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Clinical report

Phase II study of bendamustine in patients with relapsed or cisplatin-refractory germ cell cancer

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Despite generally high cure rates in patients with metastatic germ cell cancer, patients with incomplete response to first-line cisplatin-based chemotherapy or with relapsed disease following high-dose salvage therapy exhibit a very poor prognosis. We investigated the efficacy and toxicity of bendamustine, a bifunctional alkylating benzimidol derivative with only partial cross-resistance to other alkylating agents such as ifosfamide or cyclophosphamide. Nineteen patients with cisplatin-refractory germ cell tumors (GCT) or relapse after high-dose chemotherapy plus autologous stem cell support were treated with bendamustine at a dose of 120 mg/m^2 on 2 consecutive days at 3 week intervals. Patients had received a median of 9 (range 4–20) platinum-containing treatment cycles prior to bendamustine and 13 patients (68%) had previously received carboplatin/etoposide-based high-dose chemotherapy. One patient achieved a partial remission of only 6 weeks duration. No other responses were seen. Toxicity was low with one patient developing WHO grade 3 thromboyctopenia as the only WHO grade 3/4 toxicity observed. Hematologic toxicity was similar in patients pretreated with and without high-dose chemotherapy plus autologous stem cell support. We conclude that bendamustine has little or no clinically relevant activity in patients with cisplatin-refractory GCT or relapsed disease after high-dose chemotherapy. [© 2000 Lippincott Williams & Wilkins.]

Key words: Bendamustine, cisplatin-refractory germ cell cancer, palliative chemotherapy, relapse.

Introduction

Today, approximately 70–80% of patients with metastatic germ cell cancer can be cured with cisplatin-based combination chemotherapy.[1,2] Of those patients relapsing after first-line chemotherapy, only 20–40% will achieve long-term survival following platinum-containing standard-dose or high-dose salvage chemotherapy. Patients progressing during or relapsing after salvage chemotherapy exhibit an extremely poor prognosis.[3,4] The identification of new drugs with significant antitumor activity in these heavily pretreated patients, who most often have received high-dose chemotherapy with autologous stem cell support, remains a subject for clinical investigations. Phase II studies in cisplatin-refractory patients have demonstrated activity for orally administered, daily low-dose etoposide, and more recently paclitaxel and gemcitabine. Overall, responses were observed in about 20% of intensively pretreated patients with these agents.[5–9]

Bendamustine hydrochloride, a bifunctional alkylating agent, is a benzimidol derivative whose cytotoxic activity is based on cross-linking of DNA single and double strands. It was developed in the early 1960s in

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the former East Germany, and was selected for further preclinical and cinical evaluation because of its promising *in vitro* antitumor activity in transplantable animal tumor models.[10–12] Bendamustine was successfully administered to patients with multiple myeloma, and has been evaluated in a variety of solid and lymphoid malignancies since then.[13]

In vitro data, obtained by Strumberg *et al.*, demonstrated that bendamustine has only partial cross-resistance to cyclophosphamide, cisplatin or melphalan, which provides the rationale for the evaluation of bendamustine in patients pretreated with alkylating agents.[14]

The present study examined the feasibility and activity of bendamustine in heavily pretreated patients with refractory germ cell cancer.

Patients and methods

Eligibility requirements included the diagnosis of germ cell cancer with evidence of tumor progression or relapse after at least two previous cisplatin-based chemotherapies or after salvage high-dose chemotherapy with autologous stem cell support. Patients with disease progression during their initial induction chemotherapy or during salvage therapy were also eligible. Additional inclusion criteria were the presence of bidimensionally measurable disease and/or elevated tumor markers, a Karnofsky performance status $\geqslant$60%, as well as adequate hematologic (WBC $>2500/\mu$l, platelets $>75\,000/\mu$l), renal (creatinine clearance >60 ml/min) and liver function (bilirubin $\leqslant$1.5-fold upper normal value; liver enzymes $<$3-fold upper normal value). No other concomitant chemotherapy, radiotherapy or experimental medication was allowed. All patients gave their informed consent. The study was approved by the University of Tübingen Ethics Committee.

Bendamustine was administered as a 1-h infusion of 120 mg/m^2 on days 1 and 2, repeated every 3 weeks. Concomitant antiemetic therapy included 5-HT$_3$ antagonists as well as dexamethasone. A dose reduction of 50% was planned in case of WHO grade IV thrombocytopenia, granulocytopenia or neutropenic fever. No routine use of granulocyte colony stimulating factor (G-CSF) was recommended, but G-CSF could be given on an individual basis in instances of severe neutropenia. For non-hematologic toxicities, 25 and 50% dose reductions were planned in case of WHO grade III or IV organ toxicity, respectively. All patients were treated on an outpatient basis.

Response and toxicity were graded according to WHO criteria.[15] In addition, reduction of the size of a tumor and normalization of previously elevated tumor markers was considered a partial remission with tumor marker normalization (PR$^-$). A greater than 50% reduction of previously elevated tumor markers during bendamustine therapy was also considered a favorable response. All patients were scheduled for at least two cycles of bendmustine in order to be eligible for response assessment. Therapy was continued in patients with tumor response or disease stabilization for at least two more cycles after achievement of the best response or the occurrence of severe toxicity. Survival and follow-up time were calculated from the beginning of bendamustine therapy until the date of death and date of last follow-up, respectively.

Results

Nineteen patients were entered into the study between August 1998 and July 1999. Patient characteristics are listed in Table 1. A total of 36 cycles of bendamustine were applied with a median of 2 cycles (range 1–3) per patient. Most patients presented with lung and lymph node metastases. However, six patients (32%) had liver involvement and three (16%) had brain metastases. Seven patients (37%) had relapsed later than 2 years following initial therapy and 12 patients (64%) were considered to have platinum refractory or absolutely platinum refractory disease.[16] All patients were heavily pretreated with a median number of 9 (range 4–20) standard-dose cisplatin-containing chemotherapy cycles prior to bendamustine therapy. Cyclophosphamide and/or ifosfamide were administered to all patients during previous chemotherapy. Thirteen patients (68%) had previously received carboplatin/etoposide-based high-dose chemotherapy with autologous stem cell support. In addition, 12 (63%) patients were pretreated with paclitaxel and 7 (37%) with gemcitabine.

Only one patient achieved a marker-negative partial remission for a short, 6-week time period following the first cycle of bendamustine. Disease progression occurred during the third cycle of therapy. This patient was previously treated for a gonadal primary germ cell cancer with multiple retroperitoneal lymph node metastases. He had received cisplatin-containing standard chemotherapy as first-line therapy and high-dose chemotherapy with autologous stem cell support for relapsed disease. No further responses to bendamustine were achieved. All other patients progressed during the first or second cycle of therapy.

Bendamustine was well tolerated in this patient population (Table 2). Nausea/vomiting, fever and diarrhea were the main non-hematologic side effects,

Table 1. Patient characteristics ($n=19$)

No. patients included and assessable	19
Median age (years)	30 [24–56]
Gonadal/retroperitoneal/mediastinal primary	12/6/1
Sites of metastases	
lungs	16 (84%)
liver	6 (32%)
CNS	3 (16%)
bone	1 (5%)
lymph nodes	15 (79%)
Median no. of standard-dose platinum-containing cycles during previous therapy	9 [4–20]
No. of patients pretreated with at least one cyclophosphamide/ifosfamide containing chemotherapy regimen	19 (100%)
No. of patients pretreated with high-dose chemotherapy with autologous stem cell support	13 (68%)
No. patients with prior paclitaxel chemotherapy	12 (63%)
No. patients with prior gemcitabine chemotherapy	7 (37%)
Median no. of previously received chemotherapy regimens	3 [2–5]
Late relapse > 2 years	5 (26%)
Late relapse > 5 years	2 (11%)
No. of patients with platinum-refractory disease[a]	10 (53%)
No. of patients absolutely platinum-refractory disease[b]	2 (11%)
Response	
complete response	0
PR^-	1 (5%)
stable disease	0
progressive disease	18 (95%)
Status	
alive with disease	5 (26%)
dead of disease	14 (74%)

[a]Achievement of at least stable disease or better without evidence of tumor progression within 4 weeks of the last cisplatin-based chemotherapy.[16]
[b]Progressive disease despite cisplatin-based chemotherapy.[32]

Table 2. Toxicity ($n=19$)

	WHO grade I/II		WHO grade III/IV	
	No.	(%)	No.	(%)
Hematologic				
leukocytopenia	10	(53)	0	
granulocytopenia	5	(26)	0	
thrombocytopenia	4	(21)	1	(5)
anemia	1	(5)	0	
Non-hematologic				
nausea/vomiting	5	(26)	0	
fever	2	(10)	0	
diarrhea	2	(10)	0	
liver enzyme elevation	1	(5)	0	
neurotoxicity	1	(5)	0	
infection	0		0	
Hematologic toxicity in 13 patients pretreated with high dose chemotherapy plus autologous stem cell support				
leukocytopenia	7	(78)	0	
granulocytopenia	3	(23)	0	
thrombocytopenia	3	(23)	1	(8)
fever	2	(10)	0	
anemia	1	(8)	0	
infection	0		0	

but no WHO grade 3 or 4 non-hematologic toxicity was observed. Overall, hematologic toxicity was also mild and similar in patients previously treated with and without high-dose chemotherapy plus autologous stem cell support. Only one patient developed a WHO grade 3 thrombocytopenia, which was the only hematologic grade 3/4 hematologic toxicity observed. No grade 3/4 leucocytopenia occurred and there were no cases of granulocytopenic fever. None of the patients developed grade 3/4 anemia. There was no therapy-related mortality. After a median follow-up of 5 months (range 2–17), 15 patients have died (79%) and four patients are alive with disease (21%). Median overall survival for all patients was 5 months (range 2–17).

Discussion

In recent years cisplatin-refractory testicular cancer has served as a model to investigate new chemotherapeutic agents. However, only a few agents with significant clinical antiumor activity in patients suffering from cisplatin-refractory germ cell cancer have been identified to date.[17] Etoposide, particularly when given at prolonged oral schedules, was the first drug to show activity after failure of cisplatin combination chemotherapy.[5] Paclitaxel has also demonstrated activity with response rates of about 20% in heavily pretreated patients with refractory germ cell cancer.[6,7,18–20] The identification of the activity of paclitaxel has led to its investigation as part of combination chemotherapy regimens in the salvage setting and recently even in combination with standard-PEB in first-line treatment.[21,22] Only recently, gemcitabine was reported to be active in this patient population. Bokemeyer *et al.* observed a response rate of 20% in 31 assessable patients following a dose of 1000 mg/m^2 of gemcitabine once weekly for 3 consecutive weeks.[8] Similar results were obtained by investigators from Indiana University.[9]

We here report the results of a phase II study of the alkylating agent bendamustine in 19 patients with relapsed or refractory germ cell cancer. The rationale for the evaluation of alkylating agents in testis cancer is based on the activity seen for both ifosfamide and cyclophosphamide when used in standard- and high-dose regimens. *In vitro* data of bendamustine suggest only partial cross-resistance to 'classical' alkylating agents such as cyclophosphamide, melphalan or cisplatin.[14] This has subsequently been confirmed in clinical trials. Response rates of up to 70% have been reported for bendamustine monotherapy in patients with non-Hodgkin lymphomas in patients who had previously received, among other drugs, cyclophosphamide and/or ifosfamide.[23,24] In contrast to other alkylating agents such as cyclophosphamide or ifosfamide, bendamustine induces more DNA double-strand breaks. In addition, the removal of bendamustine-induced double-strand breaks was slower than for other alkylating agents. These findings may explain the activity of bendamustine in patients pretreated with alkylating agents.[14] In the present study only patients with very unfavorable prognostic characteristics were included (Table 1). However, the patient population was comparable to those who had been included in previous studies investigating paclitaxel or gemcitabine single-agent therapy.[7,8] In contrast to the studies that investigated paclitaxel and gemcitabine, only one patient achieved a partial remission of very short duration, indicating that bendamustine has no clinically significant activity in patients with refractory germ cell cancer. The present study investigated a total dose of 240 mg/m^2 given over 2 consecutive days every 3 weeks. Using similar dosages, response rates of 27, 38 and 65% have been achieved in patients with breast cancer, multiple myeloma and non-Hodgkin lymphoma, respectively.[23,25,26] Matthias *et al*. demonstrated that 215 mg/m^2 of bendamustine is the maximally tolerated dose, when administered as a single bolus dose.[27] In a second phase I study, Schöffski *et al*. recommended 140 mg/m^2 of bendamustine given on days 1 and 8 of a 4-week cycle for future phase II trials.[28] The dose intensities achieved in these studies are comparable to the dose intensity of 240 mg/m^2 every 3 weeks used in our current study. Dose-limiting toxicities in these phase I trials consisted mainly of neurotoxicity, cardiac arrhythmias, fatigue and salivary gland dysfunction, while myelosuppression was only mild with grade III or IV myelotoxicity being rarly reported.[27,28]

Despite the lack of activity in patients with relapsed or refractory germ cell cancer in our study, the good tolerability of bendamustine in a heavily pretreated group of patients was encouraging. Hematologic toxicity was mild, even in those of our patients who had previously received high-dose chemotherapy plus autologous stem cell support. No patient in the present study required a platelet or blood transfusion and no patient developed neutropenic fever or had to be hospitalized for bendamustine-related side-effects. The treatment of patients, who may have a limited bone marrow function and thus are likely to develop an increased hematologic toxicity, remains a therapeutic challenge. Only a few agents have been systematically investigated and found to be feasible in this setting, among them paclitaxel and gemcitabine.[7,29–31] Thus, bendamustine's low toxicity make it an attractive therapeutic option for the palliative treatment of those pretreated patients in whom a higher level of activity has been demonstrated.[23,25,26]

In summary, bendamustine should not be further evaluated in patients with cisplatin-refractory and intensively pretreated germ cell cancer.

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