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Clinical report

Efficacy and toxicity of bendamustine in patients with relapsed low-grade non-Hodgkin's lymphomas

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Low-grade non-Hodgkin's lymphomas (NHL) are very sensitive to a broad range of chemotherapeutic and biological agents. Relapses, however, occur even after aggressive cytostatic combinations in first-line therapy. Therefore, effective and well-tolerated salvage therapies are very important. In this single-institution trial, the efficacy and toxicity of bendamustine in the treatment of relapsed low-grade NHL was investigated. Fifty-eight patients with low-grade NHL pretreated with different cytostatic regimens were included. All patients received bendamustine at 120 mg/m^2 as a 1-h infusion on 2 consecutive days. The treatment was repeated every 3 weeks until complete remission (CR), partial remission (PR) or stable disease (SD) was confirmed on two consecutive cycles. Efficacy and toxicity were evaluated in 52 patients: CR was induced in 11%, PR in 62% and SD in another 10% of the patients. No response to treatment was seen in 17%. The median duration of remission was 16 months and the median survival time was 36 months. Side effects were generally mild, and restricted to myelosuppression, gastrointestinal toxicity and allergic reactions. Bendamustine proved to be very effective and was well tolerated in pretreated patients with relapsed or primary resistant low-grade NHL. [© 2001 Lippincott Williams & Wilkins.]

Key words: Bendamustine, chemotherapeutic pretreatment, efficacy, relapsed low-grade non-Hodgkin's lymphoma, toxicity.

Introduction

Low-grade non-Hodgkin's lymphomas (NHL) consist of a variety of subtypes. Due to their different biological behavior, median survival times range from approximately 3 to 8 years.[1,2] Cure, however, is restricted to patients with a localized stage of the disease. Although a variety of agents have demonstrated antitumor activities, high relapse rates in patients with advanced stages have led to a palliative approach. Therefore, other therapeutic concepts and drugs are needed. New effective drugs with relatively low side effects include purine analogs and antibodies, especially the anti-CD 20 monoclonal antibody rituximab.[3–11]

Bendamustine is a cytostatic drug which structurally combines a purine-like benzamidazol nucleus and a bifunctional alkylating nitrogen mustard group. The synthesis of bendamustine was completed in 1971.[12,13] Limited data were gathered during the first years, although the low toxicity of the drug had already been known. The effects of bendamustine on lymphomas and several tumors, e.g. breast cancer and small cell lung cancer, were investigated only recently.[14–19]

Bendamustine has only partial cross-resistance with other alkylating agents used in the treatment of NHL, such as cyclophosphamide, melphalan or cisplatin. Therefore, the aim of this clinical study was to examine if the administration of bendamustine is effective and well tolerated in pretreated patients with low-grade NHL.

Materials and methods

Patient selection

Patients referred to our institution with histologically confirmed low-grade NHL who had a progression or a relapse after at least one cytostatic pretreatment were consecutively included in the study. The performance status had to be WHO grade 0–2 with no age limitations. Further inclusion criteria were: leukocyte count $>3000/\mu l$ and platelet count $>100\,000/\mu l$ (unless related to bone marrow infiltration), and serum creatinine <2 mg/dl. The disease had to be measurable or evaluable according to WHO criteria.[20]

Exclusion criteria were no cytostatic pretreatment or autologous stem cell transplantation, past or current

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history of any other malignant neoplasms except for curatively treated non-melanoma skin cancer or *in situ* carcinoma of the cervix, pregnant or lactating women and active uncontrolled infections.

Treatment plan

Bendamustine was given as a 1-h infusion of 120 mg/m^2 on 2 consecutive days. Ondansetrone 8 mg and prednisone 50 mg were administered before the infusion of bendamustine to prevent nausea and vomiting. In case of body weight below 50 kg, the bendamustine dose was reduced to 60 mg/m^2. This treatment was repeated every 3 weeks. The therapy ended when complete remission (CR), partial remission (PR) or stable disease (SD) was documented on two consecutive cycles. In case of disease progression (PD), bendamustine was stopped immediately.

Evaluation of response and toxicity

Objective responses and toxicity were evaluated according to the WHO directions and the standardization for response criteria.[20,21] The response was evaluated before the beginning of every second therapy cycle (in the case of CR, there was a further response evaluation 4 weeks later) using the same baseline technique, e.g. computed tomography, radiodiagnostics, ultrasound, bone marrow biopsy or clinical examinations. Hematological toxicities were measured by weekly blood counts, non-hematological toxicities by anamnestic and clinical examinations before every new treatment cycle.

Analysis of data was done by descriptive statistical methods using Kaplan–Meier estimates for overall survival.

Results

Between January 1995 and January 2000, a total of 58 patients were consecutively enrolled into this trial. Patient characteristics are shown in Tables 1 and 2. In summary, the majority of the patients suffered from advanced disease (Ann Arbor stage III or IV), and had a long period (median 29 months) of various prior therapies (median 1) including all typical cytostatic agents in the therapy of NHL except for purine analogs and high-dose chemotherapy with stem cell support. The histological distribution according to the Kiel classification is shifted in favor of lymphocytic and centroblastic–centrocytic types.

Four patients prematurely discontinued the therapy because of non-compliance and two patients were lost to follow-up. Thus, only 52 patients were evaluable for response and toxicity. They received 1–11 cycles of bendamustine (median 6). Thirty-eight patients showed an objective response, yielding a response rate of 73% including six (11%) CRs. Another five patients (10%) achieved SD for a median of 12 months (range 5–39 months). PD was seen in nine patients (17%) after 1–5 (median 2) cycles (Table 3).

The median follow-up-time for all patients was 24 months (range 1–67) with a median remission duration of 16 months [95% confidence interval (CI) 12–

Table 1. Patient characteristics

Total number of patients	
included (*N*)	58
evaluable (*N*)	52
Sex (*N*)	
male	35
female	23
Age (years)	
median	63
range	36–82
Histological types	
lymphocytic	27
centroblastic/-cytic	22
centrocytic	6
immunocytic	3
Stages (Ann Arbor)	
I	0
II	8
III	17
IV	33

Table 2. Pretreatments of patients

Patients (*N*)/Regimens (*N*)	
33/1	
12/2	
5/3	
2/6	
Duration of pretreatment (months)	
range	2–123
median	29
Prior cytostatic drugs/combinations (*N*)	
chlorambucil/prednisone	34
cyclophosphamide/vincristine/prednisone	17
cyclophosphamide/vincristine/ methotrexate/prednisone	9
cyclophosphamide/vincristine/adriamycin/ prednisone	5
eldisine (±methotrexate)	3
bleomycin/epirubicine	3
cyclophosphamide/etoposide/methotrexate	2
cytosine-arabinoside	1
Interval between the end of pretreatment and start of bendamustine (months)	
range	1–29
median	3

Table 3. Treatment results in 52 evaluable patients

	N (%)	95% CI
CR	6 (11)	2–21
PR	32 (62)	47–75
SD	5 (10)	
PD	9 (17)	
Remission duration (months)	3–55 (median, 16; 95% CI 12–20)	
Survival (months)	3–67 (median, 36; 95% CI 23–49)	
Time to progression (months)	3–55 (median, 16; 95% CI 11–20)	

20], a median time to progression of 16 months (95% CI 11–20) and a median survival time according to Kaplan–Meier analysis (Figure 1) of 36 months (95% CI 23–49).[22]

Twelve patients are still in remission, with 19 patients still alive.

In this clinical trial, side effects were generally low with no toxic deaths (Table 4). The most common hematological and gastrointestinal toxicities were WHO grades 1 and 2, and only three patients demonstrated grade 3 leukopenia. There was neither alopecia nor cardiopulmonary or neurological adverse events. The therapy was well tolerated except for three allergic reactions (WHO grade 2) resulting in treatment interruption.

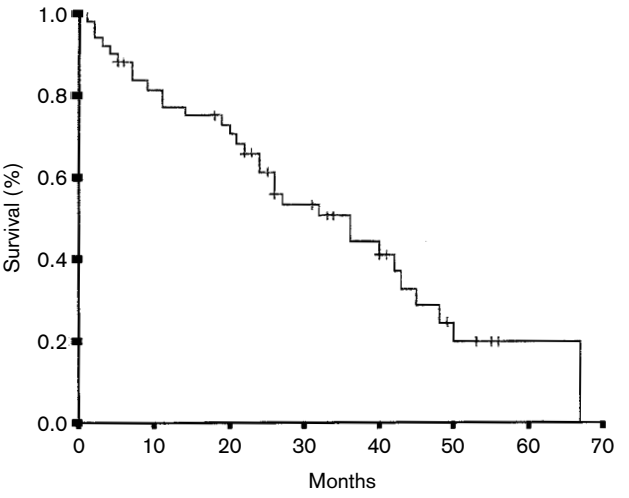

Figure 1. Overall survival according to the Kaplan–Meier method since the start of therapy with bendamustine.

Table 4. Toxicities in 52 evaluable patients

	WHO				
	0	1	2	3	4
Nausea/vomiting	23	19	10	0	0
White blood cells	8	29	12	3	0
Red blood cells	10	33	9	0	0
Platelets	30	17	5	0	0
Allergy	48	1	3	0	0
Cardiotoxicity	52	0	0	0	0
Neurotoxicity	52	0	0	0	0
Alopecia	52	0	0	0	0

Discussion

NHL are disorders with increasing prevalence and incidence, and there is considerable progress in the understanding of the pathophysiology of the different types of NHL. The so-called low-grade NHL are characterized by a low to moderate proliferative activity and a prolonged clinical course. The management of low-grade NHL is quite difficult and controversial, especially in advanced stages. Although the disease shows initial responsiveness to chemotherapy, recurrence is universal, resulting in resistance to many treatments. Therefore, low-grade NHL are considered to be incurable with standard therapy. Recent data show promising results for high-dose chemotherapy with stem cell support, but often only selected patients or subgroups of low-grade NHL are suitable for this treatment. So far, however, the studies performed do not show a clear survival benefit.[23–31]

The high efficacy and low toxicity in low-grade NHL with bendamustine as first- and second-line treatment has been known for more than 20 years. First data were evaluated in the former German Democratic Republic and recent publications confirmed the positive results.[14,18,32–37] In these studies, bendamustine was often administered as second- or third-line therapy.

In our study heavily pretreated patients with low-grade NHL were included, the majority of them in advanced stages. All patients showed PD before application of bendamustine with a median interval between the last treatment and the first administration of bendamustine of 3 months; only 12 patients (23%) had an interval of more than 6 months between the end of cytostatic pretreatment and the start of bendamustine. This shows that an unfavorable group of patients with bad prognostic factors was chosen for this trial (Table 2). Nevertheless, the majority of the patients profited from this treatment with a median remission duration of 16 months (Table 3). A correlation between the number of pretreatments and the response of bendamustine was not observed, e.g. the patient with the most extensive pretreatment

achieved a CR. One reason for this phenomenon might be the lack of complete cross-resistance to other alkylating agents and to anthracycline demonstrated in carcinoma cell lines.

It can be assumed that the response rates and the duration of remission may be higher or longer if bendamustine was used as first-line treatment of low-grade NHL. Another improvement of treatment results may be possible when combining bendamustine with other cytostatic agents. The role of bendamustine as monotherapy in relapsing NHL as compared to purine analogs or rituximab is unclear. With regard to patient compliance in a palliative treatment plan (especially duration of treatment cycle—mostly 5 days—with purine analogs) and therapy costs (rituximab), randomized studies are of great interest.

In a palliative treatment plan, especially in heavily pretreated patients, the range of side effects is of great interest. Bendamustine showed few side effects in our study (Table 4). There was no WHO grade 4 toxicity. Only three patients had a degree of white blood cells corresponding to WHO grade 3. Apart from allergic reactions (all but one patient could receive a subsequent treatment with bendamustine after pretreatment with an antihistaminic and corticosteroid), no organic toxicity appeared. The main side effects were nausea and vomiting, especially after the first therapy cycle. Due to the good tolerability, a further dose increase seems possible in order to prolong the time to progression and survival.[38]

In summary, bendamustine showed high efficacy and low side effects in the treatment of heavily pretreated patients with relapsed low-grade NHL. A complete cross-resistance to other alkylating agents was not observed. Therefore, bendamustine is an important addition to the established cytostatic agents in low-grade NHL. Further randomized clinical studies are needed to evaluate its role in the treatment of low-grade NHL.

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