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Primary treatment of stage IV gestational trophoblastic neoplasia with floxuridine, dactinomycin, etoposide and vincristine (FAEV): A report based on our 10-year clinical experiences

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HIGHLIGHTS

- Using FAEV chemotherapy as primary treatment for stage IV GTN patients achieved excellent results;
- FAEV has a low rate of toxicity, and patients treated with FAEV showed good reproductive outcomes;
- FAEV drug-resistant patients could still have chances to achieve CR by being further treated with other chemothearpy.

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ABSTRACT

Objective. To evaluate the efficacy and toxicity profile of floxuridine, dactinomycin, etoposide and vincristine (FAEV) regimen as primary treatment in stage IV gestational trophoblastic neoplasia (GTN).

Methods. From 2004 to 2014, FAEV was given to 30 stage IV GTNs as the primary treatment (at least two cycles) in Peking Union Medical College Hospital. Remission/resistance/recurrence rate, the cause of treatment failure, and the toxicity profile were analyzed.

Results. A total of 190 cycles of FAEV were administered to 30 patients; the median number of the cycles was 6 (range 3–11). The median follow up was 52.3 months (range 8–120). Of all the patients received FAEV primarily, 24 achieved complete remission after only received FAEV, with no recurrence; 6 patients later switched to EMA-CO treatment due to FAEV resistance. Among the 6 patients, 2 died of progressive disease after multiple lines of chemotherapy, the other 4 achieved complete remission after second–line or third-line chemotherapy and 1 of them relapsed 15 months later.

FAEV was well tolerated. No one died from toxicity. Severe grade 4 neutropenia and thrombocytopenia were noted in 8 (26.7%) and 2 (6.7%) cases. No secondary malignancy was observed with follow-ups from 8 to120 months. Patients treated with FAEV showed good reproductive outcomes.

Conclusions. FAEV regimen might be considered as an alternative to other chemotherapy regimen in the primary treatment of stage IV GTN, where it had a high rate of remission and a tolerable toxicity.

1. Introduction

The cure rates of Gestational trophoblastic neoplasia (GTN) can reach 100% in low risk patients and around 94% in high-risk patients (not including PSTT/ETT) due to its high sensitivity to chemotherapy [1,2]. However, stage IV GTN patients have poor prognoses caused by distant metastasis, and the survival rate of these patients reaches 69–85% [3–5]. When liver metastasis was involved, the overall survival rate was only 48% at 5 years [6]. Other factors causing the poor prognostic of high-risk patients include the interval time from the antecedent pregnancy (over 2.8 years), the number of metastasis etc [7]. In most treatment centers, high-risk GTN patients were usually treated with the regimen of etoposide, methotrexate, and actinomycin D, alternating weekly with cyclophosphamide and vincristine (EMA-CO) as the first-line therapy. More recent data shows that EMA/CO or MEA (methotrexate, etoposide, actinomycin D) treatment can reach a long-term survival rate of 94% in high-risk patients [1,2]. However, approximately 20% of the high-risk patients still need salvage chemotherapy with platinum-containing multi-agent regimens [1,8].

In China, floxuridine (FUDR) based multidrug chemotherapy was widely used. Our GTN center (Peking Union Medical College Hospital, PUMCH) also prefers to use these regimens in GTN patients, such as FAV (floxuridine, dactinomycin and vincristine) and FAEV (floxuridine,

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dactinomycin, etoposide and vincristine). In our earlier report, it is demonstrated that FAEV achieved a high complete remission (CR) rate of 60.4–63.6% on relapsed or chemo-resistant GTN patients [9,10]. In this study, the efficacy and safety of the FAEV regimen as primary treatment to stage IV GTN patients is reported.

2. Patients and methods

From January 2004 to December 2014, 30 stage IV GTN patients were registered and received primary treatment with FAEV regimen in PUMCH. All the 30 patients met the following requirements: stage IV GTN patients; never received chemotherapy before; received at least two cycles of FAEV chemotherapy as initial treatment; and no placental-site trophoblastic tumor or epithelioid trophoblastic tumor. These patients were identified through review of institutional databases, and the Institutional Review Board of PUMCH also approved this study.

2.1. Pretreatment evaluation

The primary diagnosis of stage IV GTN was made according the International Federation of Gynecology and Obstetrics (FIGO 2000) staging system. Pretreatment evaluation consisted of a complete medical history, clinical examinations, vaginal ultrasonography, computed tomography (CT), a blood sample with measurement of full blood count, coagulation studies, liver and renal function tests, and β-human serum chorionic gonadotropin (β-hCG). Patients were scored according to the FIGO scoring system 2000.

2.2. Chemotherapy regimen

The FAEV protocol with dose and schedule was listed in Table 1. Patients with brain metastases further received intrathecal methotrexate chemotherapy treatment. The regimen was repeated in 21-day intervals until β-hCG level was normalized (<2 IU/l). After normalization of β-hCG, 3–4 courses of consolidation therapy were given. The FAEV regimen was disused if patients had a plateau or an increased β-hCG level for at least two consecutive cycles, recurrent grade 4 toxicity, and any subjectively intolerable toxicity.

2.3. Evaluation after treatment

Weekly serum β-hCG was used to evaluate the therapeutic effect. A complete blood cell count, along with renal and liver function was also measured. Imaging was performed every 2–3 courses of chemotherapy. Surgery was performed to drug-resistant patients or patients with a life-threatening hemorrhage caused by tumor.

Complete Remission (CR) was defined as a normal β-hCG level for 4 consecutive weeks. After CR, β-hCG has been monthly monitored for a year. Resistance was defined as a plateau or increased β-hCG level during treatment, for at least 2 courses. Relapse was defined as increased β-hCG 3 months after CR.

Table 1
FAEV protocol with dose and schedule.

Regimen	Dose	Duration	Schedule
Vincristine	2 mg	D1	Administered by bolus intravenously 3 h before treatment with dactinomycin
Dactinomycin	200 μg/m^2	D1–5	Administered by infusion more than 30 min
Etoposide	100 mg/m^2	D1–5	Administered by infusion more than 30 min
FUDR	800 mg/m^2	D1–5	Administered by infusion more than 8 h

Toxicity was evaluated according to the National Cancer Institute (NCI) Common Toxicity criteria version 2.0. All side effects were recorded.

2.4. Statistical analysis

Statistics Analysis System version 9.2 was used in this study. The general conditions of the two groups of patients were subjected to univariate and multivariate statistical analyses to identify the resistant to FAEV related risk factors. The univariate analysis was performed using qualitative and quantitative parameters. The multivariate analysis was performed using cumulative logistic regression method. $P < 0.05$ was considered to be statistically significant.

3. Results

The features of all the 30 patients are displayed in Table 2. The mean age of the patients was 27 years (range 20–43). The antecedent pregnancy was hydatidiform mole, term delivery, or abortion, in 8 patients (26.7%), 11 patients (36.7%), and 11 patients (36.7%), respectively. Median serum β-hCG level at start was 93,984 mIU/mL (range 1250–1,244,700 mIU/mL). There were 21 patients with brain metastases, 5 with liver metastases, 3 with renal metastases; other metastases include spleen, pancreas, small intestine, stomach, abdominal wall, bone and adrenal gland. The mean FIGO score was 11 (range 7–18) and 14 with a score ≥ 12. Ten surgeries were performed prior to commencement of chemotherapy, including craniotomy in 7 cases, partial resection of the intestine in 1 case, partial hepatectomy in 1 case and abdominal wall tumor resection in1 case.

In this study, the 30 patients received a total of 190 cycles (mean 6.3, median 6, range 3–11).

3.1. Assessment of response

Of the 30 patients who received FAEV as the first-line multi-agent chemotherapy, 24 achieved β-hCG normalization after a median of 4.1 cycles (mean = 4; SD = 1.54; range 2–9). The primary remission rate with FAEV for the complete group was 80% (24/30). Among the 24 patients, 2 patients changed to EMA-CO regimen due to toxicity during consolidation treatment. The other 6 patients had a plateau or an increased β-hCG level after FAEV chemotherapy, which was interpreted as FAEV resistance, and the treatment was thus changed to EMA-CO.

Among the 6 PR patients who changed regimen, 2 (6.6%) died due to disease progression, the other 4 received additional 6–13 courses chemotherapy and got CR eventually. The features of the 6 patients are listed in Table 3.

9 patients who are sensitive to FAEV received surgical treatments while undergoing chemotherapy, among whom 1 underwent hysterectomy, 1 underwent uterine lesions resection, 4 underwent pulmonary resection, 1 underwent craniotomy, 1 underwent a lobectomy along with craniotomy, and 1 underwent abdominal wall tumor resection.

3.2. Assessment of toxicity

Toxicity was evaluated for the 30 patients (190 courses), and FAEV was well tolerated. No toxicity-related deaths occurred. Neutropenia was the most important myelosuppressive side effect. We observed 20 (66.7%) cases of neutropenia, 8 (26.7%) of them had grade 4 neutropenia. Among the 8 patients, 2 developed fever but later recovered with antibiotics and G-CSFs. 2 patients (6.7%) had grade 4 thrombocytopenia with no bleeding complications, and both received platelet transfusions. 3 patients (10%) had grades 3–4 anaemia and received packed cells. Therapy was discontinued in 2 patients during consolidation treatment due to neutropenia.