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Relapse rates after two versus three consolidation courses of methotrexate in the treatment of low-risk gestational trophoblastic neoplasia ☆

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ABSTRACT

Objective. Methotrexate (MTX) alternating with folinic acid is a commonly used treatment regimen for low-risk gestational trophoblastic neoplasia (GTN). In The Netherlands, two courses of MTX are administered after normalization of serum human chorionic gonadotrophin (hCG) levels (consolidation courses), whereas in the United Kingdom, three consolidation courses are given. In a retrospective setting we compared relapse rates of women completing MTX therapy for low-risk GTN in The Netherlands and the UK.

Methods. From 1980 to 2008, 351 patients were collected from the Dutch Central Registry for Hydatidiform Moles and records from the Dutch Working Party on Trophoblastic Disease. From the Charing Cross Hospital Trophoblast Disease Centre (London), 600 low-risk GTN patients were identified from 1992 to 2008.

Results. In 4.0% of patients relapse occurred after MTX treatment with three consolidation courses, whereas 8.3% of patients relapsed after MTX treatment with two consolidation courses ($p = 0.006$). Although patients from The Netherlands had a higher level of hCG ($p < 0.001$) and more patients had metastases before the start of treatment ($p = 0.012$), the number of courses of MTX to achieve a normal hCG did not differ significantly between patients from The Netherlands and the UK ($p = 0.375$).

Conclusions. Relapse rates were higher in patients treated with two consolidation courses of MTX. Although other factors might have influenced the observed difference in relapse rates, three courses of consolidation chemotherapy may be preferable to two in the treatment of low-risk GTN in order to decrease the risk of disease relapse. A prospective randomized study would be required to confirm these findings.

Introduction

A hydatidiform mole (HM) is an abnormal pregnancy with excessive proliferation of placental villi but severely stunted or absent embryonic development. This condition affects one to three per 1000 pregnancies in western countries [1,2] and can be classified into complete (CHM) or partial HM (PHM) [3]. Management of both CHM and PHM is similar: surgical evacuation followed by regular measurement of serum human chorionic gonadotrophin (hCG) until the levels have returned to normal. Normalization occurs in 80–90% of women. However, in the presence of three consecutive static or rising weekly hCG levels during follow-up, patients are defined as having gestational trophoblastic neoplasia (GTN). In The Netherlands, an additional criterion was added to this definition in 1993. At least one of the values should exceed the 95th percentile of the hCG regression corridor of uneventful decline as constructed by Yedema et al. [4].

GTN is an indication for chemotherapeutic treatment. Depending on the stage of the disease, patients are treated with either single-agent therapy for low-risk disease, or multi-agent therapy for high-risk disease [5]. In The Netherlands and the UK, low risk patients receive intramuscular methotrexate (MTX) (1 mg/kg or 50 mg total, respectively) on days 1, 3, 5 and 7 alternating with oral folinic acid (FA) 15 mg on days 2, 4, 6, and 8, repeated every 2 weeks [6–8]. Treatment continues until the hCG level is normal and then for a further consolidation period. The number of courses of MTX administered after normalization of serum hCG levels in order to eradicate the remaining tumor cells differs between The Netherlands and the UK. In The Netherlands, two consolidation courses are given, whereas in the UK, MTX treatment is consolidated over three further courses after normalization of hCG levels [4,8,9]. Evidence exists that relapse

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rates after MTX treatment diverge between The Netherlands and the UK, although definitions of relapse differed between these studies [10,11]. Disease relapse requires treatment with multi-agent chemotherapy, which, in contrast to MTX, is associated with an increased incidence of secondary malignancies and increases the risk of an early menopause [12–14]. Therefore an additional course of MTX would be preferred if this decreases the chance of developing relapsed disease. In the present study we have retrospectively compared the percentage of disease relapse in a large cohort of women with low-risk GTN, treated with either two (The Netherlands) or three (UK) consolidation courses of MTX.

Methods

In The Netherlands, patients with gestational trophoblastic disease (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 hCG assay service to gynecologists. Between 1977 and 2010, 3983 patients were registered at the DCRHM. Patients are treated in different referral hospitals with the Dutch Working Party on Trophoblastic Disease having a coordinative and advisory function. Data on patients with low-risk GTN were collected retrospectively from 1980 to 2008 from the DCRHM and from records of the meetings of the Dutch Working Party. According to the Dutch guideline for classification of GTN, low-risk disease is defined as GTN with as antecedent pregnancy a mole or abortion, no metastases or metastases restricted to vagina or lungs, no previous chemotherapy administered, and an interval of $\leq$12 months between the end of pregnancy and beginning of treatment. Patients who developed MTX resistant disease and therefore required additional treatment with multi-agent chemotherapy were not included. A total number of 401 low-risk GTN patients with normal hCG values after MTX treatment were selected. At the assay service of the DCRHM, all hCG concentrations are measured using an in-house developed radioimmunoassay (RIA) based on polyclonal antibody raised in rabbits. This assay detects intact hCG and free β-subunit: hCG + hCGβ. Using this assay, serum hCG concentrations of less than 2 ng/ml are considered normal. For patients whose serum hCG was measured in another hospital on a different assay, the reference values provided by the manufacturer of the assay were considered normal. After the first normalized hCG level the guidelines from the Dutch Society for Obstetrics and Gynecology recommend two additional courses of MTX [6]. Patients who received less than two consolidation courses of MTX (n = 19) or more than two consolidation courses of MTX (n = 31) were excluded from further analysis. The remaining 351 patients were included in the study.

In the United Kingdom, all patients with GTD are registered with one of three centers for hCG monitoring and, if necessary, referred to one of the two centers for treatment (Charing Cross Hospital Trophoblast Disease Centre, London or Sheffield Trophoblastic Disease Centre, Sheffield). From the Charing Cross Hospital Trophoblast Disease Centre, 610 patients were identified who were successfully treated with MTX for low-risk GTN from 1992 to 2008. Before 1992, patients were stratified in three prognostic categories according to the Charing Cross scoring system, namely high (score > 9), medium (score 6–9) or low risk (score 0–5). After 1992, patients were classified as either low-risk (score 0–8 on the Charing Cross scoring system; similar to score 0–6 on the revised prognostic scoring system of the International Federation of Gynecology and Obstetrics (FIGO)) or high risk (score > 8, corresponding to a FIGO score of > 6). In order to compare the same risk categories between The Netherlands and the UK, patients treated at the Charing Cross Hospital were included from 1992 onwards. Patients whose treatment protocol was changed due to MTX-resistance or toxicity were not included. According to the guidelines from the Royal College of Obstetricians and Gynaecologists (RCOG), three consolidation courses of MTX should be administered after normal hCG levels are obtained. At the Charing Cross Hospital, hCG detection and monitoring are done with a non-commercial, one-site, in-house, competitive hCG radioimmunoassay that uses a rabbit polyclonal antibody. Serum hCG concentrations of less than 5 IU/L are considered normal. Patients who received less than a total of four courses of methotrexate (n = 10) were also excluded from further analysis. Patients with the histology of a placental site trophoblastic tumor were excluded from the study. The remaining 600 patients were included in the study.

Indications for chemotherapy following a molar pregnancy are similar between The Netherlands and the UK. Indications for chemotherapy in The Netherlands include: a plateaued or rising hCG concentration in three consecutive weekly measurements after evacuation, or a histological diagnosis of choriocarcinoma. In addition, in the UK chemotherapy is started for a serum hCG concentration of more than 20,000 IU/L at 4 weeks or more after evacuation, lung or vaginal metastases more than 2 cm in diameter, or heavy vaginal bleeding, and until recently for a persistently raised but falling hCG at 6 months after evacuation.

Patient characteristics were compared between patients from The Netherlands and from the UK on maternal age, tumor histology, hCG level before the start of MTX, presence of lung metastases and metastases elsewhere. The hCG values before start of MTX treatment were categorized according to the FIGO 2000 prognostic scoring system into $<10^3$, 10^3–10^4, 10^4–10^5, and $>10^5$ IU/L. In addition, the number of courses of MTX required to achieve normal hCG levels was noted.

Disease relapse was defined as a rise in serum hCG values after termination of the consolidation courses of MTX, in the absence of a new pregnancy. This corresponds to 6 weeks after normalization of serum hCG for the patients who received treatment in the UK, and 4 weeks after normalization for patient treated in The Netherlands. Increasing serum hCG levels during consolidation therapy was not considered as relapsed disease. Statistical analyses were performed using SPSS 16.0 software. Differences in disease relapse between two and three consolidation courses of MTX were determined using Pearson Chi-square tests. Differences in number of courses to normalization were compared using Mann–Whitney *U* Test. Statistical differences were considered significant at $p<0.05$.

Results

From 1980 to 2008, 351 women with low-risk GTN with normalization of hCG levels after MTX treatment were collected from records from the DCRHM and the Dutch Working Party on Trophoblastic Disease. From the Charing Cross Hospital database, 600 low-risk patients successfully treated with MTX were identified from 1992 to 2008. Patient characteristics of these patients before the start of MTX treatment are shown in Table 1. Mean maternal age at diagnosis was 30.3 and 31.1 years in patients from both The Netherlands and from the UK, respectively ($p = 0.113$). In the majority of patients from The Netherlands and from the UK, the tumor histology showed a molar pregnancy (95.8% and 94.6%, respectively). The level of serum hCG before start of MTX treatment was not the same between patients from The Netherlands and from the UK ($p<0.001$). More patients with an hCG level of >100,000 IU/L were found in The Netherlands compared to the UK (7.4% versus 2.2%, respectively). The percentage of patients with metastases prior to MTX chemotherapy was 9.9% in The Netherlands and 6.0% in the United Kingdom ($p = 0.012$).

The number of MTX courses to achieve a normal hCG level was compared between patients from The Netherlands (N = 332) and the United Kingdom (N = 464). In the UK, 3.94 courses were given on average to reach normal hCG levels (median 4 courses, range 1–12), compared to an average of 4.25 MTX courses to normalization (median 4, range 1–18) in The Netherlands (Mann Whitney