Outcome of subsequent pregnancy after treatment for persistent gestational trophoblastic tumour

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BACKGROUND: This study analysed subsequent pregnancy outcome in patients treated for persistent gestational trophoblastic tumour (GTT). METHODS: Between 1974 and 1999, a total of 378 patients with GTT (83 patients with high-risk and 295 patients with low-risk GTT) were treated at Chiba University Hospital, Japan. Of these 378 patients, 363 (96.0%) achieved primary remission and 315 survivors have been followed at our hospital. RESULTS: To date, 129 patients have had 243 subsequent conceptions. While pregnancy outcome was comparable with that of the general Japanese population, the incidence of repeat molar pregnancy (2.1%) was approximately seven times higher than that of the general population. During the mandatory HCG follow-up period of 1 year, 15 patients conceived within 6 months of completion of chemotherapy. The incidence of spontaneous abortion in these 15 patients was significantly higher than that in patients who conceived after a waiting period of >6 months (P = 0.0053). CONCLUSIONS: Patients treated for GTT may anticipate a normal future reproductive outcome, although it would be better to avoid pregnancy for at least 6 months after completion of chemotherapy.

Key words: chemotherapy/gestational trophoblastic tumour/subsequent pregnancy outcome

Introduction

Since the introduction of effective chemotherapy, patients with gestational trophoblastic tumour (GTT) have been successfully treated with chemotherapy while preserving reproductive function (Newlands, 1996; Matsui et al., 1998). This tumour occurs most frequently among women in their twenties and thirties, who often desire future pregnancies after the completion of chemotherapy. However, patients with GTT may express fears related to future pregnancies, especially the possibility of GTT recurrence, abnormal pregnancy outcome and fetal anomalies resulting from anti-cancer chemotherapy. Many previous studies (Goldstein et al., 1984; Rustin et al., 1984; Ngan et al., 1988; Berkowitz et al., 1994; Kim et al., 1998; Woolas et al., 1998) have confirmed that patients with persistent GTT may anticipate a normal reproductive outcome. However, there are limited data regarding the outcome of pregnancies occurring before completion of the mandatory HCG follow-up period of 1 year (Tuncer et al., 1999).

In this paper, we studied the subsequent pregnancy outcome and recurrence in patients with persistent GTT who achieved remission after receiving methotrexate (MTX), actinomycin D (Act-D), etoposide and several combination chemotherapy regimens.

Materials and methods

From 1974 to 1999, 378 patients with GTT (83 patients with high-risk and 295 patients with low-risk GTT) were treated at Chiba University Hospital, Japan. Low-risk GTT was distinguished from high-risk GTT on the basis of modified Hammond’s criteria (Hammond et al., 1973) as antecedent molar pregnancy, short duration (<4 months), no brain or liver metastases, and no treatment history. Patients with low-risk GTT were initially treated with single-agent chemotherapy (MTX, Act-D or etoposide) and all 295 patients achieved remission. Patients with high-risk GTT were treated with combination chemotherapy [MTX, Act-D and cyclophosphamide (MAC regimen) or MTX, Act-D and etoposide (MEA regimen)] (Matsui et al., 2000).

All patients were monitored for at least 1 year. The median follow-up duration was 14.8 ± 6.9 years. Forty-two (11.1%) patients could not be traced. For women with definite foci of GTT in the uterus who had no desire to preserve fertility, we recommended adjuvant hysterectomy to reduce the total dose of drugs needed to achieve remission (Suzuka et al., 2001). Surgical removal of drug resistant foci in the uterus and metastatic sites was also performed in patients with high-risk GTT.

Remission was diagnosed when three consecutive weekly HCG levels were within the normal range, and after an additional one or two cycles for low-risk GTT or seven cycles for high-risk GTT. After remission, HCG levels were determined monthly for 6 months, every other month for another 6 months, and then every 3 or 4 months for the next 12 months. Patients were strongly advised not to become pregnant for at least 1 year after completing chemotherapy.

Statistical analyses were performed by Welch’s t-test, analysis of variance followed by Scheffe’s F-test, and the χ² test.

Results

Outcome

The primary remission rates in patients with low-risk and high-risk GTT were 100% (295/295) and 81.9% (68/83)
Table I. Initial treatment outcomes and long-term outcomes in 378 patients

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Low-risk (%)</th>
<th>High-risk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progressive disease</td>
<td>15 (4.0)</td>
<td>0</td>
<td>15 (18.1)</td>
</tr>
<tr>
<td>Primary remission</td>
<td>363 (96.0)</td>
<td>295 (100)</td>
<td>68 (18.9)</td>
</tr>
<tr>
<td>Total</td>
<td>378</td>
<td>295</td>
<td>83</td>
</tr>
<tr>
<td>Relapse</td>
<td>16 (4.4)</td>
<td>5 (1.7)</td>
<td>11 (16.2)</td>
</tr>
<tr>
<td>Cumulative risk of death</td>
<td>19 (5.0)</td>
<td>0</td>
<td>19 (22.9)</td>
</tr>
<tr>
<td>from disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death of other disease</td>
<td>2 (0.5)</td>
<td>0</td>
<td>2 (2.4)</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>42 (11.1)</td>
<td>37 (12.5)</td>
<td>5 (6.0)</td>
</tr>
<tr>
<td>Alive</td>
<td>315</td>
<td>258</td>
<td>57</td>
</tr>
</tbody>
</table>

*Twelve patients achieved remission again.

Table II. Outcome of all pregnancies and the first pregnancy occurring after completion of chemotherapy

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Total pregnancy</th>
<th>First pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Term live birth</td>
<td>169</td>
<td>69.5</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>2</td>
<td>0.8</td>
</tr>
<tr>
<td>Premature delivery</td>
<td>5</td>
<td>2.1</td>
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<tr>
<td>Spontaneous abortion</td>
<td>27</td>
<td>11.1</td>
</tr>
<tr>
<td>Therapeutic abortion</td>
<td>35</td>
<td>14.4</td>
</tr>
<tr>
<td>Repeat mole</td>
<td>5</td>
<td>2.1</td>
</tr>
<tr>
<td>Total</td>
<td>243</td>
<td>129</td>
</tr>
</tbody>
</table>

respectively (Table I). Sixteen patients who achieved primary remission relapsed subsequently, including five patients (1.7%) with low-risk GTT and 11 patients (16.2%) with high-risk GTT. Twelve of these 16 relapsed cases achieved remission again with combination chemotherapy and surgical interventions in selected cases, while four patients died after developing drug resistance. At the time of outcome evaluation, 42 (11.1%) patients (five with high-risk and 37 with low-risk GTT) were lost to follow up. There have been 21 (5.6%) deaths in our 378 patients. Nineteen patients died of disease (four widespread disease, four relapsed, nine refractory, one treatment related and one refused further treatments). Two patients with high-risk GTT died of other causes (lung cancer and traffic accident). The overall survival rate in patients with GTT at our hospital was 93.8% (315/336).

Pregnancy outcome

Among 315 survivors, 108 (34.3%) underwent hysterectomy for removal of drug resistant foci in the uterus or because the patient did not desire future pregnancy. The remaining 207 patients (65.7%) achieved remission with chemotherapy alone. Of these patients, 133 (64.3%) desired future pregnancies, and 129 patients had 243 subsequent conceptions. The 243 conceptions resulted in 169 (69.5%) term live births including two cases of twins, two (0.8%) stillbirths, five (2.1%) premature deliveries, 27 (11.1%) spontaneous abortions, 35 (14.4%) therapeutic abortions, and five (2.1%) repeat moles (Table II). The rates of stillbirths, premature deliveries and spontaneous abortions were similar to those of previous reports (Goldstein et al., 1984; Rustin et al., 1984; Ngan et al., 1988; Berkowitz et al., 1994; Kim et al., 1998; Woolas et al., 1998) and those of the general Japanese population (Ministry of Health and Welfare, 1998). Major and minor congenital anomalies (Down’s syndrome, heart anomalies and clubfoot) were detected at birth or during the nursing period in three (1.7%) infants, while the study group was not large enough to consider malformations. The mean ± SD birthweight in 167 term live births, excluding the two cases of twins, was 3205 ± 401 g (range 2130–4500). These birthweights were comparable with the standard physical growth statistics for 1998 in Japan (Ministry of Health and Welfare, 1998). The sex ratio was 85 males (50.9%) to 82 females (49.1%).

Interval to subsequent pregnancy

Among the 243 conceptions, 129 subsequent first pregnancies resulted in 102 (79.1%) term live births, one (0.8%) stillbirth, one (0.8%) premature delivery, 12 (9.3%) spontaneous abortions, nine (7.0%) therapeutic abortions and four (3.1%) repeat moles (Table II). The mean (± SD) period between completion of chemotherapy and subsequent first pregnancy was 21.7 ± 19.4 months. Although we strongly advised the patients not to become pregnant for at least 1 year after completing chemotherapy, 19 patients conceived between 6–12 months (mean ± SD, 10.0 ± 1.1; range, 7–11) and 15 patients conceived within 6 months (mean ± SD, 4.1 ± 1.7; range, 1–6) after completing chemotherapy (Table III). These 34 pregnancies resulted in 24 (70.6%) term live births, one (2.9%) stillbirth, six (17.6%) spontaneous abortions and three (8.8%) therapeutic abortions. The rate of spontaneous abortion was slightly higher than that in patients who conceived after 12 months, although there was no significant difference (P = 0.08; Fisher’s exact test). However, the spontaneous abortion rate in patients who conceived within 6 months (5/15: 33.3%) was significantly higher than that in patients who conceived >12 months after completion of chemotherapy (6/95: 6.3%) (P = 0.0069; Fisher’s exact test). Furthermore, three patients who conceived within 6 months underwent therapeutic abortion due to fear of congenital fetal anomalies resulting from anti-cancer drugs. Excluding these therapeutic abortions, the rate of spontaneous abortion was significantly higher than that of patients who conceived between 6–12 months (P = 0.022; Fisher’s exact test).
Relapse

The main fears expressed by patients and their partners were repeat mole and secondary GTT after subsequent pregnancy. Five cases of repeat molar pregnancy (2.1%) were observed in this series. The incidence of repeat molar pregnancy was approximately seven times higher than the incidence of molar pregnancy in the general Japanese population, while the incidence of repeat mole was comparable with that in patients with spontaneous resolution of HCG after evacuation of their first hydatidiform mole (Matsui et al., 2001). In 207 patients who achieved remission with conserved reproductive function, nine patients (4.3%) relapsed, including three (2.3%) who relapsed after subsequent term deliveries and six (7.7%) who relapsed without subsequent pregnancy. There was no significant difference in relapse rate in patients who had subsequent pregnancies and those who did not ($P = 0.084$; Fisher’s exact test).

Discussion

During the period 1974 to 1999, 378 patients with GTT were treated at Chiba University Hospital. In 315 survivors, 207 patients (65.7%) achieved remission with chemotherapy alone. In these potentially fertile patients, 133 (64.3%) desired future pregnancies and 129 patients had 243 subsequent conceptions. The infertility rate (3.0%; 4/133) was comparable with other reports (Goldstein et al., 1984; Rustin et al., 1984; Ngan et al., 1988; Woolas et al., 1998).

Patients with treated persistent GTT may express fears related to future pregnancies, especially the possibility of GTT recurrence or fetal anomalies. Therefore, data related to subsequent pregnancy outcome after chemotherapy for persistent GTT are essential to counsel patients and their partners concerning the potential risks of subsequent pregnancies. Many previous studies have reported that patients with persistent GTT can be assured that they may anticipate a normal reproductive outcome. In our series, the rates of term live birth, stillbirth, premature delivery, spontaneous abortion and congenital anomaly in patients who had been treated for persistent GTT were similar to the rates in the general Japanese population (Ministry of Health and Welfare, 1998) and those reported in the literature (Goldstein et al., 1984; Rustin et al., 1984; Ngan et al., 1988; Berkowitz et al., 1994; Kim et al., 1998; Woolas et al., 1998).

The other fear concerning future pregnancy, expressed by patients and their partners, is secondary development of GTT in subsequent pregnancies. The incidence of repeat molar pregnancy (2.1%) was apparently higher than that in the general population, while it was comparable with that in patients with spontaneous resolution of HCG after evacuation of their first molar pregnancy (Matsui et al., 2001). In the present series, recurrence of GTT was observed in three (2.3%) patients who conceived after remission and in six (7.7%) patients who did not conceive. There was no significant difference in relapse rate in patients who had subsequent pregnancies and those who did not ($P = 0.084$; Fisher’s exact test).

Recently, Tuncer et al. addressed the specific problem of pregnancy in patients who conceive before completion of the conventionally mandated waiting period of 12 months after chemotherapy (Tuncer et al., 1999). They reported that maternal age, parity, antecedent pregnancy, International Federation of Gynecology and Obstetrics (FIGO) stage, World Health Organization score, number of chemotherapy cycles, and interval from remission to new pregnancy had no effect on subsequent pregnancy outcome. Furthermore, they stated that pregnancy within the mandated follow-up period of 12 months was reasonably safe and therapeutic abortion was not required.

We also strongly advise patients who are treated for persistent GTT to use reliable contraception for 12 months following completion of chemotherapy, due to the anxiety and fear of fetal anomalies resulting from anti-cancer drugs. Nevertheless, 19 patients (14.7%) and 15 patients (11.6%) conceived between 6–12 months and within 6 months respectively, after the completion of chemotherapy. The cumulative spontaneous abortion rate in those patients who conceived within 6 months (33.3%) was significantly higher than that in patients who conceived after 12 months, while no significant difference was observed compared with the report of Tuncer et al. ($P = 0.08$) (Tuncer et al., 1999). However, the spontaneous abortion rate in those patients who conceived within 6 months (33.3%) was significantly higher than that in patients who conceived after 12 months. Furthermore, excluding three therapeutic abortions, the spontaneous abortion rate in the patients who conceived within 6 months was significantly higher than that in patients who conceived between 6–12 months. The mean maternal age, regimen and numbers of chemotherapy treatment were not related to the unfavourable pregnancy outcomes (data not shown). Although our study was small and retrospective, these findings suggest that it may be safer to avoid conception within 6 months after the completion of chemotherapy.

Folliculogenesis appears to be a very long process in normal women. Gougeon reported that the full span of growth from the primordial to Graafian follicle was in the order of 6–12 months (Gougeon, 1996). If anti-cancer drugs do affect the developing pre-antral follicles, ovulatory oocytes that develop within a short interval after completion of chemotherapy may be subjected to genetic damages or teratogenic effects induced by the anti-cancer drugs. Meirow et al. reported that fertilization shortly after cyclophosphamide chemotherapy could result in a high rate of pregnancy failure and high malformation rate in mice (Meirow et al., 2001). It will become vital for anti-cancer chemotherapy to define the safety period between cessation of chemotherapy and fertilization.

In conclusion, patients with treated persistent GTT may anticipate normal future reproductive outcome. As pregnancies occurring within 6 months following remission are likely to result in a more unfavourable outcome, a waiting period of at least 6 months after chemotherapy for persistent GTT is needed. Repeat molar pregnancy is also an unfavourable event in subsequent pregnancy in patients with persistent GTT, and the incidence is increased seven times compared with the general population. However, subsequent pregnancy after chemotherapy for GTT does not increase the recurrence of GTT.
References


Received on May 8, 2001; accepted on October 6, 2001