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Clinical report

Remission of refractory gestational trophoblastic disease with high-dose paclitaxel

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High-risk metastatic gestational trophoblastic disease (GTD) in patients who have failed primary chemotherapy has a very poor prognosis. About 25% of women with high-risk metastatic disease become refractory to EMA-CO (etoposide, methotrexate, actinomycin-D, cyclophosphamide and vincristine) and fail to achieve a complete remission. Currently, there is no standard salvage chemotherapeutic regime for EMA-CO failure. Paclitaxel, a taxane analog extracted from the bark of the western yew (*Taxus brevifolia*), has shown antitumor activity in a variety of cancer cell lines. High *in vivo* efficacy was confirmed in phase II trials, especially for breast and epithelial ovarian cancer patients. Recently, two *in vitro* studies have shown that paclitaxel is a highly effective antineoplastic agent in choriocarcinoma cell lines. We present the first clinical report of a serologic remission with high-dose paclitaxel (250 mg/m^2 i.v. infusion over 24 h every 3 weeks) of a highly refractory GTD in a patient who developed brain metastasis after multiple combined chemotherapeutic regimens. The patient tolerated paclitaxel with granulocyte colony stimulating factor support very well. The remission with paclitaxel in this patient confirms its preclinical activity in high-risk, refractory GTD.

Key words: Gestational trophoblastic disease, paclitaxel.

Introduction

Patients with high-risk metastatic gestational trophoblastic disease (GTD) who have failed primary chemotherapy have a very poor prognosis. Surgical extirpation of drug-resistant foci of disease must be considered in patients with limited systemic metastases.[1]

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Before cisplatin and etoposide were available, salvage regimens for patients failing the standard combination chemotherapy MAC (methotrexate, actinomycin-D and cyclophosphamide) were rarely successful. PVB regimen (cisplatin, vinblastine and bleomycin) was reported by Azab *et al.* to produce high rates of complete remission in patients with refractory GTD,[2] others have observed few remissions using this regimen unless adjuvant surgical resection or radiation therapy were used as well.[3,4] The toxic effects from this regimen are often severe among heavily pretreated patients.[3,4]

Regimens containing etoposide with and without cisplatin have definite activity in patients with refractory GTD. The EMA-CO regimen (etoposide, methotrexate, actinomycin-D, cyclophosphamide and vincristine) and EMA alternating with etoposide and cisplatin (EMA-CE) have been successfully used as salvage therapy in selected patients.[5,6] Unfortunately, about 25% of women with high-risk metastatic disease become refractory to EMA-CO and fail to achieve a complete remission.[7] Currently, there is no standard salvage chemotherapy regimen for EMA-CO failure. Etoposide and platinum combination chemotherapy is active in the treatment of refractory GTD, but has significant hematologic and renal toxicity when used as salvage therapy.[8–10] Another alternative is to give cisplatin in the EMA-POMB regimen (EMA alternating with cisplatin, vincristine, methotrexate, bleomycin).[7] A new regimen PEBA (cisplatin, etoposide, bleomycin and doxorubicin) was recently reported by Li-Pai *et al.* and was found to be effective in

EMA-CO-resistant disease.[11] A complete remission (CR) was achieved in 96% of the women and 73% had a sustained CR that lasted at least 1 year. In a small study, ifosfamide as single agent and in combination with etoposide and cisplatin (VIP) showed promise as salvage therapy in GTD.[12] The combination of ifosfamide, carboplatin and etoposide (ICE) has synergistic activity in preclinical studies.[13] High-dose ICE with autologous bone marrow transplantation has been reported to cure a number of patients with platinum-resistant germ cell tumors and metastatic GTD.[14]

Paclitaxel, at taxane analog extracted from the bark of the western yew (*Taxux brevifolia*), attracted interest because of its unique mechanism of action. It promotes the polymerization of tubulin and inhibits the disassembly of microtubules.[15,16] Paclitaxel has shown antitumor activity in multiple clinical trials in cancer of the ovary, breast, head and neck, lung, and gastrointestinal tract.[17] In epithelial ovarian cancer, multiple phase II trials have demonstrated the antitumor activity of paclitaxel in both platinum refractory and advanced recurrent disease at various dose schedules.[18–20]

This is the first clinical report of a patient with a serological partial remission of a highly refractory GTD with high-dose paclitaxel.

Case report

A 37 year old African-American woman, gravida 2, para 2, was found in 1989 to have persistent, nonmetastatic GTD which occurred after a molar pregnancy. She had remission with four cycles of methotrexate and leucovorin. Unfortunately her disease recurred 2 years later manifesting with amenorrhea and a rising serum βhCG level. She received three cycles of methotrexate and leucovorin. The serum βhCG level initially decreased but then reached a plateau. Accordingly, chemotherapy was changed to actinomycin D. Four cycles were administered, inducing complete remission. However, 2 months later the serum βhCG level once again began to rise. The metastatic investigations failed to demonstrate any lesions. However, she had empirical total abdominal hysterectomy in an attempt to eradicate any cryptic residual tumor in the uterus. The pathologic examination of the uterus showed no tumor and the serum βhCG remained abnormal. Therefore she also received three cycles of MAC, but without significant serologic response. She was then referred to the University of Texas MD Anderson Cancer Center in September of 1992 for further treatment.

On our initial evaluation, she had asymptomatic GTD. The metastatic surveys including MRI of the brain and pelvis, computed tomography (CT) scan of the abdomen, and bone scan were unremarkable. Her serum βhCG level was 260 mIU/ml. The WHO score was 9 (excluding ABO blood groups).[21] She was treated with a custom regimen consisting of high-dose methotrexate, vincristine and etoposide alternating weekly with bleomycin, 5-fluorouracil and cisplatin (Kavanagh, personal communication). She received seven courses of this regimen and went into complete remission. However, 3 months later the serum βhCG level rose again to 49 mIU/ml. The only suspicious gross disease was found by the CT scan of the abdomen and pelvis which showed left hemorrhagic ovarian cyst and hypervascularity of the vaginal cuff. In July of 1993 she underwent exploratory laparotomy with bilateral salpingo-oophorectomy and excision of the vaginal apex nodule. There was no evidence of intra-abdominal metastasis. The histologic examination of all resected tissue showed no malignancy. Postoperative serum βhCG level was 70 mIU/ml. At this time she elected to receive no further treatment.

In May of 1994 she had a transient episode of speech arrest and deviation of head and neck to the right side. MRI of the brain showed a 2 cm mass in the left posterior frontal lobe. CT scan of the chest showed a single 2.5 cm diameter nodule in the lower lobe of the right lung. Her serum βhCG level was 720 000 mIU/ml. Since only a single brain lesion was detected it was resected. The pathologic examination of resected brain tissue revealed metastatic choriocarcinoma. The serum βhCG level dropped only to 45 477 mIU/ml. She started treatment with high dose paclitaxel 250 mg/m^2 i.v. infusion over 24 h every 3 weeks. Granulocyte colony stimulating factor (G-CSF) 300 μg (approximately 5 μg/kg) was administered s.c. daily for 10 days starting 24 h after the completion of paclitaxel infusion. She received four cycles of paclitaxel and had a serologic partial response (serum βhCG level declined to less than 1/10th of the initial value, i.e. a drop of 1-log). The serum βhCG level dropped from 45 477 to 2 332 mIU/ml but then reached a plateau. Accordingly, paclitaxel was stopped. She tolerated this dose schedule of paclitaxel with G-CSF support very well. The only non-hematologic toxicity was sensory neuropathy of her lower extremities which resolved after stopping of paclitaxel. A follow-up of MRI of the brain revealed no evidence of recurrent disease in the brain.

Discussion

Although the majority of patients with metastatic GTD will be cured, there remains a subset of patients who demonstrate persistent or recurrent disease after aggressive multi-agent chemotherapy. Brain metastases which develop during or after systemic therapy are a particularly ominous sign. Such high-risk patients require special strategies including new therapeutic agents.

Paclitaxel has shown activity in a variety of cancer cell cultures.[22] High *in vivo* efficacy was confirmed in phase II trials, especially for breast and ovarian cancer patients.[20,23] Efficacy of paclitaxel in heavily pretreated patients could be explained by its unique mechanism of action. Paclitaxel inhibits cell division by promoting the assembly of microtubules and stabilizing tubulin polymers by preventing their depolymerization.[22] Paclitaxel-treated cells exhibit characteristic bundles of microtubules that are not usually associated with the microtubule organizing center, the centrosome. Mitosis is inhibited because the two centrosomes, which form the spindle poles during metaphase, do not have the necessary microtubules associated with them. Therefore mitotic cells (M phase) are sensitive to paclitaxel, whereas interphase cells (G_1, S and G_2 phase) are resistant.[24]

Although several tumor types have been evaluated, to our knowledge no information has been published about the clinical value of paclitaxel in choriocarcinoma. Recently, Marth *et al.* have shown that proliferation of choriocarcinoma cell lines JAR and BeWo was inhibited by paclitaxel in a dose-related manner and 1–3 nmol/l was sufficient to achieve 50% growth reduction.[25] Paclitaxel was found to be about 3-fold more effective in these gestational trophoblastic tumor cells than in six ovarian carcinoma cell lines. In addition to growth inhibition, cell differentiation was also induced by paclitaxel, as shown by increased human chorionic gonadotropin secretion and altered morphologic features. They concluded that paclitaxel is a highly effective antineoplastic agent in choriocarcinoma cells. Koechli *et al.* reported the activity of 10 drugs, including paclitaxel, *in vitro* in the two choriocarcinoma cell lines JAR and JEG-3 by the ATP cell viability assay and demonstrated that the three most active drugs were VP-16, paclitaxel and vincristine.[26]

This is the first report of serologic remission with paclitaxel of a highly refractory GTD in a patient who developed brain metastasis after multiple combined chemotherapeutic regimens. The patient tolerated paclitaxel very well with minor peripheral neuropathy. The remission with paclitaxel confirms its preclinical activity in GTD. Further studies of paclitaxel in patients with GTD are warranted.

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