Gynecologic Oncology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Gynecologic Oncology

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

Clinical characteristics and prognosis of ultra high-risk gestational trophoblastic neoplasia patients: A retrospective cohort study

Kong Yujia, Yang Junjun, Jiang Fang, Zhao Jun, Ren Tong, Li Jie, Wang Xiaoyu, Feng Fengzhi, Wan Xirun, Xiang Yang *

Departments of Obstetrics and Gynecology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, No.1 Shuaifuyuan, Wangfujing, Dongcheng District, 100730 Beijing, PR China

HIGHLIGHTS

- Ultra high-risk gestational trophoblastic neoplasia patients have a poor prognosis.
- The FAEV regimen is effective chemotherapy with manageable toxicity for GTN.
- Prognosis-related risk factors for ultra high-risk GTN patients are revealed.

ARTICLE INFO

Article history:
Received 26 December 2016
Received in revised form 9 April 2017
Accepted 15 April 2017
Available online xxxx

Keywords:
Gestational trophoblastic neoplasia
Ultra high-risk
Chemotherapy
Survival
Prognosis

ABSTRACT

Objective. The gestational trophoblastic neoplasia (GTN) patients with the International Federation of Gynecology and Obstetrics (FIGO) score ≥ 12 are defined as ultra high-risk GTN. This study aims to investigate the clinical characteristics, the treatment efficiency, and the prognosis of ultra high-risk GTN patients.

Methods. Between January 2002 and December 2015, medical record data of 143 GTN patients with FIGO score ≥ 12 at Peking Union Medical College Hospital (PUMCH) were reviewed. Ratios were compared using chi-square test, and prognostic risk factors were analyzed by univariate analysis and multivariate analysis.

Results. Among the 143 ultra high-risk GTN patients, 94 (65.7%) patients had achieved complete remission and 15.9% (15/94) patients relapsed after complete remission. The 5-year overall survival (OS) rate of the entire cohort approached 67.9%. The results of the multivariate analysis revealed that non-molar antecedent pregnancy [Relative risk (RR) 4.689, 95% CI 1.448–15.189, $P = 0.010$], brain metastases (RR 2.280, 95% CI 1.248–4.163, $P = 0.007$), previous failed multiagent chemotherapy (RR 5.345, 95% CI 2.222–12.857, $P = 0.000$) and surgery (RR 0.336, 95% CI 0.177–0.641, $P = 0.001$) all had influence on the prognosis of ultra high-risk GTN patients.

Conclusions. GTN patients with FIGO score ≥ 12 have a poor prognosis. More emphasis should be placed on non-molar antecedent pregnancy, brain metastases, and previous multiagent chemotherapy failure. Moreover, salvage surgery may improve the prognosis. Floxuridine-based multiagent chemotherapy is effective with manageable toxicity for ultra high-risk GTN patients.

1. Introduction

Gestational trophoblastic neoplasia (GTN) refers to a group of uncommon malignant gynecological tumors caused by abnormal proliferation of trophoblastic tissues. GTN consists of invasive mole, choriocarcinoma, placental site trophoblastic tumor (PSTT) and epitheliloid trophoblastic tumor (ETT). The International Federation of Gynecology and Obstetrics (FIGO) scoring system is used to predict prognosis of GTN patients. Low-risk GTN patients (FIGO score < 7) should be treated with single-agent. High-risk GTN patients (FIGO score ≥ 7) require multiagent chemotherapy [1]. The EMA/CO regimen (etoposide, methotrexate, actinomycin-D, cyclophosphamide, vincristine) is commonly used worldwide [2]. The overall survival (OS) rate almost approaches 100% in low-risk patients (FIGO score < 7), whereas high-risk patients (FIGO score ≥ 7) can achieve a survival rate of 80–90% [3]. However, the survival rate of high-risk patients is misleading because the prognosis of these patients is definitely different. Bolze showed that the patients with FIGO score ≥ 13 had an obviously higher

* Corresponding author.
E-mail addresses: yangjunjun@pumch.cn (J. Yang), zhaojun@pumch.cams.cn (J. Zhao), fengfz1969@sina.com (F. Feng), wanxr@pumch.cn (X. Wan), XiangY@pumch.cn (Y. Xiang).

http://dx.doi.org/10.1016/j.ygyno.2017.04.010
0090-8258/

5-year death rate than the patients with FIGO score < 13 (38.4% and 4.9%, $P < 0.001$) [4]. Other literatures also suggested that FIGO score ≥ 12 is an independent risk factor for poor prognosis [5–8]. Therefore, FIGO Cancer Report 2015 divided the GTN patients with FIGO score ≥ 7 into high-risk subgroup (7 ≤ FIGO score < 12) and ultra high-risk subgroup (FIGO score ≥ 12) [9]. However, limited information is available about ultra high-risk subgroup so far because of its rarity [10,11].

Herein we conducted the retrospective study to analyze the clinical characteristics, the treatment efficiency and the prognosis of the ultra high-risk GTN patients treated at Peking Union Medical College Hospital (PUMCH). To the best of our knowledge, this study contained the largest sample size to date, and we revealed the prognostic risk factors of ultra high-risk GTN patients for the first time.

2. Patients and methods

2.1. Patients

Between January 2002 and December 2015, a total of 1776 patients were diagnosed with GTN at Peking Union Medical College Hospital (PUMCH). Among these patients, 143 (8.1%) patients were defined as ultra high-risk patients with FIGO score ≥ 12, of whom 41 patients received initial chemotherapy in our hospital while the other 102 patients were transferred from other hospitals with a history of failed chemotherapy. The database and medical records were reviewed to extract the basic information, diagnosis, stage, FIGO score, treatment, resistance, relapse and survival information. The study was carried out with the approval of the ethics committee of Peking Union Medical College Hospital. The informed consent was waived because this was a retrospective study.

2.2. Treatment

All patients underwent an initial assessment before treatment, including medical history, physical examination, transvaginal or transabdominal sonography, chest X-ray or computed tomography (CT), blood routine test, serum biochemistry and serum β-hCG levels. Brain Magnetic Resonance Imaging (MRI) or CT was also performed if patients had neurological symptoms.

The first-line chemotherapy was the floxuridine-based multiagent chemotherapy—FAEV regimen (floxuridine, actinomycin-D, etoposide, vincristine) for these ultra high-risk patients. The details of the FAEV regimen were as follows: vincristine 2 mg was administered by bolus intravenously 3 h before actinomycin-D on day 1; actinomycin-D 200 μg/m^2, floxuridine 800 mg/m^2, and etoposide 100 mg/m^2 were administered by infusion daily on days 1–5. Chemotherapy was recycled in 21-days intervals [12]. Two to four consolidation courses were given after normalization of serum β-hCG. For those who didn't have a good response to FAEV regimen, the salvage chemotherapy regimens were considered, including EMA/CO (etoposide, methotrexate, actinomycin-D/cyclophosphamide, vincristine), EMA/EP (etoposide, methotrexate, actinomycin-D/etoposide, cisplatin), and TE/TP (paclitaxel, etoposide/paclitaxel, cisplatin). Furthermore, intrathecal methotrexate 15 mg was injected on day 1, day 3 and day 5 respectively, combined with systemic FAEV chemotherapy for GTN patients with brain metastases. Once the serum β-hCG level was normal, intrathecal methotrexate chemotherapy was stopped, but patients still received additional 2 to 4 courses of systemic consolidation chemotherapy.

2.3. Evaluation after treatment

The treatment efficiency was evaluated from three aspects, the complete remission (CR), the resistance, and the relapse. The complete remission referred to consecutive normalization of serum β-hCG for at least four weeks. The resistance was defined as a plateau or increased serum β-hCG level after two or three courses of chemotherapy, and the relapse was diagnosed if serum β-hCG increased again three months after CR.

2.4. Safety assessment

All patients who received FAEV chemotherapy were assessed for toxicity. Hematologic and non-hematologic toxicity were assessed through review of laboratory reports and medical records. Toxicity was assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.

2.5. Statistical analysis

The results were analyzed using the SPSS 19.0 statistical software (SPSS, Chicago, IL). The remission rate was compared using chi-square test. The survival time was measured from the date of diagnosis to the date of last follow-up or death, and the overall survival rate was calculated with the Kaplan-Meier method. Univariate analysis was performed with log-rank test to find out prognostic risk factors for survival. Multivariate analysis with Cox proportional regression was used to evaluate the comprehensive effect of the risk factors selected in the univariate analysis. $P < 0.05$ was considered to be statistically significant.

3. Results

3.1. Clinical characteristics

All of the 143 ultra high-risk GTN patients in this study were diagnosed with choriocarcinoma. The majority of the patients were diagnosed with choriocarcinoma based on clinical findings, including detailed medical history, physical examination, serum β-hCG levels, transvaginal or transabdominal sonography, chest X-ray or computed tomography (CT). Pathological evidence was not necessary for the diagnosis of choriocarcinoma. Only a minority of these patients had pathological evidences before the commencement of chemotherapy. Also, it should be noted that 77 patients underwent salvage surgeries after chemotherapy and got pathological diagnosis of choriocarcinoma. The mean age of the group was 33.06 years old (range 16–63), and 30 (21.0%) patients were older than 40. The median serum β-hCG was 43,049 IU/L (range 11.9–3,053,500). Antecedent pregnancy was a mole in 28 cases (19.6%), an abortion in 57 cases (39.9%), and a term in 58 cases (40.5%). Time interval from antecedent pregnancy to chemotherapy was ≥12 months in 126 cases (88.1%), and <12 months in 17 cases (11.9%). Furthermore, there were 20 (14.0%) patients with liver metastases, and 58 (40.6%) patients with brain metastases, including 8 (5.6%) cases with both liver and brain metastases; other metastases included kidney, spleen, intestine, bone, and adrenal gland. Additionally, 102 patients had previous failed chemotherapy, including 98 cases of multiagent resistance and 4 cases of single-agent resistance. According to the FIGO clinical stage system, only 4 patients (2.8%) were at stage I, 3 patients (2.1%) were at stage II, 58 patients (40.6%) were stage at III, and 78 patients (54.5%) were at stage IV. The mean FIGO score was 15 (range 12–23). The clinical characteristics of the patients were summarized in Table 1.

3.2. Treatment

Among the 143 ultra high-risk GTN patients, 4 cases died before or during the first cycle of chemotherapy and 9 cases received EMA/CO because of a history of failed FAEV chemotherapy. The other 130 patients all received FAEV chemotherapy as the first-line multiagent chemotherapy, of whom 48 cases were changed to receive salvage chemotherapy due to FAEV resistance, including EMA/CO, EMA/EP, and TE/TP. Of the 48 patients who failed on FAEV, 42 patients had a failed history of multiagent chemotherapy, and 22 patients were at stage IV. 15 patients

Please cite this article as: Y. Kong, et al., Clinical characteristics and prognosis of ultra high-risk gestational trophoblastic neoplasia patients: A retrospective cohort stu..., Gynecol Oncol (2017), http://dx.doi.org/10.1016/j.ygyno.2017.04.010