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A retrospective study to evaluate single agent methotrexate treatment in low risk gestational choriocarcinoma in the United Kingdom

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HIGHLIGHTS

- Not all low risk patients with choriocarcinoma require chemotherapy, providing hCG levels continue to fall to normal following primary intervention.
- IM MTX/FA single-agent chemotherapy was an effective curative treatment in over one third of treated low risk choriocarcinoma patients.
- Despite the development of resistance to IM MTX/FA or subsequent relapse, all patients were successfully salvaged by further treatment.

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ABSTRACT

Objective. To determine whether single agent chemotherapy with intramuscular methotrexate 50 mg administered on days 1, 3, 5, and 7 and oral folinic acid 15 mg administered on days 2, 4, 6, and 8 in 2 weekly cycles (IM MTX/FA) is an effective treatment regimen for patients with low risk gestational choriocarcinoma.

Method. Electronic databases were searched to identify patients with gestational choriocarcinoma at the Sheffield and Charing Cross supra-regional trophoblastic disease centres from January 2000 to December 2011. Clinical notes of low risk patients with FIGO score 0–6 were retrospectively reviewed to assess treatment outcomes and subsequent relapse.

Results. 65 patients were identified with low risk choriocarcinoma. Serum hCG levels normalised in 24 patients without the requirement of chemotherapy (19 with histological confirmation, 4 highly suspicious histology and 1 clinical diagnosis). Of 23 patients with histologically confirmed choriocarcinoma, 8 (35%) had a sustained complete response to IM MTX/FA and did not relapse. Both patients with FIGO score 6, and 1 patient with FIGO stage III metastatic disease developed resistance to IM MTX/FA and required further treatment. Despite the development of drug resistance or relapse all patients were successfully salvaged by subsequent treatments.

Conclusions. Not all patients with low risk choriocarcinoma that have had primary intervention prior to staging, such as surgical resection or uterine evacuation will require chemotherapy, providing hCG levels continue to decline to normal. Low risk (FIGO 0–5) patients should initially receive IM MTX/FA due to its low toxicity, outpatient administration and reasonable efficacy. Patients with FIGO score 6 or FIGO stage III disease should make an informed choice between IM MTX/FA and combination chemotherapy.

Introduction

Gestational choriocarcinoma is an aggressive, rare form of gestational trophoblastic neoplasia (GTN). Other GTN subtypes include placental site trophoblastic tumours (PSTT), epithelioid trophoblastic tumour (ETT) and persistent invasive mole [1]. Gestational choriocarcinoma (referred to as choriocarcinoma henceforth in this paper) can develop from a molar pregnancy, ectopic, still birth/miscarriage or after a preterm or term delivery, with an incidence of approximately 1:50,000 live births [2,3]. In contrast to invasive moles, choriocarcinomas develop from villous trophoblasts and are highly malignant with rapid growth and early metastases. A diagnosis of choriocarcinoma is confirmed on histology but may be presumed in the absence of tissue in the presence of classic clinical factors including very high hCG (human chorionic gonadotrophin), non-molar term pregnancy or an unknown pregnancy event.

A histological diagnosis of choriocarcinoma is considered to be an indication for chemotherapy in the United Kingdom [1,4]. However,

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not all patients will require treatment for disease eradication; patients with declining hCG levels and no metastases may be suitable for close monitoring with regular serum hCG measurements. For patients requiring systemic treatment it is vital to minimise toxicities and late effects. Patients with choriocarcinoma are young, mostly of child-bearing age, and may wish to preserve their fertility.

The FIGO (or FIGO/WHO) prognostic scoring system was developed from combining the modified WHO risk scoring system with FIGO staging [5,6]. Eight prognostic factors contribute to a final score to classify patients with GTN as low risk or high risk for the development of resistance to single agent chemotherapy, score 0–6 and ≥7 respectively. A diagnosis of choriocarcinoma is not one of the prognostic factors, despite being associated with significantly increased rates of resistance in several studies [7,8] and an independent prognostic factor for resistance to single agent chemotherapy [7]. Indeed, in Holland a diagnosis of choriocarcinoma is deemed an indication for high risk treatment with combination agent chemotherapy [9].

Our aim was to establish whether single agent therapy with intramuscular methotrexate and oral folinic acid rescue [10] (IM MTX/FA) is an appropriate treatment for patients with low risk choriocarcinoma categorised according to the FIGO prognostic staging system (score 0–6). The outcomes of patients treated with IM MTX/FA in the United Kingdom (UK) over an 11-year period were evaluated retrospectively.

Patients and methods

Patient case notes were reviewed from 1st January 2000 to 31st December 2011 at the two supra-regional tertiary trophoblastic UK treatment centres, namely the Sheffield Centre for Trophoblastic Disease (Weston Park Hospital (WPH), Sheffield) and the Trophoblastic Tumour Screening and Treatment Centre (Charing Cross Hospital, London). Patients were included in the study if they were diagnosed with choriocarcinoma and classified as low risk by the FIGO prognostic staging system (Fig. 1). Exclusion criteria were patients with FIGO score ≥ 7 or FIGO stage IV disease (Fig. 1).

Patients were staged in accordance to the site specific protocols in each hospital and standard investigations are shown in Supplementary Table 1. At each centre, a specialist pathologist in trophoblastic disease performed review of the histology and all patient cases were discussed at multidisciplinary meetings.

Patients diagnosed with low risk choriocarcinoma with FIGO score 0–6 were recommended IM MTX/FA as an outpatient. Patients were administered 50 mg IM MTX on days 1, 3, 5, and 7 and oral folinic acid 15 mg on alternate days 2, 4, 6, and 8; treatment was restarted on day 15. To assess treatment response, hCG levels were monitored 2 weekly, prior to each chemotherapy cycle, at Weston Park Hospital (WPH) and twice weekly at Charing Cross Hospital. A complete response (CR) to treatment was defined as having a normal serum hCG < 2iu/L (WPH) or <5iu/L (Charing Cross) for 3 consecutive weeks. Treatment was continued for 6 weeks after the first normal hCG level to eliminate residual tumour cells. A persistent rise or plateau of hCG levels during chemotherapy indicated resistant disease and the need for salvage treatment. Relapsed disease was defined as a rise in hCG levels ≥ 6 weeks after normalisation in the absence of pregnancy.

No further ethical approval was necessary for this study because all patients had already agreed to their clinical information being held on the local databases. Data used for this report were patient demographics, treatment details and disease outcomes including response, serial hCG levels (urine and serum), any subsequent relapse and survival.

Collated data were analysed with SPSS version 20 and to test differences in proportions, Chi-squared tests with Yates' correction and Fisher's exact tests were carried out, whilst differences in means were assessed by independent t-tests. A p value < 0.05 was considered statistically significant.

Results

In the study period from 1st January 2000 to 31st December 2011 a total of 186 patients with choriocarcinoma were identified from local databases held at each centre (135 Charing Cross, 51 WPH). 65 patients (38 Charing Cross, 27 WPH) had a FIGO score 0–6 and were staged as low risk for the development of resistance to single

FIGO Score	*0*	*1*	*2*	*4*
Age (years)	<40	≥40	-	-
Antecedent pregnancy	Mole	Abortion	Term	-
Interval months from index pregnancy	<4	4-6	7-13	>13
Pre-treatment HCG (iu/L)	<1,000	1,000-10,000	10,000-100,000	>100,000
Largest tumour mass	<3cm	3-5cm	>5cm	-
Site of metastases	Lung	Spleen, Kidney	Gastro-intestinal	Liver, Brain
Number of metastases	-	1-4	5-8	>8
Previous failed chemotherapy	-	-	Monotherapy	Combined therapy

FIGO stage	
Stage I	Disease confined to the uterus
Stage II	Extends to genital tract
Stage III	Spread to lungs with or without extension to genital tract
Stage IV	All other metastatic sites including liver, kidney, spleen and brain

Score is calculated by the addition of each variable score to gain a total score.
Total scores are classified as low risk of resistance if 0-6 and high risk if more than 7.
hCG: human chorionic gonadotrophin.

Fig. 1. FIGO prognostic scoring system (modified WHO prognostic scoring system as adapted by FIGO) and FIGO staging system for gestational trophoblastic neoplasia [5].