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Chemotherapy for gestational trophoblastic neoplasia patients with a FIGO score of 12 or greater: A multistudy analysis

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ABSTRACT

Objective: To enable a comparison of reported chemotherapy regimens in gestational trophoblastic neoplasia (GTN) patients with a International Federation of Gynecology and Obstetrics (FIGO) score ≥12.
Study design: Studies reporting cases of GTN with a FIGO score ≥12 were collected and screened for eligibility. A total of 17 studies encompassing 256 patients were included in final analysis.
Results: In the first-line setting, etoposide-methotrexate-dactinomycin alternating with cyclophosphamide-vincristine (EMA/CO), etoposide-platinum alternating with EMA (EP/EMA), and floxuridine-dactinomycin-etoposide-vincristine (FAEV) were the three most commonly used regimens. The complete response (CR) rate was 55.2% for EMA/CO, 60.0% for EP/EMA, and 63.1% for FAEV. There was no significant difference in CR rate among EMA/CO, EP/EMA and FAEV in the first-line setting. While limited by low number, the CR rate was 66.67% for methotrexate-bleomycin -etoposide (MBE), and 25% for vincristine-dactinomycin-cyclophosphamide (VAC). Of the patients who failed initial therapy, EMA/CO, EP/EMA, and paclitaxel- cisplatin alternating with paclitaxel-etoposide (TP/TE) were the three most commonly used salvage regimens. The CR rate was 39.7% for EMA/CO, 35.0% for EP/EMA, and 11.8% for TP/TE. While limited by low number, MBE was used in 5 patients and yielded a 80% CR rate. Of the fatal cases, 21 (61.8%) patients had brain metastases, and 41.2% (14/34) of the deaths were early deaths.
Conclusion: EMA/CO, EP/EMA, and FAEV yielded comparable CR rates in GTN patients with a FIGO score ≥12 in the first-line setting.

Introduction

Gestational trophoblastic neoplasia (GTN) refers to a spectrum of diseases mainly including invasive mole, choriocarcinoma, placental-site trophoblastic tumor, and epithelioid trophoblastic tumor [1]. The International of Federation of Gynecology and Obstetrics (FIGO) 2000 scoring system is used to predict prognosis and guide treatment of GTN patients [2]. Chemotherapy is the mainstay of the treatment in GTN patients. Patients with a FIGO score of 6 or less should be treated with single-agent chemotherapy [1]. A FIGO score of 7 or more denotes a high risk of developing resistance to single-agent chemotherapy, and these patients require multiagent chemotherapy [1]. The cure rates of high-risk GTN are estimated to be around 80%95% [3,4]. However, a subgroup with a FIGO score ≥12 indicates disease at high risk of treatment failure and poor prognosis [5]. Kong et al. reported a cohort of 143 GTN patients with a FIGO score ≥12 and in the entire cohort the five-year overall survival (OS) rate was 67.9% [6], which was much lower than the reported cure rates of high-risk GTN [4]. Consistently, Bolze et al. showed that a significantly higher five-year mortality rate was observed in patients with a FIGO score ≥13 compared with patients with a FIGO score <13 (38.4% v.s. 4.9%) [7]. Due to its rarity and the lack of prospective studies, management of these ultra high-risk patients has not been specifically defined. There is no consensus regarding what should be the optimal chemotherapy regimen in this specific subgroup. Thus, we performed this multistudy analysis and our aim was to synthesize existing efficacy evidence, enabling a comparison of the reported chemotherapy regimens in GTN patients with a FIGO score ≥12.

Materials and methods

Search strategy

Publications were identified by a PubMed database search from Jan. 1 st 2000 to present. The following search terms were used: ((("2000/01/01"[Date - Publication] : "3000"[Date - Publication]))

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AND (((((neoplasia[Title/Abstract]) OR neoplasm[Title/Abstract]) OR tumor[Title/Abstract]) OR tumour[Title/Abstract]) OR disease [Title/Abstract])) AND ((((high[Title/Abstract]) AND risk[Title/Abstract]) AND gestational[Title/Abstract]) AND trophoblastic [Title/Abstract]). References of the included manuscripts, critical reviews, and treatment guidelines of GTN were also screened to identify other potential relevant studies.

Eligibility criteria

Inclusion and exclusion criteria were as follows. (i) The publications reporting at least one case of GTN patients with a FIGO score ≥12 were collected and assessed for inclusion. (ii) Full text of included studies should be available. (iii) The FIGO score was calculated based on the FIGO/WHO 2000 scoring system. (iv) Studies, of which adequate information (including patient characteristics, primary treatment, FIGO score, response to chemotherapy, clinical course) were not available, were excluded from our analysis. (v) If the study populations overlapped between publications, only the most recent or most informative publication was included to avoid duplications.

Data extraction

For each included study, we extracted the first author's name, year of publication, study periods, number of patients included, patient characteristics, primary treatment, FIGO score, response to chemotherapy, and clinical course. Early death was defined as death which occurred within the first 4 weeks of treatment.

Statistical analysis

Grouped data were summarized using descriptive statistics. For categorical variables, the differences between groups were evaluated using Chi-square test or Fisher's exact test when appropriate. Statistical analyses were performed using SPSS 22.0.

Results

Identification and characteristics of eligible studies

Two hundred eighty seven articles were identified by initial search. Of these, 216 publications were excluded from further analysis because they were patently not pertinent. Of the remaining 71, 56 records were further excluded because they did not fulfill the inclusion and exclusion criteria. Two additional records were identified through reference screen of the included manuscripts, critical reviews, and treatment guidelines of GTN. In total, 17 studies were included in the final analysis. The review flow is depicted in Fig. 1. The included 17 studies encompassed 256 GTN patients with a FIGO score ≥12. The main characteristics of the included studies are shown in Supplementary Table S1.

Outcomes in GTN patients with a FIGO score ≥12 initially treated with different chemotherapy regimens

Table 1 summarizes outcomes in GTN patients with a FIGO score ≥12 initially treated with different chemotherapy regimens. Of these 196 patients, etoposide-methotrexate-dactinomycin alternating with cyclophosphamide-vincristine (EMA/CO), etoposide-platinum alternating with EMA (EP/EMA), and floxuridine-dactinomycin-etoposide-vincristine (FAEV) were the three most commonly used regimens. The complete response (CR) rate was 55.2% (16/29) for EMA/CO, 60.0% (12/20) for EP/EMA, and 63.1% (82/130) for FAEV. While limited by low number, the CR rate was 66.7% (2/3) for methotrexate-bleomycin-etoposide (MBE), and 25.0% (1/4) for vincristine-dactinomycin-cyclophosphamide (VAC). Cyclophosphamide-hydroxyurea-dactinomycin-methotrexate-vincristine (CHAMOC) (n = 4), methotrexate-dactinomycin (MA) (n = 1), cisplatin-fluorouracil (Cis-5FU) (n = 1), EP (n = 2), and methotrexate (n = 2) showed no activity in this group of patients. Six patients were not assessed for efficacy due to unaccepted toxicity. The remaining one patients received methotrexate as first-line treatment because of her poor performance status.

Outcomes in GTN patients with a FIGO score ≥12 treated with salvage chemotherapy regimens as second-line or beyond treatments

Table 2 summarizes outcomes in GTN patients with a FIGO score ≥12 treated with salvage chemotherapy regimens. EMA/CO, EP/EMA, and paclitaxel-cisplatin alternating with paclitaxel-etoposide (TP/TE) were the three most commonly used regimens in these ultra high-risk cases. The CR rate was 39.7% (25/63) for EMA/CO, 35.0% (14/40) for EP/EMA, and 11.8% (2/17) for TP/TE, respectively. Additionally, TP/TE regimens yielded PR in two patients (11.8%).While limited by low number, MBE was used in 5

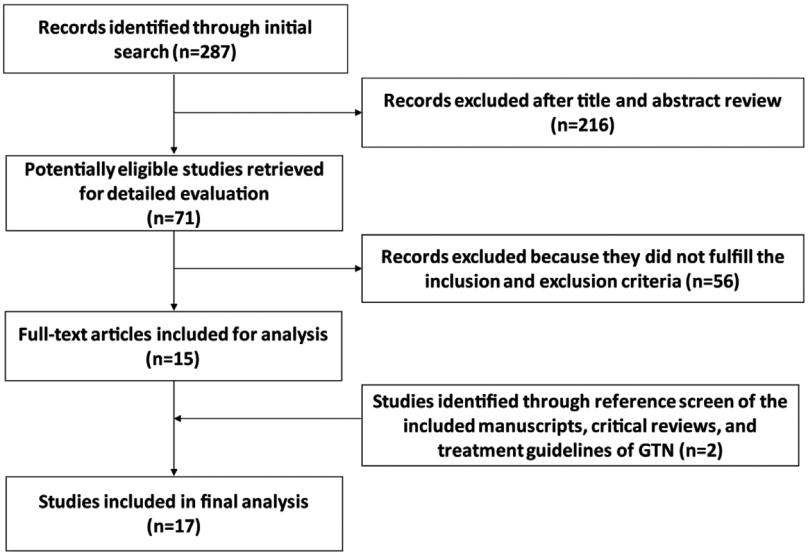

Fig. 1. Flowchart of the literature search for GTN patients with a FIGO score of 12 or greater.

Table 1
Outcomes in patients with a FIGO score of 12 or greater initially treated with different chemotherapy regimens.

Chemotherapy regimens	No. of total patients	Complete response		Resistance		Unaccepted toxicity		Others	
		No. of patients	%	No. of patients	%	No. of patients	%	No. of patients	%
EMA/CO	29	16	55.2%	10	34.5%	3	10.3%	0	0.0%
EP/EMA	20	12	60.0%	6	30.0%	2	10.0%	0	0.0%
FAEV	130	82	63.1%	48	36.9%	0	0.0%	0	0.0%
MBE	3	2	66.7%	0	0.0%	1	33.3%	0	0.0%
CHAMOC	4	0	0.0%	4	100.0%	0	0.0%	0	0.0%
MA	1	0	0.0%	1	100.0%	0	0.0%	0	0.0%
Cis-5Fu	1	0	0.0%	1	100.0%	0	0.0%	0	0.0%
VAC	4	1	25.0%	3	75.0%	0	0.0%	0	0.0%
EP	2	0	0.0%	2	100.0%	0	0.0%	0	0.0%
MTX with or without FA	2	0	0.0%	1	50.0%	0	0.0%	1	50.0%

Table 2
Outcomes in patients with a FIGO score of 12 or greater treated with salvage chemotherapy regimens as second-line or beyond treatments.

Chemotherapy regimens	No. of patients	Complete response		Partial response		Resistance		Unaccepted toxicity		Others	
		No. of patients	%	No. of patients	%	No. of patients	%	No. of patients	%	No. of patients	%
EMA/CO	63	25	39.7%	0	0.0%	38	60.3%	0	0.0%	0	0.0%
EP/EMA	40	14	35.0%	0	0.0%	23	57.5%	3	7.5%	0	0.0%
TP/TE	17	2	11.8%	2	11.8%	11	64.7%	0	0.0%	2	11.8%
MBE	5	4	80.0%	0	0.0%	0	0.0%	1	20.0%	0	0.0%
VAC	3	1	33.3%	0	0.0%	2	66.7%	0	0.0%	0	0.0%
TC	2	2	100.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Capecitabine	3	2	66.7%	0	0.0%	1	33.3%	0	0.0%	0	0.0%
BEP	2	0	0.0%	0	0.0%	2	100.0%	0	0.0%	0	0.0%
VEIP	2	0	0.0%	0	0.0%	0	0.0%	2	100.0%	0	0.0%
Paclitaxel	1	0	0.0%	0	0.0%	1	100.0%	0	0.0%	0	0.0%
EP	1	1	100.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Carboplatin/ gemcitabine	2	0	0.0%	0	0.0%	2	100.0%	0	0.0%	0	0.0%
AP	1	0	0.0%	0	0.0%	1	100.0%	0	0.0%	0	0.0%
MTX/FA	1	1	100.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
TP	1	1	100.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
VIP	1	0	0.0%	0	0.0%	1	100.0%	0	0.0%	0	0.0%
EIP	1	0	0.0%	0	0.0%	1	100.0%	0	0.0%	0	0.0%
ICE	1	0	0.0%	0	0.0%	1	100.0%	0	0.0%	0	0.0%
Oral etoposide	1	1	100.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
FAP	1	0	0.0%	0	0.0%	1	100.0%	0	0.0%	0	0.0%
Gem-TIP	1	0	0.0%	0	0.0%	1	100.0%	0	0.0%	0	0.0%
HDCT	1	0	0.0%	0	0.0%	1	100.0%	0	0.0%	0	0.0%
Pembrolizumab	2	2	100.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%

patients and yielded a 80.0% CR rate; capecitabine, paclitaxel-carboplatin (TC), Pembrolizumab, VAC, EP, MTX, TP and oral etoposide also demonstrated activity. The rest regimens, including vinblastine-ifosfamide-cisplatin (VIP), bleomycin-etoposide-cisplatin (BEP), carboplain-gemcitabine, paclitaxel, dactinomycin-platinum (AP), etoposide-ifosfamide-cisplatin (EIP), ifosfamide-carboplatin- etoposide (ICE), 5FU-dactinomycin-cisplatin (FAP), gemcitabine-paclitaxel/ifosfamide/cisplatin (Gem-TIP), and high-dose chemotherapy (HDCT) showed no activity in this group of patients. Unaccepted toxicity occurred in 3 patients for EP/EMA, 2 patients for VEIP, and 1 patients for MBE, respectively. The response status was not available in two patients receiving TP/TE.

Comparisons of CR rate between selected regimens

Table 3 summarizes comparisons of CR rate between selected regimens. EMA/CO, EP/EMA, and FAEV yielded comparable CR rates in GTN patients with a FIGO score ≥12 in the first-line setting. In the salvage setting, there was no significant difference in CR rate between EMA/CO and EP/EMA. EMA/CO yielded a higher CR rate than TP/TE, and EP/EMA also yielded a higher CR rate than TP/TE though without reaching statistical significance. Notable is that both EMA/CO and EP/EMA as first-line treatment yielded a higher CR rate than EMA/CO and EP/EMA as salvage treatment respectively, though without reaching statistical significance.

Table 3
Comparisons of CR rate between selected regimens.

Chemotherapy regimens	*P* value
First-line	
EMA/CO v.s. EP/EMA	0.737
EMA/CO v.s. FAEV	0.429
EP/EMA v.s. FAEV	0.791
Second-line or beyond	
EMA/CO v.s. EP/EMA	0.633
EMA/CO v.s. TP/TE	0.031
EP/EMA v.s. TP/TE	0.143
EMA/CO	
EMA/CO(first-line) v.s. EMA/CO(second-line or beyond)	0.165
EP/EMA	
EP/EMA(first-line) v.s. EP/EMA(second-line or beyond)	0.065

Characteristics of fatal cases of the GTN with a FIGO score ≥12

In this section, one more study containing 7 fatal cases of GTN patients with a FIGO score ≥12 and with detailed patients'

Table 4
Summarized characteristics of fatal cases of GTN with a FIGO score of 12 or greater.

Characteristics	No. of patients	%
Age		
<40	26	76.5%
≥40	6	17.6%
NA	2	5.9%
Antecedant pregnancy		
Molar	6	17.6%
Abortion	10	29.4%
Term or preterm	11	32.4%
NA	7	20.6%
FIGO stage		
I	1	2.9%
II	0	0.0%
III	4	11.8%
IV	29	85.3%
Pretreatment hCG		
<10,0000	9	26.5%
≥10,0000	15	44.1%
NA	10	29.4%
FIGO Score		
12-16	22	64.7%
17-20	11	32.4%
≥21	1	2.9%
No. of organs with metastasis		
0	1	2.9%
1	3	8.8%
2	11	32.4%
3	8	23.5%
4	4	11.8%
≥5	2	5.9%
NA	5	14.7%
Cause of death		
Progression	17	50.0%
Spesis	4	11.8%
Brain hemorrhage	4	11.8%
Brain hemorrhage, respiratory failure	1	2.9%
Brain herniation	2	5.9%
pulmonary embolism	1	2.9%
Respiratory failure, cardiac arrest	1	2.9%
Multisystem organ failure	2	5.9%
NA	2	5.9%
Early death		
Yes	14	41.2%
No	10	29.4%
NA	10	29.4%

demographic characteristics was included [8]. In total, 34 cases were included in the final analysis. The details of these patients were listed in Supplementary Table S2. Tables 4 and 5 summarized characteristics of fatal cases. The median age of patients was 29 years (range18-59 years), and 26 (76.5%) cases were younger than 40. Six (17.6%) cases developed GTN from an antecedent molar pregnancy, 10 (29.4%) cases developed GTN from an antecedent abortion, and 11 (32.4%) cases developed GTN from an antecedent pregnancy from an antecedent term or preterm pregnancy. Twenty-nine (85.3%) patients had FIGO stage IV disease. The pre-treatment human chorionic gonadotrophin (hCG) level was over 100,000 mIU/ml in 15 (44.1%) patients. In women with metastatic information, 25 (86.2%) patients had metastases in more than one organ, and brain metastases occurred in 21 (72.4%) cases. The cause of death was disease progression in 17 (50.5%) women, spesis in 4 (11.8%) women, brain hemorrhage in 4 (11.8%) women, brain herniation in 2 (5.9%) women, pulmonary embolism in 1 (2.9%) woman, multisystem organ failure in 2 (5.9%) women, respectively. One (2.9%) death resulted from brain hemorrhage and respiratory failure. One (2.9%) patient died from respiratory failure and cardiac arrest. The cause of death of the remaining 2 (5.9%) patients was not available. Early death occurred in 14 (41.2%) patients.

Discussion

Due to high chemosensitivity, the overall survival rate of high-risk GTN are now running as high as 95% [4]. However, this estimated survival rate is misleading because the prognosis of patients with a FIGO score ≥12 is significantly worse than patients with a FIGO score <12 [5,6]. FIGO Cancer Report 2015 defines patients with a FIGO score ≥12 as ultra high-risk GTN [9]. A later study showed that the mortality rate in patients with a FIGO score ≥13 was significantly higher than that in patients with a FIGO score <13 (38.4% v.s. 4.9%) [7]. FIGO Cancer Report 2018 updated the definition of ultra high-risk GTN [1]. Namely, a subgroup with a FIGO score ≥13 was defined as ultra high-risk GTN [1].

The preferred first-line chemotherapy regimen for high-risk GTN is EMA/CO which had excellent activity [1,4]. Recently, EMA/CO was also used in ultra high-risk GTN patients [10–12]. Bianconi et al. showed that patients who received EMA/CO in the first-line setting experienced good outcomes with a 75%(3/4) CR rate [10]. Shen et al. reported that 20 patients with a FIGO score ≥12 was treated with EMA/CO in the first-line setting, and 60% of the patients achieved CR [11]. In China, FAEV is was also considered to be the first-line chemotherapy in ultra-high risk GTN patients in Peking Union Medical College Hospital in China [6]. Kong et al. indicated that FAEV yielded a 63.1% (82/130) CR rate in ultra high-risk GTN patients in the first-line setting [6]. Since the introduction of the concept of ultra high-risk GTN in 2015 by FIGO, EP/EMA has been recommended as the first-line regimen for ultra high-risk GTN patients [1,9]. Cyriac et al. showed that EP/EMA yielded a 66.7% (6/9) CR rate in the first-line treatment setting [13]. Bianconi et al. reported that patients who received EP/EMA in the first-line

Table 5
Sites of metastasis in fatal cases of GTN with a FIGO score of 12 or greater.

Sites of metastasis	No. of patients	%
None	1	2.9%
Lung	2	5.9%
Liver	1	2.9%
Lung, liver	2	5.9%
Lung, brain	9	26.5%
Lung, brain, bladder	1	2.9%
Lung, brain, kidney	3	8.8%
Lung, brain, liver	3	8.8%
Lung, brain, pelvis	1	2.9%
Lung, brain, kidney, spleen	1	2.9%
Lung, brain, liver, kidney	2	5.9%
Lung, vagina, bone, muscle	1	2.9%
Lung, brain, liver, kidney, skin, meningeal	1	2.9%
Lung, mediastinum, liver, bone, muscle, skin, spinal dura	1	2.9%
NA	5	17.7%

setting achieved a 42.9%(3/7) CR rate [10]. Activity of EP/EMA in treating ultra high-risk GTN in the first-line setting was also demonstrated in several other studies [14,15]. Given the rarity of the disease, it is difficult to conduct a prospective study to compare the efficacy and safety of EMA/CO, EP/EMA and FAEV regimes, as well as other regimens in the first-line setting. So, we carried out a pooled analysis of ultra high-risk GTN patients from 17 publications. Our data showed that the pooled CR rate was 55.2% (16/29) for EMA/CO, 60.0% (12/20) for EP/EMA, and 63.1% (82/130) for FAEV, and there was no significant difference in CR rate among EMA/CO, EP/EMA and FAEV in the first-line setting. While limited by low number, other regimens also proved to be effective to some extends in treating ultra high-risk GTN. Even et al. showed that dactinomycin-cisplatin-etoposide (APE) yielded a CR rate of 85.7% (12/14) in GTN patients with a FIGO score $\geq$12 [16]. However, the study population were all free of brain metastasis, making it difficult to compare the efficacy of APE with that of other regimens used in the first-line setting.

Ultra high-risk GTN patients were at high risk of failure with first-line chemotherapy. Several regimens had been demonstrated to be effective in the salvage setting. Our pooled analysis indicated that comparable CR rates were observed between EMA/CO and EP/EMA in the salvage setting. Previous studies indicated that the efficacy of chemotherapy declined as the number of prior lines of treatment increased. Similarly, our data indicated that both EMA/CO and EP/EMA yielded a higher CR rate in the first-line setting than that in the salvage setting. This further emphasized the importance of adequate treatments in the first-line setting to reduce the occurrence of drug resistance. However, even receiving standard first-line chemotherapy, some patients still developed resistance and would have to receive multiple lines of chemotherapy. It fueled cumulative toxicity and patients with unaccepted toxicities had to switch to less toxic schemes, like single-agent chemotherapy. For example, capecitabine yielded a CR in two heavily pretreated patients [10]. More recently, Breitbach et al. reported that oral etoposide yielded a CR in one patient with a FIGO score $\geq$12 [17].

Our pooled data further indicated that nearly one-half of the deaths in GTN patients with a FIGO score $\geq$12 were early deaths. Early death of these patients could result from sudden and lethal hemorrhage in the lesions, and tumor lysis syndrome. To prevent early death, low-dose EP induction therapy was introduced and proven effective [4]. Brain metastases had been demonstrated to be a risk factor for poor prognosis, with a propensity for acute intralesional hemorrhage and cerebral herniation leading to neurologic deterioration and death [8,12]. Our pooled data indicated that 61.8% (21/34) of the fatal cases had brain metastases. Among these patients, 33.3% (7/21) of the cases died of brain hemorrhage or brain herniation. Xiao et al. showed that 84.6% (22/26) of the patients died after initial treatments died of intracranial hemorrhage with or without concurrent herniation and multiple organ failure [8]. This further emphasized the importance of salvage neurosurgery in treating such emergencies. In addition, salvage surgeries were also effective in stopping lethal bleeding in other organs such as liver, kidneys, spleen, and gastrointestinal tract, and in reducing tumor burden and removing isolated drug-resistant lesions [1,18]. In our study, we did not explore the role of salvage surgery in ultra high-risk GTN patients because the data were difficult to extract.

The present study has several limitations. First, the major one is its retrospective nature. Data in this study were mostly acquired from retrospective case series and case reports. As such, there is inherent selection bias. It makes the drawing of universally accepted guidelines unfeasible. Second, toxicity profiles for each regimen were not fully assessed, because of the lack of well reported toxicity data in included studies. Thus, it remains a subject for further research. Third, genetic testing was not systematically performed in included patients to differentiate GTN from hCG-producing non-GTN. The latter one can masquerade as GTN and exhibit features of choriocarcinoma on histologic examination, and is more aggressive than GTN in clinical course [4,19]. Thus, the presence of non-GTN patients in each group may dilute the CR rate of each chemotherapy regimen, and genetic testing are recommended to confirm the gestational origin in future study.

In conclusions, comparable CR rates were observed among EMA/CO, EP/EMA, and FAEV regimens in the first-line setting. Because of the rarity and required emergency treatment of this subgroup disease, it was difficult to envisage feasible randomized clinical trials to optimize therapy in ultra high-risk GTN patients. Our pooled analysis, despite limitations mentioned above, are useful to some extent for informed decision making in daily clinical practice and will definitely aid in the selection of chemotherapy regimens in ultra high-risk GTN patients. To maximize benefit and minimize risk to the patients, such patients are strongly recommended to be treated in specialized GTN centers with direct access to all necessary major supportive services, and multidisciplinary managements are encouraged.

Ethics approval and consent to participate

All data in this article are obtained from published studies, which have received ethics approval and consent to participate. The study was performed in accordance with the Declaration of Helsinki.

Conflict of interest

The authors declare that there are no conflicts of interest.

Authorship

Conception and design: Jun Li, Xin Lu.
Collection and assembly of data: Jun Li, Huiran Yue.
Data analysis and interpretation: All authors.
Manuscript writing: Jun Li, Xin Lu.
Final approval of manuscript: All authors.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ejogrb.2019.05.023.

References

[1] Ngan H, Seckl MJ, Berkowitz RS, Xiang Y, Golfier F, Sekharan PK, et al. Update on the diagnosis and management of gestational trophoblastic disease. Int J Gynaecol Obstet l 2018;143(Suppl. 2):79–85.
[2] Kohorn EI. The new FIGO 2000 staging and risk factor scoring system for gestational trophoblastic disease: description and critical assessment. Int J Gynecol Cancer 2001;11:73–7 l.
[3] Goldstein DP, Berkowitz RS. Current management of gestational trophoblastic neoplasia. Hematol Oncol Clin North Am 2012;26:111–31.
[4] Alifrangis C, Agarwal R, Short D, Fisher RA, Sebire NJ, Harvey R, et al. EMA/CO for high-risk gestational trophoblastic neoplasia: good outcomes with induction low-dose etoposide-cisplatin and genetic analysis. J Clin Oncol 2013;31:280–6.
[5] Yang J, Xiang Y, Wan X, Feng F, Ren T. Analysis of the prognosis and related factors for patients with stage IV gestational trophoblastic neoplasia. Int J Gynecol Cancer 2014;24:594–9.
[6] Kong Y, Yang J, Jiang F, Zhao J, Ren T, Li J, et al. Clinical characteristics and prognosis of ultra high-risk gestational trophoblastic neoplasia patients: a retrospective cohort study. Gynecol Oncol 2017;146:81–6.

[7] Bolze PA, Riedl C, Massardier J, Lotz JP, You B, Schott AM, et al. Mortality rate of gestational trophoblastic neoplasia with a FIGO score of &/=13. Am J Obstet Gynecol 2016;214(390):e1–8.
[8] Xiao C, Yang J, Zhao J, Ren T, Feng F, Wan X, et al. Management and prognosis of patients with brain metastasis from gestational trophoblastic neoplasia: a 24-year experience in Peking union medical college hospital. BMC Cancer 2015;15:318.
[9] Ngan HY, Seckl MJ, Berkowitz RS, Xiang Y, Golfier F, Sekharan PK, et al. Update on the diagnosis and management of gestational trophoblastic disease. Int J Gynaecol Obstet 2015;131(Suppl. 2):S123–6.
[10] Bianconi MI, Otero S, Moscheni O, Alvarez L, Storino C, Jankilevich G. Gestational trophoblastic disease: a 21-year review of the clinical experience at an Argentinean public hospital. J Reprod Med 2012;57:341–9.
[11] Shen T, Chen LL, Qin JL, Wang XY, Cheng XD, Xie X, et al. [EMA/CO regimen for chemotherapy 24 patients with ultra high-risk gestational trophoblastic neoplasia]. Zhonghua Fu Chan Ke Za Zhi 2018;53:371–6.
[12] Savage P, Kelpanides I, Tuthill M, Short D, Seckl MJ. Brain metastases in gestational trophoblast neoplasia: an update on incidence, management and outcome. Gynecol Oncol 2015;137:73–6.
[13] Cyriac S, Rajendranath R, Sridevi V, Sagar TG. Etoposide, cisplatin-etoposide, methotrexate, actinomycin-D as primary treatment for management of very-high-risk gestational trophoblastic neoplasia. Int J Gynaecol Obstet 2011;115:37–9.
[14] Soper JT, Spillman M, Sampson JH, Kirkpatrick JP, Wolf JK, Clarke-Pearson DL. High-risk gestational trophoblastic neoplasia with brain metastases: individualized multidisciplinary therapy in the management of four patients. Gynecol Oncol 2007;104:691–4.
[15] Ghorani E, Kaur B, Fisher RA, Short D, Joneborg U, Carlson JW, et al. Pembrolizumab is effective for drug-resistant gestational trophoblastic neoplasia. Lancet 2017;390:2343–5.
[16] Even C, Pautier P, Duvillard P, Floquet A, Kerbrat P, Troalen F, et al. Actinomycin D, cisplatin, and etoposide regimen is associated with almost universal cure in patients with high-risk gestational trophoblastic neoplasia. Eur J Cancer 2014;50:2082–9.
[17] Breitbach GP, Sklavounos P, Veith C, Costa SD, Kuhn W, Solomayer EF, et al. Oral etoposide for metastatic choriocarcinoma: a case report and review of guidelines. Arch Gynecol Obstet 2018.
[18] Lehman E, Gershenson DM, Burke TW, Levenback C, Silva EG, Morris M. Salvage surgery for chemorefractory gestational trophoblastic disease. J Clin Oncol 1994;12:2737–42.
[19] Fisher RA, Savage PM, MacDermott C, Hook J, Sebire NJ, Lindsay I, et al. The impact of molecular genetic diagnosis on the management of women with hCG-producing malignancies. Gynecol Oncol 2007;107:413–9.