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ORIGINAL ARTICLE

Bendamustine compared to fludarabine as second-line treatment in chronic lymphocytic leukemia

Norbert Niederle · Dirk Megdenberg · Leopold Balleisen · Wolfgang Heit · Wolfgang Knauf · Johann Weiß · Werner Freier · Axel Hinke · Stefan Ibach · Hartmut Eimermacher

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Abstract Bendamustine demonstrated clinical activity in pre-treated hematological malignancies due to its unique mechanism of action distinct from standard alkylating agents. This study assessed its efficacy in patients with chronic lymphocytic leukemia pre-treated with an alkylator, in comparison to fludarabine. Patients with relapsed chronic lymphocytic leukemia requiring treatment after one previous systemic regimen (usually chlorambucil-based) were randomized to either receive bendamustine 100 mg/m^2 on days 1 and 2 of a 4-week cycle or standard fludarabine treatment consisting of 25 mg/m^2 on days 1 to 5 every 4 weeks. The primary objective was to achieve non-inferior progression-free survival (PFS) with bendamustine. Out of a total of 96 patients randomized, 92 were eligible, 49 allocated to bendamustine and 43 to fludarabine. About half of the patients received six or more cycles. Overall response rates were 76 % on bendamustine and 62 % on fludarabine, with clinical complete response rates of 27 and 9 %, respectively. Median PFS was 20.1 and 14.8 months (hazard ratio, 0.87; 90 % confidence interval, 0.60–1.27), median overall survival 43.8 and 41.0 months (hazard ratio, 0.82). Thrombocytopenia and gastrointestinal toxicities were marginally more frequent on bendamustine, albeit CTC grade 3/4 event incidence was similar. These data suggest at least comparable efficacy of bendamustine vs. fludarabine, pointing to an alternative treatment option in relapsing CLL patients after chlorambucil containing initial chemotherapy.

Keywords Chronic lymphocytic leukemia · Second-line treatment · Bendamustine · Fludarabine

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N. Niederle (✉) · D. Megdenberg
Medizinische Klinik III, Klinikum Leverkusen gGmbH,
Am Gesundheitspark 11,
D-51375 Leverkusen, Germany
e-mail: niederle@klinikum-lev.de

L. Balleisen
Medizinische Klinik I, Ev. Krankenhaus Hamm, Germany

W. Heit
Hämatologicum, Essen, Germany

W. Knauf
Onkologische Gemeinschaftspraxis, Frankfurt, Germany

J. Weiß
Praxis für Hämatologie und internistische Onkologie, Weiden, Germany

W. Freier
Onkologische Schwerpunktpraxis, Hildesheim, Germany

A. Hinke · S. Ibach
WiSP Research Institute, Langenfeld, Germany

H. Eimermacher
Onkologische Schwerpunktpraxis, Olpe, Germany

Introduction

Chronic lymphocytic leukemia (CLL) is the most common type of leukemia in developed countries of the western world [1], with a yearly incidence of about 120,000 cases in the USA and Europe. As CLL often shows an indolent course and still remains an incurable disease in the vast majority of patients, therapeutic interventions are generally restricted to symptomatic patients. For many years, single alkylating agents such as chlorambucil were the cornerstone of first-line therapy. During the last two decades, the quality of tumor remissions could be raised distinctly by the introduction of purine analogues, e.g. fludarabine, and monoclonal antibodies are no purine analouges. However, a clear impact of these more aggressive

treatment approaches on overall survival could not be proven as yet; although, there are promising preliminary results on rituximab-containing regimes [2, 3]. Nevertheless, the search for further treatment options in advanced CLL is warranted.

Bendamustine, first synthesized back in the 1960s in the former German Democratic Republic [4], consists of a nitrogen–mustard moiety bound to a purine-like benzimidazole ring. Originally, bendamustine was considered to act similarly to cytostatics such as cyclophosphamide or chlorambucil. However, several preclinical and clinical findings suggested that the activity profile and the mechanism of action of the drug significantly differ from classical alkylators [5]. Recently, thorough comparative examinations on the mechanism of action revealed unique effects of bendamustine and major differences in cytotoxic effects in vitro [6]. Consequently, a lack of cross-resistance to chlorambucil and other DNA-damaging cytotoxic drugs could be detected.

Bendamustine has been shown to be clinically active in the treatment of numerous hematological and solid malignancies [7]. Based on the favorable findings of phase I and II trials in non-Hodgkin's lymphoma (NHL) and CLL [4, 8–10], both with single drug and combination treatment, several randomized trials were initiated to compare bendamustine to standard therapies.

Design and methods

This trial was registered at ClinicalTrials.gov (NCT01423032).

Patients

Patients with histologically or immunologically confirmed chronic B cell leukemia in refractory (i.e., no response or progression during initial chemotherapy) or relapsed situation after first-line treatment regimen, exhibiting disease statuses II–IV according to Rai or B/C according to Binet staging system, respectively, were enrolled. Further selection criteria included Eastern Cooperative Oncology Group (ECOG) performance status of 3 or better and at least 18 years of age. For female patients with child-bearing potential, a negative pregnancy test and willingness to use adequate contraceptional methods were required. Patients with T-CLL, prolymphocytic leukemia (PLL), presence of Richter's transformation, or first-line treatment containing either fludarabine or bendamustine were not eligible for this trial. Patients were also excluded if they presented with acute infections or distinctly reduced organ function precluding the application of chemotherapy, as for pulmonary, heart, liver (total bilirubin >5 mg/dl), renal system (creatinine >2 mg/dl), or metabolic disorders, or in case of secondary malignancy (except for curative treated basal cell carcinoma or cervical cancer). The study was approved by all ethical committees responsible for the participating study centers. All patients gave written informed consent before entering the study, in accordance with the Declaration of Helsinki, Edinburgh version, 2000.

Study design and treatment

The study was designed as an open-label, multi-center, randomized phase III trial. After registration at the central study office, patients were randomly assigned to treatment, consisting either of fludarabine or bendamustine monotherapy. Computer-generated randomization lists, created by a block randomization method with variable block size, were used. Patients were stratified according to Binet stage B or C and study center. For therapy, patients received either bendamustine 100 mg/m^2 body surface on days 1 and 2 or fludarabine 25 mg/m^2 body surface on days 1 to 5 of each 28-day treatment cycle. Treatment cycles were repeated until confirmation of best response to treatment, with a maximum of eight cycles. The duration of cycles could be extended if required for resolution of treatment-induced neutropenia or thrombocytopenia. Furthermore, dose reduction was applied in case of duration of grade 4 neutropenia for >5 days, platelet nadir $<20\times10^9$ per liter, creatinine >2.0 mg/dl, or other organ toxicities of grade 3 or higher. Grade 4 neurologic toxicity resulted in permanent termination of treatment. Bendamustine dose was decreased by increments of 20 mg/m^2 (but not more than 40 mg/m^2), fludarabine by increments of 5 mg/m^2 (but not more than 10 mg/m^2).

The primary objective was to evaluate, whether CLL treatment with bendamustine shows equivalent efficacy compared to treatment with fludarabine, with regard to progression-free survival. Secondary objectives of the trial were the comparison of antineoplastic efficacy by evaluation of remission rates and overall survival, as well as the comparison of tolerability by evaluation of frequency and grade of toxicity influencing treatment feasibility (dose reductions, cycle delays). Furthermore, frequency and duration of hospitalizations, blood transfusions, and supportive medications were evaluated.

Assessments

Baseline assessments consisted of clinical examination, tumor evaluation (clinical, by sonography and radiological imaging), and standard hematology and blood chemistry parameters including Coombs test. Additional radiologic evaluation could be performed as indicated and was left to investigator's discretion. Bone marrow biopsy and aspiration were required if not performed within 3 months prior to inclusion. Standard blood counts had to be repeated once

weekly. The complete laboratory tests as well as clinical examinations had to be repeated before the application of each treatment cycle, with complete tumor restaging (i.e., including sonography and/or radiologic evaluation) in every second cycle and 4 weeks after termination of treatment. Bone marrow biopsy was repeated at the end of therapy visit. Follow-up assessments were performed every 3 months for a duration of 2 years and every 6 months thereafter.

Response evaluation was performed on the basis of the modified National Cancer Institute Working Group response criteria [11]. In short, complete remission (CR) required all of the following for a period of at least 2 months: absence of lymphadenopathy by physical examination and appropriate radiographic techniques, no hepatomegaly or splenomegaly, normal peripheral blood count as exhibited by lymphocytes ≤4.0 per nanoliter, neutrophils ≥1.5 per nanoliter, platelets ≥100 per nanoliter, hemoglobin >11 g/dl (untransfused), <30 % lymphocytes in bone marrow with absence of nodular infiltrates. A partial remission (PR) required all of the following for a period of at least 2 months: ≥50 % decrease in peripheral blood lymphocyte count from the pretreatment baseline value, ≥50 % reduction in lymphadenopathy, and/or ≥50 % reduction in the size of the liver and/or the spleen, plus at least one of the following criteria—neutrophils ≥1.5 per nanoliter or 50 % improvement over baseline, platelets ≥100 per nanoliter or 50 % improvement over baseline, hemoglobin ≥11 g/dl or 50 % improvement over baseline, improvement of clinical Binet stage. Progressive disease was defined as the presence of at least one of the following criteria: ≥100 % increase in diameter of two enlarged lymph nodes on two consecutive determinations at least 2 months apart (one lymph node should exhibit a diameter of at least 2 cm), appearance of new pathologic enlarged lymph nodes (min. 2 cm in diameter) on two consecutive determinations at least 2 months apart, ≥50 % enlargement of liver and/or spleen (confirmed by sonography), unambiguous appearance of hepatomegaly or splenomegaly which was not previously present (size constantly ≥10 % above normal or increasing, confirmed by sonography), persisting increase of ≥100 % in absolute lymphocyte count, transformation of CLL to large B cell lymphoma (Richter's syndrome) or prolymphocytic leukemia (PLL), change of Binet stage from A to B or C or from B to C. All patients not fulfilling one of the former set of criteria were to be recorded as stable disease.

Progression-free survival was calculated from the date of randomization to the time of progressive disease or to death from any cause. Overall survival was calculated from the date of randomization until the date of death from any cause. If none of these events was recorded, the patient was censored at the date of the last examination. Adverse events were assessed at each visit and graded according to the National Cancer Institute common toxicity criteria. Causes of death were recorded as attributable to CLL, treatment toxicity, and other or unknown.

Statistical aspects

The trial was originally designed as a phase III non-inferiority trial in order to exclude a lower margin of only 30 % PFS rate after 2 years compared to an expected 45 % for the standard fludarabine arm (corresponding to a hazard ratio of 1.5), by applying a one-sided 95 % confidence interval to the hazard ratio (HR). In order to achieve a power of 80 % to claim non-inferiority in case of a truly equivalent efficacy with respect to PFS, 83 patients in each arm were to be recruited during 2 years and followed for at least another 2 years. Due to slow and continuously decreasing recruitment, predominantly caused by the lack of patients without fludarabine pre-treatment in first-line, enrollment was prematurely stopped after recruitment of 96 patients.

Response and toxicity rates were analyzed by Fisher's exact or Cochran–Armitage trend tests, as appropriate. Progression-free and overall survivals were estimated by the product limit method [12]. Univariate comparisons of these endpoints were performed using the logrank test [13]. All p values reported are two-sided. Except for the primary endpoint, all statistical tests are of exploratory nature, and hence, no adjustments for multiplicity were applied.

Results

Between September 2001 and December 2006, 96 patients from 27 centers in Germany were enrolled into the study, which had to be closed prematurely due to a lack of further referral of patients without fludarabine pre-treatment to the participating centers. Four patients did not fulfill the selection criteria and were excluded from further analysis (Fig. 1). Forty nine eligible patients were allocated to bendamustine and 43 to fludarabine. The baseline characteristics were well balanced between the treatment arms (Table 1), with the exception of performance status which was slightly less favorable in the fludarabine arm. Worthy of note, the median age of the whole patient group was 69 years, which is typical for an unselected CLL population.

Treatment

The median number of administered therapy cycles was five in both arms, with 17 and 12 % receiving the maximum number of eight bendamustine and fludarabine courses, respectively. The mean daily dose delivered by cycle was 94.6 mg/m^2 bendamustine and 24.8 mg/m^2 fludarabine. Dose reductions by patient occurred equally frequent, in 36 and 37 % on bendamustine and fludarabine, respectively.

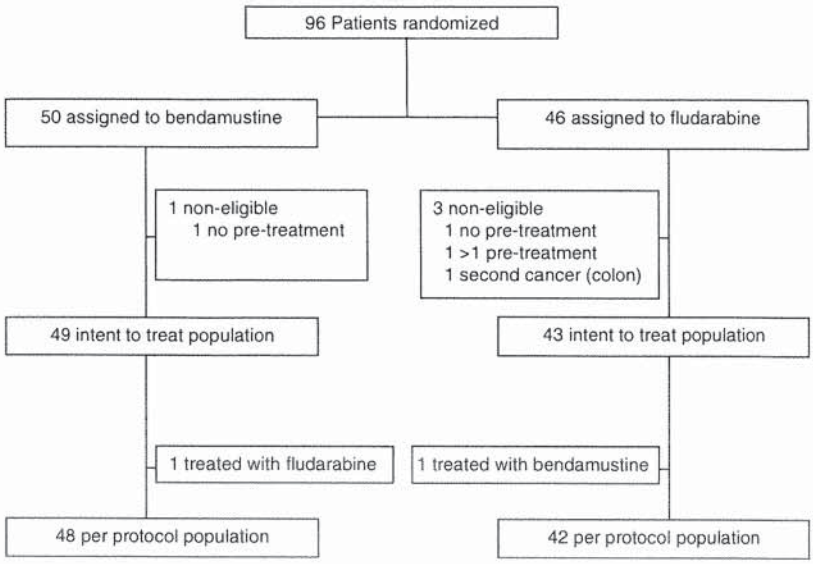

Fig. 1 CONSORT (Consolidating Standards of Reported Trials) diagram

Based on treatment courses, reductions were more frequent in the bendamustine arm (25 vs. 13 %). Bendamustine dose adjustments were predominantly caused by myelosuppression (80 %), while the most prominent reasons in the fludarabine arm were non-hematological toxicities (46 %). More often, however, cycles had to be delayed, with 56 % of patients in the total group, and equal percentages in both treatment arms, often due to patients' preference.

G-CSF and erythropoietin support was given in only 3 and 1 % of treatment courses, with no differences by chemotherapy arm. Seventy two percent of patients did not require any red blood cell transfusions during bendamustine treatment compared to 68 % on fludarabine. Platelets were substituted in about 10 % of patients in both arms. The protocol did not recommend the prophylactic use of antibiotics. Any anti-infectious therapy was administered upon the discretion of the treating physician. In total, 15 % of patients in the bendamustine arm and 12 % in the fludarabine arm had documented intravenous anti-infectious treatments while on study.

Efficacy

The overall best response rates (complete and partial remissions) on an intention-to-treat basis and counting all early protocol violations and discontinuations as failures were 76 % on bendamustine and 62 % on fludarabine, with a CR rate showing a trend in favor of bendamustine (27 vs. 9 %, p=0.057). PR rates were 49 and 53 %, while 8 and 16 % showed disease stabilization. A comparison across all response categories was not significantly different (p=0.11, Cochran–Armitage trend test).

After a median follow-up of 34 months in both arms, 81 progression events had been observed among 92 patients. Median progression-free survival was 20.1 months in the bendamustine arm compared to 14.8 months on fludarabine (Fig. 2a; logrank test, p=0.53). The hazard ratio for bendamustine is 0.87, with an upper limit of 1.27 for the one-sided 95 % confidence interval. The corresponding lower limit of confidence is 0.60. Median overall survival, based on 52 observed deaths, amounts to 43.8 months on bendamustine and 41.0 months on the purine analogue standard (Fig. 2b, HR=0.82; 95 % confidence interval 0.47 to 1.43; p=0.48).

Prognostic factors and subgroup analyses

The univariate analysis of major prognostic factors with respect to the primary endpoint shows no major impact of Binet stage B or C but distinct influences of age, resistance to first-line treatment, and performance status (Table 2). Since the baseline distribution favors the experimental arm, a subgroup analysis by ECOG status was performed. The hazard ratios of 0.97 and 0.94 for the strata with ECOG 0 and ECOG 1/2, respectively, reveal that the main unadjusted analysis result remains valid and that there is no suggestion of any interaction between performance status and treatment arm.

Toxicity

Myelosuppressive effects as well as the occurrence of fever and manifest infections occurred to a rather similar extent in the randomized groups except for decreased platelet counts (grades 1 to 2) being somewhat more prevalent in the bendamustine arm (Table 3). Febrile neutropenia was reported in 10 % of bendamustine and 15 % of fludarabine patients. Nausea and vomiting (of grades 1 and 2 only), however, were more common in the bendamustine arm, while hair loss was infrequent in both arms. Grade 3 and 4 non-hematological events were

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