Gynecologic Oncology 141 (2016) 276–280

Contents lists available at ScienceDirect

Gynecologic Oncology

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

Postmolar choriocarcinoma: An independent risk factor for chemotherapy resistance in low-risk gestational trophoblastic neoplasia

Anna E. Strohl *, John R. Lurain

John I. Brewer Trophoblastic Disease Center, Department of Obstetrics and Gynecology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

HIGHLIGHTS

- Clinicopathologic choriocarcinoma is associated with initial treatment failure in low-risk GTN.
- Low-risk choriocarcinoma is more likely to require multiagent chemotherapy or surgery for cure.
- Postmolar choriocarcinoma should be considered a poor prognostic factor in low-risk GTN.

ARTICLE INFO

Article history:
Received 17 December 2015
Received in revised form 10 February 2016
Accepted 14 February 2016
Available online 3 March 2016

Keywords:
Choriocarcinoma
Gestational trophoblastic neoplasia
Low-risk

ABSTRACT

Objective. To evaluate the effect of a clinicopathologic diagnosis of choriocarcinoma (CCA) on clinical characteristics, extent of disease, and response to chemotherapy in low-risk gestational trophoblastic neoplasia (GTN).

Methods. We reviewed the records of 678 patients with low-risk GTN (FIGO stage I and stages II—III, score < 7) treated from 1962 to 2009. Patient and disease characteristics, treatment course, as well as clinical response and survival were analyzed retrospectively. Patients with a clinicopathologic diagnosis of CCA were compared to those with a clinical diagnosis of postmolar GTN.

Results. Of 678 women with low-risk GTN, 129 (19.0%) had a clinicopathologic diagnosis of CCA. Patients with CCA had higher parity (median 1 vs. 0, $p = 0.003$), more pretreatment human chorionic gonadotropin (hCG) levels at >100,000 mIU/mL (12.7% vs. 5.9%, $p = 0.009$), longer duration of disease (19.6 vs. 9.9 weeks, $p < 0.001$), and higher FIGO scores (median 2 vs. 1, $p < 0.001$) compared with those with other histology; however, patients with CCA and postmolar GTN presented with similar stage of disease (stage I, 83.1% vs 88.2%, $p = 0.126$). Although there was no difference in survival between groups, increased resistance to first-line methotrexate chemotherapy was significantly associated with a diagnosis of postmolar CCA (OR 2.67, $p = 0.007$)), pretreatment hCG level at >10,000 mIU/mL (OR 2.62, $p = 0.002$), and higher FIGO score (3–4: OR 2.02, $p = 0.027$; 5–6: OR 5.56, $p < 0.001$) on multivariate analysis.

Conclusions. Clinicopathologic diagnosis of postmolar CCA in patients with low-risk GTN is associated with higher pretreatment hCG levels, higher FIGO scores, and increased resistance to first-line single-agent methotrexate chemotherapy.

1. Introduction

Low-risk gestational trophoblastic neoplasia (GTN) is currently defined by the International Federation of Gynecology and Obstetrics (FIGO) as non-metastatic (stage I) and metastatic (stages II and III) disease with a prognostic score of <7. Patient age, antecedent pregnancy, duration of disease, pretreatment human chorionic gonadotropin (hCG) level, site and number of metastases, size of the largest tumor, in addition to exposure to prior chemotherapy all contribute to determining the FIGO prognostic score [1]. Histopathologic diagnosis is not included in the FIGO score.

Patients with FIGO-defined low-risk GTN can be treated with initial single-agent methotrexate or actinomycin D chemotherapy with a cure rate approaching 100%, although 20–30% of low-risk patients will develop resistance to the initial chemotherapeutic agent and approximately 10% of patients will require multiagent chemotherapy with or without surgery to achieve remission [1,2]. Increased risk of initial chemotherapy resistance has been associated with older patient age, higher hCG levels, non-molar antecedent pregnancy, presence of metastatic disease, higher FIGO score, as well as differences in chemotherapy drug dosages, schedules, and routes of administration [3,4].

Although clinicopathologic diagnosis of choriocarcinoma is not included in the FIGO score, several studies have reported that a

* Corresponding author at: Division of Gynecologic Oncology, 250 E. Superior St., Suite 05-2168, Chicago, IL 60611, USA.
E-mail address: anna-strohl@northwestern.edu (A.E. Strohl).

http://dx.doi.org/10.1016/j.ygyno.2016.02.014
0090-8258/

clinicopathologic classification of choriocarcinoma versus postmolar GTN/invasive mole is also associated with an increased resistance to first-line single-agent chemotherapy in patients with low-risk GTN [5–7]. In this study, we sought to evaluate the effect of a clinicopathologic diagnosis of choriocarcinoma on clinical characteristics, extent of disease, and response to chemotherapy in FIGO-defined low-risk GTN.

2. Material and methods

We retrospectively reviewed the charts of 678 patients with FIGO-defined low-risk GTN (stage I and stages II—III, score < 7) treated at the John I. Brewer Trophoblastic Disease Center of Northwestern University from 1962 through 2009. The diagnosis of low-risk GTN (invasive mole or choriocarcinoma excluding placental site and epithelioid tumors) was made by both histologic and clinical criteria. Postmolar GTN was diagnosed after a plateau in hCG level for four consecutive tests over three weeks, a rise in hCG level by ≥10% for three consecutive tests over two weeks, any elevation in hCG level six months after molar evacuation, a histopathologic diagnosis of choriocarcinoma, or the presence of metastatic disease. The clinicopathologic diagnosis of choriocarcinoma was made by examination of tissue specimens showing hyperplastic and dysplastic trophoblast in the absence of villi, or if GTN developed in association with a non-molar pregnancy, thus excluding the possibility of invasive mole.

After the diagnosis of GTN was established, a staging evaluation was performed. Along with a complete history and physical examination, laboratory tests including complete blood count, renal and liver function panels, and quantitative serum hCG level were obtained. Routine imaging included chest X-ray and computed tomography (CT) scan of the chest if negative. If physical exam and chest X-ray were normal in the absence of symptoms, CT/MRI scans were usually not performed since metastases to other sites are uncommon. Pelvic ultrasound or MRI was occasionally useful in detecting extensive uterine disease for which hysterectomy may be of benefit.

Based on this staging evaluation, patients with GTN were categorized according to the 2002 FIGO criteria into a low-risk group that could be treated with single-agent chemotherapy with a high likelihood of success. Low-risk disease was defined as non-metastatic disease (stage I) as well as metastatic disease confined to the lungs and/or pelvis (stages II and III) with a FIGO risk factor score of less than seven. Chemotherapy protocols were standardized for all providers treating patients with GTN during the time of data collection.

Chemotherapy protocols were standardized during the time of data collection. The preferred first-line chemotherapy for patients with low-risk GTN, including both non-metastatic and metastatic disease, was methotrexate 0.4 mg/kg (max 25 mg) IV push daily for five days every other week ($N = 615$). Alternate single-agent chemotherapy in patients with a contradiction to methotrexate was actinomycin D 0.5 mg IV push daily for five days every other week ($N = 30$). Actinomycin D was also given to patients who developed resistance or toxicity to methotrexate ($N = 107$). Patients who failed sequential single-agent therapy were managed with combination drug regimens ($N = 26$). Thirty-three patients (4.9%) received initial multiagent chemotherapy, usually because of the presence of metastatic disease or an antecedent term gestation. Adjuvant surgical procedures were performed in 83 patients: hysterectomy as part of initial treatment (50) or for hCG plateau or hemorrhage (29), as well as salpingectomy (1), and uterine wedge resection (3) for resistant disease.

Routine surveillance during treatment included a history and physical examination, complete blood counts, chemistries, and hCG levels the first day of each course of treatment. Response to treatment was determined by a decrease in hCG levels. Complete response or remission was diagnosed after three consecutive weekly hCG levels were within normal range (<2 mIU/mL). Two additional courses of chemotherapy were usually given after the first normal hCG level. Follow-up after achieving remission and completing treatment consisted of one year of monthly hCG levels and use of contraception, preferably oral contraceptive pills, for pregnancy prevention.

Patient and disease characteristics, including age, clinicopathologic diagnosis, antecedent pregnancy, time to diagnosis, pretreatment hCG, extent of disease and treatment, were collected and analyzed. FIGO stage and scores were prospectively determined or calculated and assigned retrospectively in patients treated prior to 2002.

Factors associated with clinicopathologic diagnosis of choriocarcinoma were analyzed by using the Chi-square test for categorical variables and the Wilcoxon rank sum test for continuous variables. Multivariate regression analysis was performed to assess clinical and histologic predictors of resistance to first-line single-agent methotrexate. Statistical analyses were performed using SPSS Statistics Software, Version 22. The study was approved by the Institutional Review Board of Northwestern University.

3. Results

3.1. Patient characteristics (Table 1)

A total of 678 patients were treated for FIGO-defined low-risk GTN at the Brewer Trophoblastic Disease Center between 1962 and 2009. Patient and disease characteristics are presented in Table 1. The median age of patients was 27 years (range 13–53 years). Most patients had a history of hydatidiform mole (88.3%) as their antecedent pregnancy, disease duration of <4 months (85.5%), and a pretreatment hCG level of <100,000 mIU/mL (93.2%). Metastatic disease was present in 86 patients (12.7%), including lung (73), vagina (5), and lung/vagina (8). Forty-four patients (6.5%) had a FIGO score of >4. Clinicopathologic diagnosis was postmolar GTN/invasive mole in 549 patients (81.0%) and choriocarcinoma in 129 patients (19.0%).

3.2. Factors associated with clinicopathologic diagnosis of choriocarcinoma (Table 2)

A clinicopathologic diagnosis of choriocarcinoma was significantly associated with higher parity, higher pretreatment hCG levels, and longer duration of disease (Table 2). There was no difference between groups with respect to age at diagnosis, metastatic disease, or mean number of metastasis. There was also no difference in overall survival between the two groups. Survival for this cohort was 99.2% and 99.8% in patients with choriocarcinoma and postmolar GTN, respectively.

Table 1
Patient and disease characteristics.

Demographics	$N = 678$(n, (%))
Median age (years)	27 (range 13–53)
Antecedent pregnancy	
Hydatidiform mole	595 (88.3)
Spontaneous/elective abortion	54 (8.0)
Term pregnancy	25 (3.7)
Duration of disease	
<4 months	579 (85.5)
>4 months	98 (14.5)
Pretreatment hCG[a]	
<100,000	632 (93.2)
>100,000	46 (6.8)
Clinicopathologic type	
Postmolar GTN	549 (81.0)
Choriocarcinoma	129 (19.0)
FIGO stage	
Stage I	592 (87.3)
Stage II	5 (0.7)
Stage III	81 (12.0)
FIGO score	
0–2	535 (78.9)
3–4	99 (14.6)
5–6	44 (6.5)

[a] hCG = human chorionic gonadotropin (mIU/mL).