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Case report

Antitumor activity of paclitaxel after failure of high-dose chemotherapy in a patient with late relapse of a non-seminomatous germ cell tumor

Arthur Gerl[1] and Wolfgang Wilmanns[1,2]

[1]Medizinische Klinik III, Klinikum Grosshadern, University of Munich, 81377 Munich, Germany. Tel: (+49) 89 7095 1; Fax: (+49) 89 7095 8875. [2]GSF Forschungszentrum für Umwelt und Gesundheit, Munich, Germany.

Although cisplatin-based chemotherapy considerably improved the clinical outcome of patients with metastatic germ cell tumors, approximately 20% of patients fail to achieve a durable remission to first-line treatment and require effective salvage treatment. As only 20–30% of patients can expect disease-free long-term survival after conventional salvage treatment, an increasing proportion of patients has been referred to high-dose chemotherapy with autologous stem cell rescue during recent years. However, high-dose chemotherapy still fails to cure a considerable number of patients, emphasizing the need to continue the search for new active drugs. We report here the case of a patient with late relapse of a non-seminomatous germ cell tumor who failed to respond to high-dose chemotherapy after heavy pretreatment with 11 cycles of cisplatin-based chemotherapy. The patient received paclitaxel for symptomatic disease with hepatic and pulmonary metastases, and attained a partial remission. Despite the heavy pretreatment, hematologic toxicity of paclitaxel was tolerable. As recent reports described responses to single-agent paclitaxel in a quarter of pretreated patients with germ cell tumors, further clinical trials seem justified to study the role of paclitaxel in combination regimens against this cancer type.

Key words: Chemotherapy, germ cell tumor, late relapse, paclitaxel, salvage treatment.

Introduction

Approximately 20% of male patients with metastatic germ cell tumors have an incomplete response to first-line treatment or relapse from a complete remission and need effective salvage treatment. However, only approximately 25% of this patient group can expect long-term disease-free survival with conventional salvage chemotherapy.[1,2] Although high-dose chemotherapy may improve results, a considerable proportion of patients still fails to achieve a durable remission,[3,4] underscoring the necessity to continue the search for new active drugs. We studied the antitumor activity and side effects of paclitaxel in a male patient with late relapse of a non-seminomatous germ cell tumor after heavy pretreatment and failure of high-dose chemotherapy.

Correspondence to A Gerl

Case report

A 32-year-old man with a history of bilateral cryptorchism underwent partial resection of an abdominal mass in March 1990; histologic examination revealed embryonal carcinoma with seminomatous components. The right testicle was small but without any lesion, while no left testicle was found either in the left hemiscrotum or at abdominal surgery. Postoperatively serum α-fetoprotein (AFP) and lactate dehydrogenase (LDH) were elevated at 12 660 ng/ml and 337 U/l, respectively; human chorionic gonadotropin (HCG) was within the normal range. The patient underwent chemotherapy elsewhere and received four cycles of cisplatin, etoposide and bleomycin, and one further cycle consisting of vinblastine, ifosfamide and cisplatin. After normalization of AFP, a small residual mass containing necrosis/fibrosis was resected. The patient remained without evidence of disease for almost 4 years.

In May 1994 an increase of HCG to 424 U/l was noted, while AFP remained within normal limits. No mass was found at the right testicle. Moreover, thoracic and abdominal computer tomography scans did not reveal any lesions, but magnetic resonance

imaging disclosed a mass in the anterior abdominal wall and multiple hepatic lesions. Four cycles of salvage chemotherapy consisting of etoposide, ifosfamide and cisplatin were administered. HCG returned to normal and magnetic resonance imaging revealed a partial radiological remission. As tumor residuals were deemed unresectable, no further treatment was given, but the patient underwent close follow-up. Four months later HCG began to rise and regrowth of the persistent radiologic lesions was documented. The patient again underwent salvage chemotherapy consisting of etoposide, ifosfamide and cisplatin, and after the first of two cycles HCG returned to normal. High-dose chemotherapy (carboplatin 1.5 g/m^2, etoposide 2.4 g/m^2 and cyclophosphamide 6.0 g/m^2) with autologous stem cell rescue was given. Four weeks later an increase of HCG was observed and 6 weeks after high-dose chemotherapy a regrowth of hepatic lesions was documented. During the following 2 months HCG and LDH rose to 700 and 2300 U/l, respectively. Magnetic resonance imaging revealed a large number of hepatic lesions up to 8 cm and chest X-ray disclosed multiple pulmonary metastases up to 3 cm. The patient deteriorated rapidly. He lost weight and developed pain at the right upper quadrant of his abdomen.

Despite the dismal prognosis, he desired further treatment and gave his consent to chemotherapy with paclitaxel which was applied at a dose of 250 mg/m^2 as a 5 h infusion. The dose was increased in 25 mg/m^2 steps to 300 mg/m^2 during the following cycles which were given every 3 weeks in an outpatient setting. Two weeks after the first cycle the patient regained weight and his pain resolved. Re-evaluation after three cycles showed a shrinkage of hepatic lesions of approximately 80% and only minor pulmonary residuals up to 5 mm were visible on chest X-ray. Serum LDH and HCG dropped to 277 and 211 U/l, respectively. Another five cycles of paclitaxel were administered. After the eighth cycle LDH and tumor markers HCG and AFP began to rise, and magnetic resonance imaging showed new hepatic lesions, while pulmonary residuals remained stable. The patient still had a good clinical performance status. Treatment with paclitaxel was discontinued and the patient again received cisplatin-based chemotherapy.

Despite the heavy pretreatment, paclitaxel was tolerated relatively well. After the first cycle the patient developed WHO grade III leucopenia and grade II thrombocytopenia. Despite dose escalation, only grade II leucopenia and grade I thrombocytopenia were documented after the following cycles. At the end of treatment with paclitaxel the patient developed grade III peripheral neuropathy.

Discussion

A recent study by Motzer *et al.* showed a response rate of 26% to single-agent paclitaxel in 31 patients with limited pretreatment with a median number of four cycles (range: two to six) of platinum-based chemotherapy.[5] Responses were observed among patients with incomplete response to primary treatment and patients with primary mediastinal germ cell tumors; these clinical characteristics are known predictors of poor outcome of salvage treatment. However, none of five patients who had received prior treatment with high-dose chemotherapy achieved a response to paclitaxel. In a recent clinical trial by Bokemeyer *et al.* a similar response rate to paclitaxel of 25% was observed in 24 more heavily pretreated patients.[6] Before treatment with paclitaxel, patients had undergone a median of seven cycles (range: three to 12) of platinum-based chemotherapy. Twelve patients had been pretreated with high-dose chemotherapy, two of whom achieved an objective response to paclitaxel.

It is worth emphasizing that the patient described above had a late relapse of his germ cell tumor. Two recent reports described that relapses of germ cell tumors beyond 2 years from discontinuation of primary therapy show a high resistance to chemotherapy.[7,8] Considering the poor results of chemotherapy in patients with late relapses and the heavy pretreatment including high-dose chemotherapy of our patient, the response to paclitaxel is remarkable. Clinical trials currently study the role of paclitaxel in combination regimens and an expanding role for paclitaxel in the salvage treatment of germ cell tumors is anticipated.[5,6]

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