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Salvage chemotherapy for gestational trophoblastic neoplasia: Utility or futility?☆

Kathleen G. Essel [a], Amanda Bruegl [b], David M. Gershenson [c], Lois M. Ramondetta [c], R. Wendel Naumann [d], Jubilee Brown [d,*]

[a] The University of Texas, Houston Health Sciences Center, Houston, TX, USA
[b] Oregon Health Science University, Portland, OR, USA
[c] The University of Texas M.D. Anderson Cancer Center, Houston, TX, USA
[d] Levine Cancer Institute, Carolinas HealthCare System, Charlotte, NC, USA

HIGHLIGHTS

- Low-risk patients failing methotrexate should receive dactinomycin or EMA-CO.
- High-risk patients failing EMA-CO should receive etoposide-platinum combinations.
- VIP, FAC, and camptothecin did not show activity in relapsed GTN.
- EMA-EP and TP/TE showed activity in relapsed Intermediate trophoblastic tumor.
- >1/3 of high-risk patients failing initial treatment had inappropriate initial therapy.

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ABSTRACT

Objective. To determine the efficacy of chemotherapy after failed initial treatment in patients with high risk gestational trophoblastic neoplasia (GTN).

Methods. We performed a retrospective IRB-approved chart review of all patients with GTN seen at a single institution from 1985 to 2015, including all patients who failed initial treatment. We summarized clinical characteristics with descriptive statistics and estimated progression-free survival (PFS) and overall survival (OS) with the Kaplan-Meier method.

Results. Of 68 identified patients, 38 required >2 chemotherapy regimens. Patients were treated for GTN ($n = 53$), including choriocarcinoma, persistent GTN, and invasive mole; for placental site trophoblastic tumor (PSTT) ($n = 5$); and for intermediate trophoblastic tumor (ITT) ($n = 10$). Patients with GTN had a median of 2 salvage regimens, median PFS of 4.0 months, and median OS was not reached at median follow-up of 71.2 months. Active regimens included EMACO, MAC, BEP, platinum- and etoposide-based combination therapies, and ICE; 8 of 53 patients died of disease (DOD). Patients with PSTT had a median of 3 salvage regimens, median PFS of 2.8 months, and median OS of 38.8 months. Active regimens included ICE and EMA-EP; 4 of 5 patients DOD. Patients with ITT had a median of 3 salvage regimens, median PFS of 4.1 months, and median OS of 38.2 months. Active regimens included liposomal doxorubicin, platinum-containing regimens, EMA-CO, and EMA-EP; 7 of 10 patients DOD.

Conclusions. Several salvage chemotherapy regimens demonstrate activity in high risk GTN. Multiple regimens may be required and cure is not universal.

1. Introduction

Gestational trophoblastic disease (GTD) comprises a group of neoplastic disorders that arises from placental trophoblastic tissue after abnormal fertilization. It includes pre-malignant disease (complete and partial hydatidiform moles) and malignant gestational trophoblastic neoplasia (GTN), which includes choriocarcinoma, invasive mole, intermediate trophoblastic tumor (ITT), placental site trophoblastic tumor (PSTT), and epithelioid trophoblastic tumor (ETT) [1]. The malignant forms of GTD are collectively known as gestational trophoblastic neoplasia (GTN).

The discovery of effective chemotherapy has resulted in survival rates approaching 100%, and effective scoring allows the use of single agent chemotherapy agents in low-risk disease, limiting the number

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* Corresponding author at: Levine Cancer Institute, Carolinas HealthCare System, 1021 Morehead Medical Drive, Suite 2100, Charlotte, NC 28204, USA.
E-mail address: jubilee.brown@carolinashealthcare.org (J. Brown).

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of women who require more toxic multi-agent chemotherapy [2,3]. Most women who have high risk metastatic GTN (FIGO stages II and III, score > 7 and stage IV) are treated with EMACO (etoposide, methotrexate, dactinomycin, cyclophosphamide, and vincristine), resulting in eventual cure with a survival rate of 80–94% [4–9]. In contrast, up to 25% of women with high-risk metastatic GTN have refractory disease, relapse, or have extensive metastatic disease (FIGO stage IV, score > 12) and require alternate treatment strategies. These patients require identification of chemotherapy-resistant sites for surgical resection, brain irradiation, and/or alternate therapeutic regimens. The most commonly used chemotherapy regimens include EMA-EP (etoposide, methotrexate, dactinomycin, etoposide, cisplatin) and TE/TP (paclitaxel, etoposide, paclitaxel, cisplatin), resulting in a response rate of 75–80% [10].

Outcomes data in patients with high risk GTN treated with these and other regimens are scant. While several large trophoblastic treatment centers have published their experience in patients with advanced or refractory disease, the overall good prognosis yields few patients to evaluate who fail initial therapy and require salvage regimens. It is incumbent upon practicioners at large referral centers to publish their experience with these rare patients [1–3,5–9]. Therefore, the purpose of this study was to determine the efficacy of chemotherapy in patients with GTN who have failed initial therapy.

2. Materials and methods

We performed a retrospective IRB-approved chart review of all patients with GTN seen at The University of Texas M.D. Anderson Cancer Center from 1985 to 2015 and included all patients with high risk GTN who failed initial treatment. During the study period, 207 patients with GTN were treated. Of these patients, 68 failed initial treatment with chemotherapy, required further treatment and were included in this study.

Since patients with PSTT and ITT have different tumor biology and have distinct natural histories, we evaluated patients with these histologies separately from patients with other types of GTN (choriocarcinoma, invasive mole, high- and low-risk persistent GTN). Gynecologic pathologists on faculty at the M.D. Anderson Cancer Center reviewed the pathology of all cases to confirm the diagnosis. Collectively, ITT can encompass both PSTT and ETT. In some cases, PSTT could be specified. In others, the nature of the specimen, age of the case, or inability to obtain p53 status resulted in their more general classification as ITT.

Descriptive statistics were used to summarize clinical characteristics and the Kaplan-Meier method was used to estimate progression free survival (PFS) and overall survival (OS). Progression free survival (PFS) was defined as the time from the first chemotherapy of interest to physical or radiographic evidence of disease progression, death as a result of any cause, or last contact, with events defined as progressive disease or death. We calculated PFS for each regimen in every patient. Overall survival (OS) was the time from confirmation of diagnosis (sustained elevation in hCG level) to death from any cause. The log-rank test was used to compare survival curves. A complete response (CR) was defined as normalization of the hCG level maintained for at least 1 month after stopping chemotherapy. A partial hCG response (PR) was defined as a fall of hCG by > 50% sustained for > 1 month. Stable disease was defined by < 50% change in hCG > 1 month. Progressive disease was defined as a rise in hCG by > 50% sustained by > 1 month or the appearance of new metastatic disease [11].

3. Results

Sixty-eight patients who had GTN required more than one chemotherapy regimen and were included in the study. Thirty-eight patients required more than two chemotherapy regimens. The median age of diagnosis was 28 years (range 16–60 years). Patients were treated for GTN ($n = 53$), which included persistent GTN, choriocarcinoma (CC), and invasive mole; intermediate trophoblastic tumor (ITT) ($n = 10$); and placental site trophoblastic tumor (PSTT) ($n = 5$). The antecedent pregnancy was a molar pregnancy in 37 patients, term or preterm delivery in 14 patients, abortion or ectopic pregnancy in 14 patients, and was not documented in 3 patients (Table 1).

3.1. GTN (Persistent GTN, choriocarcinoma, invasive mole)

The histologic subtypes of the 53 patients with GTN included persistent GTN ($n = 29$), choriocarcinoma (CC) ($n = 22$), and invasive mole ($n = 2$). The median WHO score at the time of initial diagnosis was 4 (range, 0–18). Of the 53 patients with GTN included in the study, 23 patients had metastatic disease. The most common site of metastatic disease was the lung ($n = 22$), but other sites included brain, vagina, kidney, and spleen (Table 1). Based on the inclusion criteria of this study, patients had failed at least one cycle of therapy for GTN. The types of initial failed therapy consisted of methotrexate ($n = 29$), alternating methotrexate/dactinomycin ($n = 6$), EMACO ($n = 5$), MAC (methotrexate, dactinomycin, and cyclophosphamide) ($n = 5$), dactinomycin ($n = 4$), EMA-EP ($n = 1$), etoposide/cisplatin ($n = 1$), methotrexate/cyclophosphamide ($n = 1$), and methotrexate/dactinomycin/chlorambucil ($n = 1$).

3.2. Overall outcomes for GTN

In total, the 53 patients with GTN who failed initial therapy received a median of 2 salvage regimens (range, 1–9), with a median progression-free survival (PFS) of 4.0 months after each regimen. Median overall survival (OS) was not reached at a median follow-up of 71.2 months calculated from the date of diagnosis. At the time of most recent follow-up, 8 patients (15.1%) were dead of disease and 45 patients (84.9%) had no evidence of disease.

In total, the most active regimens based on PFS were EMACO (PFS 199.6 months, $n = 31$), dactinomycin (PFS 18.0 months, $n = 11$), platinum containing multi-agent regimens (PFS 5.6 months, $n = 22$) and

Table 1
Summary of patient characteristics ($n = 68$ patients).

	GTN ($n = 53$ patients)[2]	PSTT ($n = 5$ patients)	ITT ($n = 10$ patients)
Median age	27 years (range, 16–51)	37 years (range, 26–52)	37.5 years (range, 27–60)
Antecedent pregnancy			
Mole	34	0	2
Term/preterm	10	3	2
Abortion/ectopic/miscarriage	8	1	5
Unknown	1	1	1
Ethnicity			
Caucasian	21	4	5
Black/African American	9	1	2
Hispanic	16	0	2
Asian	7	0	1
Sites of metastases at initial diagnosis[1]			
Lung	22	3	6
Liver	3	2	1
Brain	5	0	2
Kidney	2	0	0
Other	1 (spleen)	0	4 (1 spleen, 1 pancreas, 1 thyroid, 1 adrenal)
None	30	2	3
Median number of salvage regimens	2 (range, 1–9)	3 (range, 1–5)	3 (range, 1–5)

[1] The sum of metastatic sites totals > 53 patients, as some patients had multiple sites of metastatic disease.
[2] GTN includes patients with persistent GTN, choriocarcinoma, and invasive mole

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