Original Study

A Phase I Study of Fludarabine, Cytarabine, and Oxaliplatin Therapy in Patients With Relapsed or Refractory Acute Myeloid Leukemia

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Abstract

We conducted a phase I study combining oxaliplatin with cytarabine and fludarabine for patients with relapsed or refractory AML. Oxaliplatin 30 mg/m^2/d on days 1 to 4, fludarabine 30 mg/m^2, and cytarabine 500 mg/m^2 on days 2 to 6 was the MTD. Of 27 patients who were treated, 3 had a complete remission and 2 patients had complete remission without platelet recovery.

Purpose: The combination of cytarabine and fludarabine was associated with superior clinical outcomes compared with those of high-dose cytarabine in relapse acute myeloid leukemia (AML). We conducted a phase I study combining oxaliplatin with cytarabine and fludarabine therapy for patients with relapsed or refractory AML. **Patients and Methods:** Between January 2008 and November 2009, 27 patients were registered in the study. Patients had histologically confirmed disease, performance status 0 to 2, and adequate organ function. The treatment regimen consisted of increasing doses of oxaliplatin (25, 30, or 35 mg/m^2/d) on days 1 to 4 (escalation phase), and fludarabine (30 mg/m^2) and cytarabine (500 mg/m^2) on days 2 to 6, every 28 days for $\leq$ 6 cycles. The dose-limiting toxicity was defined as any symptomatic grade $\geq$ 3 nonhematologic toxicity lasting $\geq$ 3 days and involving a major organ system. **Results:** Of 27 patients, 12 were treated in the dose-escalation phase and 15 at the maximum tolerated dose for oxaliplatin (30 mg/m^2; expansion phase). All patients were evaluable for toxicity and response. Only 1 patient received the second cycle; the remaining patients received no further study treatment, owing to slow recovery from toxicities or physician decision. Grade 3-4 drug-related toxicities included diarrhea (grade 4) and elevated levels of bilirubin (grade 3) and aspartate transaminase (grade 3). In all, 3 patients had a complete remission and 2 patients complete response without platelet recovery. **Conclusion:** Oxaliplatin, cytarabine, and fludarabine therapy had antileukemic activity in patients with poor-risk AML, but it was associated with toxicity. Different schedules and doses may be better tolerated.

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Introduction

Acute myeloid leukemia (AML) is the most common type of leukemia in adults, but it continues to be associated with the lowest overall survival rate of all leukemias. Despite progress in the understanding of the pathophysiology of AML, 20%-40% of patients are refractory to standard induction chemotherapy and 50%-70% of patients at first complete remission[1] are expected to have relapsed AML within 3 years; the prognosis following AML relapse is dismal.[2,3] High-dose cytarabine—based therapy has been the cornerstone of salvage chemotherapy for relapsed or refractory AML. The complete response (CR) rate in this clinical setting is approximately 30%.[3] The addition of other cytotoxic agents, such

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as mitoxantrone or mitoxantrone combined with etoposide, to cytarabine therapy was associated with increased toxicity without significant improvement in CR rates.[4]

Fludarabine (30 mg/m^2) and cytarabine (0.5 g/m^2/h for 2-6 h daily) therapy administered once daily for 5 days was superior to high-dose cytarabine therapy (3 g/m^2 over 2 h every 12 h for 2-6 days) for AML in relapse after an initial CR duration of $>$ 1 year.[5]

Oxaliplatin, a third-generation platinum compound, has shown activity in patients with Richter syndrome, relapsed or refractory chronic lymphocytic leukemia, and non-Hodgkin lymphoma.[6] Oxaliplatin comprises an organoplatinum complex in which the platinum atom forms a complex with 1,2-diaminocyclohexan carrier ligand and with an oxalate ligand.[7,8] In contrast to cisplatin and carboplatin, oxaliplatin causes minimal renal or auditory toxicity.[8,9] In our experience, the combination regimen of oxaliplatin, fludarabine, cytarabine, and rituximab had activity in patients with advanced lymphocytic leukemia, particularly in patients with large-cell transformation (ie, Richter syndrome), with a 58% response rate.[6]

Preclinical data have demonstrated the synergistic cytotoxicity of cisplatin in combination with the nucleoside analogues cytarabine[10] and fludarabine.[11,12] In the clinic, the timed, sequential administration of fludarabine followed by cytarabine causes an increase of 40% to 200% in the cellular concentrations of the active triphosphate of cytarabine in leukemia cells.[13,14] We hypothesized that the fludarabine–cytarabine combination would increase the sensitivity of leukemia cells to oxaliplatin by inhibiting DNA excision repair of the oxaliplatin adducts, thereby resulting in synergistic cytotoxicity in AML. In AML, increases in DNA repair processes have been suggested as the mechanism underlying resistance to agents that form DNA adducts. However, this increased capacity for excision repair could provide an opportunity for incorporation of nucleoside analogues into the DNA repair patch. Such incorporation at once blocks DNA repair and initiates signals for cell death.[15] We hypothesized that treatment of AML with nucleoside analogues and oxaliplatin would create a mechanistic interaction of these agents that would increase the killing of leukemia cells.

We therefore conducted an exploratory phase I study combining oxaliplatin with cytarabine and fludarabine for patients with relapsed or refractory AML. In patients with relapsed disease, enrollment was limited to patients in first relapse whose duration of first complete response[1] was $<$ 1 year.

The primary objectives of the study were to determine the maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) of oxaliplatin in combination with fludarabine and cytarabine; to assess the CR and CR with incomplete platelet recovery (CRp) rates; and to determine the safety and toxicity profile of combination therapy with oxaliplatin, fludarabine, and cytarabine in patients with relapsed or refractory AML.

The secondary objectives were to determine the duration of response, if any, and to assess toxicity in patients with relapsed or refractory AML.

Patients and Methods

Patient Characteristics

Eligibility criteria were histologically or cytologically confirmed relapsed or refractory AML with prior remission $<$ 1 year, performance status 0 to 2 (Zubrod scale), adequate renal and hepatic function (defined as serum creatinine level $\leq$ 2 mg/dL or creatinine clearance $>$ 40 mL/min), bilirubin level $\leq$ 2.0 mg/dL, and aspartate transaminase (AST) and alanine transaminase (ALT) values $<$ 3 $\times$ the upper limit of normal for the reference laboratory value unless due to leukemia. Uncontrolled infection, intolerance to any of the agents in the regimen, pregnancy, and lactation were reasons for exclusion. Enrollment had to be $\geq$ 4 weeks after prior chemotherapy. Before enrollment, all participants gave informed consent, and the study was approved by The University of Texas MD Anderson Cancer Center institutional review board.

Treatment

In the dose-escalation phase of the study, oxaliplatin was given at escalating doses of 25 mg/m^2 (dose level 1), 30 mg/m^2 (dose level 2), and 35 mg/m^2 (dose level 3) in a 30-minute infusion on days 1 to 4 (Table 1). Fludarabine was given at 30 mg/m^2 intravenously on days 2 to 6, and cytarabine was administered at 500 mg/m^2 by continuous intravenous infusion on days 2 to 6. Cycles were to be repeated every 28 days. All patients received antibacterial, antiviral, and tumor lysis prophylaxis as per institutional standards. In addition, each patient received the following antiemetic regimen approximately 30 minutes prior to chemotherapy during each cycle: dexamethasone at 20 mg intravenously on days 1 to 4, 5-HT3 antagonist (ondansetron at 8 mg intravenously every 8 h or granisetron at 1 mg intravenously or dolasetron at 100 mg intravenously or by mouth) administered on days 1 to 4, and lorazepam administered on days 1 to 4 at 1 to 2 mg intravenously (optional).

Table 1 Distribution of Patients, Treatment Cycles, and Dose-Limiting Toxicities Across Tested Dose Levels

Oxaliplatin Dose[a], mg/m^2 (days 1-4)	Number of Patients	Number of Patients Who Completed Cycle 1	Number of Patients With DLT	Description ofDLT[b]
25	3	3	0	
30	18	15	0	
35	6	4	3	Grade 3 elevation of ALT/AST Grade 3 high creatinine; renal insufficiency Grade 3 high bilirubin; hyperbilirubinemia

Abbreviations: ALT = alanine transaminase; AST = aspartate transaminase; DLT = dose-limiting toxicity.

[a]Fludarabine was given at 30 mg/m^2 intravenously on days 2 to 6, and cytarabine was administered at 500 mg/m^2 by continuous intravenous infusion on days 2 to 6. Cycles were to be repeated every 28 days.

[b]Dose-limiting toxicity was defined as any symptomatic $\geq$ grade 3 nonhematologic toxicity lasting $\geq$ 3 days and involving a major organ system (brain, heart, kidney, liver, or lung) in the National Cancer Institute toxicity scale, version 3.0.