A Case of Extragonadal Germ Cell Tumor with Elevated Postchemotherapy HCG Successfully Treated by Resection of a Solitary Metastasis and Chronic Oral Etoposide

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We report a 39-year-old man with disseminated extragonadal germ cell tumor (GCT), whose serum level of human chorionic gonadotropin (HCG) increased again after platinum-based combination chemotherapy, high-dose chemotherapy with autologous bone marrow rescue and radical adjunctive surgery. The increase in the HCG level was progressive in spite of multiple chemotherapy, and after a while, a coin lesion in the right lung was identified by chest roentgenography. The pulmonary lesion was refractory to additional chemotherapy. After a systematic survey to confirm that the lesion was solitary, video-assisted thoracoscopic wedge resection of the right lower lobe was performed. Because the resected tumor included viable tumor cells and the serum HCG level remained slightly high one month after the operation, oral low-dose etoposide was begun. In a short time, the level of the serum tumor marker decreased and remained normal during the subsequent 7 months of therapy and thereafter. The patient remains in complete remission 13 months after completion of the final therapy and 3 years after the initial diagnosis. Even if the level of a serum tumor marker is high, salvage resection can be a promising therapeutic option for operable tumors that are refractory to chemotherapy. The usefulness of chronic oral etoposide for patients with GCT should be examined by further clinical trials.

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Introduction

Despite the introduction of effective chemotherapy for disseminated germ cell tumor (GCT), 20–30% of patients do not achieve a complete response (CR) to cisplatin-based combination chemotherapy.\(^1\)\(^,\)\(^2\) Salvage chemotherapy or high-dose chemotherapy followed by autologous bone marrow transplantation (ABMT) can result in durable CR in a small proportion of patients showing relapse or who are refractory to conventional chemotherapy.\(^3\)\(^)\(^-\)\(^5\) However, patients whose disease continues to progress after conventional therapy or salvage chemotherapy are considered to be incurable and to have a very poor prognosis. Death is considered inevitable in patients attaining less than a CR.\(^)\(^9\)

We describe the successful treatment of a patient with GCT considered to have a poor prognosis, whose disease was refractory to first- and second-line chemotherapy and high-dose chemotherapy followed by ABMT. The role of salvage surgery in patients with high tumor marker levels and the role of chronic etoposide in the treatment of GCT are discussed.

Case Report

In November 1992, a 38-year-old man was referred with an enlarged left neck lymph node (LN), 2 cm in a diameter. Abdominal ultrasonography showed swelling of multiple paraaortic LNs, which varied in size from about 5 mm to 3 cm. A routine biological examination revealed an increased serum level of human chorionic gonadotropin.
Fig. 1. Histological appearance of the left neck LN before treatment (a) and the recurrent S8 tumor in the right lung after ABMT (b). (a) Cancer cells show vesicular or bizarre nuclei with prominent nucleoli. The proliferation pattern is papillary or solid. (b) Most cancer cells show cytotrophoblastic features, among which cancer cells with syncytiotrophoblastic features are scattered.

Fig. 2. Serum HCG levels during the course of treatment. BEP, bleomycin, etoposide, cisplatin; ICE, ifosfamide, carboplatin, etoposide; HD-Cx, high-dose chemotherapy consisting of carboplatin, etoposide and cyclophosphamide; ABMT, autologous bone marrow transplantation; multiple regimens, vinblastine, doxorubicin, methotrexate, etoposide, actinomycin D and carboplatin in combination.

(HCG). Biopsy of the left neck LN gave a final pathological diagnosis of metastatic embryonal carcinoma with a choriocarcinomatous component, with positive immunohistochemical staining for HCG and keratin (Fig. 1a). Palpation and scrotal ultrasound examination by a urologist did not detect a testis tumor.

Under a clinical diagnosis of disseminated extragonadal non-seminomatous GCT, BEP therapy consisting of bleomycin (15 mg/day, once a week), etoposide (100 mg/m²/day i.v. for 5 days) and cisplatin (120 mg/m²/day i.v. for one day) was started on December 7, 1992, when the serum HCG, β-HCG and alpha-fetoprotein (AFP) levels were 6085.8 mIU/ml, 6747.1 mIU/ml and 24.7 ng/ml, respectively. Fig. 2 shows the clinical course of the treatment and the change in the serum HCG level. BEP was repeated every 3 weeks. Initially, the serum HCG level decreased rapidly. However, the HCG decline became prolonged later and did not reach a normal value (<1 mIU/ml) after three cycles of BEP. We therefore decided to institute high-dose chemotherapy followed by ABMT at that point according to our protocol.

After additional ICE (ifosfamide, carboplatin and etoposide) chemotherapy, high-dose chemotherapy
Fig. 3. Chest roentgenography taken on December 20, 1993, showing a coin lesion in the lower field of the right lung.

consisting of carboplatin 200 mg/m²/day i.v. for 5 days, etoposide 250 mg/m²/day i.v. for 5 days and cyclophosphamide 1.2 g/m²/day i.v. for 5 days was started on March 8, when the HCG level had decreased to 2.4 mIU/ml. Three days after the chemotherapy, a previously prepared autologous bone marrow cell suspension was thawed and infused. The patient’s WBC reached 1000/µl on day +11. After recovery from severe diarrhea, liver and renal dysfunction, septicemia due to pseudomonas aeruginosa, severe mucositis, hematemesis and mild congestive heart failure, the patient’s general condition improved at the end of March, when the HCG level decreased to normal.

Because small abdominal LNs were detected by computed tomography (CT) after the ABMT, adjunctive surgery for the left neck LN and retroperitoneal LN dissection was performed on April 28. All resected LNs were proved to contain necrotic tissue and no viable tumor cells pathologically. However, the serum HCG level began to rise again just after the operation. A systemic survey of the whole body revealed no distinct recurrent lesions radiographically. Salvage chemotherapy was started on June 8. Multiple anticancer drugs including vincristine, doxorubicin, methotrexate, etoposide, actinomycin D and carboplatin were given in combination on an outpatient basis. As shown in Fig. 2, however, HCG increased gradually. In late July 1993, a follow-up chest roentgenogram revealed a small coin lesion (8 mm in diameter) in the right lung, and a CT scan confirmed a tumor in segment eight (S8). Additional salvage chemotherapy was not effective for the lung lesion, and a subsequent systemic survey found no other metastatic lesions. Up to this point, the patient had received a total of cisplatin 360 mg/m², etoposide 4.35 g/m², bleomycin 135 mg/m², carboplatin 2.4 g/m², ifosfamide 6 g/m², cyclophosphamide 6 g/m², vinblastine 21 mg, doxorubicin 420 mg/m², methotrexate 1200 mg/m² and actinomycin D 2.5 mg. Considering the patient’s prior heavy treatment, and heart and renal dysfunction, video-assisted thoracoscopic wedge resection of the lung was performed on December 20, when HCG was 2120 mIU/ml and the tumor evident on the chest roentgenography had grown to 3 cm in diameter (Fig. 3). The resected specimen in S8 of the right lung measured 8.5 x 4.5 x 3.0 cm, and microscopically the tumor was shown to contain diffuse infiltration of viable choriocarcinoma cells with both cytotrophoblastic and syncytiotrophoblastic features along with diffuse hemorrhagic necrosis (Fig. 1b).

Because the resected tumor contained viable malignant cells and the serum HCG level remained slightly high one month after the pulmonary operation, adjuvant chemotherapy was added from late January, 1994, to eradicate any residual carcinoma cells. Because the carcinoma cells had already been considered refractory to multiple conventional anticancer drugs including standard-dose or high-dose etoposide, long-term low-dose etoposide treatment was selected. Oral etoposide at 75 mg/day (42.9 mg/m²; 25 mg every 8 h) was given for 21 consecutive days every 5 weeks. Seven days after the beginning of the therapy, the serum HCG level increased slightly, and then decreased to the normal range and remained normal during the therapy for 7 months and thereafter. At present, the patient remains in complete remission 13 months after the end of the final therapy and 3 years after the initial diagnosis.

Discussion

The optimal treatment for patients with “poor risk” GCT remains an important objective of clinical research. Despite the development of effective chemotherapy, the cure rate of “poor risk” GCT is less than 50%. High-dose chemotherapy followed by ABMT has been successful in 10-20% of patients with so called “refractory GCT”. This program has provided a cure in patients who would otherwise die of the disease.

The present patient was classified as “poor risk” in view of the tumor’s extragonadal origin and high HCG values. The patient failed to achieve CR after three courses of first-line BEP therapy.
He received high-dose chemotherapy and ABMT after one cycle of an ifosfamide-containing regimen, and his serum HCG level decreased to the normal value for the first time. However, the serum HCG level began to increase soon after adjunctive surgery, where all the resected specimens were shown to contain necrotic debris, and it continued to rise even though multiple chemotherapy was administered.

The role of surgery in marker-positive patients is controversial. Generally, adjunctive surgery is recommended in patients negative for tumor markers, although recently it has been re-evaluated in highly selected patients. Table I shows the outcome of salvage surgery for chemorefractory patients positive for tumor markers in three recently reported series. Wood et al. reported that all 5 patients with an elevated HCG level had relapse, in contrast to 3 of 10 with increased AFP only. Murphy et al. and Eastham et al. showed that 10/48 (21%) and 6/16 (37%) patients remained disease-free after surgical salvage, respectively. The 16 disease-free patients included 12 with an elevated AFP level and 4 with a mildly elevated HCG level (4.7, 30, 82 and 422 mIU/ml). These might suggest that an elevated AFP level predicts a better prognosis than an elevated HCG level.

Etoposide has become one of the key drugs for treatment of GCT. The present patient had already received a considerably high dose of etoposide before salvage surgery, suggesting that the recurrent tumor was highly resistant to etoposide. As the resected tumor contained viable cells, further therapy was needed, and oral etoposide was selected as adjuvant therapy because (a) the patient had already received every possible effective drug except oral etoposide and was refractory to them, (b) his organ functions were not fully recovered and (c) we expected chronic etoposide to be effective against residual tumors which were resistant to conventionally administered etoposide. Prolonged maintenance of low plasma concentrations (>1 µg/ml) of etoposide is considered to be more important than the peak concentration. Etoposide 25 mg was given every 8 h, with the expectation that a low plasma concentration of the drug would be maintained. Seven days after the start of the therapy, the serum HCG level increased slightly, and then decreased to the normal range, suggesting the presence of residual viable cells after the salvage operation and the effectiveness of oral etoposide.

The present case demonstrated the usefulness of salvage resection for chemorefractory and resectable GCT. A phase II study of daily oral etoposide found a 14% radiographic response in addition to a 14% serological response in patients with refractory GCT. Recently, a promising outcome of oral etoposide as maintenance therapy for patients who are responsive to salvage therapy has been reported. In cases where the tumor burden is small, chronic etoposide might be worthwhile. The usefulness of chronic oral etoposide for patients with GCT as palliation, adjuvant or maintenance therapy should be examined by further clinical trials.

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