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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/m^2 days 1–5, methotrexate 300 mg/m^2 day 1, cyclophosphamide 600 mg/m^2 day 1, actinomycin D 0.6 mg/m^2 day 2 and cisplatin 60 mg/m^2 day 4, EMACP) was compared to EMA/CO (etoposide 100 mg/m^2 days 1–2, methotrexate 300 mg/m^2 day 1 and actinomycin D 0.5 mg i.v. bolus day 1 and 0.5 mg/m^2 day 2, alternating with cyclophosphamide 600 mg/m^2 day 8 and vincristine 1 mg/m^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

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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.

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