Sustainable complete remission in recurrence yolk sac tumor patient treated with tandem high-dose chemotherapy and autologous stem cell

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Summary

A 21-year-old lady diagnosed with Stage 3 ovarian yolk sac tumor (YST) underwent primary cytoreductive fertility sparing surgery, followed by conventional courses of platinum-based chemotherapy and etoposide. Recurrence at cul-da-sac was noted after a short period of remission and secondary debulking performed followed by four cycles of conventional chemotherapy. The patient's disease progressed despite courses of treatments. A joint team management including a hematologist was commenced following the failure of conventional chemotherapies. Two cycles of high-dose chemotherapy (HDCT) with ifosfamide/cisplatin/etoposide (ICE) regimen, followed by autologous stem cell transplantation (ASCT) were given. With this salvage treatment, she remained in complete remission and disease-free for more than 30 months, while maintaining her reproductive function. These approaches appear to be effective as a salvage treatment in selected cases of patients with ovarian germ cell tumor, especially those who failed primary conventional chemotherapy.

Key words: High-dose chemotherapy; Germ cell tumor; Autologous stem cell.

Introduction

Malignant ovarian germ cell tumors (MOGCT) comprise five percent of all ovarian malignancies. Dysgerminoma and yolk sac tumors (YST), account for approximately 20% of MOGCT [1]. YST are aggressive tumors with high mortality and recurrence rates, before the era of effective chemotherapy. The combination regimen with bleomycin/etoposide/cisplatin (BEP) has improved the survival of ovarian YST from 13% to 95% for Stage 1 and 75% for advanced stage [2].

However, the prognosis for chemotherapy-refractory YST is still dismal where 20% of advanced stages may experience progressive disease after BEP chemotherapy [3]. The introduction of combination high-dose chemotherapy (HDCT) and autologous stem cell transplantation (ASCT) in solid tumors appears to have promising favorable outcome for this chemo-refractory tumor. Here, the authors present a case of advanced stage YST, which was chemo-refractory and received combination HDCT and tandem ASCT.

Case Report

A 21-year-old lady presented with sudden onset of lower abdominal pain. Her past medical and gynecologic history was unremarkable. Physical examination revealed a pelvic mass. Ultrasonography and computer tomography (CT) showed complex right ovarian tumor measuring 12 cm, minimal ascites and no enlarged lymph nodes. Tumor markers were as follows: alpha-fetoprotein (AFP): 120423, CA 125: 58.8.

She underwent exploratory laparatomy, right salphingo-oophorectomy, omentectomy, appendectomy, and pelvic lymphadenectomy. The intraoperative findings included large right ovarian tumor with multiple tumor deposits at right pelvic peritoneum, uterine surface, rectal serosa, and omentum. An optimal debulking surgery was performed and staged as FIGO Stage 3C. Final pathology revealed YST. Adjuvant chemotherapy with PE (cisplatin/etoposide) regimen was given. AFP levels reduced during six courses of chemotherapy (including two courses of consolidation chemotherapy). After completed adjuvant chemotherapy, AFP was elevated, thus courses of PE regimen commenced. She was disease-free for only two months, evidenced by normalization AFP and negative CT scan findings.

An elevation of AFP level was noted after short remission and CT scan showed abnormal soft tissue lesion at pre-sacral region (Figure 1). Secondary debulking performed with intraoperative findings of pelvic recurrence at cul-de-sac. Histopathology confirmed metastatic YST. Salvage chemotherapy was commenced after surgery. She had four cycles of carboplatin (AUC 5) and etoposide. Unfortunately, her disease progressed with persistent elevation of AFP.

In view of her incurable disease, HDCT and ASCT was suggested after discussion with the hematologist. Whole body fluorine-18 2-fluoro-2-deoxy-D-glucose-positron emission tomography (FDG-PET) scan was performed for tumor assessment which revealed no evidence of recurrence. Chemotherapy regimen (carboplatin/etoposide) commenced and recombinant human granulocyte colony stimulating factor (subcutaneous RhG-CSF five ug/kg) was given every 12 hours, after completing chemotherapy. This is crucial for stem cell mobilization.

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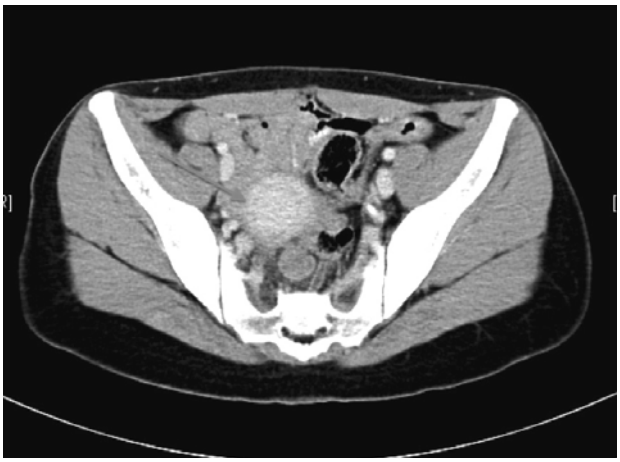

Figure 1. — Computer tomography scan of pelvic showing recurrence tumor at the pre-sacral region.

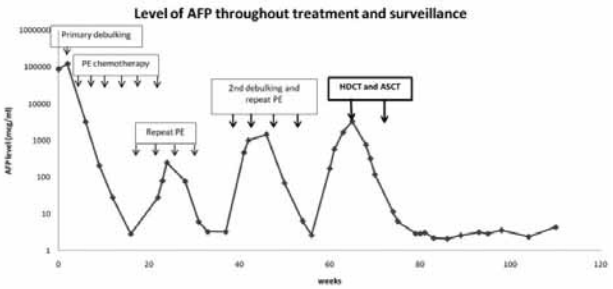

Figure 2. — A graphical representation of AFP level throughout the treatment and disease surveillance. The x-axis represents weeks of AFP taken from its initial presentation. The y-axis represents serum concentration of serial AFP.

Stem cell collection was performed on day 16 when the total white cell count reached > 10,000/ul. A double lumen catheter was inserted and Baxter-Fenwal CS 3000 cell separator was used for stem cell apheresis. A total of ten liters of whole blood was processed and CD34+ cells dose yielded which was separated into two bags and cryopreserved for future uses. Pre-transplant evaluation included cardiac blood pool image study and pulmonary diffusion capacity.

The first course of HDCT with ifosfamide/carboplatin/etoposide (ICE) was given for five days. Thawed autologous stem cells were transfused after completed ICE regimen. Recombinant human granulocyte-colony stimulating factor (RhG-CSF) (5ug/kg) was given to accelerate myeloid recovery. Leucocyte depleted blood components were transfused as indicated. The patient developed grade ¾ febrile neutropenia. The neutrophil engraftment documented by absolute neutrophil count > 500/ul was achieved at day ten. The sustained platelet recovery with transfusion-independent and platelet count > 20,000/ul was achieved at day 13. Her AFP level dropped to 11.73 ng/ml two weeks after ASCT

Her general condition and hematological profile recovered rapidly. In terms of her highly-chemosensitive disease with short duration of response, second ASCT as tandem treatment was commenced two months later with the exactly similar conditioning regimens. The use of growth factor and supportive care was similar to the first ASCT. The myeloid and platelet engraftments were achieved on days ten and 13, respectively. She was then discharged and followed up regularly as an outpatient . She had normalization of performance status and resumed her regular menstrual cycle. She did not have any premature menopausal symptoms and normal AFP level throughout the post-transplant period (Figure 2). She has now been disease-free for three years.

Discussion

YST commonly presents within the second and third decades of life. It is highly-aggressive and frequently shows early intra-abdominal dissemination and metastasis. Most of YST carry worst prognosis when compared with other MOGCT. They usually secrete AFP, which can be reliably used in monitoring effectiveness of treatment commenced and detection of recurrence [1, 3].

With the advent of platinum-based chemotherapy since the 1970's, the extent of surgery required has been progressively reduced. Whenever possible, preservation of fertility is considered. Similar menstruation and fertility rates are seen in those with ovarian YST after combination of fertility-sparing surgery and adjuvant chemotherapy when compared with the healthy population. An optimal cytoreduction surgery, presence of ascites at diagnosis, intra-peritoneal dissemination lesion, and normalization of AFP half-life were noted to have a significant effect on overall survival [4-6].

Approximately 20%-30% of the MOGCT that receive primary therapy for advanced stage will relapse or have incomplete response. Options of salvage treatment that may show curative potential in these groups are either by conventional chemotherapy or HDCT. Conventional chemotherapy only achieves 10%-40% of long-term remission, however these patients may ultimately succumb to the disease [7].

Aside from using of HDCT for patients with relapse, it is also being evaluated as first line treatment in poor prognosis disease of testicular germ cell tumor. Early HDCT studies reported longer survival rates of 15%-25%, but treatment related toxicity was formidable and treatment related death occurred in approximately ten percent of the patients [7]. While administration of HDCT alone showed severe and lethal myelosuppression, combination with bone marrow transplantation (BMT) or ASCT, and availability of hemopoeitic growth factors were used to overcome severe adverse effects of HDCT. ASCT is more favorable compared with BMT as it avoids surgical procedures and convenience for the patient.

Helw *et al*. in his review on disease-free survival for germ cell tumors treated with HDCT, revealed that long-term disease-free survival rate for refractory or heavily pre-treated GCT, first relapse GCT, and those poor-risk groups was respectively 13% (range 0%-35%), 45% (range 21%-67%), and 52% (range 36%-84%) [3]. This is supported by a German group that compared GCT patients treated with or without HDCT. The analysis showed that the benefit of HDCT was slightly more pro-

nounced and that the hazard ratio was more favorable in terms of event-free survival and overall survival [8].

The usage of two or more HDCT drugs is widely investigated. The rationale for this approach is an assumption that upfront uses of multiple HDCT may induce cell death in higher fraction of sensitive tumor cell before drug resistance develops. The choices of chemotherapic agents used for HDCT in treating MOGCT are still focused on the usual chemotherapy agents use in ovarian cancer. Among the evaluated regimens are TICE (paclitaxel/ifosfamide/cisplatin/etoposide) where complete response was seen in 56%, half of patients are free of disease at the median follow-up at > 40 months [7, 9]. This is supported by the retrospective review of advanced GCT where disease progressed after platinum-based chemotherapy. Two main active high-dose density drugs used in this setting were carboplatin and etoposide. Complete remission was observed in 63% at a median follow-up of 48 months. At two years, 90% of these patients remained free of disease [7, 10].

Phase 3 trials comparing single and sequential HDCT in relapsed or refractory disease failed to show the superiority of single HDCT regimen. One-year event-free survival rate for sequential HDCT was 55% compared with single HDCT of 37%. Further strategies to incorporate ≥ two high-dose cycles of chemotherapy may yield promising results in the future, thus becoming the preferable option for those with a second relapse [7]. In the present patient, a second cycle of HDCT with ASCT was administered as she was in the high-risk group of relapse, and these prolonged her remission.

Late complications of multiple courses of chemotherapy are of great concern as GCT patients are within reproductive age. Risk of hypothyroidism, infertility, early menopause, and secondary malignancies should be assessed during surveillance. The risk of secondary myeloid leukemia reported is two to three percent of cases treated with HDCT. Improvement of supportive care and less pre-treatment may help to reduce these morbidities [7]. The present patient did not experience any late adverse effects after treatment.

There is growing evidence on the role of combination HDCT and ASCT supported with hematopoeitic growth factor benefits in YST who failed conventional primary chemotherapy. Most of the studies and guidelines on GCT management with HDCT concentrate on testicular germ cell malignancy and further studies on recurrence MOGCT failed primary treatment managed with HDCT should be implemented in order to prolong survival and disease-free in these reproductive-aged women.

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