40+ART 12 patients (41.4%) received all six planned cycles of cisplatin 40 mg/m^2, 8 (27.6%) patients received 5 cycles, 5 patients (18.5%) 4 cycles and 4 (13.8%) patients received only 3 cycles, of whom 2 patients also received one course carboplatin. The median dose cisplatin in both arms was 200 mg/m^2.

The planned interim analysis after 30 randomized patients showed that 35% of the patients received the planned cisplatin dose during chemoradiotherapy in both arms. Therefore, the DSMB advised a second interim analysis after 50 randomized patients. This showed that only 32% of the patients received the planned cisplatin dose in the concomitant chemoradiation part of the study. Consequently, although almost all patients received at least 90% of the planned radiotherapy, the DSMB recommended stopping recruitment. At that moment 65 patients were registered instead of the planned 70 patients.

Toxicity

Chemotherapy and acute radiotherapy toxicities are listed in Table 2. Grade 3 or 4 neutropenic fever occurred in 18% of patients during TPF, despite prophylaxis with GCS-F. There was one treatment related death after 1 TPF, probably due to a cardiac event in a patient with a medical history of hypertension. During TPF there were 31 hospitalizations in 25 patients.

Table 2. Chemotherapy and acute radiotherapy toxicity

	TPF (n=62) (No. of patients)		Cis100+RT (n=27) (No. of patients)		Cis40+ART (n=29) (No. of patients)	
	all grade	grade 3+4	all grade	grade 3+4	all grade	grade 3+4
Local toxicity						
Dysphagia	15	0	23	8	25	9
Dyspnea	4	0	4	2	2	1
Hair loss	45	0	14	0	13	0
Hearing loss	11	1	15	2	8	2
Mucositis	33	2	24	7	25	17
Pain	13	0	16	2	18	2
Stridor	0	0	1	1	0	0
Taste alteration	19	0	16	0	19	0
Tinitus	9	0	8	1	7	0
Xerostomia	1	0	14	0	10	0
General toxicity						
Anorexia	28	4	13	2	20	9
Constipation	30	0	11	0	16	1
Coronary spasms	1	1	0	0	0	0
Creatinine increase	4	2	17	5	7	1
Deep vein thrombosis	2	2	0	0	0	0
Dehydration	8	6	11	7	6	4
Diarrhea	32	7	6	0	6	0
Edema	27	0	11	0	8	0
Fatigue	49	4	23	3	29	3
Infection	20	3	9	5	12	4
Nausea	44	3	21	5	23	4
Sensory neuropathy	23	0	23	4	20	1
Pneumonia	2	0	2	2	1	1
Vomiting	18	2	14	3	18	3
Weight loss	15	0	9	0	15	0
Hematological toxicity						
Febrile neutropenia	11	11	2	2	2	2
Leukopenia	8	3	10	5	6	3
Neutropenia	6	4	8	3	4	1
Trombocytopenia	3	0	3	2	7	2

Abbreviations:TPF: docetaxel/cisplatin/5-fluorouracil; Cis100+RT: cisplatinum 100mg/m^2 with conventional radiotherapy;

Ninety-six percent of the patients in arm cis100+RT and 90% in arm cis40+ART experienced one or more grade 3 toxicities, whereas grade 4 toxicity occurred in 15% versus 14% of the patients. Mucositis grade 3/4 was seen in 26% versus 59% of the patients in arm cis100+RT and arm cis40+ART, respectively ($p < 0.05$). The onset of any grade mucositis was earlier in cis40+ART than in cis100+RT: during week 1 to 3 in 72% versus 40%, respectively (p=<0.05). In arm cis40+ART 5 patients were hospitalized due to severe mucositis needing ketamine or sufentanil intravenously, versus nil in the cis100 +RT arm. Renal toxicity occurred in 62% in patients with cisplatin 100 mg/m^2 versus 14% in patients treated with weekly cisplatin (p <0.05). Main reasons for delay or discontinuation of cisplatin were in arm cis100+RT nephrotoxicity (n=7) and neutropenia (n=5) and in arm cis40+ART thrombocytopenia (n=7) and mucositis (n=3).

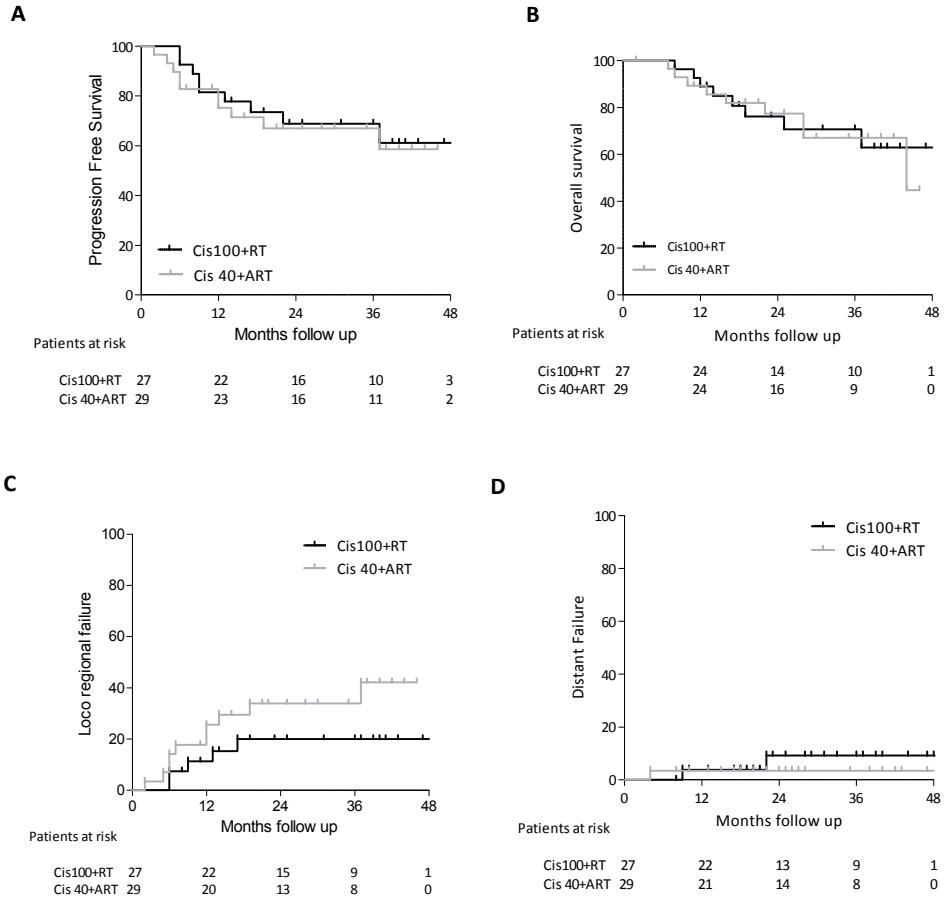
In arm cis100+RT 74% and in arm cis40+ART 90% of the patients needed a feeding tube, for median 10 versus 12 weeks, respectively (ns). During TPF most patients gained weight with a median of 2 kilograms (SD 5.42). During concomintant chemoradiotherapy patients lost weight, median 5 kilograms (SD 4.14) and median 6 kilograms (SD 3.37) in arm cis100+RT and in arm cis40+ART, respectively (ns). None of the patients needed parental feeding.

Efficacy

After TPF four patients reached CR (6.5%), 34 PR (54.8%), 14 SD with minor response (22.6%), 5 SD without any response (8.1%) and two PD (3.2%); two patients were not evaluable and 1 patient died after 1 TPF. The total response rate (CR + PR) was 61.3%. Twelve weeks after chemoradiotherapy, response rate was 81.5% in arm cis100+RT and 72.4%, in arm cis40+ART. Three patients in each arm were not evaluable for response. Elective neck dissections were performed in two of the randomized patients, 1 in each arm. First relapses occurred with local or regional disease site or both in 11%, 0% and 8% of the patients in arm cis100+RT and in 10%, 10% and 10% in arm cis40+ART, respectively. Distant metastases at first relapse were found in 2 patients in arm cis100+RT and in 1 patient in arm cis40+ART.

After a median follow-up of 38 months, two years PFS and OS for all 62 included patients were 65% and 72% respectively. For the randomized patients in arm cis100+RT 2 years PFS and OS were 70% and 78% and in arm cis40+ART 72% and 79% as shown in Figure 2 (ns). Four patients developed a second primary tumor in the follow-up. In oropharyngeal cancer patients 2 years OS was 80% in HPV negative and 92% in HPV positive patients.

Figure 2. Kaplan Meier survival plots for progression free survival (A), overall survival (B), loco regional failure (C) and distant failure (D) between the treatment arms



Discussion

Our study shows that induction chemotherapy with TPF followed by cisplatin-based chemoradiotherapy is not feasible, as only 22% of the patients treated with cis100+RT and 41% of the patients treated with cisplatin cis40+ART could receive the planned cisplatin dose during chemoradiotherapy. The planned radiotherapy could be given to 96% of the patients in each arm. TPF IC was feasible since 76% of the patients received all 4 planned cycles, whereas another 13% of the patients discontinued after two not because of toxicity.

Since there is no proven survival benefit of IC compared to concomitant chemoradiotherapy, the latter remains standard therapy in patients with LAHNC.[1,9,10] Consequently, no concessions should be made in the total dose of cisplatin during chemoradiotherapy as we know that a cumulative dose of 200 mg/m^2 is needed for optimal antitumor activity.[11,12] In two phase III studies investigating concomitant chemoradiotherapy with cisplatin 100 mg/m^2 on days 1, 22, 43 70-85% of the patients received all planned cisplatin, whereas ≥ 200 mg/m^2 cisplatin could be administered in approximately 90% of the patients.[2,13] In arm cis100+RT of our study only 85% received 200 mg/m^2 cisplatin and 69% in arm cis40+ART. We conclude that cisplatin-based CRT after IC with 4 cycles of TPF is not feasible.

There have been more studies in which IC with TPF has been studied. The TREMPLIN study investigated TPF followed by CRT with cisplatin versus bioradiotherapy for larynx preservation.[14] In this study, 47% of patients received the planned three cycles of TPF with a dropout rate after TPF of 24%. Of the 58 patients starting chemoradiotherapy with cisplatin 100 mg/m^2 only 42% completed full treatment. In both this and our study only approximately 30-40% of the patients received all planned cisplatin during chemoradiotherapy. The dropout rate after TPF in the TREMPLIN study however, was high (24% versus 10% in our study). Despite their observations, the investigators still concluded that this treatment schedule was feasible. Another study reported on a retrospective analysis of TPF followed by chemoradiotherapy with cisplatin 100 mg/m^2.[15] In that trial, only two to three courses of less-intense TPF (only 4 days of 5-fluorouracil) were planned and only 87% of the 66 patients received 3 courses. Nine patients (14%) received no CRT after TPF. Of the 59 patients receiving CRT, only 5% received all planned 3 cycles of cisplatin and only 66% of the patients could receive ≥ 200 mg/m^2 cisplatin. Grade 3 skin toxicity or mucositis occurred in 73% and 85% of the patients and there was a high rate of unplanned hospital admissions. Nevertheless, the authors stated that this schedule was feasible.

Likewise, high toxicity rates were found in our study. Main differences between the two treatment arms were a high rate of renal toxicity in patients receiving cisplatin 100 mg/m^2 with conventional radiotherapy and a high rate of mucositis in the patients who received weekly cisplatin 40 mg/m^2 with accelerated radiotherapy. The high rate of mucositis is probably caused by the accelerated radiotherapy, as described earlier.[5,16]

In our study we chose to treat patients with four courses of TPF, according to the TAX 323 regimen, which seemed less toxic than the schedule used in the TAX 324.[6,7] After TPF we decided to use the standard RTOG schedule of conventional radiotherapy with cisplatin 100 mg/m^2 versus accelerated radiotherapy with weekly cisplatin 40 mg/m^2. Accelerated radiotherapy was selected because of the better local regional control over conventional radiotherapy, albeit without any benefit in overall survival.[17,18]

We found a 2 years OS of 70% in our total population and 76% in the intention-to-treat population. This compares favourably to 2 years survival rates of 37-67% in other studies with IC and conventional chemoradiotherapy in LAHNC. [2,6,7,10,13] In the PARADIGM and DeCIDE trials, developed to compare IC directly with chemoradiotherapy, overall survival at 3 years were 70-78%.[9,10] The high survival rates, even in the control arms, of these recent studies compared to earlier trials, may be, partly, explained by HPV status. Patients with HPV positive oropharyngeal cancers have better survival rates compared to HPV negative tumours.[19] Although HPV status was not determined in the PARADIGM and DeCIDE study, more than half of the included patients presented with primary tumors in the oropharynx. We found HPV positivity in half of the patients with oropharyngeal carcinoma.

In conclusion, based on our data we do not recommend TPF induction chemotherapy followed by cisplatin-based chemoradiotherapy in routine clinical daily practice, for non-organpreservation. Still, in exceptional cases, for example in patients with N3 stages with collapse, or with cranial nerve involvement, or when rapid response is mandatory, and organpreservation, it can be considered to give one or two courses TPF induction, followed by concomitant chemoradiotherapy.

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Quality of life of patients with locally advanced head and neck cancer treated with induction chemotherapy followed by cisplatin-containing chemoradiotherapy in the Dutch Condor study, a randomized controlled trial.

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Abstract

Purpose: The CONDOR study showed that docetaxel/cisplatin/5-fluorouracil (TPF) followed by conventional radiotherapy with cisplatin 100 mg/m^2 on days 1, 22, 43 (cis100+RT; n=27) versus accelerated radiotherapy with cisplatin weekly 40 mg/m^2 (cis40+ART; n=29) in locally advanced head and neck cancer (LAHNC) patients was not feasible. Here, we report the analysis of health-related quality of life (HRQOL) of the patients entered in this study.

Methods: HRQOL was assessed at baseline, after two TPF, before start of chemoradiotherapy, and 1, 4, 8, 12 and 24 months after completion of chemoradiotherapy using the EORTC-QLQ-C30 and QLQ-H&N35 in 62 patients.

Results: Compliance with the QOL questionnaires was 94% (59/62) at baseline, and 61% (30/49) at 12 months, respectively. HRQOL decreased after TPF and further decreased during chemoradiotherapy in both arms equally. Pain and swallowing dysfunction improved significantly during TPF but deteriorated below baseline levels during chemoradiotherapy, cis40+ART > cis100+RT ($p<0.05$). HRQOL and symptoms restored to baseline within 12 months in both arms and remained at that level until 24 months.

Conclusions: After TPF, cis40+ART had a larger negative impact on symptoms than cis100+RT, probably due to the ART. HRQOL and symptoms restored to baseline levels within 12 months after end of treatment in both arms, which is an important perspective for patients during the phase of most serious acute side effects of treatment.

Introduction

In patients with locally advanced head and neck cancer (LAHNC), both disease and treatment have a great impact on quality of life (QOL). Standard treatment for these patients is concomitant chemoradiotherapy, which induces severe acute and late toxicities. Common acute toxicities of chemoradiotherapy include mucositis, dermatitis, dysphagia, ototoxicity, and polyneuropathy. Late toxicity may consist of dysphagia sometimes with aspiration, odynophagia, xerostomia, fibrosis, and occasionally osteoradionecrosis [1,2]. These toxicities negatively influence the QOL.

Induction chemotherapy, using docetaxel/cisplatin/5-fluorouracil (TPF), has been proposed as a means to improve outcome of patients with locally advanced head and neck cancer. There are only limited data on TPF followed by chemoradiotherapy using cisplatin. Although it is often stated that neo-adjuvant TPF is well tolerated, the effect of the total regimen, including the concomitant chemoradiation part, on health-related quality-of-life (HRQOL) has not been reported previously [3,4]. HRQOL comprises physical and psychosocial functioning, social interaction and disease- and treatment-related symptoms. HRQOL was studied in LAHNC patients receiving neo-adjuvant TPF versus PF followed by radiotherapy alone, showing a trend towards a better HRQOL during treatment in favor of TPF [5]. Other studies in LAHNC patients treated with chemotherapy and radiotherapy showed a pattern of decline of QOL and then return to baseline within 12 months after end of treatment [6,7]. There are no published data of QOL in LAHNC patients treated with induction chemotherapy later than 12 months after end of treatment.

We conducted a randomized phase II feasibility study, the Condor study, on induction chemotherapy with TPF followed by cisplatin-based concomitant chemoradiotherapy in two different schedules [8]. Sixty-two fit LAHNC patients started treatment with TPF. Of these patients, 56 were randomized to treatment with concomitant chemoradiotherapy with conventional chemoradiotherapy and cisplatin 100 mg/m^2 three weekly (cis100+RT) (27 patients) or concomitant CRT with accelerated radiotherapy with weekly cisplatin 40 mg/m^2 (cis40+ART) (29 patients). Ninety-six percent of the patients treated with cis100+RT and 90% of the patients treated with cis40+ART experienced grade 3 toxicity (on the Common Toxicity Criteria 3.0), whereas grade 4 toxicity occurred in 15% versus 14% of the patients. Most common grade 3-4 toxicity during TPF was febrile neutropenia (18%). During concomitant CRT grade 3-4 toxicities were mucositis in 22% vs 57%, dysphagia in 26% vs 24% and dehydration in 26% vs 14%, of patients with cis100+RT and cis40+ART, respectively. Both treatment schedules were proven not to be feasible, since the total planned dosage of cisplatin during the chemoradiotherapy could only be administered

in 32% of all patients due to severe toxicity, leading to early termination of inclusion into the study. Despite high toxicity rates, efficacy was comparable with other studies using induction chemotherapy. Response rate after TPF was 61% and 2-years overall survival was 77% in patients treated with cis100+RT and 76% for those treated with cis40+ART.

In this paper, we will focus on the HRQOL of patients treated in this phase II study with TPF induction chemotherapy followed by concomitant chemoradiotherapy, with emphasis on long-term follow-up outcome.

Methods

Trial design and participants

The CONDOR study was a randomized phase II feasibility study on induction chemotherapy with TPF followed by cisplatin-based concomitant chemoradiotherapy in two different schedules. In this study, fit LAHNC patients, stage III or IV with a WHO-performance score of 0-1 and age ≤ 65 years, were included. Patients were between 18 and 65 years of age, had a WHO performance status of 0-1, adequate bone marrow, hepatic and renal function. Exclusion criteria were active alcohol addiction, admission for chronic obstructive pulmonary disease during the last 12 months, weight loss of more than 10% during the last 3 months prior to study entry. Details on therapy schedules, and toxicity registration and grading were published recently [8].

QOL assessment

QOL data were collected using the European Organization for Research and Treatment of Cancer (EORTC) QOL questionnaire (QLQ-C30) version 3.0 and the EORTC head and neck cancer module (HN-35) [2,5,9-11]. The EORTC QLQ-C30 contains a global HRQOL score, five functional scales (physical, role, cognitive, emotional and social) and three symptom scales (fatigue, nausea/vomiting and pain), six single item scales (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea and financial difficulties). The EORTC Head and Neck module, the EORTC QLQ-H&N35 has been specifically designed and validated for head and neck cancer patients [11]. This is a 35-item questionnaire with seven symptom scales (pain, swallowing, senses, speech, social eating, social contact and sexuality), six single item scales (difficulties of teeth, mouth opening, dry mouth, sticky saliva, coughing and feeling ill) and five items about the additional use of painkillers, nutritional supplements and feeding tube and changes in body weight. All items were transformed to scales from 0 to 100, according to the EORTC scoring manual recommendations [12]. A high score on functional scale represents a better level of functioning, whereas a high score on a symptom scale indicates more severe symptoms. Differences of at least 10 points (on a scale of 0-100) on a mean value of the HRQOL parameter were classified as clinically significant [13]. Changes of ≥ 10 points are moderate, whereas changes of ≥20 points on a mean score are classified as large. The primary HRQOL analysis was based on preselected HRQOL scores: global HRQOL, pain, swallowing, speech, and coughing.

Patients completed the QOL questionnaires at baseline, after 2 cycles of TPF, before start of concomitant chemoradiotherapy (i.e., after 2, 3 or 4 TPF cycles) and 1, 4, 8, 12, 18, and 24 months after the end of chemoradiotherapy.

Statistical analysis

HRQOL was a secondary endpoint of the CONDOR study; power analysis was calculated on the primary endpoint, which was feasibility. Analyses were performed using SAS version 9.2 and SPSS version 20. Compliance rates were calculated as the number of forms received divided by the number of forms expected at each time point. Expected forms were from patients still alive at the given time point, regardless of disease state. Fishers' exact test was used to determine differences in compliance between the treatment arms. One-sided *t*-test was used to compare the baseline quality of life results of the current study with the EORTC reference values.

For the primary analyses, we used an Unstructured Covariance Model to conduct separate repeated measures analyses for each HRQOL outcome [14]. We included time, treatment, and the interaction between time and treatment as fixed factors in the linear mixed model. Time was treated as a categorical variable to allow the model to fit every possible pattern in time. The interaction between time and treatment was only defined after the start of the chemoradiotherapy. In addition, we added the baseline values of the dependent variables as possible significant covariates to the model. Residual plots from the mixed models were examined to assess model assumptions. All linear mixed model analyses were performed on all participants, including those with incomplete datasets. Differences between treatments at specific time moments were estimated from the mixed model. Two-tailed analyses were performed with a *p*-value of 0.05.

Moreover, sensitivity analysis using the proportion of patients experiencing an improvement/ worsening of more than 10 or 20 points in each selected scale was performed [13].

Results

Participants

Patient characteristics are shown in Table 1.

Table 1. Patient characteristics

	Total = 62 pts N (%)	Cis100+RT = 27 pts N (%)	Cis40+ART = 29 pts N (%)
Sex			
Male	50 (80.6)	17 (63)	27 (93.1)
Female	12 (19.4)	10 (37)	2 (6.9)
Age, years			
Mean	53,4	54.0	53.2
Range	27 – 65	32 - 65	27 - 64
WHO performance status			
0	49 (79)	23 (85.2)	23 (79.3)
1	13 (21)	4 (14.8)	6 (20.7)
Tumor site			
Oral Cavity	12 (19.4)	4 (14.8)	6 (20.7)
Oropharynx	37 (59.7)	18 (66.7)	16 (55.2)
Hypopharynx	8 (12.9)	3 (11.1)	5 (17.2)
Larynx	5 (8.1)	2 (7.4)	2 (6.9)
Disease stage			
III	5 (8.1)	2 (7.4)	3 (10.3)
IV	57 (91.9)	25 (92.6)	26 (89.7)

Abbreviations: pts: patients; Cis100+RT: cisplatinum 100mg/m^2 with conventional radiotherapy; Cis40+ART: cisplatinum 40 mg/m^2 with accelerated radiotherapy.

QOL: compliance

Data of all patients were included in this analysis. Compliance to the questionnaires was 94% at baseline, 71% after 2 TPF, 70% before start of chemoradiotherapy, 61% after chemoradiotherapy, 63% after 4 months, 66% after 12 months, 68% after 18 months, and 62% after 24 months of follow- up. Compliance was significantly lower in patients treated with cis40+ART at 4 months after end of treatment, 45% versus 81%, respectively (p=0.006). At all other time points compliance between the two treatment arms was similar.

Table 2. Baseline QOL scores and reference data

	CONDOR patients (n=59)		Reference data (n=1722)		Difference between groups
	Mean	*SD*	*Mean*	*SD*	
QLQ-30					
Global health status	75.3	19.7	63.3	22.4	$p<0.001$[a]
Physical function	92.0	15.1	81.2	20.2	$p<0.001$[a]
Role function	86.1	23.8	78.8	27.9	$p=0.035$
Emotional function	74.7	21.4	71.2	24.1	$p=0.345$
Cognitive function	91.7	15.2	86.4	19.1	$p=0.017$
Social function	87.5	18.1	82.2	24.7	$p=0.046$
Fatigue	20.8	20.9	27.6	25.0	$p=0.018$
Nausea/vomiting	2.5	8.6	5.2	13.3	$p=0.026$
Pain	25.6	29.7	24.9	26.3	$p=0.809$
Dyspnoea	6.7	14.7	18.0	26.6	$p<0.0.1$[a]
Insomnia	25.0	27.9	28.5	32.4	$p=0.388$
Appetite loss	17.2	27.8	19.4	29.3	$p=0.561$
Constipation	12.2	24.5	11.7	23.2	$p=0.910$
Diarrhoea	2.2	8.4	6.1	16.7	$p=0.001$
Financial problems	13.3	26.2	18.8	30.2	$p=0.114$
QLQ-H&N 35					
Pain	27.2	22.5	29.9	25.1	$p=0.356$
Swallowing	24.9	25.1	27.5	26.1	$p=0.454$
Senses	10.5	21.0	20.0	30.0	$p=0.002$
Speech	18.1	21.3	27.1	27.2	$p=0.003$
Social eating	21.9	26.0	23.9	26.7	$p=0.018$
Social contact	5.6	14.9	13.2	19.1	$p=0.001$
Sexuality	14.2	25.2	32.3	36.1	$p<0.001$[a]
Teeth	19.1	27.2	27.8	35.0	$p=0.029$
Opening mouth	25.4	34.1	22.4	31.9	$p=0.545$
Dry mouth	15.3	24.2	31.1	34.2	$p<0.001$[a]
Sticky saliva	19.5	31.2	32.4	35.4	$p=0.002$[a]
Coughing	18.6	25.0	34.9	32.1	$p<0.001$[a]
Feeling ill	12.4	21.4	21.7	29.2	$p=0.003$
Pain killers	61.0	49.2	52.8	49.9	$p=0.114$
Nutritional support	31.0	46.7	27.0	44.4	$p=0.590$
Feeding tube	5.1	22.2	18.3	38.7	$p<0.001$[a]
Weight loss	43.9	50.0	41.3	49.2	$p=0.620$
Weight gain	17.9	38.6	25.9	43.8	$p=0.125$

Abbreviations: EORTC: European Organisation for Research and Treatment of Cancer; QOL: quality of life; QLQ-C30: Quality of Life Questionnaire C30; QLQ-HN-35: Head and Neck Cancer-Specific Module.

[a] : Clinically significant different (10 points or more)

QOL baseline scores

Baseline QOL scores were compared to the reference values of head and neck cancer patients, stage III-IV disease (Table 2), provided by the EORTC [15]. All EORTC head and neck reference data are based on pretreatment HRQOL. A clinically and statistically significant difference in baseline scores of our patients compared to the EORTC reference values was found on global HRQOL (75.3 versus 63.3, $p<0.001$) and physical function (92.0 versus 81.2, $p<0.001$), and on the symptom scores sexuality (14.2 versus 32.2, $p< 0.001$), dry mouth (15.3 versus 31.1, $p<0.001$), sticky saliva 19.5 versus 32.4, $p<0.001$), coughing (18.6 versus 34.9, $p<0.001$), feeling ill (12.4 versus 21.7, $p=0.003$), and feeding tube (5.1 versus 18.3, $p<0.001$), in favor of the patients in our study. This indicates that in terms of QOL a relatively favorable (i.e., fit) patient group was selected for this study.

QOL during TPF

Global HRQOL decreased non-significantly after 2 TPF (70.1) and even more after the end of TPF (64.0) (Table 3, Figure 1). Pain and swallowing problems both decreased with more than 10 points after 2 TPF, but both increased before start of chemoradiotherapy (Table 3, Figure 2). Speech problems and coughing improved non-significantly after 2 TPF, but deteriorated at the end of TPF (Table 3, Figure 2).

Figure 1. Mean Global Health Scores over time by treatment arm

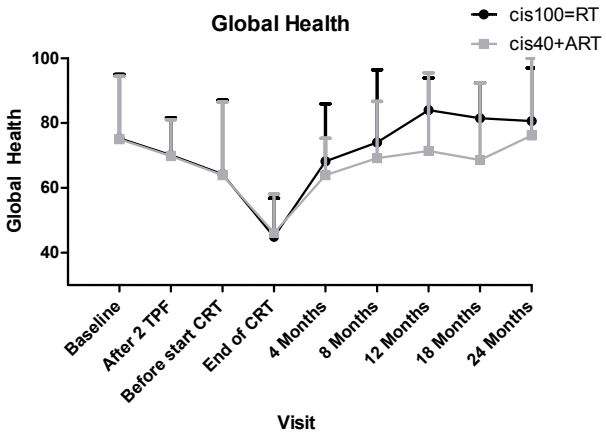


Table 3. Mean scores over time at baseline, after 2 TPF and after chemoradiotherapy

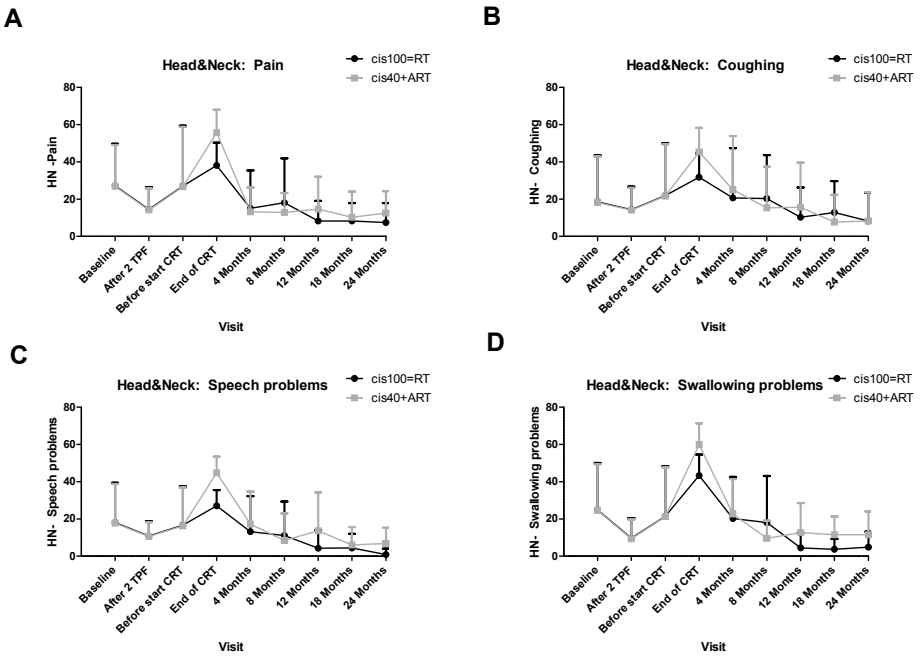
	Baseline (59/62)		After 2 TPF (42/59)		After CRT cis100+RT (18/27)		After CRT cis40+ART (16/29)		Difference between groups CRT
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	
EORTC QLQ-30									
Global health status	75.3	19.7	70.1	11.5	44.9	11.9	46.1	12.0	*p*=0.85
Physical function	92.0	15.1	80.5[a]	11.2	61.0	11.5	58.4	11.6	*p*=0.60
Role function	86.1	23.8	59.6[a]	15.2	45.0	15.9	36.0	16.2	*p*=0.32
Emotional function	74.7	21.4	84.9[a]	12.3	84.9	12.3	77.6	12.8	*p*=0.61
Cognitive function	91.7	15.2	87.6	18.0	70.2	18.2	67.4	18.3	*p*=0.61
Social function	87.5	18.1	79.6	14.5	66.4	14.9	67.1	15.1	*p*=0.91
Fatigue	20.8	20.9	35.7[a]	10.6	50.6	11.2	60.8	11.5	*p*=0.97[b]
Nausea/vomiting	2.5	8.6	8.6	5.4	30.9	6.0	37.6	6.3	*p*=0.20
Pain	25.6	29.7	11.0[a]	14.6	33.8	15.0	49.2	15.3	*p*=0.043[b]
Dyspnoea	6.7	14.7	9.0	11.2	16.0	11.4	19.9	11.6	*p*=0.45
Insomnia	25.0	27.9	18.1	11.6	27.6	12.1	27.5	12.3	*p*=0.99
Appetite loss	17.2	27.8	22.8	17.5	50.2	18.1	62.2	18.3	*p*=0.19[b]
Constipation	12.2	24.5	11.4	5.6	20.6	6.5	32.0	6.9	*p*=0.08[b]
Diarrhoea	2.2	8.4	12.9[a]	8.8	8.1	9.1	10.5	9.3	*p*=0.63
Financial problems	13.3	26.2	11.4	16.9	8.3	17.2	25.0	17.3	*p*=0.011[b]
EORTC QLQ-H&N 35									
Pain	27.2	22.5	14.5[a]	11.9	38.1	12.2	55.7	12.3	*p*=0.003b
Swallowing	24.9	25.1	9.7[a]	10.8	43.3	11.3	59.9	11.4	*p*=0.0101[b]
Senses	10.5	21.0	21.7[a]	15.2	45.0	15.6	47.3	15.8	*p*=0.74
Speech	18.1	21.3	10.9	7.9	27.1	8.5	44.8	8.7	*p*=0.004[b]
Social eating	21.9	26.0	15.3	14.3	41.4	14.6	39.9	14.8	*p*=0.82
Social contact	5.6	14.9	7.9	6.8	12.9	7.0	9.5	7.0	*p*=0.29
Sexuality	14.2	25.2	33.3[a]	19.4	53.9	20.0	55.0	20.1	*p*=0.90
Teeth	19.1	27.2	6.3[a]	14.1	10.4	14.5	15.2	14.9	*p*=0.53
Opening mouth	25.4	34.1	13.3[a]	16.8	27.2	17.3	31.5	17.4	*p*=0.58
Dry mouth	15.3	24.2	25.3[a]	18.2	44.4	18.7	56.8	18.9	*p*=0.14[b]
Sticky saliva	19.5	31.2	20.5	20.2	57.5	20.6	66.3	20.8	*p*=0.32
Coughing	18.6	25.0	14.4	12.3	31.8	12.8	45.3	13.0	*p*=0.076[b]
Feeling ill	12.4	21.4	19.8	26.6	48.1	32.8	47.9	32.1	*p*=0.98
Pain killers	61.0	49.2	41.2[a]	24.9	95.6	25.9	83.5	26.3	*p*=0.40[b]
Nutritional support	31.0	46.7	19.7[a]	18.5	83.0	19.6	66.0	20.0	*p*=0.20[b]
Feeding tube	5.1	22.2	4.8	15.7	52.3	16.6	85.0	17.0	*p*=0.003[b]
Weight loss	43.9	50.0	15.2[a]	14.6	81.3	16.1	33.3	17.1	*p*=0.0009[b]
Weight gain	17.9	38.6	50.8[a]	21.8	26.3	23.4	19.3	24.6	*p*=0.70

Abbreviations: cis100+RT: cisplatin 100 mg/m^2 on day 1,22,43 in combination with conventional radiotherapy, cis40+ART: cisplatin 40 mg/m^2 weekly in combination with accelerated radiotherapy, EORTC: European Organisation for Research and Treatment of Cancer; QLQ-C30: Quality of Life Questionnaire C30; QLQ-HN-35: Head and Neck Cancer-Specific Module.

[a] : Clinically significant different (10 points or more) after 2 TPF compared to baseline,

[b]: Clinically significant difference (10 points or more) between treatment arms after CRT

Figure 2. Mean symptom scores over time by treatment arm, A =pain, B = coughed, C= speech problems, D = swallowing problems



QOL: differences between treatment arms during chemoradiotherapy and changes over time

Global HRQOL decreased during chemoradiotherapy, equally in both arms (Table 3, Figure 1). Four months after end of treatment, global HRQOL increased and it was restored to baseline levels within 12 months after end of treatment. Beyond 12 months however, patients treated with cis100+RT had a higher score than the patients treated with cis40+ART, albeit not significant. Twenty-four months after end of treatment global HRQOL was equal in both arms (Table 4). Pain, swallowing problems, speech problems and coughing all worsened during chemoradiotherapy. A clinically and statistically significant difference between the treatment arms at end of treatment was found in all these symptom scores in favor of the patients treated with cis100+RT (Table 3, Figure 2). In both treatment arms, pain, swallowing problems and speech problems recovered to baseline level 4 months after treatment. There were no differences in mean scores of pain, swallowing problems, speech problems and coughing between the treatment arms at 12 and 24 months after end of treatment (Table 4).

Table 4. Mean scores over time at 1 and 2 years after treatment

	1 year follow up cis100+RT		1 year follow up cis40+ART		Difference between groups	2 year follow up cis100+RT		2 year follow up cis40+ART		Difference between groups
	Mean	*SD*	*Mean*	*SD*		*Mean*	*SD*	*Mean*	*SD*	
EORTC QLQ-30										
Global health status	84.0	9.9	71.4	24.1	*p*=0.07[a]	80.6	16.4	76.2	23.8	*p*=0.64
Physical function	91.3	10.7	85.1	16.1	*p*=0.22	92.8	7.8	88.6	11.4	*p*=0.35
Role function	87.2	15.4	73.5	37.7	*p*=0.19[a]	83.3	22.5	73.8	30.2	*p*=0.44
Emotional function	91.0	10.5	78.6	24.9	*p*=0.09[a]	83.3	25.1	88.1	16.6	*p*=0.66
Cognitive function	93.6	8.4	81.3	25.7	*p*=0.09[a]	88.9	16.4	69.0	33.9	*p*=0.19[b]
Social function	91.0	12.9	81.3	29.7	*p*=0.28	93.1	13.2	88.1	15.9	*p*=0.47
Fatigue	16.2	17.9	23.5	24.5	*p*=0.37	22.2	21.7	28.6	31.3	*p*=0.61
Nausea/vomiting	0.0	0.0	3.92	11.1	*p*=0.16	0.0	0.0	7.1	18.9	*p*=0.36
Pain	5.1	10.5	16.7	30.0	*p*=0.16[a]	8.3	16.7	7.1	18.9	*p*=0.89
Dyspnoea	2.6	9.2	13.7	20.6	*p*=0.08[a]	2.8	9.6	9.5	16.3	*p*=0.35
Insomnia	2.6	9.2	17.6	20.8	*p*=0.02[a]	11.1	21.7	14.3	17.8	*p*=0.75
Appetite loss	7.7	20.0	17.6	26.7	*p*=0.25	5.6	13.0	14.3	26.2	*p*=0.44
Constipation	0.0	0.0	11.8	20.2	*p*=0.046[a]	5.6	13.0	0.0	0.0	*p*=0.17
Diarrhoea	0.0	0.0	2.1	8.3	*p*=0.33	0.0	0.0	4.8	12.6	*p*=0.36
Financial problems	10.3	16.0	14.6	29.7	*p*=0.62	0.0	0.0	4.8	12.6	*p*=0.36
EORTC QLQ-H&N 35										
Pain	8.3	10.8	14.7	17.3	*p*=0.23	7.4	10.5	12.5	11.8	*p*=0.33
Swallowing	4.5	8.1	12.7	15.9	*p*=0.08	4.9	8.3	11.5	12.5	*p*=0.17
Senses	17.9	17.3	17.6	21.6	p=1.00	16.7	26.6	12.5	7.7	*p*=0.62
Speech	4.3	9.7	13.7	20.6	p=0.11	0.9	3.2	6.9	8.3	*p*=0.08
Social eating	10.9	11.0	19.1	24.6	p=0.19	6.9	12.7	17.7	22.0	*p*=0.18[b]
Social contact	0.5	1.8	7.3	14.8	p=0.23	0.6	1.9	1.7	4.7	*p*=0.47
Sexuality	12.5	16.1	27.8	26.5	p=0.09[a]	11.1	17.9	13.9	16.4	*p*=0.75
Teeth	2.6	9.2	14.6	27.1	p=0.11[a]	5.6	13.0	8.3	23.6	*p*=0.74
Opening mouth	12.8	16.9	15.7	20.8	p=0.69	13.9	22.3	20.8	24.8	*p*=0.52
Dry mouth	43.6	21.0	49.0	29.1	p=0.58	33.3	24.6	41.7	23.6	*p*=0.46
Sticky saliva	17.9	22.0	31.3	28.5	p=0.18[a]	16.7	22.5	37.5	21.4	*p*=0.05[b]
Coughing	10.3	16.0	15.7	23.9	p=0.49	8.3	15.1	8.3	15.4	*p*=1.00
Feeling ill	2.6	9.2	17.6	31.4	p=0.08[a]	8.3	20.7	4.2	11.8	*p*=0.61
Pain killers	7.7	27.7	23.5	43.7	p=0.24[a]	16.7	38.9	25.0	46.3	*p*=0.67
Nutritional support	15.4	37.6	23.5	43.7	p=0.60	0.0	0.0	12.5	35.4	*p*=0.35[b]
Feeding tube	0.0	0.0	5.9	24.3	p=0.39	0.0	0.0	12.5	35.4	*p*=0.35[b]
Weight loss	0.0	0.0	25.0	44.7	p=0.04[a]	8.3	28.9	12.5	35.4	*p*=0.78
Weight gain	46.2	51.9	31.3	47.9	p=0.43[a]	41.7	51.5	25.0	46.3	*p*=0.47[b]

Abbreviations: cis100+RT: cisplatin 100 mg/m^2 on day 1,22,43 in combination with conventional radiotherapy, cis40+ART: cisplatin 40 mg/m^2 weekly in combination with accelerated radiotherapy, EORTC: European Organisation for Research and Treatment of Cancer; QLQ-C30: Quality of Life Questionnaire C30; QLQ-HN-35: Head and Neck Cancer-Specific Module.

[a] : Clinically significant different (10 points or more) 1 year after treatment between treatment arms, [b]: Clinically significant difference (10 points or more) between treatment arms after 2 years.

Other HRQOL scales

All other HRQOL items were analyzed on an exploratory basis. Patients treated with cis40+ART scored clinically and statistically significantly worse on feeding tube dependence after CRT, but significantly better on nutritional support and use of painkillers. Patients treated with cis100+RT scored clinically and statistically significant worse on weight loss. Moreover, a clinically significant difference (> 10 points) was found for fatigue, appetite loss, constipation and dry mouth in favor of cis100+RT.

Furthermore, after two years follow-up patients treated with cis100+RT had clinically significant (> 10 points) better cognitive function and less sticky saliva compared to patients treated with cis40+ART. Patients treated with cis40+ART scored clinically significant worse on nutritional support and feeding tube than patients in arm cis100+RT (Table 4).

Sensitivity analyses

The proportion of patients experiencing an improvement or worsening of 10 or 20 points on the selected scales between baseline and end of chemoradiotherapy were compared between the treatment arms. These analyses showed the same trend of more pain in patients treated with cis40+ART compared to cis100+RT (Table 5). Moreover, a higher percentage of patients experienced a worsening in speech and swallowing problems in the group treated with cis40+ART, whereas more patients experienced improvement in the group treated with cis100+RT (Table 5).

Table 5. Sensitivity analysis: proportion of patients experiencing improvement/ worsening of selected scales after chemoradiotherapy compared to baseline

	Cis100 +RT (N=27) N (%)	Cis40+ART (N=29) N (%)	*p*-value for difference
Global qualiy of life[a]			
≥16.6 points worsening	15 (83.3)	10 (71.4)	0.669
≥ 25 points worsening	13 (72.2)	8 (57.1)	0.465
≥16.6 points improvement	0 (0)	1 (7.1)	0.437
≥ 25 points improvement	0 (0)	0	1.00
Coughing[b]			
≥33.3 points worsening	10 (58.8)	8 (57.1)	1.00
≥ 33.3 points improvement	3 (17.6)	3 (21.4)	1.00
Pain[c]			
≥11.1 points worsening	8 (47.1)	12 (85.7)	0.057
≥ 22.2 points worsening	7 (41.2)	11 (78.6)	0.067
≥11.1 points improvement	4 (23.5)	2 (14.3)	0.664
≥ 22.2 points improvement	2 (11.8)	1 (7.1)	1.00
Speech problems[d]			
≥11.1 points worsening	8 (47.1)	10 (71.4)	0.275
≥ 22.2 points worsening	6 (35.3)	8 (57.1)	0.289
≥11.1 points improvement	5 (29.4)	2 (14.3)	0.412
≥ 22.2 points improvement	4 (23.5)	2 (14.3)	0.664
Swallowing[e]			
≥11.1 points worsening	12 (70.6)	11 (78.6)	0.698
≥ 22.2 points worsening	11 (64.7)	10 (71.4)	1.00
≥11.1 points improvement	4 (23.5)	2 (14.3)	0.664
≥ 22.2 points improvement	3 (17.6)	1 (7.1)	0.607

Abbreviations: cis100+RT: cisplatin 100 mg/m^2 on day 1,22,43 in combination with conventional radiotherapy, cis40+ART: cisplatin 40 mg/m^2 weekly in combination with accelerated radiotherapy, [a]Global QoL score may take all values from 0 to 100 distant by 8.3 points (0, 8.3, 16.6, and so on). A shift of more than 10 points means a shift of 16.6 points or more. A shift of more than 20 points means a shift of 25 points or more. [b]Coughing score may take all values from 0 to 100 distant by 33.3 points (0, 33.3, 66.6, and so on). [c]Pain score may take all values from 0 to 100 distant by 2.8 points. [d]Speech score may take all values from 0 to 100 distant by 5.5 points. [e]Swallowing score may take all values from 0 to 100 distant by 2.8 points.

Discussion

HRQOL was assessed as secondary endpoint of the randomized phase II CONDOR study in patients with locally advanced head and neck cancer treated with TPF induction chemotherapy followed by cisplatin 100 mg/m^2 with conventional radiotherapy versus cisplatin 40 mg/m^2 with accelerated radiotherapy. Our study patients had a clinically and statistically significant better global HRQOL and physical function compared to the EORTC reference values for head and neck cancer patients with stage III-IV disease, which data were obtained during standard treatment[15]. Global HRQOL in our patients was also better than the patients included in the EORTC 24971/TAX 323 study [5]. This is a reflection of our selection criteria to include only very fit LAHNC patients, *i.e.,* no admissions for COPD in the past year, WHO 0-1, no weight loss more than 10% in the past three months, no active alcohol addiction and adequate bone marrow, liver and kidney function. Despite the excellent clinical condition of our patients at baseline reflected by the good global HRQOL, both treatment schedules were shown not feasible [8].

Global HRQOL declined during TPF and more during chemoradiotherapy, without any difference between the two treatment arms. The declining global HRQOL is in contrast with the results of the EORTC 24971/TAX 323 study, where global HRQOL improved during TPF[5]. In that study however, baseline global HRQOL was significantly lower than in our study (61.2 versus 75.3, respectively, p<0.001). After 2 cycles of TPF though, global HRQOL scores in the CONDOR and TAX 323 cohorts were comparable, 70.1 and 69.3, respectively. However, before start with CRT the global HRQOL scores of the CONDOR cohort decreased further (64.0) while the TAX 323 cohort remained stable (70.7; p<0.05). This is in agreement with Tribius et al who reported a significant greater deterioration in global HRQOL in patients with the highest baseline scores [16].

Global HRQOL restored to baseline levels within 12 months after end of treatment and remained at that level after 24 months. This is in line with other QOL in head and neck cancer studies[6,9,17] and is not very satisfying, because an improvement in QOL is desirable in cured patients. This pattern of no improvement in quality of life could be hypothetically caused by substitution of tumor-associated complaints at presentation by therapy sequelae-associated complaints leading to high symptom scores after the end of treatment [18]. Other studies concerning induction chemotherapy in head and neck cancer did not include QOL analysis [19-21].

In contrast to the declining global HRQOL scores, we found improvement of symptom scores, especially for pain and swallowing problems during TPF. This is in line with the results of the EORTC 24971/TAX 323 study [5] and presumably reflects tumor response, which is consistent with our efficacy results; 62% of the patients had partial or complete responses after TPF. The improvement in pain and swallowing problems did not lead to better global health. Probably the increase of other symptom scores such as fatigue, constipation and feeling ill plays a role in declining global health score.

Patients in the CONDOR study showed differences in physician rated toxicity scores of mucositis and dysphagia between the two treatment arms, showing more grade 3 and 4 mucositis in the patients treated with cis40+ART (59% versus 26%). The differences in symptom scores on speech problems, swallowing problems and pain in favor of the patients treated with cis100+RT are in line with this. As described earlier, the difference in mucositis can be explained by the toxicity caused by accelerated radiotherapy and the weekly radio-sensitizing effect of cisplatin [8,22]. High toxicity rates were observed with this treatment schedule, causing increasing symptom scores and decreasing global HRQOL during treatment. Despite this, all symptom scores in both treatment arms returned to baseline level at 12 months after end of treatment.

The main limitations of this study are the relatively small patient population and the difference in compliance between the two treatment arms at 4 months after chemoradiotherapy namely 45% versus 81% in cis40+ART and cis100+RT respectively. This difference in compliance rate at 4 months could have led to selection bias, since patients treated with cis40+ART experienced more toxicity during chemoradiotherapy and had worse symptom scores. Assuming that the patients treated with cis40+ART who had more symptoms were less likely to return the questionnaires, possibly the QoL scores at 4 months for this group are overestimated.

Our study has several strengths. It has a randomized design and it is the first study reporting on QOL in patients treated with induction chemotherapy followed by concomitant cisplatin-based chemoradiotherapy. Because we used standard and validated questionnaires, comparison of our results with other studies in locally advanced head and neck cancer is possible. Overall compliance in our study was high, with more than 60% returned questionnaires during treatment as well as after one and two years after end of treatment. This is much higher than the compliance rate of 45% after 9 months in the EORTC 24971/TAX 323 study [5].

In summary, in our patients with locally advanced head and neck cancer we found high baseline HRQOL scores. However, despite this initial high global health score, reflecting the good condition of the patients participating in the Condor study, both chemoradiation treatment schedules after prior TPF chemotherapy were shown not feasible. Especially patients treated with cis40+ART experienced high rates of grade 3 and 4 mucositis and consequently high symptom scores (pain, swallowing problems and feeding tube dependence) during treatment.

Importantly, global health and all the symptom scores, restored to baseline levels within 12 months after end of treatment in both arms and remained at that level at two years of follow up after end of treatment. This is remarkable given the impressive toxicity the patients have gone through, and important with regard to the quality of the survivorship of these patients who presented with such advanced localized head and neck carcinomas.

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Ototoxicity in locally advanced head and neck cancer patients treated with induction chemotherapy followed by intermediate or high dose cisplatin-based chemoradiotherapy

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Abstract

Background: This study evaluated ototoxicity in locally advanced head and neck cancer patients treated in the CONDOR study with docetaxel/cisplatin/5-fluorouracil (TPF) followed by conventional radiotherapy with concomitant cisplatin 100 mg/m^2 on days 1, 22, 43 (cis100+RT) versus accelerated radiotherapy with concomitant cisplatin weekly 40 mg/m^2 (cis40+ART).

Methods: Sixty-two patients were treated in this study. Audiometry was performed at baseline, during TPF, before start of chemoradiotherapy, and 1, 4, 8 and 12 months after treatment.

Results: A complete dataset of audiometric data was available of 12 patients treated with high dose cisplatin and of 11 patients treated with intermediate dose cisplatin. Patients in the high dose group showed significant more hearing loss than in the intermediate group at 4 kHz ((z=1.98; *p*=0.04) and 8 kHz (z=2.07; p<0.03)). Interindividual variation was high in both groups.

Conclusions: After induction TPF, more ototoxicity was observed in chemoradiotherapy with cis100+RT than after chemoradiotherapy with cis40+ART.

Introduction

Cisplatin-based concomitant chemoradiotherapy is the cornerstone of the treatment of patients with locally advanced head and neck cancer (LAHNC). [1] Several chemoradiation schedules are used, including the most common used RTOG schedule with cisplatin 100mg/m^2 on days 1, 22 and 43 and a weekly schedule with cisplatin 40 mg/m^2.[2-6] Cisplatin containing induction chemotherapy is being promoted as an attempt to further improve survival of these patients.[1,7,8] However, studies exploring a combination of induction chemotherapy and concomitant chemoradiotherapy, did not use the standard cisplatin-based chemoradiotherapy, i.e. cisplatin 100 mg/m^2 on day 1, 22 and 43. Therefore, a randomized phase II feasibility study was performed of induction chemotherapy with docetaxel/cisplatin/5-fluorouracil (TPF) followed by concomitant cisplatin-based chemoradiotherapy, with the two most commonly used cisplatin schedules, the CONDOR study.[9] After induction treatment with TPF, patients were randomized to either high dose cisplatin, i.e. 100mg/m^2 on days 1, 22 and 43 in combination with conventional RT or intermediate dose cisplatin, i.e. 40 mg/m^2 weekly during 6 weeks in combination with accelerated radiotherapy. The aim of this study was to evaluate the feasibility and toxicity of these schedules. The main conclusion of the study was that induction chemotherapy with 4 cycles of TPF followed by cisplatin-based concomitant chemoradiotherapy was not feasible, since the total planned dose of cisplatin during the concomitant chemoradiotherapy could only be administered in 32% of the patients due to severe toxicity, i.e. febrile neutropenia, dehydration, dysphagia and mucositis, which led to premature closure of the study. Induction chemotherapy followed by chemoradiotherapy with cisplatin is not standard of care.

The most common, well-known, and potentially permanent side effects encountered in patients treated with high dose cisplatin are ototoxicity, nephrotoxicity and neurotoxicity. Ototoxicity caused by cisplatin is related to both dose and schedule and mainly affects the high-frequency area.[10,11] Most studies on cisplatin-induced ototoxicity in LAHNC have been performed in patients treated with high dose cisplatin, i.e. 100 mg/m^2 on days 1, 22 and 43.[12] The incidence of sensorineural hearing loss after chemoradiotherapy in LAHNC patients is 17-88%.[13] This wide range is due to heterogeneity of the population, different definitions of ototoxicity and different treatment schedules. Daily low dose cisplatin chemoradiotherapy leads to less acute hearing loss as compared to high dose cisplatin in a pooled analysis.[14] However, no prospective studies were performed to compare ototoxicity using different schedules of cisplatin-based chemoradiation. Moreover, no data are available on TPF-induced hearing loss.

Besides cisplatin-induced ototoxicity, radiotherapy can also lead to hearing loss. This sensorineural hearing loss is correlated with the radiation dose to the cochlea and affects mainly the high-frequency area. Another type of radiotherapy associated hearing loss may be conductive hearing loss. This can be caused by middle ear effusion secondary to loss of Eustachian tube competence if the tube included in the radiation treatment volume.
In the CONDOR study the effect on ototoxicity of two concomitant, high dose and intermediate dose, cisplatin schedules was prospectively evaluated. It was hypothesized that patients treated with intermediate dose cisplatin would develop less hearing deterioration than those treated with high dose cisplatin.

Methods

Treatment schedules

From 2008 until 2012, 62 LAHNC patients were included in this randomized phase II study in three centers in the Netherlands. The main study results were published before.[9] Induction chemotherapy consisted of docetaxel 75 mg/m^2 on day 1, followed by cisplatin of 75 mg/m^2, day 1 and fluorouracil 750 mg/m^2 per day, by continuous infusion on days 1-5. This treatment was administered every three weeks for 4 cycles in case of a good response, or 2 cycles in case of no response. Thereafter, patients were randomly assigned to either concomitant chemoradiotherapy with high dose cisplatin, 100mg/m^2 on days 1, 22 and 43, combined with conventional radiotherapy or concomitant chemoradiotherapy with weekly intermediate dose cisplatin, 40 mg/m^2 for 6 cycles, with accelerated radiotherapy. Thus, in total patients could receive up to 600 mg/m^2 cisplatin in the high dose cisplatin group and 540 mg/m2 in the intermediate group. Conventional radiotherapy consisted of 5 fractions per week with a total treatment time of 7 weeks. Accelerated radiotherapy was given in 6 fractions per week, with a total treatment time of 6 weeks. During one of the week days two fractions were delivered with an interval of at least 6 hours. In both arms intensity-modulated radiation therapy (IMRT) was mandatory. Dose to gross tumor volume was 70Gy in 35 fractions, dose to elective nodal areas was 46 Gy in 23 fractions in both arms.

Audiometry

Audiometry was performed according to standard procedures using standard equipment. Air-conduction thresholds were determined in 1, 2, 4 and 8 kHz. Bone-conduction thresholds were measured, from 1 kHz to 4 kHz. The equipment was calibrated according to ISO 389-1 (ISO, 1998). All measurements were carried out in special sound treated double-walled booths.

According to the study protocol, audiometry was carried out at baseline, during and after TPF before start of chemoradiotherapy, and 1, 4, 8 and 12 months after the ending of treatment. To increase the accuracy, hearing thresholds of the two ears were averaged. In case of asymmetry in thresholds at the base-line measurement exceeding 15 dB HL (hearing loss), only the data of the best hearing ear were considered.

Statistics

To compare hearing deterioration in the two groups statistically, non-parametric testing was applied. The hypothesis was that high dose group patients would show more hearing deterioration than those in the intermediate group. Audiometric data at a frequency of 1, 2, 4 and 8 kHz of 4 months' post-chemoradiotherapy and 1-year post-chemoradiotherapy were compared to baseline, in those patients were data were available.

Furthermore, we analyzed the patients based on their baseline thresholds. We divided our patients in two categories based on their baseline thresholds. Category 1 contained all the data of patients with baseline threshold at or below 50 dB HL, whereas category 2 contained the data of patients with baseline threshold above 50 dB HL(at 2, 4 and 8 kHz). We compared our results with those of Zuur et al.. She treated LAHNC patients with intra arterial cisplatin and used sodium thiosulphate rescue.[15]

Results

Patients and treatment characteristics

Sixty-two patients participated in the study. Of these 62 patients 32% received the planned dose of cisplatin during concomitant chemoradiotherapy. We did not have complete audiometric datasets of all patients at the different time points, which was mostly caused by no shows due to physical conditions. The 4 months' post-chemoradiotherapy audiometric data were available of 13 patients treated with high dose and of 12 patients treated with intermediate dose cisplatin. One patient in each group was excluded because of lack of baseline audiometric data or drop out before randomization, which led to 12 patients in the high dose group and 11 in the intermediate dose group and these two groups were used to test the research hypothesis. Moreover, of 8 and 7 patients of these groups, respectively, also the 1 year's post chemoradiotherapy audiometric results were available. Table 1 shows the baseline and treatment characteristics of the patients included in this analysis. Patients had a median age of 57 years. The majority of patients was male and had oropharyngeal cancer. Eighty-seven percent of the patients included in this analysis received all 4 planned cycles of TPF induction chemotherapy. Ten patients in the high dose group received all 3 cycles and 2 pts received 2 of the planned cycles cisplatin, with a mean cisplatin dose during treatment of 497.7 mg/m^2. In the intermediate dose group, 3 patients received all planned 6 cycles, 4 patients received 5 cycles, the others received less cycles with a median total cisplatin dose during all treatment of 482.2 mg/m^2. The median cisplatin dose during all treatment was not significantly different between the treatment arms.

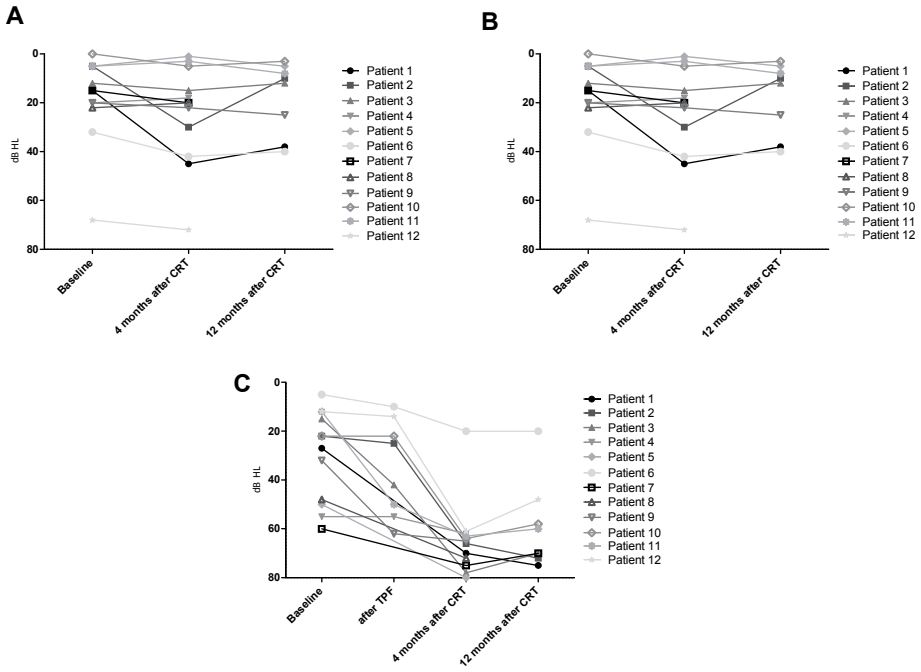
Audiometry

With regard to the high and intermediate cisplatin dose groups, per frequency, the 4-months and 1-year post chemoradiotherapy threshold were compared to the baseline threshold. Figures 1 and 2 present the individual data. At 8 kHz and 4 kHz, the patients treated with high dose cisplatin showed more severe deteriorations in hearing than the group treated with intermediate dose cisplatin (z=2.07; p<0.03 and z=1.98; p=0.04, respectively) (Figure 1 and 2). At 2 kHz level a similar trend was observed, albeit less prominent and non-significant. In each group there was a large variation between individuals.

Table 1. Characteristics of patients participating in the audiometric analyses and their treatments

Variables	High dose group N(%)	Intermediate dose group N (%)
Sex		
Male	7 (58.3)	10 (90.9)
Female	5 (41.7)	1 (9.1)
Age, years		
Mean	52.7	53.4
Range	37 – 64	27 - 64
WHO performance status		
PS 0	12 (100)	10 (90.9)
PS 1	0 (0)	1 (9.1)
Tumor site		
Oral Cavity	2 (16.7)	1 (9.1)
Oropharynx	7 (58.3)	6 (54.5)
Hypopharynx	2 (16.7)	3 (27.3)
Larynx	1 (8.3)	1 (9.1)
T classification		
T 1	0 (0)	1 (9.1)
T 2	2 (16.7)	0 (0)
T 3	3 (25.0)	8 (72.7)
T 4	7 (58.3)	2 (18.2)
N classification		
N 0	3 (25.0)	3 (27.3)
N 1	2 (16.7)	0 (0)
N 2a	2 (16.7)	2 (18.2)
N 2b	2 (16.7)	4 (36.4)
N 2c	3 (25.0)	2 (18.2)
TPF cycles		
1	0 (0)	0 (0)
2	1 (8.3)	0 (0)
3	1 (8.3)	1 (9.1)
4	10 (83.3)	10 (90.9)
Cisplatin dose during CRT		
300 mg/m^2	2 (16.7) 3 cycli	0 (0)
240 mg/m^2	0 (0)	3 (27.3) 6 cycli
200 mg/m^2	10 (83.3) 2 cycli	4 (36.4) 5 cycli
160 mg/m^2	0 (0)	2 (18.2) 4 cycli
120 mg/m^2	0 (0)	2 (18.2) 3 cycli
Median	217 mg/m^2	189 mg/m^2
Mean RT dose	67.3 Gy	69.3 Gy
Cumulative cisplatin dose (total treatment)	497.9 mg/m^2	482.2 mg/m^2

Figure 1: Hearing capability (in dB HL) at different frequencies in high dose cisplatin group over time (n=12)



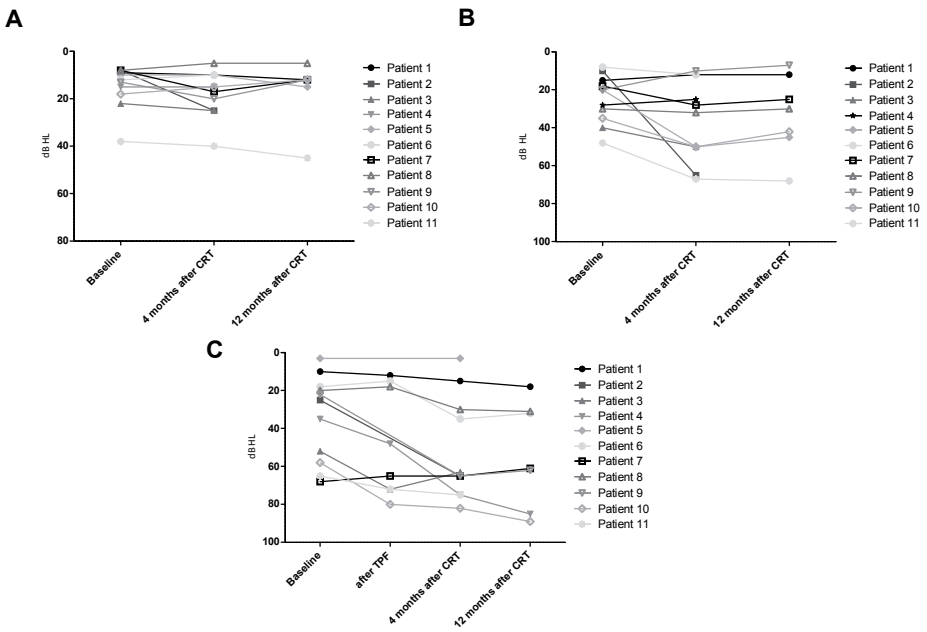
A = 2 kHz, B= 4 kHz and C = 8 kHz

Long-term data, 1-year post chemoradiotherapy, were available for 15 patients, 8 in the high dose and 7 in the intermediate dose group. Overall in all these 15 patients, limited improvements in hearing thresholds were found of (mean with standard deviations) 2.9 +/- 6.3 dB, 4.7 +/- 4.9 dB and 1.7 +/- 5.9 dB at 8kHz, 4kHz and 2 kHz, respectively. On an individual level, a large spread was seen (Figures 1 and 2). It should be kept in mind that the standard deviation of test-retest hearing thresholds is 6.2 dB [16]. As the thresholds of the left and right ear were averaged, theoretically, the standard deviation decreases to 4.4 dB. Therefore, the 95% confidence interval for threshold measurements as carried out in this study equals 8.8 dB (twice the standard deviation). With this in mind, one patient from the high dose group showed a significant improvement in hearing of 13, 17, 20 dB HL for the 3 frequencies. One further patient from the high dose group had a significant improvement at 4 kHz (of 14 dB) and one patient from the intermediate group had a significant deterioration of 10 dB at 8kHz only. For all the others no significant changes were found.

Bone-conduction testing revealed no air-bone gap in any of these patients, suggesting that the observed changes over time in hearing thresholds were due to cochlear functioning only.

The effect of radiation on hearing deterioration was also studied. An asymmetry in radiation dose on the middle ear was found in eight patients. In 5 of these 8 patients there was no difference in hearing deterioration between both ears. In two patients however, hearing loss was more prominent in the ear that received the highest radiation dose, 15 and 23 dB, respectively. Remarkably, in 1 patient in the intermediate dose group, we found a decline of 15 dB in the ear that received the lowest radiation dose.

Figure 2: Hearing capability (in dB HL) at different frequencies in intermediate dose cisplatin group over time (n=11)



A = 2 kHz, B= 4 kHz and C = 8 kHz

The data presented in the figures were analyzed in more detail, taking into account that the amount of deterioration in hearing threshold depends on the baseline value. Table 2 shows the mean deterioration of our patients with baseline thresholds in the category 1 (baseline hearing thresholds at or below 50 dB HL). Mean deterioration data of Zuur et al. (averaged data quartiles 1 and 2) is added for comparison[15]. Again, hearing deterioration is mostly modest in the intermediate dose group while that of the high dose group is more prominent.

Table 2. Mean deterioration in hearing thresholds (in dB) for the subgroups of patients in quartiles 1 and 2 from the high (100 mg/m2) and intermediate dose (40 mg/m2) cisplatin groups compared to Zuur et al. [15] (intra-arterial cisplatin, high dose, 150 mg/m2 with sodium thiosulphate rescue)

Frequency	High dose cisplatin	Intermediate dose cisplatin	Zuur et al. intra-arterial cisplatin
8 kHz	41 dB	20 dB	38 dB
4 kHz	30 dB	12 dB	22 dB
2 Khz	8 dB	3 dB	6 dB

The data of Zuur et al., were calculated from their Figure 5. Per subgroup, the mean deterioration over time was calculated and the mean data of the quartiles 1 and 2 subgroups were subsequently average as well as those of the quartiles 3 and 4 subgroups.

Discussion

We show that after induction chemotherapy with TPF, chemoradiotherapy with high dose cisplatin seems to be more ototoxic than chemoradiotherapy with intermediate dose cisplatin in a limited number of LAHNC patients. The cumulative dose of cisplatin was similar. We showed a significant difference with more hearing loss at hearing threshold at 4 and 8 kHz in chemoradiotherapy with high dose versus intermediate dose cisplatin. Furthermore, no structural improvement in hearing thresholds was found during 1-year's follow-up after the end of treatment. The variation in hearing loss between individuals was large. Hearing deterioration caused by the treatment mainly affects the high frequencies, as has been described before.[11,15]

Differences between cisplatin schedules on ototoxicity have been described earlier. Vermorken et al. studied ototoxicity in 48 patients treated with different doses of cisplatin.[17] They found higher incidences of ototoxicity in patients treated with higher cumulative doses, but also in patients treated with higher dosages per infusion and also with rapid infusion. Rademakers-Lakhai et al. studied ototoxicity in a cohort of non-small cell lung cancer patients treated with a dose-escalating schedule of cisplatin in combination with gemcitabine. [18] Cisplatin doses ranged from weekly 25 mg/m^2 to 105 mg/m^2 every two weeks. They concluded that hearing loss after cisplatin was dose, schedule and frequency dependent, with the highest losses at a dose of cisplatin ≥ 60 mg/m^2 per cycle. Niemensivu et al. also compared ototoxicity in LANHC patients treated with chemoradiotherapy with high and intermediated dose cisplatin.[19] They collected a prospective cohort of 22 patients treated with intermediate dose cisplatin and compared that with a retrospective cohort of 9 patients treated with high dose cisplatin. This comparison showed more hearing problems in patients in the high dose group, especially at the higher frequencies.

Analysis based on baseline thresholds also showed more ototoxicity in the high dose group. Zuur et al. who treated patients with cisplatin intra-arterially 150 mg/m^2 on days 1, 8, 15 and 22, divided their patients in 4 quartiles based on baseline thresholds. They reported an obvious deterioration in the 8 kHz threshold after treatment for patients in quartiles 1 and 2 (patients with favorable pretreatment hearing) of 41 dB and 35 dB, respectively.[15] For quartiles 3 and 4, thus baseline threshold above 50 dB HL, the mean deterioration was significantly less, approx. 10 dB for either quartile. Our patients treated with high dose cisplatin showed somewhat more hearing deterioration than the patients of Zuur et al. treated with intra-arterial cisplatin 150mg/m^2 with sodium thiosulfate cisplatin rescue.

Not only higher dosages of cisplatin can cause differences in ototoxicity, co-medication can also be of influence. As described earlier, furosemide is known to induce ototoxicity especially when combined with cisplatin.[17,20] Unfortunately, the use of furosemide was not registered in our population. Patients treated with high dose cisplatin receive more fluid for pre- and posthydration than patients with intermediate dose cisplatin, which conceivably could have led to more furosemide use.

Theoretically, the different radiation schedules in our study could also have played a role in the differences in ototoxicity between the treatment arms. We did not find data in literature on LAHNC patients, but in a cohort of patients with glioblastoma multiforme, ototoxicity of two different treatment schedules with cisplatin 30 mg/m^2 weekly combined with standard radiotherapy versus accelerated radiotherapy was studied.[21] They found no statistically or clinically differences in ototoxicity between both arms, suggesting that acceleration of radiation did not change susceptibility to hearing loss.

Compared with the data of Zuur et al, who treated patients with four courses of intra-arterial cisplatin 150 mg/m^2 with sodium thiosulfate cisplatin neutralization or three courses of high dose chemoradiotherapy 100 mg/m^2, our results in patients with high dose cisplatin are in the same range as their patients, which is remarkable, because our patients also had received prior TPF induction therapy with cisplatin with a maximum of 300 mg/m^2 in total, 75 mg/m2 per cycle.

Theunissen et al. showed discrete progressive hearing loss in long-term follow up (median 4.5 years) in patients treated with high dose chemoradiotherapy.[22] Also, Ho et al. found progressive hearing loss in long-term follow up of patients with nasopharyngeal cancer treated with radiotherapy and chemoradiotherapy with cisplatin. However, in the latter study, radiotherapy may have played a large role in the hearing loss because of the higher dose of radiation on the Eustachian tube and middle ear in patients with nasopharyngeal cancer.[23]

Ototoxicity caused by chemoradiotherapy is a serious problem, sometimes even dose-limiting. Although there are some known risk factors, such as age, baseline hearing thresholds and cumulative dose of cisplatin, it is still impossible to predict which patient will suffer from hearing loss.

Genetic variations of drug-processing genes, pharmacogenetics, may play a role in the difference of experienced toxicity. Genetic variants of single nucleotide polymorphisms, SNPs, are studied in this regard. For example, an association of genetic variants in Thiopurine S-methyltransferase (TPMT) and Catechol-O-methyltransferase (COMPT) with

cisplatin-induced hearing loss in children was described by Ros et al.[24] Moreover, Vos et al, showed a significant correlation between ACYP2 variant rs1872328 and cisplatin-induced ototoxicity in children with osteocarcoma.[25] The ACYP2 is a gene that encodes an acylphosphatase expressed in muscle and the cochlea and may be involved in hair cell development.

Other studies found an association with other polymorphisms, for example in the genes megalin, glutathione-S-transferases.[26,27] A potentially protective effect for ototoxicity was described for genetic variants of the Otos gene.[28]

The main strength of our study is the randomized design, with prospective audiometrics at predefined moments during treatment. As far as we know, this is the first study which compares audiological data in a prospective randomized trial in patients receiving high and intermediate dose cisplatin combined with radiotherapy, after TPF induction chemotherapy.

Unfortunately, because of a poor performance status during treatment, not all subjects participated in all audiological measurements. Consequently, the analysis had to be carried out in a relatively limited number of patients.

In summary, we have observed more frequent and more severe ototoxicity in patients treated with high dose cisplatin, although the number of patients was limited. From a toxicity perspective, our current data on ototoxicity and our previous data on nephrotoxicity do not support high dose cisplatin schedules over intermediate doses in LAHNC patients.[29]

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Genetic variants as predictive markers for ototoxicity and nephrotoxicity in patients with locally advanced head and neck cancer treated with cisplatin-containing chemoradiotherapy (the PRONE study)

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Submitted

Abstract

Objectives

Ototoxicity and nephrotoxicity are well-known, potentially irreversible side effects of cisplatin-containing chemoradiotherapy in locally advanced head and neck cancer (LAHNC) patients. Several predictive genetic variants have been described, but unknown in a well-defined group of LAHNC patients. The aim of this study is to investigate these genetic variants as predictors for ototoxicity and nephrotoxicity in LAHNC patients treated with cisplatin-containing chemoradiotherapy.

Methods

A prospective cohort of 102 LAHNC patients treated with cisplatin-containing chemoradiotherapy was genotyped for 10 genetic variants in the genes *ACYP2, COMT, TPMT, WFS1, OCT2, MATE1* and *XPD* and evaluated for their association with cisplatin-induced ototoxicity (*ACYP2, COMT, TPMT* and *WFS1)* and nephrotoxicity (*OCT2, MATE* and *XPD*). Ototoxicity was determined by patient-reported complaints according to CTCAE v 4.03 as well as tone audiometrical assessments. Nephrotoxicity was defined as a decrease of ≥25% in creatinine clearance by the MDRD during treatment compared to baseline.

Results

A significant association was observed between carriership of the A allele for rs1872328 in the *ACYP2* gene (0.019) and cisplatin-induced clinically determined ototoxicity, but not with ototoxicity measured by tone audiometrical assessments (p=0.449). Carriership of a T allele for rs316019 in the *OCT2* gene was significantly associated with a decrease of more than 25% in creatinine clearance at any time during chemoradiotherapy (p=0.022), but not with nephrotoxicity at the end of the chemoradiotherapy. No associations were found with the other genes.

Conclusion

We showed prospectively that in LAHNC patients genetic variants in *ACYP2* and *OCT2* are significantly associated with ototoxicity and nephrotoxicity, respectively. Validation studies are necessary to prove the added value for individualized treatments plans in these patients.

Introduction

Head and neck cancer is a common type of cancer worldwide, with an estimation of 61,670 new patients diagnosed in the United States and 139,531 new cases in Europe in 2016 [1,2]. The most frequently used treatment for patients with locally advanced head and neck cancer (LAHNC) is concomitant chemoradiotherapy with cisplatin, which improves loco-regional control as well as overall survival compared to radiotherapy alone. [3] [4] Chemoradiotherapy can also be applied as adjuvant treatment in case of a high recurrence risk after surgery. Concomitant chemoradiotherapy with cisplatin however, induces a high rate of acute toxicities such as mucositis, dysphagia and dermatitis, most of which will recover with time, but can also induce irreversible ototoxicity and nephrotoxicity. [3,5-7]

Ototoxicity, characterized by sensorineural hearing loss, can be an adverse effect of either systemically administered cisplatin or radiotherapy to the inner ear. Both chemotherapy and radiotherapy cause lesions in the cochlea, which may lead to ototoxicity. [8] Ototoxicity caused by cisplatin begins with high frequency loss and is often bilateral, permanent and can be progressive also after the end of administration of cisplatin. [8,9] Chemotherapy with cisplatin is applied either at a dose of 100mg/m^2 every 3 weeks for 3 cycles (high dose) or at a dose of 40mg/m^2 every week for 6 or 7 cycles (intermediate dose). [5,6] The incidence of ototoxicity is dependent on the cisplatin dose per course and cumulative dose (79% with high dose and 31% with 6mg/m^2 daily). [10,11] Besides ototoxicity, another common side effect of cisplatin is nephrotoxicity that also can be irreversible. However, unlike ototoxicity, part of the nephrotoxicity can be reduced by prophylactic measures such as hyperhydration with high Natrium Chloride dose regimens. The occurrence and the severity of nephrotoxicity is also related to the cisplatin dose; 100% of the patients treated with high dose cisplatin experienced nephrotoxicity of any grade compared with 75% of the patients with intermediate dose cisplatin. [7]

With the aim to prevent ototoxicity and nephrotoxicity, several studies have been performed to identify risk factors and predictive markers. Known clinical risk factors for ototoxicity after chemoradiation in LAHNC patients are the cumulative dose of cisplatin and cumulative radiation dose to the cochlea, younger age, good pretreatment hearing, administration of furosemide and low levels of serum albumin and hemoglobin. [12] [13] However, cisplatin-induced toxicity cannot totally be predicted by these factors. Recently, various studies found genetic variants, i.e., single nucleotide polymorphisms (SNPs), that are associated with cisplatin-induced side-effects. Genetic variants in *ACYP2* (Acylphosphatase 2) and *WFS1* (Wolframin ER transmembrane glycoprotein) were identified as predictive markers for hearing loss. [14-18] The *ACYP2* gene is expressed in the cochlea.[15] Mutations in *WFS1* can cause progressive deafness after administration of cisplatin. [19] Cisplatin-

induced ototoxicity could be related to increased levels of S-adenosylmethionine through reduced thiopurine S-methyltransferase *(TPMT)* or catechol O-methyltransferase (*COMT)* activity, however, their predictive value for ototoxicity is controversial. [20,21] With respect to nephrotoxicity, genetic variants in *OCT2* (organic cation transporter 2), *MATE1* (multidrug and toxin extrusion 1) and *XPD* (xeroderma pigmentosum group D), are believed to be of predictive value.[22-25] *OCT2* and *MATE1* are expressed in the human kidney at the basolateral membrane of renal proximal tubules, and are involved in the secretion of various cationic substances from the circulation into tubular cells. In that way *OCT2* and *MATE1* are involved in the cellular uptake of cisplatin.[22,24] *XPD* is part of the nucleotide excision repair pathway and is involved in removal of cisplatin and radiotherapy induced DNA damage. [25,26]

However, most of the above-mentioned studies showed correlations in a limited number of patients and thus confirmation of the association between the SNPs and cisplatin related side effect is needed. Furthermore, the studies were performed in patients with other cancers than head and neck cancer. Therefore, the aim of this study is to investigate the relationship between the different SNPs and cisplatin-induced ototoxicity and nephrotoxicity in LAHNC patients.

Materials and methods

Patients and treatment

A cohort of Dutch patients with pathologically proven LAHNC and treated with cisplatin-based concomitant chemoradiotherapy was prospectively recruited at the Radboud university medical center, Nijmegen, and the Erasmus University Medical Center, Rotterdam, in the Netherlands. Eligibility criteria included a minimum age of 18 years and a WHO performance score of 0 or 1. Patients with distant metastasis and renal dysfunction were not considered eligible. Before inclusion, written informed consent was obtained from all patients. The local ethical committee waived the study from ethical approval.

Patients were treated with cisplatin-based concomitant chemoradiotherapy for either primary treatment or adjuvant treatment. Concomitant chemoradiotherapy was administered in three different treatment schedules; *1.* Conventional radiotherapy in combination with cisplatin 100 mg/m^2 on days 1, 22 and 43; *2.* Accelerated radiotherapy combined with cisplatin 40 mg/m^2 on a weekly basis for 6 weeks; *3.* Conventional radiotherapy combined with cisplatin 40 mg/m^2 on a weekly basis for 7 weeks. Intensity-modulated radiation therapy (IMRT) was mandatory. Dose to gross tumor volume was 70 Gy/35 fractions, dose to elective nodal areas 46 Gy/23 fractions.

Cisplatin was given by infusion in combination with standard prehydration, posthydration and anti-emetics. If during the weeks of treatment the creatinine clearance was below 60 mL/min because of dehydration, cisplatin was only administered if the creatinine clearance recovered to 60 mL/min after rehydration. Dose modifications and discontinuation of cisplatin were performed according to standard local practice.

Measurements

Tone audiometry was performed according to standard procedures under standardized conditions. Air-conduction and thresholds were determined in 1, 2, 4, 8, 10, 12.5 and 16 kHz. Bone-conduction thresholds were measured, from 1 kHz to 8 kHz. According to the study protocol, audiometry was carried out at baseline, during chemoradiotherapy after 100 mg/m^2 or 120 mg/m^2 cisplatin as total dosage at that moment and within 2 months after completion of treatment.

Ototoxicity was scored utilizing two different approaches. In the first approach, clinically determined ototoxicity, physicians asked their patients to the hearing loss according to the CTCAE 4.03 (grade 1: no hearing loss, grade 2: hearing loss but hearing aid or intervention not indicated, grade 3: hearing loss with hearing aid or intervention indicated). In the second approach, hearing loss was classified using the tone audiometric data from baseline and end of treatment based on the ear with the worst hearing loss. Hearing

loss was defined by threshold shifts at 2,4 or 8 kHz of ≤ 25 dB (grade 1; no hearing loss), threshold shift of 26-40 dB (grade 2; mild hearing loss) or threshold shift of ≥ 40 dB (grade 3; moderate-profound hearing loss). [16]

Additionally, weekly laboratory tests were performed including creatinine and the creatinine clearance by use of calculation of the Modification of Diet in Renal Disease (MDRD). Nephrotoxicity was defined as a decrease of 25% or more in creatinine clearance by the MDRD at any point during treatment compared to baseline. We used a decrease of 25% or more in creatinine clearance as definition for nephrotoxicity based on the international accepted Risk, Injury, Failure, Loss and End Stage Renal Disease (RIFLE) criteria.[7] Blood or saliva (Oragene saliva collection kit (DNA Genotek, Kanata, Ontario, Canada)) were used for DNA extraction.

Genotyping

Genotyping of genetic variant in *TPMT* (rs12201199, rs1800460, rs1142345) and *COMT* (rs9332377) were performed using Taqman SNP genotyping according to the instructions of the manufacturer (ThermoFisher, Nieuwerkerk aan den IJssel, The Netherlands). The other genetic variants (*COMT* rs4646316, *ACYP2* rs1872328, *OCT2/SLC22A2* rs316019, *WFS1* rs62283056, *XPD/ERCC2* rs13181 and *MATE1* rs2289669) were genotyped using Kompetitive Allele Specific PCR (KASP™) (KASPar-On_Demand assays (Laboratory of the Government Chemist (LGC) Genomics, Hoddesdon, UK)) according to the instructions of the manufacturer [14,27]. Analysis of the Taqman and KASP assay was carried out on a 7500FAST Real-Time PCR System (ThermoFisher). Genotypes were scored using 7500 software (v2.0.6, ThermoFisher). Negative controls as well duplicates (8%) were included as quality controls for genotyping.

Statistics

A sample size calculation showed that the inclusion of 100 patients in our study would give us 80% power to identify a statistically significant association between a SNP and our outcome of ototoxicity, assuming a 40% ototoxicity rate, an alpha of 0.05, an allelic OR of 3 and a minor allele frequency of 10%. [20,21]

The association between the SNPs and clinically relevant hearing loss ("yes" versus "no") and between the SNPs and nephrotoxicity ("yes" versus "no" decrease in MDRD ≥ 25%) were analyzed with a Pearson's chi-square or Fisher-exact tests. P-values were tested two-sided and were considered as statistically significant when <0.05. SPSS version 22 was used for performing the analyses.

Meta-analysis of the data of ototoxicity and *ACYP2* was performed using a fixed-effects model in review Manager version 5.3 (The Cochrane Collaboration, Oxford, UK).

Results

Between August 2013 and February 2017, 103 patients were included in this study. One patient withdrew consent. In 10 cases no blood or saliva samples were available for DNA analysis. Thus, in total 92 patients were included in the final analysis. Thirty-eight patients and eighteen patients were treated with low dose cisplatin 40mg/m² weekly for 6 and 7 weeks, respectively, and thirty-five patients were treated with high dose cisplatin 100mg/m² on days 1, 22 and 43. Baseline characteristics are shown in Table 1.

Table 1. Patient characteristics of the 92 patients analyzed

	Number of patients (%)
Age mean (range)	57.8 (28-69)
Gender	
Male	67 (72.8)
Female	25 (27.2)
WHO score	
0	63 (68.5)
1	28 (30.4)
2	1 (1.1)
Treatment indication	
Primary treatment	62 (67.4)
Postoperative treatment	29 (31.5)
Primary treatment tumor, postoperative treatment for lymph nodes	1 (1.1)
Primary site	
Oral cavity	21 (22.8)
Oropharynx	42 (45.7)
Hypopharynx	10 (10.9)
Larynx	13 (14.1)
Unknown primary	4 (4.3)
Nasal vestibule	2 (2.2)
Cisplatin dose	
40 mg/m²	57 (61.3)
100 mg/m²	35 (37.6)
Cumulative cisplatin dose (median, range)	240mg (80-300)

Ototoxicity

In all 92 patients, data on clinically-determined ototoxicity were available, whereas hearing loss after treatment based on tone audiometric measurements was available for 79 patients. Of all the 92 patients, six patients reported new hearing loss without a hearing

aid or intervention indicated (grade 2) and one patient reported hearing loss for which a hearing aid or intervention was indicated (grade 3) at end of treatment. Of these 7 patients, 4 were treated with cisplatin 40 mg/m^2 and 3 were treated with cisplatin 100 mg/m^2. Based on audiometric measurements, of the 85 patients included in the analysis, 52 patients (55.9%) were graded no hearing loss (grade 1), whereas 16 patients (17%) and 11 patients (12%) were graded mild (grade 2) and moderate-profound (grade 3) hearing loss, respectively. Nine of the 11 patients with moderate-profound hearing loss were treated with cisplatin 100 mg/m^2. There was no statistically difference in cumulative cisplatin dose in patients with or without hearing loss when measured clinically or audiometrically (p=0.231 and p=0.142).

Unfortunately, bone conduction was only available in 55 patients. Of these 41 patients (74%) showed no hearing loss, 11 patients (20%) showed mild hearing loss, 3 patients (6%) suffered moderate-profound hearing loss. (Table 2)

Table 2. Ototoxicity and nephrotoxicity

	Number of patients (%)
Ototoxicity clinically at the end of treatment (N=92)	
None (grade 0 or grade 1)	85 (92.4)
Hearing loss without hearing aid indicated (grade 2)	6 (6.5)
Hearing loss with hearing aid indicated (grade 3)	1 (1.1)
Ototoxicity by tone audiometry (N=79)	
None (≤25 dB loss)	52 (65.8)
Mild (26-40 dB loss)	16 (20.3)
Moderate (≥40 dB loss)	11 (13.9)
Ototoxicity by audiometry, only bone conduction (N=55)	
None (≤25 dB loss)	41 (74.5)
Mild (26-40 dB loss)	11 (20)
Moderate (≥40 dB loss)	3 (5.5)
Nephrotoxicity any time during study (N=92)	
MDRD < 25% decrease	39 (42.4)
MDRD ≥25 % decrease	53 (57.6)
Nephrotoxicity at the end of study (N=86)	
MDRD < 25% decrease	78 (84.8)
MDRD ≥25 % decrease	8 (8.7)

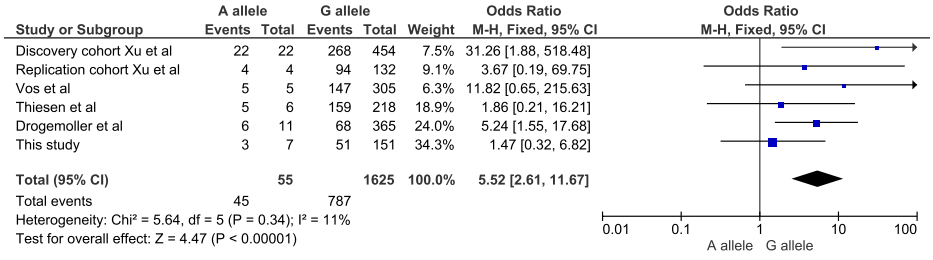
Nephrotoxicity

Of the 92 patients included, 53 patients (58%) had a decrease of 25% or more in creatinine clearance at any time during treatment. Cumulative cisplatin dose was not different between those patients groups intentionally treated with high dose or intermediate dose cisplatin (*p*=0.107*)*. In 86 patients end of treatment creatinine clearance was available. Of these patients, 8 (9%) had a decrease of 25% or more in creatinine clearance relative to baseline. All these 8 patients (100%) were treated with cisplatin 100 mg/m^2. (Table 2)

SNP and ototoxicity

Nine patients were heterozygous GA for the *ACYP2* variant rs1872328; all other patients (n=83) were homozygous GG. Forty-three percent of the patients reporting clinically hearing loss grade 2 or 3 (3 out of 7 patients) were carrying an A allele, whereas 7% of the patients without clinically hearing loss (grade 0 or 1) were carrier of the A allele. Association analysis showed a statistically significant difference between the groups (*p*=0.019, OR 9.9 95%CI [1.8-54.7]). We found no differences between carriership of the A allele and ototoxicity based on tone audiometrical measurements. (Table 3) A meta-analysis of the cohorts of the previous published studies performed in humans also indicated a significant association of the *ACYP2* variant with ototoxicity. For this analysis we used the data of the audiometrical assessments in our patients to compare with the other performed studies. (Figure 1)

Figure 1. Forest plot of meta-analysis of *ACYP2* rs1872328. Meta-analysis of published cohorts in humans and present study using a fixed-effects model. 95% CI, 95% confidence interval of odds ratio; M-H, Mantel-Haenszel method



For the tested genetic variants in *TPMT*, *COMT* and *WFS1* no statistically differences were found in either clinically or tone audiometrically assessed hearing loss. (Table 3) Also, the association analysis in patients with hearing loss using bone conduction as outcome, showed no statically significant difference.

Table 3. Significance levels for genetic variants related to ototoxicity. *=significantly different

Genotype	Clinical no ototoxicity N (%)	Clinical ototoxicity N (%)	*p*-value
TPMT:rs12201199			
AA	77 (91.6)	7 (8.3)	*p*=1.0
AT/TT	8 (100)	0 (0)	
TPMT:rs1142345			
TT	77 (91.6)	7 (8.3)	*p*=1.0
TC/CC	8 (100)	0 (0)	
TPMT:rs1800460			
CC	77 (91.6)	7 (8.3)	*p*=1.0
CT/TT	8 (100)	0 (0)	
COMT:rs4646316			
CC	49 (94)	3 (6)	*p*=0.463
CT/TT	36 (90)	4 (10)	
COMT:rs9332377			
CC	66 (93)	5 (7)	*p*=0.657
CT/TT	19 (90)	2 (10)	
ACYP2:rs1872328			
GG	79 (95)	4 (5)	*p*=0.019*
GA	6 (67)	3 (33)	
WFS1:rs62283056			
GG	53 (88)	7 (12)	*p*=0.090
GC/CC	30 (100)	0 (0)	

Table 4. Significance levels for genetic variants related to nephrotoxicity. *=significantly different (*p*<0.05)

Genotype	No nephrotoxicity during treatment N (%)	Nephrotoxicity during treatment N (%)	*p*-value
OCT2/SLC22A2:rs316019			
GG	35 (48.6)	37 (51.4)	*p*=0.022*
GT/TT	4 (20.0)	16 (80)	
MATE1:rs2289669			
GG	15 (42.9)	20 (57)	*p*=0.867
GA/AA	23 (41.1)	33 (58)	
XPD/ERCC2:rs13181			
TT	18 (53)	17 (47)	*p*=0.139
TG/GG	20 (36)	36 (64)	

Table 5. Overview of performed studies to ototoxicity and cisplatin

	Discovery Xu[15]	Replication Xu[15]	Vos[14]
Patients	Children with brain tumours	Children with brain tumours	Children (3-43 yrs) with osteosarcoma
Number of patients	238	68	156
Cummulative dose cisplatin (median, range)	287 mg/m2 (unknown)	Unknown*	480 mg/m2 (140-720)
Concomitant drugs	Vincristine, amisfostine, cyclofosfamide	Vinblastin, carboplatin	Vincristine, carboplatin in some pts
Radiation	Craniospinal	Focal in some pts	0

***** But same cisplatin dose as discovery cohort

	Audiometrical no ototoxicity N (%)	Audiometrical mild ototoxicity N (%)	Audiometrical moderate ototoxicity N (%)	*p*-value
	47 (66) 5 (63)	14 (20) 2 (25)	10 (14) 1 (12)	*p*=0.939
	47 (66) 5 (63)	14 (20) 2 (25)	10 (14) 1 (12)	*p*=0.863
	47 (66) 5 (63)	14 (20) 2 (25)	10 (14) 1 (12)	*p*=0.863
	31 (67) 21 (64)	10 (22) 6 (18)	5 (11) 6 (18)	*p*=0.863
	40 (66) 12 (67)	11 (18) 5 (28)	10 (16) 1 (5)	*p*=0.666
	48 (67) 4 (57)	15 (21) 1 (14)	9 (12) 2 (29)	*p*=0.499
	34 (65) 16 (64)	12 (23) 4 (16)	6 (12) 5 (20)	*p*=0.522

	No nephrotoxicity at end of treatment N (%)	Nephrotoxicity at end of treatment N (%)	*p*-value
	61 (91.0) 18 (89.5)	6 (9.0) 2 (10.5)	*p*=1.00
	29 (90.6) 49 (90.6)	3 (9.4) 5 (9.4)	*p*=1.00
	31 (96.9) 45 (86.8)	1 (3.1) 7 (13.2)	*p*=0.249

Thiesen[17]	Drogemoller[16]	Our study
Children with different tumours	Testicular cancer	Head and neck cancer
149	229	92
378 mg/m2 (60-800)	400 mg/m2 (200-920)	240mg/m2 (80-300)
Vincristine, carboplatin	Etoposide, bleomycine	-
Some pts	0	IMRT

SNP and nephrotoxicity

Data on the *OCT2* gene were available in 92 patients. Eighteen patients were heterozygous GT for the *OCT2* variant rs316019; 2 patients were homozygous TT and all other 72 patients were homozygous GG. Thirty percent of the patients with a decrease of 25% or more in creatinine clearance during treatment were carrying a T allele, whereas 10% of the patients without nephrotoxicity, which was significantly different (p=0.049, OR 3.78 95%CI [1.1-12.4]). No association was found between carriers of the T allele and a decrease in creatinine clearance of more than 25% at end of treatment compared to baseline (p=0.845*)*. Creatinine clearance was not significantly associated with the analyzed genetic variants in *MATE1* and *XDP*. (Table 4)

Discussion

Since a high percentage of LAHNC patients treated with cisplatin-based chemoradiotherapy develop irreversible ototoxicity and nephrotoxicity, to avoid these it would be worthwhile to add predictive biomarkers for toxicity to treatment decision-making. In this study we investigated whether germline genetic variants were associated to ototoxicity and nephrotoxicity, we focused on 10 SNPs in 7 genes which were previously reported to be related to these adverse effects[16,17,20,22]. We could confirm the association between a genetic variant in *ACYP2* and clinical reported hearing loss, but not with tone audiometrical measurements. Moreover, we found an association with *OCT2* and nephrotoxicity during treatment with cisplatin, but not with nephrotoxicity at end of treatment, which makes it not very useful in clinical practice. Furthermore, in these chemoradiation treated patients we were unable to replicate the association between genetic variants in *TPMT, COMT, WSF1* and ototoxicity and variation in the *MATE1* and *XDP* genes and nephrotoxicity.

With our findings we are the fifth to report on the association between genetic variation in the *ACYP2* gene and cisplatin-induced ototoxicity [14-17]. The initial studies of Xu and Vos reported that the A allele of the genetic variants rs1872328 in the *ACYP2* gene was only present in patients with ototoxicity, i.e., 13.8% and 6.5%, respectively, carried the A allele. More recent studies, also identified the A allele in patients without hearing loss, but only in a low percentage (1%).[16] In contrast to these studies we found that 57% of the patients without audiometrical measured ototoxicity carried the A allele and 43% of the patients with mild to moderate audiometrical measured ototoxicity. Compared to all the other studies, we found relatively high frequencies of carriership of the A allele, namely in 10% of our patients.

We could not find an association between the other variants investigated and ototoxicity. This is in line with previous studies which already showed variable results[16,20,21]. (Table 5) A possible confounder in ototoxicity rate in our patient population is radiation in the head and neck region, because radiation can induce conductive hearing loss as a result of inflammation and edema as well as sensorineural hearing loss caused by radiation on the inner ear. [12] Although some patients in the studies by Xu et al. and Ross et al. received cranial radiation as well.[15,28]

There is a great variance in the used scoring systems for ototoxicity between the studies, as the initial studies were done in children, most systems are only validated in children. [29] We decided to perform two analyses, one based on clinical hearing loss and the other on objective audiometrical assessments. For the audiometrical assessments we used the same scoring system as Drogemoller, because this system can be applied to adults,

in contrast to the Chang scoring system which is only used for children[14,16]. We are the first to use clinically-determined ototoxicity scored by the CTCAE as well, as this is a clinically relevant outcome measure reflecting the patients' perspective. Interestingly we could detect an association between the genetic variant in *ACYP2* when using the clinical measure but not for audiometrically determined ototoxicity. In the meta-analysis which we performed, our study had the same direction of effect (OR>1) as the other studies, however we did not find a significant association between carriership of the A allele in *ACYP2* and audiometrically determined ototoxicity. Nevertheless our study supports the association based on the direction of the effect.

Cisplatin-induced sensorineural hearing loss can best be evaluated with bone conduction measurements. Theunissen et al. argued that air conduction measurements also include information on bone conduction as these reflect the functionality of the whole auditory system. [30] To optimize our study, we decided to perform an association analysis using both outcomes, but we did not find any association between the studies genetic variants and the two ototoxicity outcomes.

With respect to SNPs as predictive markers for nephrotoxicity, the genetic variant in *OCT2* was found to be associated with a significant decrease of 25% or more in MDRD at any point during chemoradiotherapy, but not with nephrotoxicity at end of treatment. *OCT2* has been suggested as a marker for nephrotoxicity in other studies. [22] [24]. To our knowledge, only two studies have been performed to assess the relationship between *OCT2* and cisplatin-induced nephrotoxicity in humans. [22,31]. Filipski et al. investigated the effect of the rs316019 variant in *OCT2* in 78 cancer patients receiving cisplatin. Renal function was determined 1 day before and 1-8 days after the first dose cisplatin. Iwata et al. investigated the rs316019 variant of *OCT2* in 53 patients receiving cisplatin during more cycles. Remarkably, both Iwata et al. and Filipski et al. showed that the presence of T of the genetic variant rs316019 in *OCT2* was ameliorating cisplatin-induced nephrotoxicity, whereas our study found the opposite. The variation in the results might be related to the different endpoints for nephrotoxicity that have been used. Based on the previous studies and ours we believe that at the moment the use of this SNP does not seem to be relevant for clinical practice.

In our study, patients treated with high dose cisplatin and intermediate dose cisplatin were taken together, because of the small number of patients treated with the high dose schedule. Therefore we cannot draw conclusion regarding association between SNPs and toxicity for specific cisplatin dosages, while we know from previous studies that high dose cisplatin induces higher rates of ototoxicity as well as nephrotoxicity.

A limitation of our study is that we were not able to reach the planned sample size of 100 patients, due to lack of DNA of 10 patients, resulting in a somewhat smaller patient cohort. Besides this, in our power calculation we estimated an ototoxicity rate of 40%, but only 34% of our patient experienced ototoxicity based on audiometrical assessment. Furthermore, because of the relative small patient population, we did not correct for multiple testing and could not perform subgroup analyses. Therefore this study should be viewed as the first steps in the link between the studied genes and toxicities in LAHNC patients.

In conclusion, we are the first to report an association of *ACYP2* and cisplatin-induced ototoxicity in LAHNC patients and the fifth to describe the possible predictive value of *ACYP2* regarding cisplatin-induced ototoxicity. These findings should be validated in a large cohort, to finally determine the predictive value of *ACYP2* in ototoxicity. As personalized medicine is getting more important, these findings could eventually lead to individualized treatment for LAHNC patients.

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Summary, general discussion and future perspectives

Summary

The majority of locally advanced head and neck cancer (LAHNC) patients are treated with concomitant chemoradiotherapy with cisplatin 100mg/m^2 on days 1, 22 and 43. This intensive treatment can induce high rates of acute and late toxicities leading to a negative impact on quality of life. Despite this intensive treatment, LAHNC is associated with a poor prognosis with 5-years overall survival rates ranging from 30-50%. The main objective of this thesis is to evaluate options to improve efficacy and decrease toxicity of concomitant chemoradiotherapy in LAHNC patients.

Since toxicity of chemoradiotherapy is partly dependent on cisplatin, a possible way to reduce this toxicity is decreasing the cisplatin dose and by acceleration of radiotherapy, efficacy may be increased. **Chapter 2** describes a retrospective study in 106 LAHNC patients treated with accelerated radiotherapy up to a dose of 68 Gy in 5.5 weeks combined with cisplatin 40 mg/m^2 weekly for 6 weeks. Radiotherapy either consisted of intensity-modulated radiation therapy (IMRT) or of 3D-conformal radiotherapy. Treatment compliance was high, 99% of the patients received all planned radiotherapy and 90% received five or more cycles of cisplatin. Local toxicity rates were high, with confluent mucositis in 77% and moist dermatitis in 27% of the patients treated with IMRT, whereas toxicity rates were even higher in patients treated with 3D-conformal radiotherapy. Cisplatin-based toxicity was relatively mild, with low rates of grade 3 and 4 toxicity. Three-year loco-regional control, disease-free (DFS) and overall survival (OS) were 72%, 54% and 61%, respectively. Despite a high rate of confluent mucositis, treatment feasibility was excellent, without compromising on survival when compared to the high dose cisplatin regimen. Ideally, a multicenter phase III study of this treatment regime versus radiotherapy with cisplatin 100 mg/m^2 should be performed.

A common side effect of cisplatin is nephrotoxicity. **Chapter 3** shows the results of a retrospective study in which nephrotoxicity of both cisplatin-based chemoradiotherapy schedules as described above, are compared. Furthermore, different grading systems for nephrotoxicity were evaluated. Forty patients were treated with radiotherapy in combination with 3 cycles of cisplatin 100 mg/m^2 (high dose) and 104 were treated with accelerated radiotherapy combined with cisplatin 40 mg/m^2 during 6 weeks (intermediate dose). Nephrotoxicity, defined as an increase in serum creatinine of ≥50% relative to baseline was found in 60% of the patients in the high-dose versus 7% in the intermediate dose group (p=<.001). Using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 grade 2 and 3 nephrotoxicity was present in 53% and 8% of the high dose versus 7% and 0% in the intermediate dose group, respectively. When grading nephrotoxicity according to CTCAE version 3.0 underreporting of renal toxicity is found, with grade 2 and 3 nephrotoxicity in 8% and 3% in the high dose group versus 0% and 0%

in the intermediate dose group, respectively. The Risk, Injury, Failure, Loss and End stage (RIFLE) kidney disease criteria are an international widely accepted classification in grading acute kidney injury. Using these criteria, 43% of the patients treated with high dose and 7% in the intermediate dose group were classified as Risk, whereas 10% and 8% scored Injury and Failure in the high dose group compared to none in the intermediate dose group. These numbers are in line with those using the CTCAE 4.03 criteria. In conclusion, intermediate dose cisplatin causes significantly less nephrotoxicity, which is best graded using the CTCAE version 4.03.

As described before, adding induction chemotherapy to radiotherapy or chemoradiotherapy is another attempt to improve survival of LAHNC patients. Docetaxel, 5-fluorouracil and cisplatin (TPF) is the most effective and used induction chemotherapy schedule in LAHNC, but this has never been studied followed by cisplatin-based chemoradiotherapy. That is why we performed the CONDOR study, a randomized phase II study in which LAHNC patients received TPF followed by randomization to either concomitant chemoradiotherapy with cisplatin 100mg/m^2 once every three weeks with conventional radiotherapy (cis100+RT) or chemoradiotherapy with weekly cisplatin 40 mg/^{2} and accelerated radiotherapy (cis40+ART), as described in **Chapter 4.** Sixty-two patients were included, 27 patients were randomized to cis100+RT and 29 to cis40+ART. This treatment schedule was not feasible, since only 32% of the patients could receive the total planned cisplatin dose during the concomitant chemoradiotherapy due to toxicity. During TPF grade 3 or 4 neutropenic fever occurred in 18% of the patients, during chemoradiotherapy most common toxicities were dehydration, dysphagia and mucositis. There was one treatment related death. Despite high toxicity rates, two years progression free and overall survival were 70% and 78% versus 72% and 79% for cis100+RT and cis40+ART, respectively. **Chapter 5** describes the health-related quality of life data of the patients treated in the CONDOR study, a secondary endpoint of the study. Health-related quality of life was assessed at baseline, after 2 TPF, before start of chemoradiotherapy and 1, 4, 8, 12 and 24 months after completion of therapy using the EORTC-QLQC30 and QLQ-H&N35. Baseline scores were relatively high, reflecting the good clinical condition of the patients. Health-related quality of life decreased after TPF and even more during chemoradiotherapy, in both arms equally. Pain and swallowing dysfunction deteriorated significantly more below baseline levels during chemoradiotherapy with cis40+ART compared to cis100+RT. Health-related quality of life and symptom scores restored to baseline levels within 12 months after end of treatment in both arms. In **Chapter 6** the audiological data of the patients treated in the CONDOR study are described. A complete dataset of audiometric data was available of 12 patients treated with cis100+RT and of 11 patients treated with cis40+ART. Patients treated with cis100+RT showed significant more hearing loss than those treated with cis40+ART at 4 kHz ((z=1.98; p=0.04) and 8 kHz (z=2.07; p<0.03)). There was a large inter-individual variation in both groups.

Chapter 7 describes the use of genetic variants to predict cisplatin-induced ototoxicity and nephrotoxicity in LAHNC patients. One-hundred and two patients entered the study and genetic data were available of 92 of them. Single nucleotide polymorphisms, (SNPs) in *OCT2 and ACYP2* were significantly related to nephrotoxicity and ototoxicity (patient reported) as determined by CTC v4.03. We did not find an association with hearing loss measured with tone audiometry. Further research is needed before determination of SNPs can be used to individualized treatments plans and to take this potential predictive factor for ototoxicity into account in the process of shared decision-making with the patients.

General discussion

Chemoradiotherapy in locally advanced head and neck cancer; the optimal schedule
Cisplatin-based chemoradiotherapy is one of the cornerstones of the primary treatment of LAHNC. The most widely used treatment schedule is the *Radiation Therapy Oncology Group* (RTOG) schedule with conventional radiotherapy with concomitant cisplatin 100 mg/m^2 on days 1, 22 and 43, offered with curative intention, but associated with high toxicity rates, especially mucositis and dysphagia leading to feeding tube dependence, and furthermore hematological toxicity, nephrotoxicity and ototoxicity.[1-3] This has a huge impact on the health-related quality of life of LAHNC patients due to a high rate of acute and late toxicities. Because of the high acute toxicity rate, as illustrated by the fact that only 70% of patients complete all 3 planned cycles of chemotherapy, other chemoradiotherapy schedules have been investigated. One of those is a chemoradiotherapy schedule consisting of cisplatin 40 mg/m^2 weekly, often combined with hyperfractionated or accelerated radiotherapy.[4-7] In our retrospective analysis of 104 patients treated with accelerated radiotherapy combined with 6 cycles of weekly cisplatin 40 mg/m^2 we found high treatment compliance.[8] Treatment was well tolerated, with low rates of hematological toxicity. Furthermore, we showed that concomitant chemoradiotherapy with weekly cisplatin 40mg/m^2 induces significantly less nephrotoxicity compared to concomitant chemoradiotherapy with cisplatin 100mg/m^2 every three weeks.[9] However, in 80% of the patients confluent mucositis was observed, which most likely was due to the accelerated radiotherapy, which notoriously leads to a higher rate and severity of mucositis.[10]

Recently, in 2017, two phase III trials were presented comparing weekly intermediate dose cisplatin to high dose cisplatin every 3 weeks in combination with radiotherapy. In the first study two cycles of cisplatin 100 mg/m^2 were compared to weekly cisplatin 40 mg/m^2 in combination with IMRT in locally advanced nasopharyngeal cancer patients.[11] This trial included 529 patients, 267 were randomized to the weekly schedule and 259 to cisplatin every three weeks. The primary endpoint, failure free survival, showed no significant difference at median follow up time of 17.5 months (92% versus 88%; hazard ratio 1.056). Remarkably, significantly more leucopenia and thrombocytopenia were found in patients treated with weekly cisplatin, but other grade 3 and 4 toxicities did not differ between the treatment arms. The second phase III study was a non-inferiority phase III trial in LAHNC patients and compared chemoradiotherapy with cisplatin 100 mg/m^2 every three weeks for 3 cycles to cisplatin 30 mg/m^2 weekly for 7 cycles.[12,13] Three-hundred patients were included, 150 in each arm; 93% received treatment in the adjuvant setting, and 87% were oral cavity tumors. Median cisplatin dose was 300 mg/m^2 in the high dose versus 210 mg/m^2 in the intermediate dose group. In the high dose

group, 60% of the patients received all 3 cycles of chemotherapy and in the intermediate dose group 65% of the patients received all 6 cycles. The primary endpoint, locoregional relapse rate, showed a significant difference in favor of the high dose three-weekly schedule, 42.2% versus 29.6%, hazard ratio 1.58 with a median follow up of 20 months. Acute toxicity of grade 3 and higher and number of hospitalizations were significantly higher in the high dose cisplatin schedule. The intermediate dose cisplatin of 30 mg/m^2 was not a logical choice, since more data are available on cisplatin 40 mg/m^2 that is far more widely used. Moreover, in this study when patients could only receive six cycles of cisplatin they did not receive a cumulative dose of at least 200 mg/m^2 cisplatin, which is assumed to be the required total dose for optimal synergistic antitumor effect in combination with radiotherapy.[14]For both phase III studies no data on late toxicity and health-related quality of life are available yet.

In conclusion, treatment with high dose cisplatin induces more ototoxicity, nephrotoxicity and leads to more hospitalizations in comparison with weekly intermediate dose cisplatin. In nasopharyngeal cancer efficacy of both schedules is shown to be comparable. Since high dose cisplatin leads to more ototoxicity and nephrotoxicity, intermediate dose cisplatin with radiotherapy is recommended in nasopharyngeal cancer.

However, In LAHNC data on primary definite chemoradiotherapy comparing high dose cisplatin with intermediate dose 40 mg/m^2 are needed in a randomized multicenter phase III trial for definitive conclusions on efficacy, toxicity and quality of life.

The role of induction chemotherapy in treatment of locally advanced head and neck cancer

In a meta-analysis, published in 2009, induction chemotherapy in LAHNC showed no significant improvement of survival.[15] In this analysis however, a lot of different, and nowadays regarded as suboptimal, chemotherapy schedules were included. Also, there was a large heterogeneity in patient and tumor characteristics. None of the studies included in this meta-analysis used cisplatin-based concomitant chemoradiotherapy, the most effective cytotoxic drug for head and neck cancer. We showed in our CONDOR study, described in Chapter 4, that induction chemotherapy with TPF followed by cisplatin-based chemoradiotherapy was not feasible.

In the Tremplin study, published in 2013, 3 cycles of TPF followed by randomization to chemoradiotherapy with cisplatin 100 mg/m^2 or bioradiotherapy with cetuximab was studied in 153 patients.[16] The primary endpoint of this study was the feasibility of preservation of the larynx. In this study only 40% of the patients completed all planned cisplatin in the chemoradiotherapy arm. Although the authors concluded that this was

a feasible treatment option, the 40% is within the range of our result of 32%, which we ranked in our LAHNC study as unfeasible. The primary endpoint, laryngeal preservation 3 months post induction and bio-or chemoradiotherapy, did not show significant difference between treatment with cisplatin or cetuximab.

More recently, two phase III trials published in 2013 and 2014 evaluated the efficacy of induction therapy followed by chemoradiotherapy compared to chemoradiotherapy alone.[17,18] The DeCIDE study randomized LAHNC patients to either chemoradiotherapy with docetaxel, fluorouracil and hydroxyurea (DFHX), or two cycles of TPF followed by chemoradiotherapy with DFHX. Only 285 patients were included, instead of the planned 400 patients. Toxicity during TPF included myelosuppression, mucositis and dehydration and there were 4 toxic deaths during TPF (2.9%). No significant differences between both arms were found in overall survival, recurrence free survival or distant failure free survival. Overall survival was higher than expected in both arms, with 2-years overall survival of approximately 80%. In the PARADIGM trial three cycles of TPF followed by chemoradiotherapy with either docetaxel or carboplatin as experimental treatment were compared to standard treatment consisting of concomitant chemoradiotherapy with cisplatin 100 mg/m^2 on days 1 and 22. Instead of the planned 300 patients, only 145 patients were included. Patients randomized to TPF followed by chemoradiotherapy suffered from significant more grade 3-4 febrile neutropenia and mucositis than those randomized to chemoradiotherapy alone. In this study also no significant difference was found in overall and progression free survival. Three-year overall survival rates were 73% and 78% for TPF followed by chemoradiotherapy versus chemoradiotherapy, respectively. Both studies did not meet their planned accrual (due to slow recruitment) and survival rates were higher than expected, which makes interpretation of the results challenging. Nevertheless, both studies showed that induction chemotherapy followed by chemoradiotherapy is a toxic treatment without any benefit in survival.

In conclusion, the randomized phase II CONDOR study, described in Chapter 4, and other published phase III studies, do not support the combination of induction chemotherapy followed by concomitant chemoradiotherapy in LAHNC patients. Selected patients, however, may have benefit from (short lasting) induction chemotherapy before offering concomitant chemoradiotherapy. TPF induction can cause rapid disease response, which can be used in highly symptomatic patients with LAHNC or nasopharyngeal cancer patients.

Future perspectives

In LAHNC there are three important challenges: 1. to improve overall survival in patients with a poor prognosis by intensifying therapy or by use of new treatment approaches and 2. to decrease toxicity in patients with a good prognosis by de-intensifying therapy, and 3. improving management of toxicity in general. With this in mind I will discuss (*i*) the use of immunotherapy, (*ii*) radiosensitizing drugs, (*iii*) de-intensifying therapy; (*iv*) improving management of toxicity, (*v*) use of pharmacogenetics to predict toxicity, and (*vi*) patient reported outcomes measures

(i) Immunotherapy

The growing understanding of the immune system in tumor suppression has led to the development of immunotherapy in cancer treatment. Our immune system has checkpoints that induce tolerance of lymphocytes to antigens that otherwise activate apoptosis and cytotoxic tumor suppression. These checkpoints are used by malignant cells to suppress the immune response against tumors leading to an escape of immune surveillance. One of the most important checkpoints is PD-L1, programmed death-ligand 1, which is a transmembrane protein. Binding of PDL1 on the tumor cell to PD1 on the lymphocyte leads to immune suppression. Pembrolizumab is a monoclonal PD-1 antibody and blocks the PD1 to PDL1 binding, which can lead to an immune response to cancer cells. In the KEYNOTE-012 study, a phase I-b trial, pembrolizumab was given to recurrent or metastatic head and neck squamous cell carcinoma patients with PD-L1 expression.[19]. In 60 patients treated with pembrolizumab, the overall response was 18%. In 82% of these responders the response lasted more than 6 months. In a single arm phase II study that did not take into account PDL-1 expression of the tumors, pembrolizumab was studied in 171 recurrent or metastatic head and neck cancer patients, who were progressive after treatment with platinum and cetuximab.[20] The overall response rate was 16% with a median duration of response of 8 months. Grade ≥ 3 toxicity was found in 15% of the patients.

Nivolumab, a monoclonal PD-1 antibody, was investigated in a phase III trial in patients with recurrent or metastatic head and neck cancer whose disease was progressive within 6 months after platinum treatment.[21] Three hunderd sixty-one patients were randomized 2:1 to nivolumab or standard systemic therapy (methotrexate, docetaxel or cetuximab). Overall survival, the primary endpoint, was significantly longer in the nivolumab group 7.5 months versus 5.1 months (hazard ratio for death 0.70) in the standard treatment arm. The 1-year survival rate was 36% in the nivolumab group and 17% in the standard of care group. Treatment-related adverse events grade 3 or 4 occurred in 13% of the nivolumab group, versus 35% in the standard of care group. Moreover, in an exploratory

analysis of quality of life data, nivolumab stabilized symptoms and functioning up to week 15 whereas standard therapy led to clinically meaningful deterioration.

Both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) approved nivolumab and the FDA also approved pembrolizumab for treatment of patients with recurrent or metastatic head and neck cancer. Based on the results of the phase III trial with nivolumab the committee 'Beoordeling van Oncologische Middelen' (BOM) in The Netherlands, which evaluates the value of new and EMA approved oncological medications, did not approve nivolumab for treatment of head and neck cancer patients, because it did not meet the so-called PASKWIL criteria, criteria set by the Dutch Society of Medical Oncology to evaluate new drugs.[22]

The first data on the use of pembrolizumab in combination with chemoradiotherapy in LAHNC patients show that it is a safe combination not impairing chemotherapy or radiation dose.[23] In a phase II trial patients with resectable, HPV-negative LAHNC were treated with one gift of pembrolizumab neo-adjuvant and only patients with extracapsular extension or positive margins received post-operative chemoradiation followed by pembrolizumab.[24] In the first 21 patients enrolled in this study, in only 38% extracapsular extension or positive margins were found, compared to 80% expected. Moreover, 43% of the patients showed pathological treatment response to the neoadjuvant pembrolizumab. These preliminary results make the use of anti-PD1 in LAHNC patients promising.

Since only a subset of patients responds to anti-PD1 therapy, there is a need for predictive biomarkers for response. Biomarkers that are of interest in head and neck cancer patients treated with anti-PD1 are PDL-1 and PDL-2 expression, HPV status, microsatellite instability and mutational load.[19,25]

Currently, phase III trials of anti-PD1 in (neo-) adjuvant setting, in combination with radiotherapy and combination with chemoradiotherapy in LAHNC patients are recruiting. Tumor irradiation stimulates the immune system by release of apoptotic cell bodies which act as tumor associated antigens and danger signals, which can prime and activate new antitumor T cells. This suggests the synergistic function of radiotherapy and immune checkpoint inhibitors.

Hopefully this will lead to better survival for LAHNC patients. If immunotherapy will substitute cisplatin in next future this will probably lead to a better quality of life.

(ii) Radiosensitizing drugs

In addition to being cytotoxic by itself, cisplatin also has a radiosensitizing effect, albeit small when given three-weekly. Another treatment strategy is the combination with, hopefully more potential, radiosensitizing drugs. Radiotherapy induces cell death by single- and double-strand DNA breaks (ratio 25:1).[26] The ability of the tumor cells to repair this DNA damage limits the effect of radiotherapy. Poly ADP-ribose polymerase (PARP) is an essential enzyme in base excision repair and single-strand break DNA. Double-strand breaks are the most cytotoxic lesions, while the effect on single-strand breaks repair has minimal impact on survival of non-replicating cells. PARP inhibition increases the level of double-strand breaks of replicating cells, by delayed repair of radiation induced single-strand breaks which convert into double-strand breaks. This makes that PARP-inhibitors increase radiosensitivity in replicating cells, i.e. tumour cells. This was tested in head and neck cancer cell lines with positive results.[27-29] PARP-inhibitors in combination with radiotherapy are currently tested in phase I studies in head and neck cancer patients (NCT02229656, NCT02308072).

(iii) De-intensifying therapy

It is known that patients with HPV-associated oropharyngeal cancer with a minimal smoking history have a good 3-years overall survival of 94% when treated with chemoradiotherapy.[30] Probably, these patients can be treated with less intensive treatment without compromising survival.

Cisplatin-based chemoradiotherapy is known to induce significant toxicity, including ototoxicity, neuropathy, nephrotoxicity and myelosuppression. An alternative treatment could be cetuximab in combination with radiotherapy, which is probably better tolerated, as shown in a phase III trial in 2006.[31] In addition to radiotherapy, cetuximab toxicity comprises acneiform rash and radiation dermatitis. A retrospective analysis of the oropharyngeal patients included in this trial with respect to HPV, based on p16 status, was performed.[32] This analysis showed a longer overall survival of p16-positive oropharyngeal cancer patients compared to p16-negative oropharyngeal cancer patients, as expected. Furthermore, the addition of cetuximab to radiotherapy, increased 3-years overall survival in both p16-positive and –negative patients. Therefore, currently several ongoing phase III trials are investigating outcomes in locally advanced oropharyngeal HPV-positive patients comparing standard cisplatin-based chemoradiotherapy to cetuximab in combination with radiotherapy, as for example the De-ESCALaTE (NCT01874171), the RTOG1016 (NCT01302834) and the TROG HPVOropharynx (NCT01855451).

Another way of de-intensifying treatment in HPV-positive oropharyngeal cancer is de-escalating the radiation dose to the primary tumor or elective nodes. Standard radiation is 70Gy in 35 fractions.

A phase II study was performed in 43 HPV/p16 positive oropharyngeal patients (T0 to T3, N0 to N2c, M0) with a minimal smoking history to evaluate efficacy of 60 Gy radiotherapy with IMRT concurrent with weekly cisplatin 30 mg/m^2.[33] Although the locoregional control rate, disease free and overall survival are not known, yet, the complete response rate of 86% is promising. Moreover, acute toxicity seems to be mild, with 11% grade 3-4 hematological toxicity and only 39% temporally feeding tube dependency, which makes this treatment promising. At this time, phase II studies are ongoing to evaluate if decreasing radiation dose can achieve a similar excellent survival in this patient group (NCT03215719 and NCT02254278).

(iv) Improving management of toxicity

Swallowing dysfunction and aspiration are seen in a high proportion (30%-100%) of LANHC patients treated with chemoradiotherapy, which has an immense impact on quality of life.[34,35] Cisplatin-based chemoradiotherapy induces dysphagia and aspiration pneumonia. Around half of the patients will develop an aspiration pneumonia during or shortly after the treatment. Aspiration pneumonia leads to hospitalization and reduced quality of life. The use of prophylactic antibiotics to prevent aspiration pneumonia in LAHNC patients treated with chemoradiotherapy has been assessed in a multicentre trial, which was initiated in our hospital.[36] Patients were randomized to standard management or to prophylactic amoxicillin/clavulanic acid from day 29 until 14 days after end of chemoradiotherapy. The rate of pneumonia did not differ between the two treatment groups in the 94 randomized patients (p=0.56). However, significant less fever of any grade was seen in patients treated with prophylactic antibiotics. In addition, patients treated with prophylactic antibiotics needed less hospitalizations compared to those in the standard treatment group (20% versus 35%, p=0.08). There was a trend in decreased use of painkillers and improvement of general health related quality of life in patients using the prophylactic antibiotics. The reduction in hospitalizations led to a significant reduction in costs.[37] There was no difference in quality of life between the treatment groups and no adverse events associated with antibiotic use were reported. Based on this study, a recommendation can be made to use prophylactic antibiotics in LAHNC patients during and after chemoradiotherapy according to the schedule used in the study.

(v) Use of pharmacogenetics to predict toxicity

It has been suggested that genetic variants in genes involved in cisplatin metabolism can predict the development of cisplatin-induced toxicity, especially ototoxicity and nephrotoxicity.

As described in Chapter 7, we found a significant correlation between carriers of the A allele in the *ACYP2* gene and cisplatin induced ototoxicity clinically determined based on the CTCAE 4.03. We could not confirm this for ototoxicity based on tone audiometrical data.[38-41] The predictive value of *ACYP2* in cisplatin-induced ototoxicity needs to be determined by a large cohort validation study, before it can be used in clinical practice. Other single nucleotide polymorphisms (SNPs) that have been reported in relation to cisplatin-induced ototoxicity, such as *TPMT, COMT and WFS1,* could not be replicated and this makes them not useful in clinical practice.

For cisplatin-induced nephrotoxicity we found an association between carriership of the T allele in the *OCT2* gene. However, 2 other studies investigating genetic variants in the *OCT2* gene, showed that carriership of the T allele was protective in developing renal damage by cisplatin.[42,43] The role of these SNPs in predicting nephrotoxicity is therefore unclear. Further research is needed before determination of SNPs can be used for individualized treatments plans.

(vi) Patient reported outcomes

Cancer patients undergoing treatment suffer from symptoms, which are often not documented by their clinicians.[44] Therefore, there is a growing interest in patient reported outcomes (PROs); patients are asked to report their symptoms on a routine base and when there is a severe or worsening of symptoms, a trigger is given to the treating physician. Moreover, a report of symptom burden is used during the clinic visits. Recently, the integration of PROs in the care of metastastic cancer patients was proven to induce overall survival benefit compared to usual standard practice.[45] Probably, the early response to patients symptoms, prevented adverse downstream interventions.

Data of the use of patient reported outcome measures (PROMs) in head and neck cancer patients are scarce. The agreement between patient-reported and practitioner-reported toxic effect during chemoradiotherapy in patients with oropharyngeal cancer has been studied.[46] Forty-four patients with oropharyngeal cancer were treated with concomitant chemoradiotherapy. Toxic effects were scored using the Common Terminology Criteria for Adverse Events (CTCAE) and the Patient-reported Outcome version of the CTCAE (PRO-CTCAE). At baseline when most symptoms were absent, there was a high agreement between patient- and practitioner reported symptom

severity. However, during treatment, practitioners reported lower severity of toxic effects, especially for domains that are not easily evaluated by physical examination, such as anxiety and fatigue.

The use of PROMs in patients treated with cetuximab and panitumumab was investigated.[47] Sixty patients (69%) in this study had head and neck cancer, and 52 of these patients had LAHNC treated with cetuximab in combination with radiotherapy. These patients showed a decrease in well-being during the first five weeks of treatment. Moreover, dose-modifications were comparable as described by Bonner et al.[31] The use of PRO could not prevent dose discontinuation. More studies on evaluation of PRO to improve toxicity management and quality of life of LAHNC patients treated with chemoradiotherapy are needed. The use of PROMs should be more implemented in new clinical studies.

In our multidisciplinary head and neck chain care of the Radboud university medical center we will start with using PROMs in head and neck cancer patients in 2018 to investigate if we can further improve care for these patients.

Conclusion

The survival of LAHNC patients varies widely, with for example 3-year overall survival rates that range between 10 and 95%, which mostly depends on stage, HPV-status and smoking habits. HPV-associated oropharyngeal carcinoma has the best prognosis. Most LAHNC patients are treated with cisplatin-based concomitant chemoradiotherapy, which is complicated by a high rate of serious toxicities and negative impact on health-related quality of life. In the future, treatment needs to be more individualized, based on known prognostic indicators such as stage, HPV-status and smoking. In addition, other novel potential predictive factors for tumor response or toxicity, such as tumor immunogenicity, pharmacogenetics and tumor microenvironmental characteristics, need to be explored. If possible, treatments need to be adapted to reduce toxicity, on the other hand they need to be intensified where necessary. Well-informed patients take better decisions, and shared decision making should be part of routine medical care before starting any treatment. Finally, implementation of PROMs and related adequate actions could further improve the outcome of LAHNC patients.

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Nederlandse samenvatting

Hoofd-hals kanker

Hoofd-hals kanker bestaat uit een groep van verschillende maligniteiten, gelokaliseerd op de lip, in de mondholte, neusholte, paranasale sinussen, farynx (orofarynx, hypofarynx en nasofarynx), larynx en de speekselklieren. Met uitzondering van tumoren in de speekselklieren en de nasofarynx, zijn deze tumoren in het algemeen plaveiselcelcarcinomen. Dit proefschrift beschrijft resultaten van onderzoek bij patiënten met plaveiselcelcarcinomen van de mondholte, orofarynx, hypofarynx en larynx, die ik verder zal aanduiden als patiënten met 'hoofd-hals kanker'.

In Nederland werden er in 2016 3192 nieuwe patiënten met hoofd- hals kanker gediagnosticeerd. Risicofactoren voor het ontwikkelen van hoofd-hals kanker zijn roken, alcohol gebruik/misbruik, en met name bij het orofarynxcarcinoom een infectie met het humaan papillomavirus (HPV).

De overleving van patiënten met hoofd-hals kanker is vooral afhankelijk van het ziektestadium bij presentatie. Ongeveer de helft van de patiënten presenteert zich met lokaal uitgebreide ziekte (stadium III of IV). Zij moeten een intensieve behandeling ondergaan die vaak uit meerdere modaliteiten bestaat, zoals (*i*) chirurgie al dan niet gevolgd door radiotherapie of chemoradiotherapie, (*ii*) primaire chemoradiotherapie of (*iii*) radiotherapie in combinatie met cetuximab (bioradiotherapie). Ondanks deze intensieve behandeling is de prognose van deze patiëntengroep slecht, met een 5-jaars overleving van 30-50%. Een uitzondering hierop zijn patiënten met een lokaal uitgebreid HPV-positief orofarynxcarcinoom zonder een voorgeschiedenis van roken, waarbij een 3-jaarsoverleving na chemoradiotherapie behaald wordt van 94%.

De behandeling

Primaire chemoradiotherapie is de behandeling van keuze bij patiënten met een lokaal uitgebreid orofarynx-, hypofarynx- of larynxcarcinoom. De keuze voor deze behandeling wordt gemaakt om orgaansparend te zijn, dus om tong, spraak- of slikfunctie te behouden, of omdat de ziekte chirurgisch niet in zijn geheel te verwijderen is.

Het meest gebruikte schema ter wereld voor chemoradiotherapie is het zogenaamde "Radiation Therapy Oncology Group" (RTOG) schema, waarbij conventionele radiotherapie (70Gy in 35 fracties gedurende 7 weken) gecombineerd wordt met cisplatin 100 mg/m^2 op dag 1, 22 en 43. Dit is een behandeling die gepaard gaat met veel bijwerkingen, zowel acuut als ook op latere termijn. De acute bijwerkingen die kunnen ontstaan zijn vooral lokale problemen zoals slikproblemen, mucositis (kapotte slijmvliezen), pijn, en

een droge mond waardoor er een verminderde inname van voedsel en vocht is, alsmede dermatitis (ontsteking van de huid). Daarnaast kan er gehoorschade optreden door de radiotherapie en door de chemotherapie en kan de chemotherapie, naast misselijkheid en braken, ook nierschade en perifere neuropathie (schade aan de zenuwen) veroorzaken. Late bijwerkingen van de behandeling ontstaan maanden tot jaren na het einde van de behandeling en kunnen blijvend zijn. Xerostomie, een droge mond, is de meest bekende en meest voorkomende late bijwerking, welke ontstaat door beschadiging van de speekselklieren. Andere late bijwerkingen zijn osteoradionecrose, schildklierproblemen, atherosclerose van de halsvaten, gehoorschade, polyneuropathie, nierschade en fibrose. Verder hebben deze patiënten een verhoogd risico op het ontstaan van andere vormen van kanker, met name een tweede primaire hoofd-hals tumor of longkanker. Dit risico is vooral verhoogd door roken en alcohol gebruik, maar is, is zeer veel mindere mate, ook gerelateerd aan bestraling.

De huidige chemoradiotherapie voor hoofd-hals kanker is beperkt effectief en gaat gepaard met aanzienlijke bijwerkingen. Daarom is het doel van mijn onderzoek, zoals beschreven in dit proefschrift, om te bestuderen of er mogelijkheden zijn om enerzijds de behandeling effectiever te maken en anderzijds de toxiciteit te verminderen.

Eén van de mogelijkheden om de behandeling effectiever te maken is de radiotherapie te intensiveren, bijvoorbeeld door het geven van geaccelereerde radiotherapie. Bij geaccelereerde therapie, wordt een even grote dosis bestraling gegeven, maar in een kortere tijdsduur. Hierdoor is de kans op lokale controle groter en is de 3-jaarsoverleving iets beter. Doordat de geïntensiveerde radiotherapie periode is ingekort tot 35 dagen, is dit schema niet te combineren met de chemotherapie van het RTOG schema, waarbij cisplatin 100 mg/m^2 op dag 1, 22 en 43 wordt gegeven omdat op dag 43 de radiotherapie is beëindigd. Daarom is, in combinatie met geaccelereerde radiotherapie, een alternatief cisplatin schema bestudeerd, waarin patiënten wekelijks cisplatin 40 mg/m^2 krijgen gedurende 6 weken.

In **hoofdstuk 2** van dit proefschrift beschrijf ik een retrospectieve studie waarin 106 patiënten met lokaal uitgebreide kanker zijn behandeld met geaccelereerde radiotherapie met wekelijks cisplatin 40 mg/m^2. Bijna alle patiënten konden de gehele radiotherapie afronden (99% van de patiënten) en 90% van de patiënten kregen minimaal 5 kuren cisplatin. Er werd veel lokale toxiciteit gezien, meer dan drie kwart van de patiënten kreeg een ernstige confluerende mucositis en ruim een kwart een vochtige dermatitis. De bijwerkingen van de cisplatin waren relatief mild. De lokale controle en de overleving na 3 jaar waren respectievelijk 72% en 61%. De conclusie van deze studie was dat, ondanks het veel vóórkomen van lokale acute toxiciteit, de behandeling, mits vergezeld van

adqueate supportive care, goed werd verdragen en afgerond, zonder afbreuk te doen aan de overleving, voor zover het mogelijk is die te vergelijken met studies waarin het RTOG schema werd gebruikt. De twee behandelschema's, conventionele radiotherapie met cisplatin 100 mg/m^2 op dag 1, 22 en 43 versus geaccelereerde radiotherapie met wekelijks cisplatin 40 mg/m^2, zijn namelijk niet in een fase III studie met elkaar vergeleken.

Zoals eerder beschreven is nefrotoxiciteit, ofwel nierschade, een bekende en beperkende bijwerking van cisplatin. Deze bijwerking is afhankelijk van de dosis en de frequentie van de cisplatin kuren. Het verschil in nefrotoxiciteit tussen de twee cisplatin-gebaseerde chemoradiotherapie schema's heb ik beschreven in **hoofdstuk 3.** Hierbij heb ik ook gekeken naar verschillende manieren om de nefrotoxiciteit te graderen. Veertig patiënten werden behandeld met de hoge dosis cisplatin (cisplatin 100 mg/m^2 op dag 1,22 en 43) en 104 patiënten werden behandeld met de intermediaire dosis cisplatin (wekelijks cisplatin 40 mg/m^2). Nefrotoxiciteit, gedefinieerd als een stijging van het serum kreatinine van meer dan 50% ten opzichte van de uitgangswaarde, werd gevonden in 60% van de patiënten die werden behandeld met de hoge dosis cisplatin versus in 7% van de patiënten die behandeld werden met de intermediaire dosis cisplatin. Ook met de andere graderingssystemen, de Common Terminology Criteria for Adverse Events (CTCAE) versie 3.0 en versie 4.03 en de Risk, Injury, Failure, Loss and End stage (RIFLE) criteria werden grote verschillen gezien tussen beide groepen, ten nadele van de hoge dosis cisplatin. De intermediaire dosis cisplatin is dus duidelijk minder nefrotoxisch en geconcludeerd werd dat de CTCAE 4.03 criteria de beste criteria zijn om nefrotoxiciteit van cisplatin in deze patiëntengroep te scoren.

Een andere manier om de overleving van patiënten met lokaal uitgebreide hoofd-hals kanker te verbeteren is om voorafgaand aan de chemoradiotherapie, chemotherapie toe te voegen. Het doel van deze inductie ofwel neo-adjuvante chemotherapie is om het volume van de tumor te verkleinen en de eventueel aanwezige micrometastasen te laten verdwijnen.

Er zijn in het verleden meerdere studies geweest om te onderzoeken welk schema het best gebruikt kan worden als inductie chemotherapie bij hoofd-hals kanker. Het meest effectieve schema is een combinatie van docetaxel, cisplatin en 5-fluorouracil (TPF) gebleken, zoals beschreven in de TAX 323 en TAX 324 studies. In deze twee studies werd TPF gevolgd door radiotherapie alleen of chemoradiotherapie met carboplatin. Een studie waarin inductie chemotherapie, bestaande uit TPF, gecombineerd werd met cisplatin-bevattende chemoradiotherapie was toentertijd nog niet verricht.

In de CONDOR studie, een gerandomiseerde fase II studie, onderzochten wij of het haalbaar is om TPF inductie chemotherapie te combineren met cisplatin-bevattende chemoradiotherapie. In **hoofdstuk 4** worden de resultaten van deze studie beschreven. Patiënten met lokaal uitgebreide hoofd-hals kanker kregen 2 tot 4 TPF kuren en werden daarna gerandomiseerd tussen conventionele radiotherapie met cisplatin 100 mg/m^2 op dag 1, 22 en 43 of geaccelereerde radiotherapie met wekelijks cisplatin 40 mg/m^2.

In deze studie werden 62 patiënten geïncludeerd, 27 patiënten werden behandeld met de hoge dosis cisplatin en 29 met de intermediaire dosis cisplatin. Ten gevolge van toxiciteit kon slechts 22% en 41% (32% in totaal) van de patiënten met de hoge versus intermediaire dosis alle geplande doseringen van cisplatin krijgen tijdens het chemoradiotherapie gedeelte, daarom werd er besloten om de studie voortijdig te staken. Er werd geconcludeerd dat TPF gevolgd door cisplatin-bevattende chemoradiotherapie niet haalbaar is. De radiotherapie kon in beide studiearmen wel bij vrijwel alle patiënten volledig gegeven worden.

Kwaliteit van leven was een van de secundaire eindpunten van de CONDOR studie en de resultaten van onderzoek hiernaar worden beschreven in **hoofdstuk 5**. De kwaliteit van leven werd door middel van twee verschillende gevalideerde vragenlijsten gemeten vóór de start van de behandeling, na 2 kuren TPF, voor de start van de chemoradiotherapie en 1, 4, 8, 12 en 24 maanden na afronden van de behandeling. De uitgangsscores waren hoog, wat betekent dat het patiënten betreft die voorafgaand aan de behandeling in een relatief goede conditie waren. De globale kwaliteit van leven daalde tijdens de TPF inductie chemotherapie en nog verder tijdens de chemoradiotherapie. Patiënten die werden behandeld met de geaccelereerde radiotherapie met intermediaire dosis cisplatin ervoeren significant meer slikklachten en pijn tijdens de chemoradiotherapie ten opzichte van de patiënten die werden behandeld met de conventionele radiotherapie met hoge dosis cisplatin. Dit verschil wordt het meest waarschijnlijk veroorzaakt door de geaccelereerde radiotherapie. Een jaar na het beëindigen van de behandeling was de kwaliteit van leven weer op hetzelfde niveau als voor de start van de behandeling in beide armen.

Zoals eerder beschreven is ototoxiciteit een bekende en soms ook dosis beperkende bijwerking van cisplatin. De ernst van cisplatin geïnduceerde ototoxiteit is afhankelijk van de dosering en het schema.

In **hoofdstuk 6** beschrijf ik de audiologische data van de patiënten behandeld in de CONDOR studie. Tijdens de studie werden op meerdere momenten audiogrammen verricht. Een complete data set van audiogrammen was beschikbaar van 12 patiënten

die behandeld werden met hoge dosis cisplatin en van 11 patiënten die werden behandeld met intermediaire dosis cisplatin. Patiënten die werden behandeld met hoge dosis cisplatin hadden significant meer gehoorverlies dan de patiënten die werden behandeld met intermediaire dosis cisplatin op toonhoogte 4 kHz en 8 kHz; dit zijn de hoge tonen.

Vooralsnog is het niet mogelijk om te voorspellen welke patiënten die behandeld gaan worden met cisplatin bijwerkingen, zoals nefrotoxiciteit en ototoxiciteit, gaan ervaren. Verschillen in het DNA zijn mogelijk van invloed op de bijwerkingen die door cisplatin worden veroorzaakt en heten 'single nucleotide polymorfisms' (SNPs). In **hoofdstuk 7** wordt de studie beschreven die de relatie tussen verschillende van deze genetische varianten en cisplatin geïnduceerde nefrotoxiciteit en ototoxicieit beschrijft. Er werden 102 patiënten geïncludeerd in de studie, de genetische data waren beschikbaar van 92 patiënten. De SNP in *ACYP2* was significant gecorreleerd aan het door de patiënt aangegeven gehoorverlies, maar niet aan het gehoorvlies gemeten met een audiogram. Verder onderzoek is nodig om te bekijken of het gebruik van SNPs ingezet kan worden als een predictieve factor en uiteindelijk kan worden ingezet bij het maken van een geïndividualiseerde keuze voor behandeling, wat inhoudt dat bij een genetisch bepaald hoog risico op gehoorschade ten gevolge van cisplatin een alternatieve behandeling zou kunnen worden overwogen.

De toekomst

De overleving van lokaal uitgebreide hoofd-hals kanker patiënten varieert sterk, met 3-jaars overlevingspercentages van 10 tot 95%, die meestal afhankelijk zijn van het stadium van de ziekte, HPV-status en rookgewoonten. Het HPV-geassocieerde orofarynxcarcinoom bij patiënten die nooit gerookt hebben, heeft de beste prognose. De meeste patiënten met lokaal uitgebreide hoofd-hals kanker worden behandeld met cisplatin-bevattende chemoradiotherapie, wat gepaard gaat met een hoog percentage ernstige toxiciteit en een, tijdelijk, negatieve impact op de kwaliteit van leven. In de toekomst moet de behandeling meer geïndividualiseerd worden, gebaseerd op bekende prognostische indicatoren zoals stadium, HPV-status en roken. Daarnaast moeten andere nieuwe potentiële voorspellende factoren voor tumorrespons of toxiciteit, zoals tumorimmunogeniciteit, farmacogenetica en micro-omgevingseigenschappen van tumoren, worden onderzocht. Indien mogelijk moeten behandelingen worden aangepast om de toxiciteit te verminderen bij patiënten met een goede prognose, aan de andere kant moeten ze waar nodig worden geïntensiveerd bij patiënten met een slechte prognose. Goed geïnformeerde patiënten nemen betere beslissingen en gedeelde besluitvorming moet deel uitmaken van de standaard medische zorg voordat een behandeling wordt gestart.

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Curriculum vitae

Chantal Driessen werd geboren op 3 januari 1984 te Venlo. Ze behaalde haar VWO-diploma in 2002 aan het Valuascollege te Venlo. Ze begon datzelfde jaar aan haar opleiding Geneeskunde aan de Universiteit Maastricht en behaalde in 2008 haar artsexamen. Na haar artsexamen werkte ze 4 maanden als arts-assistent interne geneeskunde niet in opleiding in het Maxima Medisch Centrum te Veldhoven. In 2009 startte ze met de opleiding Interne Geneeskunde. Het eerste deel van de opleiding vond plaats in het TweeSteden Ziekenhuis Tilburg (opleiders: dr. H. Goei, dr. H.H. van Oijk en dr. T.K.A. Wierema). In 2011 onderbrak ze haar opleiding om te starten met het promotieonderzoek zoals beschreven in dit proefschrift. Tijdens haar onderzoeksperiode kreeg ze een persoonlijke KWF onderzoeksbeurs voor arts-assistenten voor het onderzoek getiteld 'Prediction of ototoxicity and nephrotoxicity in patients with locally advanced head and neck cancer treated with chemoradiotherapy'. In 2015 hervatte ze haar opleiding tot Internist in het Radboudumc (hoofdopleider prof. dr. J. de Graaf). Vanaf april 2016 startte ze met haar differentiatie Medische Oncologie in het Radboudumc met als opleiders prof. dr. Ir. J.J.M. van der Hoeven en dr. I.M.E. Desar. Dit opleidingstraject wisselde zij af met het vervolg van haar promotie onderzoek. Per 1 januari 2019 zal zij haar opleiding tot internist oncoloog afronden, waarna zij als internist-oncoloog aan het Radboudumc verbonden zal blijven.

Chantal woont samen met Rens van de Weyer. Ze hebben samen 2 kinderen, Max (2014) en Tom (2017).