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Comparing cisplatin-based combination chemotherapy with EMA/CO chemotherapy for the treatment of high risk gestational trophoblastic neoplasia

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Abstract Background: Cisplatin-based chemotherapy (etoposide 100 mg/m² days 1–5, methotrexate 300 mg/m² day 1, cyclophosphamide 600 mg/m² day 1, actinomycin D 0.6 mg/m² day 2 and cisplatin 60 mg/m² day 4, EMACP) was compared to EMA/CO (etoposide 100 mg/m² days 1–2, methotrexate 300 mg/m² day 1 and actinomycin D 0.5 mg i.v. bolus day 1 and 0.5 mg/m² day 2, alternating with cyclophosphamide 600 mg/m² day 8 and vincristine 1 mg/m² day 8) for the treatment of high-risk gestational trophoblastic neoplasia (GTN).

Patients and methods: In the Netherlands, 83 patients were treated with EMACP and 103 patients with EMA/CO. Outcome measures were remission rate, median number of courses to achieve normal human chorionic gonadotrophin (hCG) concentrations, toxicity, recurrent disease rate and disease specific survival.

Results: Remission rates were similar (EMACP 91.6%, EMA/CO 85.4%). The median number of courses of EMA/CO to reach hCG normalisation for single-agent resistant disease and primary high-risk disease was three and five courses, respectively, compared to 1.5 ($p = 0.001$) and three ($p < 0.001$) courses of EMACP. Patients treated with EMACP more often developed

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fever, renal toxicity, nausea and diarrhoea compared to patients treated with EMA/CO. Patients treated with EMA/CO more often had anaemia, neuropathy and hepatotoxicity.

Conclusion: EMACP combination chemotherapy is an effective treatment for high-risk GTN, with a remission rate comparable to EMA/CO. However, the difference in duration of treatment is only slightly shorter with EMACP. Cisplatin-based chemotherapy in the form of EMACP in this study was not proven more effective than EMA/CO.

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1. Introduction

Gestational trophoblastic disease (GTD) comprises a spectrum of disorders, ranging from the premalignant complete and partial hydatidiform moles (CHM and PHM, respectively), to gestational trophoblastic neoplasia (GTN) consisting of invasive moles, choriocarcinoma, placental site trophoblastic tumours (PSTT) and the rare epithelioid trophoblastic tumour (ETT). Patients with GTN are classified as having low-risk or high-risk disease using the modified WHO prognostic scoring system as adapted by FIGO.¹ Patients with a score of 0–6 are defined as having low-risk disease. These patients are treated with single-agent chemotherapy, consisting of either methotrexate (MTX) or actinomycin D. For high-risk patients (prognostic score of 7 or more) single-agent chemotherapy is considered insufficient treatment and they are therefore treated with multi-agent chemotherapy.²

Before the introduction of multi-agent chemotherapy in the 1970s, only 31% of the high-risk patients would be cured with single-agent chemotherapy.³ Throughout the late 1970s, the combination of MTX, actinomycin D and cyclophosphamide or chlorambucil (MAC) became the preferred first-line chemotherapy, followed by the combination regimen of cyclophosphamide, hydroxyurea, actinomycin D, MTX, vincristine and doxorubicin (CHAMOCA) in the early 1980s.^{2,4,5} In 1982, an alternative schedule to CHAMOCA was designed by the Dutch Working Party on Trophoblastic Disease, consisting of etoposide, MTX, actinomycin D, cyclophosphamide and cisplatin (EMACP), aiming to design a schedule that could be repeated frequently with a short interval between two courses, causing less myelosuppression and containing the new agents etoposide and cisplatin.^{6,7} Today, the most widely accepted initial treatment for high-risk trophoblastic tumour is EMA/CO chemotherapy (etoposide, MTX and actinomycin D, alternating with cyclophosphamide and vincristine) introduced in 1979 by Newlands and Bagshawe, showing complete remission rates ranging from 69% to 86%.^{8–11} However, due to the favourable outcome following treatment, some centres in the Netherlands preferred to continue application of the EMACP schedule after the introduction of EMA/CO. The aim of the present study was to evaluate the efficacy and safety of cisplatin-based combination chemotherapy (EMACP) as

compared to the EMA/CO schedule for the treatment of high risk GTN.

2. Patients and methods

2.1. Patients

In the Netherlands, patients with GTD are registered at the Dutch Central Registry for Hydatidiform Moles (DCRHM) residing at the Radboud University Nijmegen Medical Centre (RUNMC). This voluntary registry serves as an epidemiological database and provides a national human chorionic gonadotrophin (hCG) assay service to gynaecologists. Patients with GTD, and even GTN are treated in various referral hospitals. The Dutch Working Party on Trophoblastic Disease, founded in 1971, has a registration and advisory function. The Dutch classification system for trophoblastic tumours scores for previous failure to chemotherapy, localisation of metastases, antecedent pregnancy and the interval between end of pregnancy and beginning of treatment (Table 1). Patients treated with EMACP or EMA/CO from 1982 to 2009 were identified from the databases of the DCRHM and the Dutch Working Party on Trophoblastic Disease. Patients treated with other multi-agent chemotherapy administered before the start of EMACP or EMA/CO, patients diagnosed with PSTT and patients with a non-gestational tumour were excluded. In total, 83 patients treated with EMACP and 103 patients treated with EMA/CO were included in this study. Medical records of all patients were reviewed for age at diagnosis, antecedent pregnancy, date of evacuation, histology of the tumour, localisation of metastases, indication for treatment with first multi-agent chemotherapy and duration of follow-up.

2.2. Treatment

The EMACP and EMA/CO chemotherapy regimens are shown in Table 2. In the EMACP regimen, the interval between courses is 21 days. After normalisation of the serum hCG concentration generally two courses of chemotherapy were given to prevent disease relapse. In the EMA/CO regimen, interval between courses is 15 days. After normalisation of the serum hCG the national guideline advises three courses of consolidation chemotherapy.¹² Drug resistance was defined as steady

Table 1
Risk classification of GTN by the Dutch Working Party on Trophoblastic Disease.

Low-risk GTN	Demands all of the following conditions: <ol style="list-style-type: none"> 1. Antecedent pregnancy: hydatidiform mole or abortion^a 2. No metastases or metastases in vagina or lung 3. No previous chemotherapy 4. Interval between evacuation and start of chemotherapy less than 12 months
High-risk GTN	Demands one or more of the following conditions: <ol style="list-style-type: none"> 1. Failure of previous (mono-) chemotherapy 2. Metastases in more than one site (outside the uterus) 3. Metastases in one or more of the following organs: liver, spleen, kidney, gastrointestinal tract, bones or brain 4. Antecedent pregnancy: term 5. Interval between end of antecedent pregnancy and start of chemotherapy more than 12 months

^a There is no consensus on classification of non-molar abortion as low- or high-risk disease.

or increasing serum hCG during treatment. When drug resistance occurred most patients were treated with surgery, salvage chemotherapy treatment or both.

2.3. Outcome measures

Outcome measures were the percentage of patients that achieved a complete remission, defined as a normal hCG value after completion of treatment (without consolidation courses), and the median number of chemotherapy courses required to achieve complete remission. Also, the percentage of patients with recurrent disease and the disease specific survival was registered after 24 months of follow-up from the start of treatment. The cut-off point of 24 months was chosen because the national guidelines recommend 2 years of follow-up after treatment for high-risk GTN, since the chance of relapsed disease is the highest within the first year of remission, and 85% of all episodes of disease relapse occur within 18 months of remission.^{12,13} Short-term toxicities were registered according to the Common Terminology Criteria for Adverse Events v3.0 (CTCAE). Also long-term toxicities, including secondary malignancies were registered. Data on toxicity were obtained from the medical records and if used, from the Systemic Therapy Checklist designed by the EORTC.¹⁴

2.4. Statistical analysis

Statistical analysis was performed using SPSS software (version 18). Patient characteristics, remission rates and toxicity were compared using Chi-square test. Mean age was compared using Student *t*-test. The median

number of chemotherapy courses to hCG normalisation was compared using the non-parametric independent-samples median test. *p* values of less than 0.05 were considered statistically significant.

3. Results

Patient characteristics are shown in Table 3. In total, 83 patients were treated with EMACP, of which 16 patients received a modified schedule without MTX (ECAP). Patients treated with EMA/CO were significantly older (mean 32 years) than patients treated with EMACP (mean 29 years, *p* = 0.008). The antecedent pregnancies from patients treated with EMACP were not significantly different from patients treated with EMA/CO. The indications for treatment were significantly different between patients treated with EMACP and those treated with EMA/CO (*p* = 0.023). Patients treated with EMACP more often were treated for single-agent resistant disease (63.9%) compared to EMA/CO patients (43.7%). More patients treated with EMA/CO had primary high-risk disease (42.7%) compared to patients treated with EMACP (27.7%). Seven patients (8.4%) were treated with EMACP and 14 patients (13.6%) with EMA/CO because of disease relapse after single-agent chemotherapy. Median follow-up from the start of treatment was 33.3 months (range 3.9–246.9 months).

3.1. Acute toxicity

Table 4 shows toxicity profiles for EMACP and EMA/CO. Three patients died from sepsis related to treatment, of which one patient was treated with EMACP and two were treated with EMA/CO. Patients treated with EMACP more often developed fever (22.9% versus 11.7%, *p* = 0.041), renal toxicity (15.7% versus 4.9%, *p* = 0.013), nausea (48.2% versus 28.2%, *p* = 0.005) and diarrhoea (13.3% versus 3.9% *p* = 0.02) compared to patients treated with EMA/CO. Patients treated with EMA/CO more often had anaemia (28.8% versus 7.2%, *p* < 0.001), although the incidence of leucopenia and thrombocytopenia was not significantly different. In addition, they more often developed neuropathy (26.2% versus 6.0%, *p* < 0.001) and hepatotoxicity (16.5% versus 6.0%, *p* = 0.028).

The number of patients in whom the dose of chemotherapy had to be reduced was not significantly different between EMA/CO and EMACP (21.4% versus 27.7%), but in more patients treated with EMACP one or more courses had to be delayed due to toxicity or myelosuppression (36.1% versus 20.4%, *p* = 0.017). In patients treated with EMACP, a total of 330 courses were administered. Patients treated with EMA/CO received a total of 688 courses. Dose reduction occurred in 39 (11.8%) of EMACP courses and in 60 (8.7%) of EMA/

Table 2

(a) EMACP regimen and EMA/CO regimen for high-risk gestational trophoblastic neoplasia and (b) the accumulated dosage per week. Interval between courses is 21 and 15 days, respectively.

(a) EMACP regimen			EMA/CO regimen		
Day	Chemotherapy	Dose (i.v.)	Day	Chemotherapy	Dose (i.v.)
1	Etoposide	100 mg/m ²	1	Etoposide	100 mg/m ²
	Methotrexate	300 mg/m ²		Methotrexate	300 mg/m ²
	Cyclophosphamide	600 mg/m ²		Actinomycin D	0.5 mg
2	Etoposide	100 mg/m ²	2	Etoposide	100 mg/m ²
	Actinomycin D	0.6 mg/m ²		Actinomycin D	0.5 mg
3	Etoposide	100 mg/m ²	8	Vincristine	1 mg/m ²
4	Etoposide	100 mg/m ²		Cyclophosphamide	600 mg/m ²
	Cisplatin	60 mg/m ²			
5	Etoposide	100 mg/m ²			
(b) EMACP regimen			EMA/CO regimen		
Etoposide 166.7 mg/m ²			Etoposide 100 mg/m ²		
Methotrexate 100 mg/m ²			Methotrexate 150 mg/m ²		
Cyclophosphamide 200 mg/m ²			Cyclophosphamide 300 mg/m ²		
Actinomycin D 0.2 mg/m ²			Actinomycin D 0.5 mg		
Cisplatin 20 mg/m ²			Vincristine 0.5 mg/m ²		

CO courses (mostly removal of vincristine due to neuropathy) ($p = 0.119$). Delay of chemotherapy was required in 45 courses (13.6%) of EMACP, compared to 33 (4.8%) of EMA/CO courses that were given with delay ($p < 0.001$).

3.2. Late toxicity

In total, seven patients developed secondary malignancies, of which two patients died. After EMA/CO, four patients developed a secondary malignancy (3.9%): two Acute Myeloid Leukaemia (AML), one patient developed Chronic Myeloid Leukaemia (CML) and one patient died from multiple myeloma 16 years after treatment with EMA/CO. Three patients developed a secondary tumour after EMACP (3.6%). One developed myelodysplastic syndrome (refractory anaemia with excess blasts (RAEB)), and two patients developed AML, of which one patient died, 40 months after start of treatment. None of the patients had a cumulative etoposide dose exceeding 2 g/m².

3.3. Response to treatment

Table 5 shows remission rates achieved with EMACP and EMA/CO for single-agent resistant disease, primary high-risk disease and relapsed disease after initial remission on single-agent chemotherapy. In total, 76 out of 83 patients achieved disease remission with EMACP (91.6%), compared to 88 out of 103 patients treated with EMA/CO (85.4%), which was not significantly different. Remission was achieved in 52 of 53 (98.1%) patients that were treated with EMACP after failure of initial single-agent chemotherapy, compared to 44 of 45 (97.8%) in patients treated with EMA/CO, which was not significantly different. Median number of EMACP courses to achieve normal serum hCG concentrations in these

patients was 1.5 (range 1–5) compared to a median of three (range 1–6) courses of EMA/CO ($p = 0.001$). In 78.3% (18 out of 23) and 72.7% (32 out of 44) of patients that were primarily classified as high-risk GTN, disease remission was achieved with EMACP and EMA/CO, respectively (not significant). They received a median of three EMACP courses (range 2–7) and five EMA/CO courses (range 3–13) to achieve normal serum hCG concentrations ($p < 0.001$). In 85.7% (six out of seven) of patients treated for disease relapse after single-agent chemotherapy disease remission was achieved with a median of one course of EMACP. Complete remission was also achieved in 85.7% (12 out of 14) of these patients treated with EMA/CO, but with a median of two (range 1–4) courses (not significantly different). The median duration of treatment to achieve disease remission for single-agent resistant disease, primary high risk disease and relapsed disease, respectively, is 6, 10 and 4 weeks with EMA/CO, compared to 4.5, 9 and 3 weeks with EMACP.

Of the 17 patients treated with EMACP for post-term GTN, 14 went into remission (82.4%) with a median of three courses. Of the 38 patients treated with EMA/CO that had an antecedent term pregnancy, 28 patients (73.7%) went in remission (data not shown). These patients received a median of five courses of EMA/CO to achieve normalisation of the hCG concentration (range 1–13). During follow-up, 10 patients out of 76 patients that initially went into remission with EMACP subsequently developed recurrent disease (13.2%), compared to four out of 88 patients that achieved disease remission with EMA/CO (4.5%, $p = 0.049$).

Seven patients did not achieve disease remission with EMACP. Two patients had an additional hysterectomy and one patient was switched to EMA/CO due to severe toxicity of EMACP. One patient developed a severe sepsis and died after the first EMACP course. Another

Table 3
Patient characteristics.

	EMACP (<i>n</i> = 83)	EMA/CO (<i>n</i> = 103)	<i>p</i>
Age at diagnosis (years)			0.008
Mean (SD)	29 (6)	32 (6.2)	
Antecedent pregnancy			NS
Hydatidiform mole	62 (74.7%)	59 (57.3%)	
Term pregnancy	17 (20.5%)	38 (36.9%)	
Non-molar abortion	2 (2.4%)	4 (3.9%)	
Uncertain	2 (2.4%)	2 (1.9%)	
Indication for treatment			0.023
Single-agent resistant disease	53 (63.9%)	45 (43.7%)	
Primary high-risk disease	23 (27.7%)	44 (42.7%)	
Disease relapse after MTX	7 (8.4%)	14 (13.6%)	

SD, standard deviation; MTX, methotrexate.

Table 4
Toxicity profile for EMACP (*n* = 83) and EMA/CO (*n* = 103).

Toxicity	EMACP Number of patients (%)	EMA/CO Number of patients (%)	<i>p</i>
Myelosuppression			
Anaemia	6 (7.2%)	29 (28.2%)	<0.001
Leucopenia	50 (60.2%)	50 (48.5%)	NS
Thrombocytopenia	6 (7.2%)	4 (3.9%)	NS
Fever	19 (22.9%)	12 (11.7%)	0.041
Neuropathy	5 (6.0%)	27 (26.2%)	<0.001
Renal toxicity	13 (15.7%)	5 (4.9%)	0.013
Hepatotoxicity	5 (6.0%)	17 (16.5%)	0.028
Gastro-intestinal			
Mucositis	16 (19.3%)	10 (9.7%)	NS
Nausea	40 (48.2%)	29 (28.2%)	0.005
Diarrhoea	11 (13.3%)	4 (3.9%)	0.02
Dose reduction	23 (27.7%)	22 (21.4%)	NS
Delay in courses	30 (36.1%)	21 (20.4%)	0.017
Secondary malignancy	3 (3.6%)	4 (3.9%)	NS
Death	1 (1.2%)	2 (1.9%)	NS

NS, not significant.

patient was wrongfully switched to EMACO due to presumed drug resistance, however, this was due to the use of another hCG assay. In one patient the hCG concentration was decreasing but upfront she agreed on performing a hysterectomy if after four courses of EMACP the hCG was not normalised. One patient initially treated with EMACP, died from metastatic disease 23 months after diagnosis. She presented with a choriocarcinoma after a term pregnancy with metastases to liver and lungs, and was treated with extensive chemotherapy and radiotherapy but subsequently developed bone and brain metastases.

Fifteen patients did not achieve disease remission with EMA/CO. Seven patients were switched to a platinum-containing chemotherapy regimen. Five patients were treated with a platinum-containing chemotherapy regimen and hysterectomy. Two patients died during EMA/CO due to sepsis, and one patient was cured with hysterectomy only.

Five patients died from GTN or the given treatment within the 24 months of follow-up. Disease specific survival of EMACP patients was 96.4% (80 out of 83) and 98.1% (101 out of 103) of patients initially treated with EMA/CO.

4. Discussion

The present study showed that 91.6% of patients treated with EMACP achieved disease remission compared to 85.4% of patients treated with EMA/CO. Patients treated for primary high-risk disease, single-agent resistant disease and relapsed disease all required less courses of EMACP to achieve normalisation of serum hCG compared to patients treated with EMA/CO. Patients treated with EMACP more often developed fever, renal toxicity and gastro-intestinal toxicity, and significantly more courses had to be delayed compared to EMA/CO. However, patients treated with EMA/CO more

Table 5

Remission rates in patients treated with EMACP and EMA/CO for single-agent resistant disease, primary high-risk disease and relapsed disease after initial remission on single-agent chemotherapy.

Treatment indication	EMACP			EMA/CO		
	n	CRR (%)	Number of courses to disease remission (median)	n	CRR (%)	Number of courses to disease remission (median)
Single-agent resistant disease	53	52 (98.1%)	1.5 (4.5 weeks)	45	44 (97.8%)	3 (6 weeks)
Primary high-risk disease	23	18 (78.3%)	3 (9 weeks)	44	32 (72.7%)	5 (10 weeks)
Disease relapse after MTX	7	6 (85.7%)	1 (3 weeks)	14	12 (85.7%)	2 (4 weeks)
Total	83	76 (91.6%)		103	88 (85.4%)	

CRR, complete remission rates.

often had anaemia, neuropathy and hepatotoxicity. The number of patients that died from sepsis during treatment and of patients that developed secondary tumours was comparable in EMA/CO en EMACP.

In previous studies evaluating EMA/CO combination chemotherapy, a remission rate of 69–86% was obtained.^{8–10,15–18} The disease specific survival rate varies from 85% to 90.9%.^{8,9,16,17} The remission rate and disease specific survival of all EMA/CO patients in our study were 85.4% and 98.1%, respectively. In the present study more patients treated with EMA/CO had primary high-risk disease compared to patients treated with EMACP. Remission rates were higher in patients who received prior single-agent chemotherapy compared to patients that received EMA/CO as first treatment for primary high-risk disease (97.8% versus 72.7% respectively). For comparison, Escobar et al. found that the complete response to EMA/CO was higher in patients who received EMA/CO as primary treatment (76%) than in patients who were treated secondarily with EMA/CO (65%).¹⁸ In contrast, Bower et al. reported that the complete remission rate after EMA/CO was not different if women received prior chemotherapy (78% and 79% for first and second line treatment).⁸ Lu et al. also found the same remission rates in patients receiving EMA/CO as first-line treatment and as secondary treatment (77.8%).¹⁶ The differences found in our study might result from a difference in prior chemotherapy. Patients that received prior chemotherapy in the studies by Bower et al. and Lu et al. had received either single-agent MTX or combination chemotherapy, whereas all patients in our study only received previous single-agent MTX or actinomycin D.

Although less courses of EMACP than EMA/CO were needed to achieve normal serum hCG, EMACP is a 3-weekly schedule whereas EMA/CO is a 2-weekly schedule. Still, the duration of chemotherapeutic treatment, although minimal, is shorter with EMACP. However, each course of EMA/CO requires only 1 day of hospital admittance every 2 weeks for the administration of the EMA part of the course, since the CO part on day 8 can be given in the outpatient clinic. In contrast, administration of the EMACP schedule requires

5 days of hospital admittance (days 1–5) every 3 weeks, which is a higher burden for the patient and is less cost-effective. In this respect, EMA/CO therefore seems preferable over EMACP. If the difference in number of consolidation courses would be included, patients treated with EMA/CO, who received two consolidation courses, would have received 3.5, 5 and 3 courses for single-agent resistant disease, primary high risk disease and relapsed disease, respectively, compared to 6, 8 and 5 courses of EMA/CO, since for the EMA/CO regimen three consolidation courses are advised. However, significantly more patients developed recurrent disease after EMACP (13.2%) than after EMA/CO (4.5%), which may warrant the need for three courses of consolidation therapy of EMACP to obtain sustained remission.

The relatively high risk of developing secondary malignancy found is most likely brought about by etoposide.¹⁹ Pedersen-Bjergaard et al. reported on five patients with leukaemic complications among 82 patients who received a cumulative dose of more than 2 g/m² etoposide, whereas no leukaemias were observed among 130 patients who had received up to 2 g/m².^{20,21} Each course of EMA/CO contains 200 mg/m² of etoposide compared to 500 mg/m² in the EMACP schedule. Therefore the cumulative dose of 2 g/m² is reached after four courses of EMACP and only after 10 courses of EMA/CO. All three patients that developed secondary tumours after EMACP received four courses of EMACP. Of the four patients who developed secondary malignancies after EMA/CO, in none of the patients this dose was reached. However, more recent reports suggest that the risk estimate after moderate cumulative doses (1.5–3 g/m²) was virtually identical to the risk estimate for patients who received etoposide at a dose of less than 2.0 g/m².²² Etoposide is a cell-cycle specific agent, and large differences have been reported for different schedules. A schedule of five consecutive daily infusions is much more active than 24-h infusion of the same total dose.²³ Similarly, increased leukaemogenicity was suggested for these intermittent administration schedules.

Cisplatin has previously been identified as an active agent for high-risk GTN.²⁴ Currently, it is used in patients who have failed initial combination chemotherapy

in particular, such as the EMA/EP regimen, substituting etoposide and cisplatin for cyclophosphamide and vincristine in the EMA/CO protocol. EP and EMA are alternated at weekly intervals.²⁴ In contrast to EMACP, EMA/EP does not contain cyclophosphamide. In addition, EMA/EP contains a cumulative dose of 250 mg/m² etoposide in each course, compared to 500 mg/m² in the EMACP schedule. However, EMA/EP contains 75 mg/m² cisplatin in each course compared to 60 mg/m² cisplatin in the EMACP schedule. Previously, Newlands et al. reported significant toxicity of EMA/EP chemotherapy in patients who have relapsed after or who have become refractory to EMA/CO, with patients suffering from neutropenia (68%), thrombocytopenia (40%), anaemia (21%) and renal toxicity (41%). Myelosuppression caused delays in chemotherapy in 88% of EMA/EP patients and 38% of patients required dose reductions.²⁵ Mao et al. reported myelosuppression and gastro-intestinal problems as the main adverse effects in 18 patients treated with 74 cycles of EMA/EP. Because of myelosuppression and hepatotoxicity, 32 courses (43.2%) were delayed.²⁶ This is a much higher toxicity than the observed toxicity of EMACP in our study. Adding cisplatin after previous multi-agent chemotherapy leads to an impaired bone marrow reserve. It might therefore be advantageous to start chemotherapy with cisplatin earlier in the course of treatment.

In conclusion, EMACP combination chemotherapy is an effective treatment for high-risk GTN. The remission rate of EMACP was comparable to EMA/CO, and although less courses of EMACP were required to achieve disease remission, the difference in duration of chemotherapeutic treatment is only slightly shorter with EMACP. Short term toxicity was alternating different between EMACP and EMA/CO, but overall not significantly more common in either of them, whereas long-term toxicity was not different between both regimens. Cisplatin-based chemotherapy in the form of EMACP in this study was not proven more effective than EMA/CO. From the results of this study no arguments could be found to change the current standard with EMACO.

Conflict of interest statement

None declared.

References

- FIGO Oncology Committee. FIGO staging for gestational trophoblastic neoplasia 2000. *Int J Gynaecol Obstet* 2002;**77**:285–7.
- Lurain JR. Gestational trophoblastic disease: II. Classification and management of gestational trophoblastic neoplasia. *Am J Obstet Gynecol* 2010;**204**:11–8.
- Bagshawe KD, Dent J, Newlands ES, et al. The role of low-dose methotrexate and folinic acid in gestational trophoblastic tumours (GTT). *Br J Obstet Gynaecol* 1989;**96**:795–802.
- Begent RH, Bagshawe KD. The management of high-risk choriocarcinoma. *Semin Oncol* 1982;**9**:198–203.
- Lurain JR, Brewer JI. Treatment of high-risk gestational trophoblastic disease with methotrexate, actinomycin D, and cyclophosphamide chemotherapy. *Obstet Gynecol* 1985;**65**:830–6.
- Einhorn LH, Donohue J. Cis-diamminedichloroplatinum, vincristine, and bleomycin combination chemotherapy in disseminated testicular cancer. *Ann Intern Med* 1977;**87**:293–8.
- Newlands ES, Bagshawe KD. Activity of high-dose cis-platinum (NCI 119875) in combination with vincristine and methotrexate in drug-resistant gestational choriocarcinoma. A report of 17 cases. *Br J Cancer* 1979;**40**:943–5.
- Bower M, Newlands ES, Holden L, et al. EMA/CO for high-risk gestational trophoblastic tumours: results from a cohort of 272 patients. *J Clin Oncol* 1997;**15**:2636–43.
- Newlands ES, Bagshawe KD, Begent RH, et al. Results with the EMA/CO (etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine) regimen in high risk gestational trophoblastic tumours, 1979 to 1989. *Br J Obstet Gynaecol* 1991;**98**:550–7.
- Bolis G, Bonazzi C, Landoni F, et al. EMA/CO regimen in high-risk gestational trophoblastic tumor (GTT). *Gynecol Oncol* 1988;**31**:439–44.
- Newlands ES, Bagshawe KD, Begent RH, et al. Developments in chemotherapy for medium- and high-risk patients with gestational trophoblastic tumours (1979–1984). *Br J Obstet Gynaecol* 1986;**93**:63–9.
- Werkgroep Oncologische Gynaecologie (WOG). Landelijke Richtlijn Persistentere trofoblast en choriocarcinoom. Available from: www.oncoline.nl, July 13, 2010 (version 1.3).
- Mutch DG, Soper JT, Babcock CJ, et al. Recurrent gestational trophoblastic disease. Experience of the Southeastern Regional Trophoblastic Disease Center. *Cancer* 1990;**66**:978–82.
- Verweij J, Nielsen OS, Therasse P, van Oosterom AT. The use of a systemic therapy checklist improves the quality of data acquisition and recording in multicentre trials. A study of the EORTC Soft Tissue and Bone Sarcoma Group. *Eur J Cancer* 1997;**33**:1045–9.
- Soper JT, Evans AC, Clarke-Pearson DL, et al. Alternating weekly chemotherapy with etoposide–methotrexate–dactinomycin/cyclophosphamide–vincristine for high-risk gestational trophoblastic disease. *Obstet Gynecol* 1994;**83**:113–7.
- Lu WG, Ye F, Shen YM, et al. EMA-CO chemotherapy for high-risk gestational trophoblastic neoplasia: a clinical analysis of 54 patients. *Int J Gynecol Cancer* 2008;**18**:357–62.
- Turan T, Karacay O, Tulunay G, et al. Results with EMA/CO (etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine) chemotherapy in gestational trophoblastic neoplasia. *Int J Gynecol Cancer* 2006;**16**:1432–8.
- Escobar PF, Lurain JR, Singh DK, et al. Treatment of high-risk gestational trophoblastic neoplasia with etoposide, methotrexate, actinomycin D, cyclophosphamide, and vincristine chemotherapy. *Gynecol Oncol* 2003;**91**:552–7.
- Grunberg SM, Warr D, Gralla RJ, et al. Evaluation of new antiemetic agents and definition of antiemetic agent emetogenicity – state of the art. *Support Care Cancer* 2011;**19**:43–7.
- Rustin GJ, Newlands ES, Lutz JM, et al. Combination but not single-agent methotrexate chemotherapy for gestational trophoblastic tumors increases the incidence of second tumors. *J Clin Oncol* 1996;**14**:2769–73.
- Smith MA, Rubinstein L, Anderson JR, et al. Secondary leukemia or myelodysplastic syndrome after treatment with epipodophyltoxins. *J Clin Oncol* 1999;**17**:569–77.
- Pedersen-Bjergaard J, Daugaard G, Hansen SW, et al. Increased risk of myelodysplasia and leukaemia after etoposide, cisplatin, and bleomycin for germ-cell tumours. *Lancet* 1991;**338**:359–63.
- Slevin ML, Clark PI, Joel SP, et al. A randomized trial to evaluate the effect of schedule on the activity of etoposide in small-cell lung cancer. *J Clin Oncol* 1989;**7**:1333–40.

24. Theodore C, Azab M, Droz JP, et al. Treatment of high-risk gestational trophoblastic disease with chemotherapy combinations containing cisplatin and etoposide. *Cancer* 1989;**64**:1824–8.
25. Newlands ES, Mulholland PJ, Holden L, et al. Etoposide and cisplatin/etoposide, methotrexate, and actinomycin D (EMA) chemotherapy for patients with high-risk gestational trophoblastic tumors refractory to EMA/cyclophosphamide and vincristine chemotherapy and patients presenting with metastatic placental site trophoblastic tumors. *J Clin Oncol* 2000;**18**:854–9.
26. Mao Y, Wan X, Lv W, Xie X. Relapsed or refractory gestational trophoblastic neoplasia treated with the etoposide and cisplatin/etoposide, methotrexate, and actinomycin D (EP-EMA) regimen. *Int J Gynaecol Obstet* 2007;**98**:44–7.