Optimizing Premedications in the Prevention of Bendamustine Infusion-Related Reactions

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Background: Bendamustine is indicated for the treatment of chronic lymphocytic leukemia (CLL) and rituximab-refractory indolent non-Hodgkin lymphoma. Clinical trials have reported a 25% incidence of infusion-related reactions (IRRs) in patients receiving bendamustine. While these reactions are well documented, there is no consensus on the optimal premedication regimen for the prevention of these adverse effects. At our center, we utilize a regimen of ondansetron 16 mg orally and dexamethasone 10 mg IV push prior to each infusion of bendamustine. This report describes our experience with our current premedication regimen with regard to IRRs and the incidence of febrile neutropenia (FN).

Methods: We retrospectively analyzed 73 consecutive patients receiving bendamustine infusions at our institute from June 2008 to June 2010 to determine the incidence of IRRs and FN. The primary objective was to determine the incidence of IRRs. Secondary objectives included incidence of FN and hospital admission rate.

Results: A total of 478 infusions of bendamustine were administered to 73 consecutive patients. The median patient age was 69 years. IRRs affected 19% of our population, and 10.9% experienced FN. Notably, all IRRs were attributed to rituximab infusions and no patients experienced an IRR when receiving bendamustine alone. This compares favorably to the initial reported IRRs of 25% with bendamustine alone.

Conclusions: Based on our experience with bendamustine, ondansetron and dexamethasone provide a safe and effective prevention of IRRs associated with bendamustine. By avoiding the use of other premedications, the likelihood of additional complications or adverse effects can be minimized.

Introduction

Bendamustine first demonstrated promising activity in non-Hodgkin lymphoma (NHL) over 30 years ago. First synthesized in 1963 in the German Democratic Republic, the intention was to create an agent with less toxicity that would retain the efficacy of nitrogen mustard compounds. While used extensively in Germany for several years, bendamustine was not approved for use in the United States until 2008.

Bendamustine is a chemotherapeutic agent that is structurally similar to both alkylating agents and antimetabolites. However, in vivo and in vitro studies have demonstrated an incomplete cross-resistance with other alkylating agents such as cyclophosphamide, melphalan, and carmustine. A benzimidazole ring system may confer nucleoside-like properties and provide stability that correlates with longer-lasting DNA damage by bendamustine. Additionally, increased stability has been noted when compared to other nitrogen mustards, along with slower repair of DNA damage than with other alkylating agents.

Phase II studies in East Germany were conducted with bendamustine in a small group of patients diagnosed with chronic lymphocytic leukemia (CLL). These initial studies demonstrated response rates of 65% to 93% and a favorable adverse event profile. A European intergroup CLL study later reported the superiority of bendamustine over chlorambucil as first-line treatment in CLL patients. Overall response rates (ORRs) in 156 patients receiving bendamustine and 149 patients receiving chlorambucil were 68% and 39%, respectively. Additionally, median progression-free survival (PFS) was 21.7 months in patients treated with bendamustine vs 9.3 months in patients treated with chlorambucil. The median duration of remission was 18.9 months and 6.1 months, respectively. The results of this trial led to approval of bendamustine by the US Food and Drug Administration for the treatment of CLL.

The efficacy of bendamustine in NHL was also demonstrated in two North American trials that reported responses in chemotherapy and rituximab-refractory NHL at greater than 70%. It has also been shown to be efficacious in patients with follicular and mantle cell lymphoma, with response rates of 90% to 92% and complete remission rates of 55% to 60% when utilized in combination with rituximab.

Bendamustine is associated with several adverse effects, including significant infusion-related reactions (IRRs). Clinical trials report IRRs of all grades for fever of 24% to 34% (2% grade 3/4), chills 1% to 14% (0% to 1% grade 3/4), pruritus 6% (0% grade 3/4), and rash 5% to 16% (1% to 3% grade 3/4). An IRR was defined as a disorder characterized by adverse reaction to the infusion of pharmacological or biological substances according to Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. While these reactions are well documented, there is no consensus on the optimal premedication regimen for
The primary objective was to assess patient tolerance of bendamustine infusion with designated premedications and efficacy of the current premedication regimen employed at our center with regard to the occurrence of IRRs. Secondary objectives included determination of the hospital admission rate, incidence of febrile neutropenia (FN), incidence of neutropenia and resulting growth factor use, discontinuation rate, and reasons for discontinuation. A retrospective review of electronic medical records was used to obtain necessary demographic, clinical, and laboratory data. Demographic data collected included age, height, weight, body surface area, and gender. Clinical and laboratory data collected included baseline laboratory values, primary diagnosis, dosing, the number of doses received, concurrent rituximab use if applicable, growth factor utilization, premedication administration, as well as safety data including the rate of adverse reactions, interventions, and hospitalization. Data specific to IRR were found in outpatient nursing notes documenting any adverse events occurring throughout the infusion time. The data were coded and extracted for analysis using SPSS version 17.0. Data were analyzed using descriptive statistics.

**Results**

Seventy-three patients received a total of 478 infusions of bendamustine. Baseline patient characteristics are summarized in the Table. Adherence to dexamethasone and ondansetron as premedications was 97.7% and 99.5%, respectively. Overall there were 41 reports of nonhematologic adverse reactions in 34 of the 73 patients (46.5%).

**Infusion-Related Reactions**

IRRs affected 19% of our population. Our analysis revealed that 82% of IRRs occurred in the first cycle of bendamustine/rituximab regimen. More importantly, 100% of IRRs were attributed directly to the concurrent rituximab infusion and no IRRs occurred in patients receiving bendamustine alone. In comparison to available data from the manufacturer, the frequency of IRRs at our center is lower in terms of fever (22% vs 36% to 59%), chills (6.8% vs 9%), rash (11% vs 12%), and pruritus (2.5% vs 8%). Based on these data, the premedication regimen with ondansetron and dexamethasone appears to be effective in the prevention of IRRs occurring with the administration of bendamustine.

**Adverse Reactions**

Thirty-four patients (46.5%) experienced a nonhematologic adverse reaction during treatment with bendamustine. Approximately half of the reactions occurred with the first cycle of bendamustine and could be directly attributed to rituximab administration. After accounting for rituximab-related infusions, only 19 patients (26%) experienced a nonhematologic adverse reaction to bendamustine. Fever was the most common adverse reaction reported, affecting 22% of the overall population (Fig 1). However, only 10.9% of our patients experienced FN, which is less than the proportion reported in previous studies.

A total of 35 patients received colony-stimulating factors during treatment with bendamustine (Fig 2). They were utilized as primary prophylaxis for neutropenia in 35.6% of patients (32.9% received pegfilgrastim and 2.7% received filgrastim).
filgrastim. Eight of the 73 patients (11%) required a dose reduction in order to continue treatment with bendamustine. Hospitalization was required in 18 patients (24.6%), with median admission duration of 4 days. Hospitalization occurred secondary to FN in 9.5%, non-neutropenic fever in 8.2%, shortness of breath in 2.7%, abdominal pain/constipation in 1.3%, nausea/vomiting in 1.3%, and hypotension in 1.3%.

**Bendamustine Administration and Discontinuation**

Patients completed a median of 3 courses of therapy with bendamustine administration. The most common reasons for discontinuation were completion of therapy (23.2%), disease progression (13.6%), and myelosuppression (absolute neutrophil count < 1,000; 13.6%). Other reasons for halting therapy with bendamustine included fatigue (6.8%) and infection (4.1%). These reported rates are consistent with those found in post-marketing experience with bendamustine. However, we postulate the large number of patients discontinuing therapy secondary to disease progression may be a result of the heavily pretreated patient population.

**Discussion**

Based on our findings, ondansetron and dexamethasone provide a safe and effective strategy for the prevention of IRRs while minimizing the likelihood of additional complications. The premedication regimen of ondansetron and dexamethasone has proven to be a safe and effective strategy for the prevention of IRRs with bendamustine administration and has been adopted as our institutional standard.

**References**