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Health-related quality of life of patients treated with chemoradiotherapy plus or minus prophylactic antibiotics to reduce the number of pneumonias for locally advanced head and neck cancer, the PANTAP study

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ABSTRACT

Objectives: The recent PANTAP trial showed that administration of prophylactic antibiotics in locally advanced head and neck carcinoma (LAHNC) patients treated with chemoradiotherapy reduced fever, hospitalization and costs. The current study describes the effect of prophylactic antibiotics on health-related quality of life (HRQoL), another secondary endpoint of the trial.

Materials and methods: In this multicenter randomized trial, LAHNC patients treated with chemoradiotherapy received prophylactic antibiotics or standard care. HRQoL was assessed at baseline (before chemoradiotherapy), day 28 of chemoradiotherapy (one day before starting prophylactic antibiotics), the final day of radiotherapy, and 3.5 months after the end of chemoradiotherapy, using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30, EORTC H&N35 module, and the Performance Status Scale for Head & Neck cancer patients (PSS-HN).

Results: Ninety-five patients were randomized: 48 patients were allocated to the standard group and 47 patients to the prophylaxis group. Thirty-four patients in the standard group (70.8%) and 28 patients in the prophylaxis group (59.6%) completed the questionnaires at baseline and at follow-up. No significant differences in HRQoL were found at baseline and at day 28. At the end of radiotherapy, the prophylaxis group performed better on almost all functional subscales of the EORTC QLQ-C30 and reported less symptoms. At the end of follow up, almost no differences were seen between the two treatment groups.

Conclusion: Prophylactic antibiotics during chemoradiotherapy for LAHNC patients improved HRQoL at the end of the radiotherapy, however no differences were found 3.5 months after the end of chemoradiotherapy.

Introduction

Head and neck cancer is the sixth most common type of cancer with an annual incidence of 686,328 new cases worldwide [1,2]. Locally advanced head and neck cancer (LAHNC) itself, as well as the side effects of treatment, can negatively influence health-related quality of life (HRQoL). Social and emotional interactions are important aspects of an individual's HRQoL and largely depend on structural and functional capacity of organs in the head and neck region that are affected by the tumour and its treatment [3]. Rettig et al. showed that HRQoL begins to decline in the 2–5 years before a diagnosis of LAHNC with a steep reduction in the 24 months before diagnosis [4]. At presentation, disease-related symptoms may comprise of hoarseness, pain, otalgia, dysphagia,

cough and stridor [5], which likely to account for decreased HRQoL prior to diagnosis.

The treatment for LAHNC often consists of concomitant platinum-based chemoradiotherapy. However, this treatment is associated with a high rate of acute toxicities. Radiotherapy causes mucositis, dermatitis, dysphagia, anorexia and pain [6,7], whereas chemotherapy may cause nausea, neutropenia and thrombocytopenia and worsen radiotherapy-related toxicities, in particular mucositis and dysphagia [6]. In a previous study, the incidence of grade 3 or 4 acute toxicities among LAHNC patients treated with radiotherapy alone was 47%, while this was 77% among patients treated with concomitant chemoradiotherapy [6]. Due to these acute adverse events, there is a significant deterioration of HRQoL during treatment [8], that may be worse for

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patients treated with chemoradiotherapy compared to those treated with radiotherapy alone [9]. Immediately (4–6 weeks) after radiotherapy HRQoL declines even further [10,11], however gradual improvement is during the following period [4,9–12]. In general, most HRQoL domains recover to baseline levels around 12 months after treatment [9,13].

Dysphagia and aspiration during and after chemoradiotherapy for head and neck cancer are usually underreported [14–16]. In LAHNC patients, the incidence of aspiration at diagnosis ranges from 9% to 53% [14,17], and the aspiration rate during and after chemoradiotherapy is between 13% and 69% [16–18]. As a consequence, aspiration pneumonia during chemoradiotherapy is a relatively frequent complication (46%) [19]. In the recently conducted PANTAP-trial, prophylactic antibiotics during chemoradiotherapy in LAHNC did not result in a reduction in the number of patients with a pneumonia (45.8% of the patients in the standard group versus 46.8% of the patients in the prophylaxis group), however prophylactic antibiotics led to a significant reduction in the rate of hospitalization, episodes of fever and costs per patient [19,20]. It could be hypothesized that prophylactic antibiotics have a protective effect on HRQoL as they may reduce acute toxicities such as mucositis and pain, which were previously shown to have a negative impact on HRQoL [21]. One of the secondary objectives of the PANTAP trial, and the aim of the current study, was to assess the effects of prophylactic antibiotics during chemoradiotherapy on the HRQoL among LAHNC patients compared with those who did not receive prophylactic antibiotics. We hypothesized that the group receiving prophylactic antibiotics would report a better HRQoL at the end of radiotherapy due to the positive effects of prophylactic antibiotics. In addition, our study aims to describe HRQoL changes during treatment in both treatment groups.

Methods

Patients and study design

The PANTAP-study was a randomized, multicenter phase II study for patients with LAHNC who were treated with chemoradiotherapy, either as primary treatment or postoperative treatment. Chemotherapy consisted of cisplatin, given at a dose of 100 mg/m² every 3 weeks for 3 cycles, or 40–50 mg/m² given every week for 6 or 7 cycles. Radiotherapy was given with intensity-modulated radiation therapy and an accelerated (68 Gy in 34 fractions of 2 Gy over 5.5 weeks) or conventional scheme (70 Gy in 35 fractions of 2 Gy over 7 weeks) [6,7]. Patients were enrolled before start of the chemoradiotherapy. Exclusion criteria for registration included an allergy to amoxicillin, the use of maintenance antibiotics or immunodeficiency. Patients were randomized after 21–28 days of chemoradiotherapy, unless complications such as pneumonia, other infections or antibiotic treatment had occurred within the 14 days preceding randomization. Patients were randomized to receive either standard care alone, (the standard group), or to receive prophylactic oral amoxicillin/clavulanic acid 625 mg three times daily from day 29 until 14 days after the end of chemoradiotherapy in addition to standard care (the prophylaxis group). Patients were allocated equally to the two treatment groups by minimization, which is a method of adaptive stratification allowing a higher numbers of stratification factors: smoking, Chronic Obstructive Pulmonary Disease (Gold 0–2 or Gold 3–4), weight loss (more than 10% versus less than 10%), primary site of the tumour (oral cavity, oropharyngeal, or hypopharyngeal and laryngeal cancer), participating centre, and human papillomavirus positivity [22].

The primary endpoint was to evaluate the number of patients who developed pneumonia. Secondary endpoints were to determine the number and duration of hospital admissions, to assess toxicity and adverse events including side effects of amoxicillin/clavulanic acid, to evaluate cost-effectiveness, and to explore HRQoL.

The study protocol was approved by the local ethical committee and

Table 1

Patient characteristics at baseline (no statistically significant differences between the study groups).

	All patients		Patients with complete HRQoL questionnaires	
	Standard group (n = 48)	Prophylaxis group (n = 47)	Standard group (n = 34)	Prophylaxis group (n = 28)
Age-yr (range)	58.5 (43–68)	57.0 (23–68)	58.5 (48–68)	58.1 (29–68)
Sex – no. (%)				
Female	14 (29.2)	11 (23.4)	10 (29.4)	7 (25.0)
Male	34 (70.8)	36 (76.6)	24 (70.6)	21 (75.0)
WHO– no. (%)				
0	35 (72.9)	32 (68.1)	26 (76.5)	19 (67.9)
1	11 (22.9)	11 (23.4)	7 (20.6)	7 (25.0)
Unknown	2 (4.2)	4 (8.5)	1 (2.9)	2 (7.1)
Tumor site– no. (%)				
Oral cavity	14 (29.2)	13 (27.7)	9 (26.5)	6 (21.4)
Oropharynx	20 (41.7)	20 (42.6)	14 (41.2)	14 (50.0)
Hypopharynx	5 (10.4)	11 (23.4)	4 (11.8)	7 (25.0)
Larynx	8 (16.7)	3 (6.4)	7 (20.6)	1 (3.6)
Unknown	1 (2.1)	0	0	0
primary				
Indication CRT– no. (%)				
Primary treatment	26 (54.2)	34 (72.3)	19 (55.9)	20 (71.4)
Postoperative treatment	22 (45.8)	13 (27.7)	15 (44.1)	8 (28.6)

registered at <http://clinicaltrials.gov> (NCT01598402).

Assessments

HRQoL was assessed at baseline, day 28 of chemoradiotherapy (one day before starting prophylactic antibiotics), on the final day of radiotherapy, and 3.5 months after the end of chemoradiotherapy. Questionnaires included the 30-item core European Organization for the Research and Treatment of Cancer Quality-of-Life Questionnaire (EORTC QLQ-C30) [23], the EORTC QLQ Head and Neck Cancer-Specific Module (EORTC H&N35) [23], and the Performance Status Scale for Head & Neck cancer patients (PSS-HN) [24].

The EORTC QLQ-C30 is a 30-item questionnaire that assesses HRQoL in cancer patients across five functioning scales (physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning), three multi-item symptom scales (fatigue, pain, nausea and vomiting), six single-item symptom scales (dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial problems) and global QoL [23]. Patients provide their answers on a 4-point scale (from 1 [not at all] to 4 [very much]), except for global QoL, which has a 7-point scale (from 1 [very poor] to 7 [excellent]). By linear transformation the raw scores are standardized, so that overall scores range from 0 to 100. A higher score on the functioning scales and on global QoL represent a better level of quality of life and functioning, and a higher score on the symptom scales means a worse level of symptoms [25]. According to EORTC Quality of Life Group guidelines, clinically important differences between the two treatment groups were divided into four classes based on size: large (representing unequivocal clinical relevance), medium (likely to be clinically relevant, but to a lesser extent), small (subtle but, nevertheless, clinically relevant) and trivial (circumstances unlikely to have any clinical relevance, or where there was no difference). For each subscale criteria to fit each of the four classes were composed [26]. Within each treatment group clinical relevant differences over time were defined as a difference of at least 10 points [27].

The EORTC H&N35, a disease-specific HRQoL questionnaire,

Table 2
Baseline scores in HRQoL measured by the EORTC QLQ-C30 and QLQ-H&N35. (N) after each subscales means the number of available questionnaires.

	Baseline			Δ	p
	EORTC stage III-IV (mean) ^F	Standard group (n = 34)	Prophylaxis group (n = 28)		
PSS-HN					
Normalcy of diet (N)	NA	77.5 (32)	68.8 (25)	-8.7	0.253
Eating in public(N)	NA	93.8 (32)	84.0 (25)	-9.8	0.126
Understandability of speech(N)	NA	89.8 (32)	90.0 (25)	0.2	0.977
QLQ-C30					
Physical functioning (N)	81.2	89.4 (34)	89.0 (28)	-0.4	0.895
Role functioning(N)	78.8	74.0 (34)	79.8 (28)	5.8	0.413
Emotional functioning(N)	71.2	77.7 (34)	82.1 (28)	4.4	0.382
Cognitive functioning(N)	86.4	89.7 (34)	94.0 (28)	4.3*	0.267
Social functioning (N)	82.2	79.4 (34)	88.7 (28)	9.3*	0.104
Global health status (N)	63.1	72.2 (33)	72.0 (28)	-0.2	0.968
Fatigue(N)	27.6	16.7 (34)	21.0 (28)	4.3	0.415
Nausea/vomiting (N)	5.2	0.5 (33)	5.4 (28)	4.9*	0.075
Pain(N)	24.9	18.1 (34)	18.5 (28)	0.4	0.962
Dyspnoea(N)	18.0	8.8 (34)	6.0 (28)	-2.8	0.548
Insomnia(N)	28.5	27.5 (34)	23.8 (28)	-3.7	0.629
Appetite loss(N)	19.4	10.8 (34)	19.0 (28)	8.2	0.230
Constipation(N)	11.7	12.7 (34)	10.7 (28)	-2	0.719
Diarrhea(N)	6.1	1.0 (34)	6.0 (28)	5*	0.068
Financial problems (N)	18.8	18.6 (34)	11.9 (28)	-6.7*	0.289
QLQ-H&N35 ^a					
Pain(N)	NA	18.8 (34)	25.3 (27)	6.5	0.203
Swallowing(N)	NA	16.3 (34)	28.7 (27)	12.4 [†]	0.024 [‡]
Senses problems(N)	NA	16.2 (34)	7.4 (27)	-8.8	0.090
Speech problems(N)	NA	16.5 (33)	14.0 (27)	-2.5	0.643
Social eating(N)	NA	13.1 (33)	24.4 (26)	11.3 [†]	0.027 [‡]
Social contact(N)	NA	4.0 (33)	7.7 (27)	3.7	0.302
Sexuality(N)	NA	20.6 (30)	13.8 (23)	-6.8	0.428
Teeth(N)	NA	13.7 (34)	14.7 (25)	1	0.891
Opening mouth(N)	NA	26.5 (34)	24.4 (26)	-2.1	0.800
Dry mouth(N)	NA	17.6 (34)	18.5 (27)	0.9	0.886
Sticky saliva(N)	NA	21.6 (34)	20.5 (26)	-1.1	0.887
Coughing(N)	NA	24.5 (34)	22.2 (27)	-2.3	0.704
Felt ill(N)	NA	6.9 (33)	6.2 (26)	-0.7	0.890
Pain killers(N)	NA	48.5 (33)	37.0 (27)	-11.5 [†]	0.110
Nutritional supplements(N)	NA	27.3 (33)	37.0 (27)	9.7	0.427
Feeding tube(N)	NA	9.1 (33)	7.7 (26)	-1.4	0.851

NA = not available.

* Small clinically important difference.

† Clinically relevant difference of more than 10 points.

‡ Statistically significant.

^F EORTC reference data from patients with stage III or IV head and neck cancer [32].

^a Weight gain and weight loss not reported due to difficult interpretation.

comprises 35 questions assessing symptoms and side effects of treatment, social function and body image/sexuality, and incorporates seven multi-item scales (pain, swallowing, senses (taste and smell), speech, social eating, social contact, sexuality), and 11 single item scales (teeth, opening mouth, dry mouth, sticky saliva, coughing, felt ill, pain killers, nutritional supplements, feeding tube, weight loss, weight gain). After linear transformation, all symptom scales range in score from 0 to 100, where a higher score means more complaints [23]. A difference of at least 10 points between the two treatment groups, as well as within the

groups, was considered to be a clinically significant difference [27].

The PSS-HN was designed to measure unique disabilities of head and neck cancer patients. Surgery and/or systemic therapies in head and neck cancer patients often introduce cosmetic and functional deficits leading to problems with speech and eating [28]. The PSS-HN was developed as a simple and practical assessment and consists of three subscales: ‘normalcy of diet’, ‘understandability of speech’, and ‘eating in public’. Each is rated from 0 to 100, with higher scores indicating better performance, and 100 representing normal function [24]. The ‘normalcy of diet’ subscale assesses the extent to which the patient is able to eat a regular diet. The ‘understandability of speech’ subscale rates the degree to which a listener is able to understand the patient’s speech. The ‘eating in public’ subscale scores swallowing-related QoL issues by documenting the patient’s ability to share a meal with others, and in which type of environment. The PSS-HN has been shown to have adequate inter-rater reliability and to be sensitive to differences in performance and change over time [24]. There are no studies performed to determine clinically relevant differences on the three subscales, as with the QLQ-C30 and QLQ-H&N35, however, a score of 50 or less on the different scales seems to correlate with a lower Karnofsky performance scale [24]. Norman’s rule of thumb was used for the PSS-HN, whereby a ±0.5 standard deviation difference (i.e. 12.8 points) indicated a clinically relevant difference [29,30].

Statistics

Differences between the groups were calculated at every time point. Independent t-tests were performed to find any statistical significant differences between the two treatment groups for each symptom or functioning scale. For HRQoL during treatment compared with baseline (both groups) no statistical tests were performed and therefore results are descriptive. As described above, for all the separate questionnaires, we have not only reported statistical significant differences, but also (minimal) clinically important differences, because statistical significance does not provide information about clinical meaningfulness i.e. whether the observed effect is larger than the smallest clinically important effect [31,32].

The change in HRQoL and symptom burden (separate models for each scale) by treatment group was analyzed using linear mixed-effects models (i.e. covariance pattern model with an unstructured error variance matrix and maximum likelihood estimation) [33]. This technique uses data efficiently by including incomplete cases in the analysis. As a result, bias is limited and statistical power is preserved. Time was analyzed as a regular categorical predictor with four levels (i.e. four time points). The interaction of treatment group and time was tested separately. Analyses were performed in IBM SPSS 22.0 with a significance level of α = 0.05.

Results

Patients

A total of 106 patients were included from six centres between January 2012 and July 2015. At randomization, 48 patients were allocated to standard group and 47 patients to the prophylaxis group. Nine included patients could not be randomized (e.g. due to the use of antibiotics 14 days prior to randomization). Both groups were well balanced with respect to baseline clinical and sociodemographic characteristics (Table 1).

HRQoL completion rate and baseline scores

Only patients who completed the questionnaires at baseline as well as at follow up were included in analyses (complete case analysis). Therefore, a total of 34 patients in the standard group (70.8%) and 28 patients in the prophylaxis group (59.6%) were included in final

Table 3
 Scores in HRQL at four time points during the study measured by the EORTC QLQ-C30 and QLQ-H&N35. (N) after each subscales means the number of available questionnaires. At baseline, 34 questionnaires in the standard group (70.8%) and 28 in the prophylaxis group (59.6%) could be analyzed, at day 28, 70.8% and 55.3%, at the end of radiotherapy 52.1% and 40.4% and at follow up 70.8% and 69.6% in the standard group and prophylaxis group, respectively.

	Baseline				Day 28				After RT				FU				
	Standard group (n = 34)	Prophylaxis group (n = 28)	Δ	p	Standard group (n = 34)	Prophylaxis group (n = 28)	Δ	p	Standard group (n = 34)	Prophylaxis group (n = 28)	Δ	p	Standard group (n = 34)	Prophylaxis group (n = 28)	Δ	p	
PSS-HN																	
Normalcy of diet(N)	77.5 (32)	68.8 (25)	-8.7	0.253	45.5 (31)	37.6 (25)	-7.9	0.294	39.2 (24)	28.9 (18)	-10.3	0.210	72.0 (32)	56.9 (26)	-15.1 [#]	0.090	
Eating in public(N)	93.8 (32)	84.0 (25)	-9.8	0.126	67.5 (30)	56.8 (22)	-10.7	0.274	69.6 (23)	68.8 (16)	-0.8	0.946	87.5 (32)	72.9 (24)	-14.6 [#]	0.094	
Understandability of speech(N)	89.8 (32)	90.0 (25)	0.2	0.977	79.8 (31)	80.0 (25)	0.2	0.981	71.9 (24)	84.7 (18)	12.8 [#]	0.175	91.9 (31)	90.0 (25)	-1.9	0.607	
QLQ-C30																	
Physical functioning(N)	89.4 (34)	89.0 (28)	-0.4	0.895	82.0 (34)	84.2 (26)	2.2	0.539	76.0 (25)	83.2 (19)	7.2 [*]	0.167	87.1 (34)	84.6 (28)	-2.5	0.473	
Role functioning(N)	74.0 (34)	79.8 (28)	5.8	0.413	62.3 (34)	64.7 (26)	2.4	0.708	55.3 (25)	68.4 (19)	13.1 [*]	0.127	73.5 (34)	73.8 (28)	0.3	0.965	
Emotional functioning(N)	77.7 (34)	82.1 (28)	4.4	0.382	81.4 (34)	78.2 (26)	-3.2	0.536	78.7 (25)	83.8 (19)	5.1	0.335	85.9 (33)	81.3 (28)	-4.6	0.304	
Cognitive functioning(N)	89.7 (34)	94.0 (28)	4.3 [*]	0.267	81.9 (34)	86.5 (26)	4.6 [*]	0.382	77.3 (25)	89.5 (19)	12.2 [†]	0.047 [*]	88.4 (33)	91.7 (28)	3.3 [*]	0.389	
Social functioning(N)	79.4 (34)	88.7 (28)	9.3 [*]	0.104	73.0 (34)	75.6 (26)	2.6	0.693	66.7 (25)	86.0 (19)	19.3 [†]	0.023 [*]	84.3 (33)	83.3 (28)	-1	0.851	
Global QoL(N)	72.2 (33)	72.0 (28)	-0.2	0.968	57.4 (34)	59.6 (26)	2.2	0.679	50.3 (25)	59.6 (19)	9.3 [*]	0.194	71.7 (33)	64.9 (28)	-6.8 [*]	0.179	
Fatigue(N)	16.7 (34)	21.0 (28)	4.3	0.415	41.5 (34)	41.9 (26)	0.4	0.950	46.7 (25)	38.6 (19)	-8.1 [*]	0.808	28.9 (34)	27.0 (28)	-1.9	0.736	
Nausea/vomiting(N)	0.5 (33)	5.4 (28)	4.9	0.075	27.0 (34)	15.4 (26)	-11.6 [*]	0.091	29.3 (25)	27.2 (19)	-2.1	0.808	6.9 (34)	5.4 (28)	-1.5	0.659	
Pain(N)	18.1 (34)	18.5 (28)	0.4	0.962	28.9 (34)	34.0 (26)	5.1	0.440	35.3 (25)	37.7 (19)	2.4	0.782	17.6 (34)	18.5 (28)	0.9	0.897	
Dyspnoea(N)	8.8 (34)	6.0 (28)	-2.8	0.548	7.8 (34)	11.5 (26)	3.7	0.390	8.0 (25)	8.8 (19)	0.8	0.864	7.8 (34)	11.9 (28)	4.1 [*]	0.384	
Insomnia(N)	27.5 (34)	23.8 (28)	-3.7	0.629	22.2 (33)	18.7 (25)	-3.5	0.642	22.7 (25)	15.8 (19)	-6.9 [*]	0.443	16.7 (34)	28.4 (27)	11.7 [*]	0.158	
Appetite loss(N)	10.8 (34)	19.0 (28)	8.2	0.230	49.0 (34)	50.7 (25)	1.7	0.854	53.3 (25)	42.1 (19)	-11.2	0.284	22.5 (34)	33.3 (28)	10.8	0.176	
Constipation(N)	12.7 (34)	10.7 (28)	-2	0.719	22.5 (34)	23.1 (26)	0.6	0.927	29.3 (25)	29.8 (19)	0.5	0.955	6.9 (34)	9.5 (28)	2.6	0.583	
Diarrhea(N)	1.0 (34)	6.0 (28)	5 [*]	0.068	9.8 (34)	7.7 (26)	-2.1	0.618	10.7 (25)	15.8 (19)	5.1 [*]	0.390	1.0 (33)	4.8 (28)	3.8 [*]	0.136	
Financial problems(N)	18.6 (34)	11.9 (28)	-6.7 [*]	0.289	15.7 (34)	12.8 (26)	-2.9	0.614	20.0 (25)	12.3 (19)	-7.7 [*]	0.343	17.2 (33)	21.4 (28)	4.2 [*]	0.552	
QLQ-H&N35[‡]																	
Pain(N)	18.8 (34)	25.3 (27)	6.5	0.203	39.2 (34)	44.3 (25)	5.1	0.418	46.2(24)	41.2 (18)	-5	0.501	26.5 (34)	28.7 (27)	2.2	0.704	
Swallowing(N)	16.3 (34)	28.7 (27)	12.4 [†]	0.024 [†]	45.9 (34)	46.7 (25)	0.8	0.907	53.8 (24)	47.2 (18)	-6.6	0.396	22.7 (34)	29.9 (27)	7.2	0.263	
Senses problems(N)	16.2 (34)	7.4 (27)	-8.8	0.090	51.0 (34)	40.7 (25)	-10.3 [†]	0.159	46.5 (24)	40.7 (18)	-5.8	0.468	28.4 (34)	30.9 (27)	2.5	0.729	
Speech problems(N)	16.5 (33)	14.0 (27)	-2.5	0.643	25.7 (34)	28.4 (26)	2.7	0.690	42.4 (25)	26.9 (19)	-15.5 [†]	0.051	14.4 (34)	19.0 (28)	4.6	0.354	
Social eating(N)	13.1 (33)	24.4 (26)	11.3 [†]	0.027 [*]	35.9 (34)	39.4 (26)	3.5	0.487	41.9 (25)	38.7 (19)	-3.2	0.643	17.6 (34)	34.3 (27)	16.7 [†]	0.017 [*]	
Social contact(N)	4.0 (33)	7.7 (27)	3.7	0.302	12.7 (34)	9.6 (26)	-3.1	0.479	22.1 (25)	9.4 (19)	-12.7 [†]	0.041 [*]	6.3 (34)	8.8 (28)	2.5	0.446	
Sexuality(N)	20.6 (30)	13.8 (23)	-6.8	0.428	38.0 (32)	41.7 (22)	3.7	0.711	43.5 (23)	42.2 (17)	-1.3	0.908	29.6 (31)	27.8 (24)	-1.8	0.845	
Teeth(N)	13.7 (34)	14.7 (25)	1	0.891	13.7 (34)	14.5 (23)	0.8	0.888	26.4 (24)	21.6 (17)	-4.8	0.616	10.1 (33)	26.9 (26)	16.8 [†]	0.019 [*]	
Opening mouth(N)	26.5 (34)	24.4 (26)	-2.1	0.800	37.3 (34)	34.7 (25)	-2.6	0.764	47.2 (24)	35.2 (18)	-12	0.165	30.4 (34)	34.6 (27)	4.2	0.583	
Dry mouth(N)	17.6 (34)	18.5 (27)	0.9	0.886	52.0 (34)	50.7 (25)	-1.3	0.881	52.8 (24)	48.1 (18)	-4.7	0.643	54.9 (34)	56.8 (27)	1.9	0.835	
Sticky saliva(N)	21.6 (34)	20.5 (26)	-1.1	0.887	58.8 (34)	68.0 (25)	9.2	0.255	66.7 (24)	70.4 (19)	3.7	0.682	45.1 (34)	43.2 (27)	-1.9	0.789	

(continued on next page)

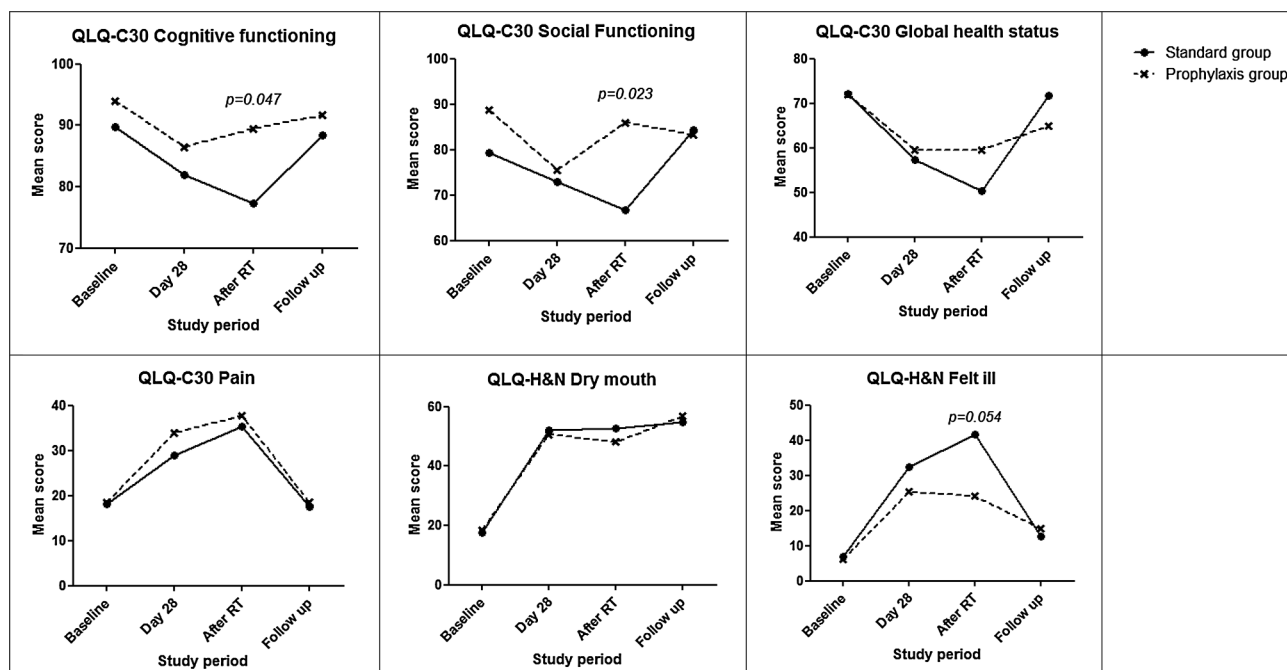


Fig. 1. On the top three functional items of the QLQ-C30 showing a decrease during chemoradiotherapy, and an increase at follow up, whereas the prophylaxis group in general had a less steep decline after radiotherapy compared with the standard group. On the bottom three symptom subscales, showing an increase in symptoms during radiotherapy, with improvement of symptoms at follow up, except for some specific subscales like dry mouth. The prophylaxis group felt less ill during chemoradiotherapy.

and 3.5 months follow-up, with no difference between the two treatment groups. Patients also scored significantly higher on ‘Nausea and vomiting’ at the end of radiotherapy compared with all other time-points. The symptoms of the EORTC QLQ-H&N35 ‘pain’, ‘swallowing’, ‘sticky saliva’, changed significantly between the end of radiotherapy and baseline and end of radiotherapy and end of follow-up, with significantly higher scores at the end of radiotherapy. The symptoms ‘senses problems’, ‘speech problems’, ‘social eating’, ‘sexuality’, ‘dry mouth’, ‘coughing’, ‘felt ill’ and the need of ‘a feeding tube’ scores all significantly higher at the end of radiotherapy compared with baseline. On the ‘cognitive functioning’ and ‘social functioning’ scales of the EORTC QLQ-C30 and the ‘social contact’ and ‘feeling ill’ symptom scales of the EORTC QLQ-H&N35 the standard group experienced significantly more problems over time compared to the prophylaxis group (Table 4).

Discussion

HRQoL was an important secondary objective of the PANTAP-study, which showed that prophylactic administration of amoxicillin/clavulanic acid reduced the number of hospital admissions, episodes of fever and healthcare costs without lowering the incidence of pneumonias. This study showed that prophylactic antibiotics also seemed to improve most aspects of HRQoL at the end of radiotherapy compared to standard care alone, although not all subscales were statistically significantly different.

At baseline some small clinically relevant differences were found between the two treatment groups, though most disappeared before the start of the prophylactic antibiotics at day 28. However, at the end of radiotherapy, when patients in the prophylaxis group were still taking the prophylactic antibiotics, the prophylaxis group reported a better HRQoL on most items compared to the standard group. At the end of follow up, 3.5 months after the end of chemoradiotherapy, few differences still existed between the two treatment groups. This suggests the advantage of the prophylaxis, with respect to the HRQoL, is experienced between the start of the antibiotics and the end of radiotherapy,

as seen in the decreased decline in functional subscales. During the study, HRQoL deteriorated from baseline to day 28 and the end of radiotherapy; patients experienced a significantly higher symptom burden at the end of radiotherapy compared to baseline on 10 of the 18 symptoms covered by the EORTC QLQ-H&N35 reflects the high level of toxicity at the end of chemoradiotherapy. This confirms findings in the literature that show a decline in HRQoL during and at the end of (chemo)radiotherapy [9,11]. This deterioration can be explained by treatment toxicities.

Interestingly, we observed no difference in reported levels of diarrhoea in the prophylaxis group compared to the standard group. This is surprising given the relatively long use of antibiotics in the prophylaxis group.

At follow-up, 3.5 months after the end of chemoradiotherapy, most subscales returned to baseline-values or better, which has been previously described in other studies [4,9,12]. Only the ‘senses problems’, ‘dry mouth’, and ‘sticky saliva’ symptom scales saw no improvement at follow up. This is also agrees with previous studies by Vergeer et al. and Jellema et al. that showed dry mouth, sticky saliva and diminished taste can be long lasting or even permanent [10,35], due to permanent damage to the salivary glands caused by the radiotherapy. The fact that patients in the prophylaxis group scored significantly higher on the subscales ‘social eating’ and ‘teeth’ at follow-up, cannot be explained by the use of prophylactic antibiotics. This may be due to statistical issues related to the small number of completed questionnaires.

Slightly more patients included in the prophylaxis group had hypopharyngeal cancer, although not statistically different. Hypopharyngeal cancer is associated with a greater risk of aspiration and pneumonia. This may have influenced the number of aspiration pneumonias in both groups. But as the number of pneumonias were not different between the two groups, it likely would not have had any consequence on the HRQoL outcomes.

To the best of our knowledge, the PANTAP study is the first study to investigate the effect of prophylactic antibiotics on the occurrence of pneumonias, the number of hospital admissions and healthcare costs in LAHNC patients treated with chemoradiotherapy. The strength of the

Table 4
 Linear mixed-effects model of the functional scales of the EORTC QLQ-C30 (4a) and the EORTC QLQ-H&N35 (4b). The item financial problems of the EORTC QLQ-C30 and the items nutritional supplements, feeding tube, weight loss and weight of the EORTC H&N-35 are not reported, because they are based on single item-questions, and in that way difficult to interpret and because of the small number of patients easy to vary in outcome.

4a.		Physical functioning	Role functioning	Emotional functioning	Cognitive functioning	Social functioning	Global QoL	Fatigue	Nausea	Pain	Dyspnoea	Insomnia	Appetite loss	Constipation	Diarrhea	
		Beta	Beta	Beta	Beta	Beta	Beta	Beta	Beta	Beta	Beta	Beta	Beta	Beta	Beta	Beta
<i>Time variables</i>																
Time																
T3 versus T1		6.69*	13.14*	-1.45	4.74	4.90	13.06*	-19.27*	-21.17*	-19.30*	-3.92	6.52	-27.01*	-19.17*	-9.05*	
T3 versus T2		1.88	-2.92	-5.65	-3.05	-7.81	-0.04	1.59	-11.20*	-4.56	1.50	1.30	4.67	-6.64	-7.04	
T3 versus T4		2.34	7.19	-2.34	2.36	-0.45	5.92	-13.32*	-21.17*	-19.30*	2.04	11.16	-12.72	-20.36*	-10.24*	
<i>Treatment</i>																
Arm B versus Arm A		-6.16	-10.30	-5.67	-11.91*	-16.37*	-7.78	6.71	4.02	-3.06	-2.03	4.63	8.66	0.64	-3.58	
<i>A</i>																
4b.																
		Pain	Swallowing	Senses problems	Speech problems	Social eating	Social contact	Sexuality	Teeth	Opening mouth	Dry mouth	Sticky saliva	Coughing	Felt ill	Pain killers	
		Beta	Beta	Beta	Beta	Beta	Beta	Beta	Beta	Beta	Beta	Beta	Beta	Beta	Beta	
<i>Time variables</i>																
Time																
T3 versus T1		-15.44*	-20.60*	-35.79*	-14.33*	-16.95*	-2.52	-29.21*	-3.08	-12.26	-28.47*	-49.40*	-11.05*	-19.98*	-14.59	
T3 versus T2		3.04	-2.73	-0.15	-0.24	-1.88	-0.82	-1.30	-4.43	-2.33	6.01	-0.53	5.92	-0.14	1.97	
T3 versus T4		-12.31*	-19.26*	-11.30	-9.52	-6.56	-1.20	-15.28	6.68	-1.66	10.99	-26.22*	-2.78	-10.48	-55.98*	
<i>Treatment</i>																
Arm B versus Arm A		4.03	4.63	7.81	13.36	1.19	11.51*	0.50	5.83	5.95	7.38	-3.44	-2.87	16.24*	-6.97	

* Indicating a clinically significant difference (<0.05).

current study is the focus on the effect of prophylactic antibiotics on HRQoL in this patient group. As far as we know, only one other study has looked at the effect of antibiotics on HRQoL. Braimah et al. investigated the effect of oral antibiotics on HRQoL after mandibular third molar surgery and showed that extended oral use of amoxicillin/clavulanic acid was correlated with a better, though not statistically significant, HRQoL [36].

A limitation of this study is the relative low compliance of completed HRQoL questionnaires, particularly at the end of radiotherapy. In addition, fewer questionnaires were completed by the prophylaxis group (at baseline 70.8% versus 59.6% for standard versus prophylaxis groups, respectively). Because of this, the number of included questionnaires was too low to perform multivariate analyses and no conclusions could be drawn on the impact of pneumonia or hospital admission on HRQoL. The explorative nature of this study also made it impossible to correct for multiple comparisons or confounders such as comorbidity. Furthermore, the last follow-up questionnaire was at 3.5 months after the end of chemoradiotherapy, limiting our ability to assess the long-term effects of prophylactic antibiotics on HRQoL. However, as HRQoL largely returned to baseline values at 3.5 months follow up with almost no differences between the groups, no large clinically relevant differences would be expected in future.

In conclusion, prophylactic antibiotics in LAHNC patients treated with chemoradiotherapy may mitigate deterioration of HRQoL at the end of the radiotherapy compared to standard care alone. However, no differences were found between groups at the end of follow up. This study should be replicated with larger numbers and more potential covariates. However, given the fact that prophylactic antibiotics, compared to standard treatment, reduced the number of hospital admissions and costs and also seemed to help maintain HRQoL at the end of the chemoradiotherapy, prophylactic antibiotics in this patients group can be considered.

Declaration of Competing Interest

None declared.

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