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Case report

Gemcitabine after bone marrow transplantation for refractory juvenile granulosa cell tumor

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A 19-year-old woman with refractory juvenile granulosa cell tumors had persistent disease after PVB (cisplatin, vinblastine and bleomycin) and multiple high doses of ICE (ifosfamide, carboplatin and etoposide) with peripheral stem cell support. She achieved stable disease for 4 months with low dose intensity gemcitabine of 500 mg/m^2/week. The planned dose had been 1250 mg/m^2/week. The dose intensity was limited by myelosuppression especially thrombocytopenia. The use of thrombopoietic, in addition to erythropoietic and myelopoietic, agents may permit higher dose intensity of gemcitabine after bone marrow ablative therapy with resulting greater anti-tumor activity. [© 1998 Lippincott Williams & Wilkins.]

Key words: Gemcitabine, juvenile granulosa cell tumor, post bone marrow transplantation.

Introduction

Granulosa cell tumors constitute 1–3% of ovarian neoplasms. Most of them are of the adult subtype. The juvenile subtype, which was first classified by Scully *et al.*, is usually found in women under the age of 30 and has a different clinicopathological profile.[1] The prognosis of juvenile granulosa cell tumor (JGCT) with early stage of disease is favorable. Surgery is the cornerstone of treatment. Beyond FIGO stage Ia, adjuvant chemotherapy or radiotherapy is recommended. Platinum-based chemotherapy is the standard treatment in advanced or recurrent disease.

We report herein a case of a patient with recurrent JGCT who had platinum-based chemotherapy and high dose chemotherapy with stem cell support. She then received gemcitabine with 4 months of stable disease and good non-hematologic tolerance.

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Case report

A 19-year-old, G_0P_0, white female was diagnosed with stage Ia, JGCT, in 1994. She underwent left unilateral salpingo-oophorectomy. After surgery, she received no adjuvant therapy as she was felt to have good disease prognosis. She did well until October 1996, when she developed abdominal distension and pain. She was then referred to the University of Texas MD Anderson Cancer Center. On physical examination, her abdomen was markedly distended with ascites and a large abdominal mass was palpable. Her CA-125 was 66.5 mIU/ml. Alphafetoprotein and β-HCG were normal. There was no evidence of metastatic disease on her chest X-ray. The computerized tomography (CT) scan of the abdomen and pelvis confirmed an extensive tumor in the pelvis and in the peritoneal cavity consistent with recurrent JGCT. She had an exploratory laparotomy in October 1996 which revealed multiple omental masses, three perihepatic nodules, a large right pelvic mass (9×7 cm), a 6×4 cm mass at the splenic hilum and multiple implants in the pelvis (diameter less than 1 cm). All lesions, except for the splenic hilar mass and the multiple implants in the pelvis, were removed. The pathology confirmed recurrent JGCT of the ovary. She subsequently received four courses of PVB (cisplatin, vinblastine and bleomycin) chemotherapy as per Colombo *et al.*,[2] from October 1996 to January 1997, achieving a minor response. Afterwards she was treated with high dose ICE (ifosfamide, carboplatin and etoposide) and autologous peripheral blood stem cell support.[3] She received four courses of this treatment, with the last course ending in May 1997. The patient achieved a partial remission, as demonstrated by serial CT scans of the abdomen and pelvis,

with a plateau in response. The patient was then started on gemcitabine with a planned dose schedule of 1250 mg/m^2 on day 1, 8 and 15 every 28 days. The patient received gemcitabine for 18 weeks and should have received 14 doses. She received 11 doses and the deleted doses are designated as 0 mg. The median dose was 500 mg/m^2 [95% confidence interval (CI): 370–800 mg/m^2] with a range of 0–1250 mg/m^2. Dose reductions and omissions were necessitated by myelosuppression. The median nadir platelet count was 25 000 μl (range 13 000–49 000). The median nadir granulocyte count was 1000 μl (range 700–1700). The median hemoglobin over 4 months was 9.9 g/dl (range 7.4–11.2). The patient received prophylactic granulocyte colony stimulating factor and after 2 months of treatment erythropoietin support was added. However, no thrombopoietic cytokines were available for her at that time. Erythropoietin increased her median pre-erythropoietin hemoglobin from 7.9 g/dl to a post-erythropoietin median hemoglobin level of 10.0 g/dl. She had no significant non-hematologic toxicity during this gemcitabine treatment, and resumed full time university studies, swimming and aerobic exercise. The patient had stable disease as evidenced by CT scan of the abdomen and pelvis. Gemcitabine was stopped in November 1997 due to progression of disease.

Discussion

Data on advanced or recurrent JGCT are scanty since most JGCT present at early stage.[1] Radiotherapy is established as an effective modality for treatment of adult-type GCT. However, its role in the treatment of JGCT is still controversial.[2] At the present time platinum-based chemotherapy is the standard systemic treatment in advanced or recurrent JGCT.[4,5] Gershenson *et al.* reported five responses (two complete and three partial) among six patients with poor prognosis sex cord-stromal ovarian tumors treated with BEP (bleomycin, etoposide and cisplatin).[4] The authors noted that the responses were not durable. Most studies demonstrate worse prognosis among patients with advanced or recurrent JGCT.[1,2,4] Only few anecdotal reports showed long-term survival.[6–8] In platinum refractory JGCT, high dose chemotherapy is one of the options. Paclitaxel is another promising approach with some reports of paclitaxel salvage therapy in platinum-resistant ovarian sex cord-stromal tumors.[5,9]

Gemcitabine (2′, 2′-difluorodeoxycytidine), a novel nucleoside analog, has shown overall response rates of 19% as a single agent in the treatment of platinum-resistant ovarian cancer.[10] There was one case report of a short-term response with gemcitabine in a platinum-resistant ovarian germ cell tumor.[11] Larry Einhorn has reported (personal communication) the activity and safety of gemcitabine in patients with refractory testicular cancer after relapse from high dose chemotherapy and bone marrow transplantation. The fact that gemcitabine led to stabilization of a poor prognosis JGCT in a patient after bone marrow transplantation, despite severely compromised dose intensity (one half of the planned one), suggests that further studies to evaluate its activity in sex-cord stromal ovarian tumors are warranted. The introduction of interleukin-11 may permit higher dose intensity of gemcitabine in this setting and perhaps a greater anti-tumor activity.

Conclusion

This is a patient with refractory recurrent JGCT who had failed PVB and high dose ICE chemotherapy, and then achieved stabilization of progressive disease for 4 months with low dose intensity gemcitabine chemotherapy. The patient tolerated treatment well without significant non-hematopoietic side effects. The use of a thrombopoietic agent may permit higher dose intensity and perhaps a superior anti-tumor response. Further studies of gemcitabine in this setting are warranted.

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