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Bendamustine is effective in relapsed or refractory aggressive non-Hodgkin's lymphoma

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Background: Bendamustine, an alkylating agent with a nitrogen mustard group and a purine-like benzimidazol group, has been shown to be effective in several solid tumors and indolent non-Hodgkin's lymphomas, but has not yet been studied for efficacy in aggressive lymphomas.

Patients and methods: We conducted a phase II study in patients with relapsed or refractory high-grade non-Hodgkin's lymphomas, using bendamustine at a dose of 120 mg/m^2 on days 1 and 2, every 3 weeks for up to six cycles. Twenty-one patients were enrolled; 18 were evaluable for response and toxicity, 10 of whom were refractory to previous chemotherapy.

Results: With three patients achieving a complete response (at 6, ≥8 and ≥22 months) and five a partial response (three at 2 months, one at 3 months and one at 10 months), the total response rate of the evaluable patients was 44% (eight out of 18; 38% of all patients). Two complete and two partial responders were refractory to prior treatment. In 10 patients, treatment had to be stopped after one to three cycles due to progressive disease or hematological toxicity ($n = 2$). Non-hematological side effects were mild. Eight (13%) WHO grade 3 and no grade 4 events were observed in 60 evaluable treatment cycles. Hematologic toxicity was moderate (grade 3 and 4): anemia in five cycles (8%), leukopenia in seven (12%) and thrombocytopenia in eight (13%).

Conclusions: Bendamustine as a single agent is effective against aggressive lymphoma, even in cases of refractory disease. Further studies are warranted to determine the significance of bendamustine in the treatment of aggressive lymphomas.

Key words: aggressive lymphoma, bendamustine, refractory disease, relapse

Introduction

Although a significant proportion of patients with aggressive non-Hodgkin's lymphomas is curable by standard combination chemotherapy, the majority of the patients eventually die of the disease. In particular, patients with refractory disease and those in relapse with concomitant diseases or older age have a dismal prognosis [1, 2]. For this group of patients a palliative treatment option with manageable toxicity and possibly high efficacy seems adequate. Although such treatment approaches are commonly used on an individual basis, there is a paucity of information on this issue from palliative studies. Recently, well-tolerated substances such as gemcitabine or rituximab have been used in relapsed or refractory patients with some success [3–6]. Because of its proven efficacy against solid tumors and low-grade lymphomas, the nitrogen mustard derivative bendamustine was explored in the present study.

Bendamustine hydrochloride was developed in the 1960s in former East Germany, but was never systematically studied in patients until the 1990s. The drug consists of an alkylating nitrogen mustard group and a purine-like benzimidazol compound with a suggested purine-analog effect [7]. Bendamustine has been shown to have substantial activity against low-grade lymphomas [8], multiple myelomas [9] and several solid tumors [10, 11]. We recently reported that bendamustine effectively induces apoptosis in lymphoma cells [12].

The main toxicities of bendamustine are hematological WHO grade 3 and 4 events, occurring in 6–40% of patients [9, 13]. Subjective toxicity, which is usually low, includes nausea and emesis (usually well manageable with serotonine antagonists), diarrhea and allergy-like skin reactions, but hardly any alopecia [7].

Herein we report the results of the first study using bendamustine as a single agent in aggressive non-Hodgkin's lymphoma.

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Patients and methods

Patients were eligible if a curative treatment option (i.e. high-dose therapy) was not appropriate. Patients with the following conditions were entered into the study: refractory lymphoma [defined by progression during chemotherapy, relapse within 6 months after induction of therapy with a complete response (CR), a partial response (PR) or less response after completed first-line therapy], early relapse (within 12 months of last treatment), second relapse, relapse after high-dose therapy, or relapsed or refractory HIV-associated lymphoma. Pretreatment investigations included physical examination, computed tomography (CT) scan of the thorax and the abdomen or other involved regions, ultrasound of the abdomen, bone marrow histology and electrocardiogram (ECG). Response was evaluated after two, four and six cycles, and every 3 months after completion of treatment including the aforementioned examinations. Bone marrow biopsy was repeated in cases of initial infiltration or when bone marrow involvement during the treatment course was suspected. Evaluation of toxicity was performed according to WHO criteria and response assessment by the International Workshop Criteria [14]. The study was approved by the ethics committees of the participating institutions.

Bendamustine 120 mg/m^2 was administered as a 30-min infusion on two consecutive days once every 3 weeks. The dose was reduced to 75% in cases of thrombocytopenia <10 cells/nl or granulocytopenia <0.1 cells/nl for >5 days. A serotonine antagonist was administered before every infusion. Blood cell counts, blood smears and biochemistry profiles were determined at least once a week.

Results

Of 21 patients enrolled, 18 were evaluable for response and toxicity. Three patients had to be excluded, one due to protocol violations, one because of unevaluable tumor parameters and one because the initial bone marrow histology was revised to secondary acute myeloblastic leukaemia. Median age was 66 years (range 38–84 years; Table 1). Three patients were HIV positive, 16 had aggressive B-cell lymphomas, one a peripheral T-cell lymphoma (unspecified) and one an angioimmunoblastic T-cell lymphoma (Table 1). At the time treatment with bendamustine was initiated, the majority of the patients presented with advanced stages of disease and extranodal manifestations. The median number of risk factors according to the 'International Prognostic Index' was 2.5 (Table 1). Twelve patients had previously received two or more chemotherapeutic regimens, some with additional irradiation, two had relapsed after autologous stem cell transplantation, four had refractory disease after first-line treatment, and six had refractory disease after treatment of first or second relapse (Table 1).

Five of 18 evaluable patients (all of them responders) completed all six planned cycles of therapy. Reasons for previous discontinuation of treatment were: progressive disease in the 10 non-responding patients, progressive disease after initial PR in one patient, and hematological toxicity in two responding patients.

Toxicity

Subjective toxicity was moderate to low. No WHO grade 4 toxicity was observed with respect to nausea/emesis, fever, infections, alopecia or diarrhea, and grade 3 toxicity for these side effects was <10% of all evaluated treatment cycles (Table 2). Hepatic, renal, pulmonary or cardiac toxicity was unremarkable (Table 2). Hematological WHO grade 3 and 4 toxicity was generally moderate (8–13% of all treatment cycles; Table 2). In two patients, however, bendamustine had to be stopped due to prolonged grade 4 thrombo- and leukocytopenia. Altogether, hematological toxicities resulted in delays or dose reduction in 13 (21.7%) of the scheduled treatment cycles. None of the patients received myeloid growth factors. No treatment-related deaths were observed.

Response

Objective responses were observed in eight patients [44%, confidence interval (CI) 21.5%–69%], with five patients (27.8%) achieving a partial remission (lasting 2, 2, 2, 3 and 10 months) and three achieving complete remission. Of the latter, CR lasted 6 months in one patient (Table 3). Two patients, one of whom relapsed within 6 months of achieving CR and the other who achieved only partial remission after six cycles of a CHOP-like regimen, are in ongoing complete remission after ≥8 and ≥27 months, respectively (total CR rate 16.7%; Table 3). In the group of primary refractory patients and the population of relapsed patients, two CRs and two PRs, and one CR and three PRs were achieved, respectively. The median time from last treatment in the responding patients was 5.5 months (range 1–48 months; data not shown).

Ten of 18 evaluable patients (56%) progressed during treatment: in five (28%) this occurred within the first two treatment cycles, while the remaining five (28%) experienced a short phase of stable disease with relief of lymphoma-associated symptoms (Table 3). None of these patients received more than three cycles of bendamustine treatment. In this group of patients, the median time from last treatment was 3.5 months (range 1–60 months; data not shown).

Discussion

The results of our study of the use of bendamustine in refractory or relapsed aggressive non-Hodgkin's lymphoma patients without a curative treatment option show that objective and durable responses can be achieved in this high-risk population. Bendamustine was chosen for this primary palliative setting because of its known effect against low-grade lymphomas [8, 15], its low toxicity profile [7], the assumption of no or little cross-resistance with other alkylating agents [13] and its manageability on an outpatient basis. The rationale for the given dose of bendamustine was the expectation that the majority of the patients had undergone intense prior treatment. Due to myelotoxicity, higher doses of the drug are usually administered only in previously untreated patients [9].

Table 1. Characteristics of the evaluable patients[a]

Characteristic		No. of patients (%)
Sex		
Male		14 (77.8)
Female		4 (22.2)
Age (years)		
Median	66	
Range	38–84	
HIV positive		3 (16.7)
Diagnosis		
Diffuse large cell		12 (66.7)
Follicular B cell, grade 3		1 (5.6)
Aggressive B cell, unspecified		3 (16,7)
Angioimmunoblastic T cell		1 (5.6)
Peripheral T cell, unspecified		1 (5.6)
International prognostic index (not age-adjusted)		
Low		3 (16.7)
Low–intermediate		6 (33.3)
High–intermediate		6 (33.3)
High		3 (16.7)
Prior chemotherapeutic regimens		
1		6 (33.3)
2		9 (50.0)
3		1 (5.6)
4		2 (11.1)
Prior irradiation		8 (44.4)
Prior autograft		2 (11.1)
Stage III or IV at enrollment		12 (66.7)
Extranodal manifestations at enrollment		11 (61.1)
Resistant to last chemotherapeutic regimen		10 (55.6)

[a]Three patients were not evaluable: one 50-year-old female with diffuse large cell B-cell lymphoma who received additional chemotherapeutic drugs, one 75-year-old male with aggressive B-cell lymphoma (unspecified) whose lymphoma parameters were not evaluable, and one 65-year-old male with initial diagnosis of diffuse large cell B-cell lymphoma, in whom the diagnosis of relapse was revised to secondary acute myeloblastic leukaemia (AML).

The patient population had an extremely poor prognosis, defined by criteria as having a high rate of refractory aggressive lymphoma, heavy pretreatment, advanced stage disease or extranodal manifestations in the majority of the patients, relapse or resistant disease in three HIV-positive individuals, and a high median age. The response rate of 44% is somewhat higher than could be expected with other single agent therapies in this palliative setting. For example, with the CD20 antibodies rituximab or gemcitabine, response rates of ~30% have been described in comparable patient populations [3, 6]. In comparison with salvage treatment regimens, the response rates of bendamustine are certainly inferior [16]; however, one has to consider that our patient population did not qualify for aggressive regimens, mostly due to age or previously performed salvage therapy without response in younger patients.

From the results obtained in the present study, with responses to bendamustine therapy in heavily pretreated patients or patients with refractory disease, we can definitely conclude that it has substantial activity against aggressive lymphomas and that consideration of bendamustine as a treatment option in such patients is justified.

The palliative concept of using bendamustine in cases of aggressive lymphoma is supported by some patients, who did not achieve objective responses, but experienced short periods of relief of lymphoma-associated symptoms, while the non-hematological toxicity was mild, resulting in a short-term

Table 2. Toxicity of bendamustine in 60 evaluable treatment cycles

	WHO toxicity grade			
	1	2	3	4
Anemia	20 (33.3)	4 (6.7)	3 (5.0)	2 (3.3)
Thrombocytopenia	6 (10.0)	6 (10.0)	3 (5.0)	5 (8.3)
Leukocytopenia	17 (28.3)	8 (13.3)	3 (5.0)	4 (6.7)
Granulocytopenia	10 (16.7)	6 (10.0)	2 (3.3)	4 (6.7)
Nausea/emesis	20 (33.3)	3 (5.0)	1 (1.7)	0 (0.0)
Fever	7 (11.7)	9 (15.0)	1 (1.7)	0 (0.0)
Infections	8 (13.3)	1 (1.7)	2 (3.3)	0 (0.0)
Alopecia	0 (0.0)	1 (1.7)	4 (6.7)	0 (0.0)
Diarrhea	10 (16.7)	5 (8.3)	0 (0.0)	0 (0.0)

Shown are numbers of cycles and percentage of total cycles in which the respective toxicity occurred. Other toxicities (grade 1 and 2, <10% of the total number of treatment cycles) included obstipation, erythema, phlebitis, peripheral neuropathy and elevated creatinine.

Table 3. Response to bendamustine treatment in patients with relapsed or refractory aggressive lymphoma

Response	No. of patients	Percentage of evaluable patients (n = 18)	Percentage of included patients (n = 21)	Response duration (months)
Total response	8	44.4	38.1	
Complete remission	3	16.7	14.3	6, 8+, 27+
Partial remission	5	27.8	23.8	2, 2, 2, 3, 10
Progressive disease	10	55.6	47.6	
Primary progressive	5	27.8	23.8	
Progressive after relief of lymphoma-associated symptoms[a]	5	27.8	23.8	
Not evaluable	3			

[a]Relief of lymphoma-associated symptoms, including reduction of systemic symptoms in four cases and of lymphedema in one case, lasted between 2 and 8 weeks.

increase in quality of life. Subjective toxicity was generally mild, as reported in previous studies [7], and comparable to that of gemcitabine or rituximab [3, 6]. In most patients, hematological toxicity was moderate. In two patients, however, treatment had to be discontinued due to long lasting hematologic toxicity, most likely due to intense pretreatment.

Different schedules, ranging from daily administration of low doses of bendamustine (i.e. 25 mg/m^2 for 14–21 days) to single doses of 150 mg/m^2 on two consecutive days every 3 weeks have been used arbitrarily [7, 9], but effective doses with tolerable toxicities have not been well defined. A recent report demonstrated rather low hematological toxicity using a weekly administration of 60 mg/m^2 in advanced progressive solid tumors [13]. Thus, dose modifications in order to reduce adverse effects may be possible. Whether the response in aggressive lymphomas can be maintained with such regimens needs to be evaluated.

Due to the efficacy and tolerability of bendamustine, the question arises of whether the drug should be included in combination chemotherapy regimens for treatment of aggressive non-Hodgkin's lymphoma prior to the palliative situation. We recently published an *in vitro* study demonstrating the synergistic effects of bendamustine with cladribine on apoptosis of lymphoma cells [12]. Unpublished data from our group demonstrate that rituximab sensitizes lymphoma cells for bendamustine-induced apoptosis. Therefore, it seems possible that by combining bendamustine with other chemotherapeutic agents or antibody therapy, the anti-lymphoma effect may be further increased.

In conclusion, bendamustine is effective in aggressive lymphoma and can be recommended for the palliative situation. Further studies will have to define its role for chemotherapy and chemotherapy/antibody combinations in this setting, as well as in patients in the earlier stages of disease.

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