Original Study

A Phase 2 Trial of Fludarabine Combined With Subcutaneous Alemtuzumab for the Treatment of Relapsed/Refractory B-Cell Chronic Lymphocytic Leukemia

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Abstract

We evaluated alemtuzumab in combination with fludarabine for patients with relapsed chronic lymphocytic leukemia. Sixty patients were enrolled onto this phase 2 study; the complete response rate was 8.3%, with an overall response rate of 28.3%. Although many patients developed cytomegalovirus reactivation, these episodes were manageable. This regimen should be considered only for fit patients refractory to available therapies.

Background: Alemtuzumab is effective in fludarabine-refractory patients with chronic lymphocytic leukemia. We performed a phase 2 study of alemtuzumab in combination with fludarabine in patients with relapsed disease. **Patients and Methods:** Patients received alemtuzumab and fludarabine daily on days 1 to 5 of a 28-day cycle for up to 6 cycles with the primary objective of determining the rate of complete response. Of 60 enrolled patients, 51 had previously received fludarabine, and 60% had received 3 or more prior therapies. **Results:** Five patients experienced complete response (8.3%) and 12 experienced partial response, yielding an overall response rate of 28.3% for the intention-to-treat population. Among the 41 patients who completed at least 4 cycles of therapy, the complete response rate was 20%. Median progression-free survival was 211 days. Forty-seven percent of patients experienced cytomegalovirus viremia, including 4 patients with symptomatic cytomegalovirus disease. All patients responded to antiviral therapy. **Conclusion:** Despite some evidence of efficacy in this setting, the primary end point for the study was not met. In the era of targeted agents that are well tolerated, the combination of fludarabine and alemtuzumab should be used rarely for a select group of fit patients who are refractory to standard therapies.

Clinical Lymphoma, Myeloma & Leukemia, Vol. 15, No. 11, 694-8
Keywords: Alemtuzumab, Chronic lymphocytic leukemia, Fludarabine, Minimal residual disease, Small lymphocytic lymphoma

Introduction

Chronic lymphocytic leukemia (CLL) is the most common adult leukemia in the United States, with an estimated 16,060 new cases diagnosed in 2012.[1] It is generally considered incurable outside of allogeneic stem cell transplantation. For young, fit patients who require front-line therapy, fludarabine-based regimens are often administered, with a median progression-free survival of 51.8 months for fludarabine, cyclophosphamide, and rituximab and 42 months for fludarabine and rituximab.[2,3] However, patients who have evidence of early relapse or whose disease fails to respond to initial treatment with a fludarabine-based regimen have a poor prognosis, with a median survival of 10 months.[4]

Alemtuzumab is a recombinant humanized monoclonal antibody directed against CD52, which is effective in fludarabine-refractory CLL, with an overall response rate (ORR) of 33% (complete response [CR], 2%; partial response [PR], 31%) and a median overall survival (OS) of 16 months via intravenous administration.[5]

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Submitted: May 2, 2015; Revised: Jul 1, 2015; Accepted: Jul 28, 2015; Epub: Aug 05, 2015

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2152-2650/$ - see frontmatter
http://dx.doi.org/10.1016/j.clml.2015.07.640

Subcutaneous administration of alemtuzumab may alleviate infusion-related adverse events, which affect up to 90% of patients, and has been evaluated in subsequent trials with evidence of efficacy and decreased risk of infusion reactions.[5] In the CLL2H study of subcutaneous alemtuzumab in fludarabine-refractory CLL, the ORR was 34%, with a median OS of 19.1 months.[6] Grade 1/2 injection-site skin reactions occurred in 34% of patients, but the rate of infusion-related complications was decreased in the subcutaneous group compared to patients receiving intravenous alemtuzumab.[6]

In addition to infusion and skin reactions, infectious complications are common in patients treated with alemtuzumab. Cytomegalovirus (CMV) infections complicate 24% of patients treated, while bacterial infections affect 29% of patients, including 16% of patients experiencing sepsis.[7] The role of alemtuzumab in CLL remains a topic of controversy, especially in the era of novel oral therapies. It is highly effective: patients with *TP53* mutations or deletions, for example, have an ORR of 40% with a median response duration of 8 months.[8]

Fludarabine and alemtuzumab have been evaluated in combination both in the front-line and relapsed settings. In a randomized study comparing fludarabine and alemtuzumab to fludarabine alone in relapsed/refractory CLL, the median progression-free survival for the combination was 23.7 months, with both agents administered intravenously. The ORR was 82% and the CR rate was 13%. In addition, 6 patients with a clinical CR were confirmed to have no evidence of minimal residual disease (MRD) in bone marrow samples obtained at the conclusion of induction therapy. Infusion-related adverse events occurred in 62% of enrolled patients, and the majority of grade 3/4 toxicities were hematologic.[9]

We conducted a multicenter phase 2 study to assess the efficacy of fludarabine and alemtuzumab in relapsed/refractory CLL, utilizing subcutaneous administration of alemtuzumab. In addition to response rate, we assessed patients experiencing a response after induction for MRD and monitored alemtuzumab-related adverse events, including infusion reactions and infectious complications.

Materials and Methods

Patients

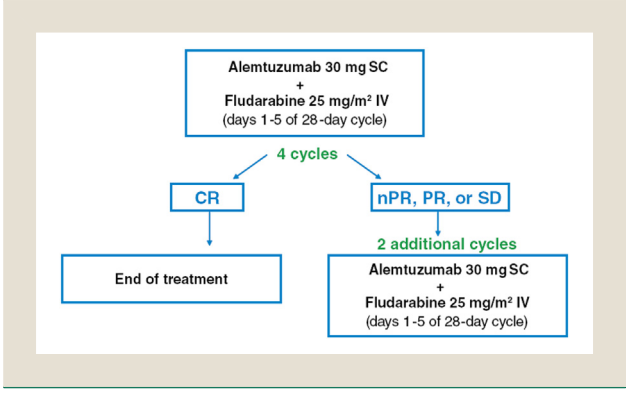
Patients with confirmed B-cell CLL (B-CLL) who had received at least 1 prior therapy were eligible. Patients needed to be at least 18 years of age, have disease that failed to respond to 1 prior therapy, have an Eastern Cooperative Oncology Group performance status of 0 or 1, and creatinine and total bilirubin $\leq$ 1.5 times the upper limit of normal. Women were excluded if pregnant or breast-feeding, unwilling to use an acceptable form of contraception, or of childbearing potential. Additional exclusion criteria included treatment with any anticancer agents (eg, chemotherapies, monoclonal antibodies) within 4 weeks of start of study, history of HIV positivity, or other current infection requiring treatment with antibiotic, antiviral, or antifungal agents. Patients with central nervous system involvement with CLL were also excluded. The study was conducted in accordance with the International Conference on Harmonization/Good Clinical Practice as required by 21 Code of Federal Regulations parts 50, 56, and 312, and the standard operating procedures for clinical investigation and documentation applicable at Bayer HealthCare Pharmaceuticals Inc. The conduct of this study was in accordance with the Declaration of Helsinki, and informed consent was obtained from all patients. The protocol and all amendments were reviewed and approved by each site's institutional review board. This clinical trial was indexed on ClinicalTrials.gov (NCT00206726).

Treatment and Scheduled Follow-up

This was a multicenter, phase 2, open-label, single-arm study evaluating the efficacy and safety of alemtuzumab and fludarabine in the treatment of B-CLL subjects who have received at least 1 prior therapy. Alemtuzumab was administered in a single subcutaneous dose of 30 mg at least 30 minutes before fludarabine infusion on days 1 to 5 of each 28-day cycle for 4 to 6 cycles. In this study, cumulative weekly exposure to subcutaneous alemtuzumab was 150 mg, which is higher than the recommended 90 mg for intravenous administration. The choice of the higher cumulative dose was supported by the findings of Hale et al,[10] who demonstrated that 150 mg was the mean cumulative dose needed to reach an alemtuzumab blood level of 1 μg/mL.

Vital signs (temperature, blood pressure, and pulse) were measured before administration of alemtuzumab. To help minimize injection site reactions, the site of injection was rotated daily. After alemtuzumab administration, fludarabine treatment was administered at 25 mg/m^2 intravenously over a period of 30 minutes on days 1 to 5 of each 28-day cycle for 4 to 6 cycles. Dose reductions were permitted for hematologic and nonhematologic toxicities. Toxicity was defined by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events, version 3. The disease of all patients was restaged after cycle 4. The National Cancer Institute–sponsored Working Group guidelines for CLL were used for assessment of response.[11] Those subjects experiencing a PR or stable disease were provided an additional 2 cycles of treatment (total of 6 cycles), and subjects demonstrating presumptive signs of a CR received no further treatment but were followed for response (Figure 1). Subjects with CR, PR, or stable disease at either evaluation underwent confirmatory biopsy 2 months after their posttreatment assessment. No subject received more than 6 cycles of therapy. Individual subjects were followed off treatment until documented disease progression or until they completed 9 months of follow-up.

Figure 1 Trial Schema



Abbreviations: nPR = nodular partial response; PR = partial response; SD = stable disease.