The following full text is a publisher's version.

For additional information about this publication click this link.
http://hdl.handle.net/2066/118179

Please be advised that this information was generated on 2019-11-16 and may be subject to change.
Comparing cisplatin-based combination chemotherapy with EMA/CO chemotherapy for the treatment of high risk gestational trophoblastic neoplasia

C. Lybol\textsuperscript{a,b,*}, C.M.G. Thomas\textsuperscript{b}, E.A. Blanken\textsuperscript{c}, F.C.G.J. Sweep\textsuperscript{b,†}, R.H. Verheijen\textsuperscript{d,†}, A.M. Westermann\textsuperscript{e}, I.A. Boere\textsuperscript{f}, A.K.L. Reyners\textsuperscript{g}, L.F.A.G. Massuger\textsuperscript{a,†}, R.Q.G.C.M. van Hoesel\textsuperscript{c}, P.B. Ottevanger\textsuperscript{c,†}

\textsuperscript{a} Department of Obstetrics and Gynaecology, Radboud University Nijmegen Medical Centre, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands
\textsuperscript{b} Department of Laboratory Medicine, Radboud University Nijmegen Medical Centre, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands
\textsuperscript{c} Department of Medical Oncology, Radboud University Nijmegen Medical Centre, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands
\textsuperscript{d} Division of Woman & Baby, Gynaecological Oncology, University Medical Centre Utrecht, Utrecht, The Netherlands
\textsuperscript{e} Department of Medical Oncology, Academic Medical Centre, Amsterdam, The Netherlands
\textsuperscript{f} Department of Medical Oncology, Erasmus University Medical Centre, Rotterdam, The Netherlands
\textsuperscript{g} Department of Medical Oncology, University of Groningen, University Medical Centre Groningen, The Netherlands

Available online 23 October 2012

Abstract  Background: Cisplatin-based chemotherapy (etoposide 100 mg/m\textsuperscript{2} days 1–5, methotrexate 300 mg/m\textsuperscript{2} day 1, cyclophosphamide 600 mg/m\textsuperscript{2} day 1, actinomycin D 0.6 mg/m\textsuperscript{2} day 2 and cisplatin 60 mg/m\textsuperscript{2} day 4, EMACP) was compared to EMA/CO (etoposide 100 mg/m\textsuperscript{2} days 1–2, methotrexate 300 mg/m\textsuperscript{2} day 1 and actinomycin D 0.5 mg i.v. bolus day 1 and 0.5 mg/m\textsuperscript{2} day 2, alternating with cyclophosphamide 600 mg/m\textsuperscript{2} day 8 and vincristine 1 mg/m\textsuperscript{2} 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...
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.

© 2012 Elsevier Ltd. Open access under the Elsevier OA license.

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. 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. 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. Before the introduction of multi-agent chemotherapy in the 1970s, only 31% of the high-risk patients would be cured with single-agent chemotherapy. 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. 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. 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%. 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. Drug resistance was defined as steady.
High-risk GTN Demands one or more of the following conditions:  
1. Antecedent pregnancy: hydatidiform mole or abortion*  
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  

Low-risk GTN Demands all of the following conditions:  
1. Antecedent pregnancy: hydatidiform mole or abortion*  
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  

* 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 EMACP. 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/
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 septis and died after the first EMACP course. Another
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.

4. Discussion
The disease specific survival rate varied from 85% to 90.9% 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. also found the same remission rates in patients who received EMA/CO as primary treatment (76%) than in patients who were treated secondarily with EMA/CO (65%). 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). Lu et al. also found the same remission rates in patients receiving EMA/CO as first-line treatment and as secondary treatment (77.8%). 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/CP, 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. 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. 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. 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. Similarly, increased leukaemogenicity was suggested for these intermittent administration schedules.

Cisplatin has previously been identified as an active agent for high-risk GTN. 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 vin-
cristine 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 addi-
tion, 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, New-
lands et al. reported significant toxicity of EMA/EP che-
motherapy in patients who have relapsed after or who
have become refractory to EMA/CO, with patients suf-
ferring from neutropenia (68%), thrombocytopenia
(40%), anaemia (21%) and renal toxicity (41%). Myelo-
suppression 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 che-
motherapy leads to an impaired bone marrow reserve.
It might therefore be advantageous to start chemother-
apy 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 signifi-
cantly 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

1. FIGO Oncology Committee. FIGO staging for gestational
2. Lurain JR. Gestational trophoblastic disease: II. Classification and
management of gestational trophoblastic neoplasia. Am J Obstet
Gynecol 2010;204:11–8.
methotrexate and folic acid in gestational trophoblastic tumours
4. Begent RH, Bagshawe KD. The management of high-risk chorio-
5. Lurain JR, Brewer JI. Treatment of high-risk gestational tropho-
blastic disease with methotrexate, actinomycin D, and cyclophas-
6. Einhorn LH, Donohue J. Cis-diamminedichloroplatinum, vin-
blastine, and bleomycin combination chemotherapy in dissemi-
7. 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.
gestational trophoblastic tumors: results from a cohort of 272
9. Newlands ES, Bagshawe KD, Begent RH, et al. Results with the
EMA/CO (etoposide, methotrexate, actinomycin D, cyclophos-
phamide, vincristine) regimen in high risk gestational trophoblas-
11. Newlands ES, Bagshawe KD, Begent RH, et al. Developments in chemotherap-
y for medium- and high-risk patients with gestational
12. Werkgroep Oncologische Gynaecologie (WOG). Landelijke Rich-
tlijn Persisteerende trofolast in choriocarcinoom. Available from:
www.oncoline.nl, July 13, 2010 (version 1.3).
trophoblastic disease. Experience of the Southeastern Regional
systemic therapy checklist improves the quality of data acquisition
and recording in multicentre trials. A study of the EORTC Soft
weekly chemotherapy with etoposide-methotrexate-actinomycin/
cyclophosphamide-vincristine for high-risk gestational
16. Lu WG, Ye F, Shen YM, et al. EMA-CO chemotherapy for high-
risk gestational trophoblastic neoplasia: a clinical analysis of 54
(etoposide, methotrexate, actinomycin D, cyclophosphamide,
vincristine) chemotherapy in gestational trophoblastic neoplasia.
gestational trophoblastic neoplasm with etoposide, methotrexate,
actinomycin D, cyclophosphamide, and vincristine chemotherapy.
antiemetic agents and definition of antineoplastic agent emetoge-
20. Rustin GJ, Newlands ES, Lutz JM, et al. Combination but not
single-agent methotrexate chemotherapy for gestational tropho-
blastic tumors increases the incidence of second tumors. J Clin
Oncol 1996;14:2769–73.
or myelodysplastic syndrome after treatment with epipodophylo-
risk of myelodysplasia and leukaemia after etoposide, cisplatin,
23. 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
