Original Study

Phase I-II Clinical Trial of Oxaliplatin, Fludarabine, Cytarabine, and Rituximab Therapy in Aggressive Relapsed/Refractory Chronic Lymphocytic Leukemia or Richter Syndrome

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Abstract

We found that of 102 patients with relapsed/refractory chronic lymphocytic leukemia (CLL) (n = 67) or Richter syndrome (RS) (n = 35) treated with the OFAR2 (oxaliplatin, fludarabine, cytarabine, and rituximab) regimen, response rates (phase II) were 38.7% for RS (complete response [CR], 6.5%) and 50.8% for relapsed/refractory CLL (CR, 4.6%), and the median survival durations were 6.6 (RS) and 20.6 (CLL) months. Among patients who underwent allogeneic stem cell transplantation (SCT) as post-remission therapy, none has died with a median follow-up of 15.9 months.

Background: To improve outcomes of patients with Richter syndrome (RS) and relapsed/refractory chronic lymphocytic leukemia (CLL), we modified the OFAR1 regimen (oxaliplatin and cytarabine doses of the oxaliplatin, fludarabine, cytarabine, and rituximab) for this phase I-II study (OFAR2). **Patients and Methods:** OFAR2 consisted of oxaliplatin at 30 mg/m^2 on days 1 to 4, fludarabine at 30 mg/m^2, cytarabine at 0.5 g/m^2, rituximab at 375 mg/m^2 on day 3, and pegfilgrastim at 6 mg on day 6. Fludarabine and cytarabine were given on days 2 and 3 (cohort 1), days 2 to 4 (cohort 2), or days 2 to 5 (cohort 3) every 4 weeks. Phase II followed the "3 + 3" design of phase I. **Results:** The 102 patients (CLL, 67; RS, 35) treated had heavily pretreated high-risk disease. Twelve patients were treated in phase I; cohort 2 was the phase II recommended dose. The most common toxicities were hematologic. Response rates (phase II) were 38.7% for RS (complete response [CR], 6.5%) and 50.8% for relapsed/refractory CLL (CR, 4.6%). The median survival durations were 6.6 (RS) and 20.6 (CLL) months. Among 9 patients who underwent allogeneic stem cell transplantation (SCT) as post-remission therapy, none has died (median follow-up, 15.9 months). **Conclusion:** OFAR2 had significant antileukemic activity in RS and relapsed/refractory CLL. Patients undergoing SCT as post-remission therapy had favorable outcomes.

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Introduction

The clinical outcomes of patients with Richter syndrome (RS) and aggressive relapsed chronic lymphocytic leukemia (CLL) are generally poor. Even if these diseases respond to initial therapy, they eventually relapse and patients die of their disease.[1,2] However, the recent identification of prognostic factors and the development of newer therapies promise to improve treatment outcomes for patients with these diseases.[3] Platinum compounds, rituximab, fludarabine, and cytarabine are active agents against lymphoproliferative disorders, and platinum-based chemotherapy has shown significant activity in relapsed/refractory lymphoproliferative disorders.[4-10] Oxaliplatin is a third-generation platinum compound that is comprised of an organoplatinum complex in which the platinum atom is complexed with a 1,2-diaminocyclohexane carrier ligand and an oxalate ligand.[11,12] It is associated with more favorable renal and auditory toxicity profiles than seen with cisplatin.[12,13] The rationale for combining oxaliplatin with fludarabine and cytarabine is based on preclinical data demonstrating synergistic cytotoxicity between these nucleoside analogs and cisplatin.[14-17] In the clinic, sequential administration of fludarabine followed by cytarabine increased the leukemic cellular concentrations of the active cytarabine triphosphate by 40% to 200%.[18] The rationale for the design of the OFAR regimens was based on the hypothesis that fludarabine and cytarabine combined would inhibit DNA excision repair of the oxaliplatin adducts, resulting in synergistic cytotoxicity in RS and CLL.[19]

The results of our first phase I-II clinical trial of oxaliplatin, fludarabine, cytarabine, and rituximab (OFAR1) were encouraging.[19] The OFAR1 regimen (phase II) consisted of oxaliplatin at 25 mg/m^2/d (days 1-4), fludarabine at 30 mg/m^2 (days 2 and 3), cytarabine at 1 g/m^2 (days 2 and 3), and rituximab at 375 mg/m^2 (day 3). OFAR1 resulted in response rates of 50% and 36% in patients with RS and fludarabine-refractory CLL, respectively, but it was associated with myelosuppression.[19]

The OFAR1 phase I-II trial evaluated 3 doses of oxaliplatin. Although the combination was effective, the myelosuppression that was observed was felt to be caused by cytarabine. Thus, in OFAR2, the cytarabine dose was reduced from 1 to 0.5 g/m^2. Because of this decrease, it was judged that increasing the dose of oxaliplatin from 25 to 30 mg/m^2 would be tolerable and could contribute to additional antileukemic activity. The rationale for using oxaliplatin with fludarabine in CLL was based on previously published data demonstrating that fludarabine increases oxaliplatin cytotoxicity in normal and CLL lymphocytes by suppressing interstrand DNA cross-link removal.[20]

To increase the antileukemic activity and decrease the myelosuppression of this regimen, we designed a modified phase I-II study of OFAR1 (OFAR2). In OFAR2, the starting dose of oxaliplatin was increased from 25 mg/m^2 to 30 mg/m^2, and the daily dose of cytarabine was decreased from 1 g/m^2 to 0.5 g/m^2. In the phase I portion of OFAR2, 3 dose-escalation cohorts were evaluated (3 + 3 design) by increasing the number of days of cytarabine and fludarabine treatment (2, 3, or 4 days).

The objective of the phase I portion of OFAR2 was to determine the phase II recommended dose of fludarabine and cytarabine in combination with oxaliplatin and rituximab. The objectives of phase II were to assess the response rates, to define the safety and toxicity profile, and to determine the failure-free and overall survival durations.

Patients and Methods

Patients

Eligible patients were at least 18 years old and had histologically or cytologically confirmed Richter transformation, prolymphocytic leukemia, or aggressive, relapsed, or refractory B-cell CLL. Other eligibility criteria were performance status 0 to 2 (Zubrod scale); serum creatinine level $\leq$ 2 mg/dL or calculated creatinine clearance $>$ 50 mL/min; bilirubin level $\leq$ 2 mg/dL; and alanine aminotransferase or aspartate aminotransferase levels $<$ 2.5 times the upper limit of normal for the reference laboratory unless higher levels were caused by leukemia or congenital hemolytic disorder (for bilirubin); and platelet counts $> 20 \times 10^9$/L, unless lower counts were caused by disease involvement or autoimmune disorders. Patients were excluded if they were pregnant; had a history of oxaliplatin, fludarabine, cytarabine, or rituximab intolerance; had received chemotherapy and/or radiation therapy in the preceding 4 weeks; or had any other medical condition deemed by the investigator to be likely to interfere with their ability to give informed consent or cooperate/participate in the study or to interfere with the interpretation of the results. Signed informed consent forms explaining the investigational nature of the trial were obtained from all patients in accordance with institutional policy. The phase I portion of the trial was conducted at MD Anderson and the phase II portion included MD Anderson and other members of the CLL Research Consortium: Moore's Cancer Center, the University of California, San Diego, and Ohio State University Medical Center. The protocol was approved by the institutional review boards of the participating centers. The trial was conducted in accordance with the Declaration of Helsinki.

Data were analyzed by a biostatistician (S.W.) and all authors had access to primary clinical trial data. The study was registered in www.clinicaltrials.gov (registration No. NCT00472849).

Treatment

In the phase I portion of this study, oxaliplatin was administered intravenously (IV) at 30 mg/m^2 daily on days 1 through 4 (2-hour infusion). Rituximab at 375 mg/m^2 IV (4- to 6-hour infusion) was administered on day 3 of the first cycle and day 1 of subsequent cycles. Pegfilgrastim at 6 mg subcutaneously was administered on day 6. Three dose-escalation cohorts were evaluated using a "3 + 3" design that increased the number of days of cytarabine and fludarabine treatment from 2 days (days 2 and 3; cohort 1) to 3 days (days 2-4; cohort 2) to 4 days (days 2-5; cohort 3). The daily dose of fludarabine was 30 mg/m^2 IV (30-minute infusion starting after oxaliplatin completion), and the daily dose of cytarabine was 0.5 g/m^2 IV (2-hour infusion starting approximately 4 hours after fludarabine was started).

Patients were to receive a subsequent cycle of treatment no less than 4 weeks from the initiation of the previous cycle if no drug-related grade 3 or 4 nonhematologic life-threatening adverse events had occurred and drug-related nonhematologic toxicity had resolved to baseline or $<$ grade 2.