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Risk adapted single-agent dactinomycin or carboplatin for second-line treatment of methotrexate resistant low-risk gestational trophoblastic neoplasia

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HIGHLIGHTS

- Methotrexate-resistance develops in approximately one-third of low-risk GTN patients.
- Subsequent use of single-agent dactinomycin or carboplatin results in an 80–90% complete hCG response rate.
- Multi-agent chemotherapy, associated with greater toxicity, can be reserved for sequential single-agent chemotherapy failure.
- Overall survival should approximate 100%.

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ABSTRACT

Objective. To evaluate the outcome of patients treated with second-line chemotherapy for methotrexate-resistant low-risk GTN at the Sheffield Centre, UK between 2001 and 2015, including the novel use of single-agent carboplatin as a strategy to reduce exposure to combination chemotherapy.

Methods. 392 low-risk GTN patients were treated with first-line methotrexate. The selection of chemotherapy regimen following methotrexate-resistance depended on the volume of residual disease as indicated by the serum hCG value at the time, with patients switching to either single-agent dactinomycin at an hCG level < 150 IU/L from 2001–2010 and <300 IU/L since 2010, or to combination treatment with etoposide/dactinomycin (EA) above these thresholds. In order to reduce exposure to more toxic combination chemotherapy regimens, our treatment policy was revised in 2011, with the recommendation of single-agent carboplatin as an alternative to EA at hCG levels >300 IU/L.

Results. 136 (35%) of 392 received second-line chemotherapy following methotrexate-resistance. 59 patients received single-agent dactinomycin with 53 (90%) patients achieving complete hCG response, 3 patients requiring combination chemotherapy or surgery, and 3 patients subsequently spontaneously resolving. 56 patients received EA chemotherapy with hCG complete response in 50 (89%) patients, and the remaining 6 patients were cured with further multi-agent chemotherapy or surgery. With carboplatin, 17/21 (81%) achieved an overall complete hCG response rate, with 4 patients requiring third-line EA. Carboplatin was well tolerated with no significant alopecia; myelosuppression was the most significant toxicity. Overall survival for all patients was 100%.

Conclusion. These data show the continued excellent outcomes for methotrexate-resistant low-risk patients treated with single-agent dactinomycin or EA. Our experience with carboplatin is promising and provides an alternative regimen for methotrexate-resistant low-risk disease that avoids alopecia and in-patient treatment.

1. Introduction

Gestational trophoblastic disease encompasses a spectrum of pregnancy-related disorders ranging from the pre-malignant conditions of partial (PM) and complete mole (CM) to the neoplastic conditions of invasive mole, choriocarcinoma or more rarely, placental site and epithelioid trophoblastic tumours. All cases in the UK are registered for hCG monitoring at one of three designated screening centres, and if subsequent treatment is required, patients are treated at the Charing Cross Hospital Trophoblast Disease Centre, London, or at the Trophoblastic Disease Centre at Weston Park Hospital, Sheffield. The onset of persistence, or malignant change, is termed gestational trophoblastic neoplasia (GTN) and is almost always identified by a rising or plateau in serum

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hCG concentration, occurring in approximately 15% of CMs and 0.5–1% of PMs [1,2].

Clinicians treating GTN usually use the International Federation of Gynaecology and Obstetrics (FIGO 2000) scoring system to guide first-line treatment decisions and allow comparison of data [3]. A score of 0–6 predicts for a low-risk of resistance to single-agent chemotherapy with methotrexate (MTX) or dactinomycin. Scores of ≥7 are deemed high-risk, with almost no chance of complete response to single-agent chemotherapy and therefore receive combination chemotherapy from the outset.

GTN is highly chemo-sensitive and the prognosis, particularly in low-risk disease, is excellent. These tumours have been readily curable for over 50 years and effective therapy quite considerably predates the modern era of randomized clinical trials [4]. Current standard treatment protocols are based on empirical evidence robustly supported by large treatment outcome series from several centres [4–8]. Overall survival in low-risk disease is almost 100% and therefore a key aim is to optimise treatment by reducing exposure to both short and longer-term toxicities and minimise serious long-term adverse events including premature menopause and the small increased risk of leukaemia [9].

Overall, approximately 75% of all women with low-risk GTN achieve complete marker remission with first-line treatment [10], with the risk of resistance to initial MTX chemotherapy increasing with higher FIGO scores [4], a diagnosis of choriocarcinoma [11], a higher pre-treatment hCG [12] and the presence of metastatic disease [13]. The selection of chemotherapy regimen in MTX-resistance depends on the volume of residual disease as indicated by the serum hCG value at the time. In the UK, at lower levels of serum hCG (<150 IU/L historically, increased to <300 IU/L in 2010) we have utilised a switch to single-agent dactinomycin. Above these levels, a switch to combination chemotherapy using a regimen of etoposide/dactinomycin (EA), delivered over a three-day inpatient stay at the Sheffield Centre was our standard recommendation. As a strategy to reduce exposure to combination chemotherapy, avoid in-patient treatment and minimise the risk of alopecia, our treatment policy was revised in August 2011 and, based on the significant activity of carboplatin in seminoma [14–16], EA was replaced by single-agent carboplatin on a 3-weekly schedule.

We present here the clinico-pathologic details, prognostic scores, toxicity, treatment and subsequent outcomes for all women treated with second-line chemotherapy between 2001–2015 at the Sheffield Centre, and also our novel results from the use of single-agent carboplatin in patients with methotrexate-resistance with hCG levels >300 IU/L.

2. Patients and methods

Patients registered from 2001 to 2015 and defined as low-risk GTN according to the International FIGO/WHO (2000) scoring system were identified from the electronic database. Patients were included if they had attended the treatment centre for staging and received first-line chemotherapy. The indications for staging and criteria for chemotherapy at the Sheffield Centre have previously been published [6]. All cases had centrally reviewed histology. Written informed consent was obtained for all chemotherapy treatment regimens.

Case-notes were individually retrospectively reviewed and data collected included patient demographics, type of antecedent pregnancy, FIGO/WHO score and stage, first and second-line chemotherapy treatment details, serum hCG level prior to both initial treatment and the change to second-line treatment, overall response, relapse, and subsequent fertility or secondary malignancy. Case-notes were also reviewed to evaluate toxicity where possible, retrospectively graded according to Common Terminology Criteria for Adverse Events (Version 4, 2009). Adverse events secondary to carboplatin were prospectively collected using the same criteria. All patients had previously given permission for clinical information to be held on the database and therefore no further ethics committee approval was required.

All patients had previously received intramuscular MTX (50 mg every 48 h for 4 doses) with calcium folinate (folinic acid) rescue (15 mg orally 30 h after MTX) as first-line treatment, with courses being repeated every 2-weeks. Serum hCG was measured prior to the start of each cycle.

The development of treatment resistance was defined as a serial rise in ≥2 serum hCG readings over 4 weeks or ≥3 consecutive hCG levels that had failed to adequately fall (approximately 25%) over the same time period. Serum hCG was measured with a 2-site chemoluminescent immulite immunoassay (Siemens Immulite 2000). Patients were not routinely re-imaged on development of treatment resistance.

From 2001 to July 2010 at the Sheffield Centre, patients received single-agent dactinomycin if the serum hCG level was <150 IU/L at the time of the development of MTX-resistance. Dactinomycin was administered as an intravenous bolus at a dose of 1.25 mg/m^2 every 2 weeks. Following the first normal hCG level, patients received 6-weeks of consolidation treatment (3 cycles). If MTX-resistance developed with a serum hCG level >150 IU/L, patients received combination chemotherapy with etoposide/dactinomycin [EA (E:100 mg/m^2 iv Days 1–3, A:0.5 mg iv Days 1–3)], involving a 2-night hospital stay for patients every 10-days, with a further 6-weeks (4 cycles) of consolidation treatment following the first normal hCG level. Hysterectomy was also considered for organ-confined disease. In July 2010, in order to reduce the number of women being exposed to greater toxicity from combination chemotherapy, the UK national GTD service increased the hCG threshold at which combination chemotherapy was recommended and allowed a switch to single-agent dactinomycin for MTX-resistance up to an hCG level of 300 IU/L.

Our treatment policy was further modified in 2011 by introducing single-agent carboplatin on a 3-weekly schedule instead of EA for patients developing resistance with an hCG level of ≥300 IU/L. Dosing for each carboplatin cycle was calculated using the Calvert formula [17] and according to pre-treatment creatinine clearance (based on serum creatinine and use of the Cockcroft-Gault formula) to deliver a dose estimated to achieve a target area under the concentration curve (AUC) value of 6 mg/mLs/min. Treatment was delayed in the event of neutropenia ($<1.0 \times 10^9$/L) or thrombocytopenia ($<75 \times 10^9$/L) until recovery and carboplatin dose reduced to an estimated AUC of 5 mg/mLs/min for subsequent doses. Serum hCG was measured weekly and treatment continued until a normal hCG plus 6-weeks of consolidation treatment (two cycles). For patients failing to respond adequately, chemotherapy was changed to third-line EA. Response rates to carboplatin were regularly reviewed.

Following complete response to treatment and completion of six weeks consolidation treatment, all patients were followed-up by weekly serum hCG for 6-weeks, then monthly serum and urinary hCG levels for 6-months, 13-weekly urinary hCG from 6 to 24 months and then 6-monthly urinary hCG for life.

Data were collected and descriptive statistics generated using IBM SPSS statistics, version 21.

3. Results

From 2001–2015, 7672 patients were registered at the Sheffield Centre. Patients with a diagnosis of atypical trophoblastic tumour were excluded. 458 (6.0%) patients received chemotherapy, with 392 patients (5.1% of all registered patients) treated with intramuscular MTX for low-risk disease, and 66 patients (0.9% of all registered patients) received combination chemotherapy for high-risk disease. Of the 392 patients receiving treatment for low-risk disease, 167 patients required a change in treatment, mainly due to MTX-resistance (n = 140, 35.7%) or due to MTX-toxicity (n = 27, 6.9%). Four patients opted for a hysterectomy rather than second-line chemotherapy following development of MTX-resistance, and 136 patients went on to second-line chemotherapy (Fig. 1). Patients switched due to MTX-toxicity are not included in further analyses.

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