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Fatal gestational trophoblastic neoplasia: An analysis of treatment failures at the Brewer Trophoblastic Disease Center from 1979–2012 compared to 1962–1978

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HIGHLIGHTS

- The overall survival rate is improving for patients with gestational trophoblastic neoplasia.
- Deaths from gestational trophoblastic neoplasia are now most often due to widespread chemotherapy-resistant disease.
- Early deaths from hemorrhagic complications of gestational trophoblastic neoplasia are becoming less common.

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ABSTRACT

Objective. To determine clinical factors that contributed to death from gestational trophoblastic neoplasia (GTN) at the Brewer Trophoblastic Disease Center from 1979–2012 compared to 1962–1978.

Methods. Nineteen women who died of GTN from 1979–2012 were retrospectively identified and compared to 45 women previously reported on who died of GTN from 1962–1978. Clinical factors analyzed included demographics, pretreatment human chorionic gonadotropin (hCG) level, duration of disease, antecedent pregnancy, number and sites of metastases, FIGO stage and score, treatment, and cause of death.

Results. Death from GTN occurred in 19 (4%) of 483 patients treated from 1979–2012 compared to 45 (11%) of 396 patients treated from 1962–1978 ($P < 0.001$). Pretreatment hCG level >100,000 mIU/mL, time from pregnancy event to treatment >4 months, nonmolar antecedent pregnancy and use of surgery to control metastatic disease were similar between the two treatment eras. Patients in the recent series were more likely to have presented with FIGO IV disease or brain metastasis, been initially treated with multiagent chemotherapy, and received treatment before referral to our center compared to the earlier series. The most common causes of death from 1979–2012 and 1962–1978 were hemorrhage from one or more metastatic sites (11% vs. 42%), respiratory failure (37% vs. 31%), and multiorgan failure due to widespread chemoresistant disease (42% vs. 8%), respectively.

Conclusions. Our overall survival rate in patients with gestational trophoblastic neoplasia improved from 89% in 1962–1978 to 96% in 1979–2012. More patients treated between 1979–2012 died from widespread chemoresistant disease rather than hemorrhagic complications.

1. Introduction

Deaths from gestational trophoblastic neoplasia (GTN) are now rare events, with the overall cure rate exceeding 90%. Virtually all patients with nonmetastatic and metastatic low-risk disease will be cured whereas up to 20% of patients with metastatic high-risk choriocarcinoma will die from their disease. Risk factors related to fatal GTN include histolopathologic diagnosis of choriocarcinoma, high initial human chorionic gonadotropin (hCG) level, long duration of disease, multiple sites and increasing number of metastases, antecedent nonmolar pregnancy, and extent of prior treatment [1–5]. An understanding of treatments utilized, sites of failure, and causes of death in cases of fatal GTN is important in preventing future deaths from GTN [6–9]. The objective of the present study was to determine clinical factors that contributed to death from gestational trophoblastic neoplasia (GTN) at the Brewer Trophoblastic Disease Center from 1979–2012 compared to 1962–1978 [10,11].

2. Materials and methods

The records of the John I. Brewer Trophoblastic Disease Center of Northwestern University were searched for all deaths from gestational

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trophoblastic neoplasia between 1979 and 2012. A total of nineteen patients who received treatment at the Brewer Center and subsequently died of gestational trophoblastic neoplasia were retrospectively identified, representing 4% of the 443 patients with GTN referred to our center for treatment during that time. Clinical factors analyzed included demographics, pretreatment hCG level, duration of disease, time from pregnancy event to treatment, number and sites of metastasis, FIGO stage and score, treatment, and cause of death. Duration of disease was assessed from the time of diagnosis to death. The final cause of death reflected combined clinical and autopsy data. Results were compared to 45 previously reported cases of women who died of GTN between 1962 and 1978 [10]. Differences between the two groups were analyzed by Chi-square. The study was approved by the Institutional Review Board of Northwestern University.

3. Results

3.1. Clinical data

Nineteen (4%) of 443 women who were treated at the Brewer Center between 1979 and 2012 died of gestational trophoblastic neoplasia (Table 1). Eighteen patients (95%) had presumed or histologically-confirmed choriocarcinoma. One patient had placental site trophoblastic tumor (PSTT). The mean age was 29.5 years (range 18 to 42 years). All nineteen patients had FIGO stage III (7) or IV (12) disease at the time of diagnosis. FIGO scores ranged from 9–19 (mean = 14). Twelve patients (63%) had a nonmolar index pregnancy. Pretreatment hCG levels ranged from 23 to 7,000,000 mIU/mL (mean = 605, 324 mIU/mL; median 178,000 mIU/mL). Thirteen patients (68%) received first-line multiagent chemotherapy at our center, consisting of methotrexate, actinomycin D, and cyclophosphamide (MAC) in 7 patients, cyclophosphamide, hydroxyurea, actinomycin D, methotrexate, vincristine, and doxorubicin (CHAMOCA) in 1 patient, and etoposide, methotrexate, actinomycin D, cyclophosphamide and vincristine (EMA-CO) in 5 patients. Six patients (32%) had failed treatment elsewhere before referral to the Brewer Center. Salvage chemotherapy usually consisted of etoposide and platinum in combination with bleomycin or ifosfamide. Seven patients (37%) received adjuvant brain radiation, usually 3000 cGy to the whole brain in 200 cGy fractions. Thirteen patients (68%) underwent 14 surgical procedures, including 11 hysterectomies, one splenectomy, one liver resection, and one pulmonary resection. All patients had metastases present at the start of the treatment: 18 (98%) had lung metastases, 6 (33%) had brain metastases, and 3 (17%) had liver metastases. Median overall survival from diagnosis to time of death was 22 months (range <1 to 134 months).

3.2. Causes of death

In general, causes of death were primarily related to widespread chemotherapy-resistant disease (8, 42%) or respiratory failure due to progressive disease in the lungs (7, 37%). Two patients (11%) died as a direct result of hemorrhage: one intracranial from brain metastasis and one intraabdominal from hepatic rupture related to liver metastasis. One patient died from hepatitis-related liver cancer with no evidence of active choriocarcinoma as a result of blood transfusion received during treatment for GTN. One patient who had a rising hCG level and multiple sites of metastatic disease refused further treatment. No patient died directly of chemotherapy-related complications.

3.3. Comparison of 1962–1979 to 1979–2012

Overall survival from GTN improved from 89% in 1962–1978 to 96% in 1979–2012 ($P < 0.001$). Presentation of disease was similar between the cohorts in regards to hCG level > 100,000 mIU/mL (53% vs. 54%), pregnancy event to treatment time greater than 4 months (58% vs. 62%) and nonmolar antecedent pregnancy (63% vs. 68%). Patients in the most recent treatment group were twice as likely to have received first-line multiagent chemotherapy (68% vs. 31%) and were less likely to have received treatment before being referred to the Brewer Center (26% vs. 32%) compared to the previous group. Finally, those who died between 1979 and 2012 were more likely to have presented with FIGO stage IV disease (63% vs. 49%) and brain metastases at the time of diagnosis (31% vs. 18%) compared to those who died between 1962 and 1978 (Table 2). The patients from our current series more often died from chemotherapy-resistant disease leading to multiorgan failure or pulmonary insufficiency (79% vs. 40%, $P < 0.01$), while patients

Table 1
Patient and disease characteristics, treatment, and cause of death, 1979–2012.

Case no.	Age	Index pregnancy	hCG level (mIU/ml)	Metastatic disease at diagnosis	Duration of disease	FIGO stage	First line multiagent chemo	Adjuvant treatment	Cause of death
1	24	Preterm	23,805	Lungs	36 months	III:16	N	TLH	Pulmonary
2	33	Molar	81,833	Lungs, brain	52 months	IV:14	Y	RT	Progressive disease
3	32	Unknown	35,712	Liver	12 months	IV:12	Y	–	Progressive disease
4	20	Molar	500,000	Lungs, liver	14 months	IV:16	Y	TAH	Progressive disease
5	23	Term	28,900	Lungs	5 months	III:9	Y	TAH	Pulmonary
6	18	Molar	415,000	Lungs, brain	6 months	IV:13	Y	RT	Pulmonary
7	39	Molar	7,000,000	Lungs, brain, spleen	56 months	IV:19	N	TAH	Intracranial hemorrhage
8	29	SAB	13,000	Lungs	15 months	III:11	N	RT/TAH	Pulmonary
9	32	Term	280,000	Lungs, brain, spleen	134 months	IV:18	Y	RT/splenectomy	Hepatitis-related liver cancer*
10	26	Term	1250	Lungs, small bowel	22 months	III:15	N	TAH	Lost to follow-up
11	35	Molar	400,000	Lungs, liver, spleen, kidney	<1 month	IV:12	Y	TAH/BSO, liver resection	Progressive disease
12	40	Unknown	23	Lung	32 months	III:9	Y	RT/TVH	Pulmonary
13	24	Term	3281	Lung	56 months	III:11	Y	Pulmonary lobectomy	Progressive disease
14	34	Term	6239	Lung	22 months	III:11	N	TAH	Progressive disease
15	25	SAB	154	Lung, brain, spleen, heart	34 months	IV:17	N	TAH	Progressive disease
16	29	Molar	170,000	Lung, vagina, brain	127 months	IV:16	Y	–	Pulmonary
17	27	Preterm	240,000	Lung, brain	14 months	IV:18	Y	RT/TAH	Pulmonary
18	29	Molar	1,124,000	Lung, brain, liver	–	IV:12	Y	RT	Progressive disease
19	42	SAB	178,000	Lung, liver, spleen	1 month	IV:13	Y	–	Pulmonary

SAB: spontaneous abortion.
RT: brain radiotherapy.
TAH: total abdominal hysterectomy.
TLH: total laparoscopic hysterectomy.
TVH: total vaginal hysterectomy.
* Thought to be secondary to blood transfusions.