Gynecologic Oncology 137 (2015) 73–76

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Brain metastases in gestational trophoblast neoplasia: An update on incidence, management and outcome

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HIGHLIGHTS

- Brain metastases are exceptionally rare in GTN occurring after a molar pregnancy.
- In non-molar choriocarcinoma brain metastases occur in approximately 20% of patients.
- Standard chemotherapy with enhanced doses of methotrexate is curative in 85% of patients.

ARTICLE INFO

Article history:
Received 20 September 2014
Accepted 9 January 2015
Available online 15 January 2015

Keywords:
Trophoblast
Brain
Metastases
Chemotherapy

ABSTRACT

Objective. To update the demographic data, treatment details and outcomes for GTN patients with brain metastases managed with the modern treatment protocols at the UK centre for gestational trophoblast neoplasia at Charing Cross Hospital in London.

Methods. The hospital database and pharmacy records were reviewed to identify GTN patients treated with brain metastases. Data was assembled on the specific GTN diagnosis, staging, prognostic scores, chemotherapy regimens, additional interventions and outcomes.

Results. During the 22 year study period, 27 GTN patients with brain metastases were treated. One case clearly resulted from a prior molar pregnancy, 3 were of uncertain aetiology and 23 cases had no prior molar pregnancy. The standard chemotherapy regimens were EMA-CO or EMA-EP given with an enhanced CNS methotrexate dose combined with intrathecal methotrexate. Five patients required emergency neurosurgery and routine radiotherapy was not employed.

Twenty three (85%) patients are long term survivors and four patients died. Of the patients who died, all four had chemotherapy refractive disease and two had extended intervals of 18 and 30 years from their antecedent pregnancy.

Conclusion. The incidence of brain metastases in postmolar pregnancy GTN is extremely low. Patients with non-molar choriocarcinoma have an approximate 20% risk of CNS disease and should have routine CNS imaging. Treatment with CNS doses of EMA-CO or EMA-EP appears curative for most patients.

Introduction

Gestational trophoblast neoplasia (GTN) arises from the cells of conception, constitutively makes human chorionic gonadotropin (hCG), is rare but routinely curable with chemotherapy treatment [1]. The most frequent form of the diagnosis, postmolar pregnancy trophoblast tumours occurs mostly after a complete molar pregnancy and in modern series has a cure rate of 100%, with patients predominantly treated with single agent chemotherapy [2,3]. At the more complex end of the disease spectrum, non-molar choriocarcinoma has an incidence of approximately 1 in 50,000 pregnancies and is also routinely curable with cure rates of 91% and 94% reported in modern series [4,5].

GTN patients with CNS involvement are rare and information on the optimal treatment and patient outcome is limited [6]. Currently there is little data describing the overall incidence and prognosis of CNS disease in GTN and the relative risk for CNS involvement in the differing forms of GTN particularly comparing the incidence between postmolar pregnancy GTN and cases of non-molar choriocarcinoma.

A number of case series have indicated that CNS disease in GTN patients generally retains a favourable prognosis, with effective treatment and routine cures being delivered with a range of drug regimens and in some cases supported with radiation therapy [7–9]. At present there is no consensus on the optimal therapy, previous historical retrospective studies have suggested improved outcomes with the combination of chemotherapy with whole brain radiation therapy compared to

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http://dx.doi.org/10.1016/j.ygyno.2015.01.530
0090-8258/

chemotherapy alone [10]. However more recent series give improved results for both approaches with larger series reporting cure rates of 64% for combined modality therapy [11] and 79.5% with combination chemotherapy alone [7].

In the UK, the care of all patients with GTN has been centralized to two hospitals, Weston Park Hospital in Sheffield and Charing Cross Hospital in London for the past 40 years. This arrangement has allowed the two units to gain significant expertise in the management of these rare malignancies and to develop regimens and treatment protocols specifically for GTN patients with CNS disease. In this study we have reviewed the demographics, treatment and outcome for GTN patients with CNS disease treated at Charing Cross Hospital in London between 1991 and 2013.

Patients and methods

The study cohort consisted of the UK based GTN patients with the CNS involvement who received the first line chemotherapy treatment at Charing Cross Hospital within the period 1991–2013. Cases were identified from the Charing Cross Hospital GTN database and the hospital pharmacy chemotherapy treatment records.

During the study period the standard imaging at Charing Cross Hospital for new postmolar pregnancy GTN patients was a Doppler pelvic ultrasound and chest x-ray, with CNS imaging being only performed for patients with lung metastases visible on the chest x-ray. For patients with a likely diagnosis of non-molar choriocarcinoma the standard imaging was extended to include CT scans of the thorax, abdomen and pelvis and MRI scans of the brain and pelvis.

Since the early 1990s the chemotherapy treatment protocol at Charing Cross Hospital for GTN patients with CNS disease has been based on the standards of either etoposide, methotrexate and dactinomycin alternating weekly with cyclophosphamide and vincristine (EMA-CO) or where the disease involves the liver too, EMA alternating weekly with etoposide and cisplatin (EP) chemotherapy. However, the methotrexate dose is increased from the standard 300 mg/m^2 to 1000 mg/m^2 and intrathecal methotrexate is given alternate weeks with either CO or EP [7,12,13]. In patients who were unwell with significant CNS or other organ dysfunction at presentation, treatment was commenced with 1–2 days of low dose etoposide (100 mg/m^2) and cisplatin (20 mg/m^2), prior to the introduction of definitive treatment [5]. In the absence of proven additional benefit and to minimise long term toxicity, patients did not receive whole brain radiotherapy as part of their routine management.

The standard chemotherapy drug regimens employed were;

EMA (CNS)-CO

Week 1

Day 1 Dactinomycin 0.5 mg iv
Etoposide 100 mg/m^2 iv
Methotrexate 500 mg/m^2 in 1000 ml N/Saline over 12 h iv
Methotrexate 500 mg/m^2 in 1000 ml N/Saline over 12 h iv

Day 2 Dactinomycin 0.5 mg iv
Etoposide 100 mg/m^2 iv
Folinic acid 30 mg po 6 hourly × 12 doses, starting 32 h after commencing methotrexate

Week 2

Day 8 Vincristine 0.8 mg/m^2 (max 2 mg)
Cyclophosphamide 600 mg/m^2

EMA (CNS)-EP

Week 1

Day 1 Dactinomycin 0.5 mg iv
Etoposide 100 mg/m^2 iv
Methotrexate 500 mg/m^2 in 1000 ml N/Saline over 12 h iv
Methotrexate 500 mg/m^2 in 1000 ml N/Saline over 12 h iv

Day 2 Folinic acid 30 mg po 6 hourly × 12 doses, starting 32 h after commencing methotrexate

Week 2

Day 8 Etoposide 150 mg/m^2 iv
Cisplatin 75 mg/m^2 iv.

Intrathecal methotrexate was also given at a dose of 12.5 mg on the non-EMA week until the serum and CSF hCG had reached the normal range at which point it is discontinued.

Chemotherapy was delivered according to these standard protocols and for 8 additional weeks treatment after the serum hCG level reached the normal range. Routine neurosurgery or whole brain radiation therapy was not employed, but individual patients underwent emergency neurosurgery to decompress raised intracranial pressure or to manage bleeding. In addition, patients who had residual radiographic CNS abnormalities went on to complete their care with stereotactic radiotherapy following completion of chemotherapy.

Results

Demographics

During the period 1991–2013, 27 UK based GTN patients with brain metastases received the first line chemotherapy treatment at Charing Cross Hospital. As shown in Table 1 the patient's ages ranged between 18 and 59 with a median age of 32. The pathological and genetic identity

Table 1
The demographics and clinical features of the 27 gestational trophoblast neoplasia patients with CNS metastases treated at Charing Cross Hospital 1991–2013.

Age group	Patients
Age 18–25	7 (26%)
Age 26–35	11 (41%)
Age 36–45	6 (22%)
Age 46+	3 (11%)
GTT origin	
Molar pregnancy	1 (4%)
Uncertain aetiology	3 (11%)
Non-molar choriocarcinoma	23 (85%)
Pregnancy interval	
<4 months	10 (37%)
4–7 months	6 (22%)
7–12 months	3 (11%)
>12 months	8 (30%)
hCG level at diagnosis (IU/L)	
<5000	3 (11%)
5000–50,000	8 (30%)
50,000–500,000	11 (41%)
500,000–1,000,000	2 (7%)
>1,000,000	3 (11%)
FIGO score	
9–12	5 (18.5%)
13–16	17 (63%)
17–21	5 (18.5%)
Metastatic disease sites	
Lung	24 (89%)
Hepatic	5 (18.5%)
Renal	5 (18.5%)
Spleen	4 (15%)
CNS only	3 (11%)