A Phase I/II Study of the Janus Kinase (JAK)1 and 2 Inhibitor Ruxolitinib in Patients With Relapsed or Refractory Acute Myeloid Leukemia

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Abstract

Ruxolitinib is a potent and specific Janus kinase (JAK)1/JAK2 inhibitor recently approved for the treatment of myelofibrosis. We enrolled 27 patients older than 14 years with relapsed or refractory acute myeloid leukemia (n = 26) or acute lymphoid leukemia (n = 1). One patient with multiple relapses after 7 lines of therapy achieved a complete remission with incomplete recovery of peripheral blood counts (CRp) at a ruxolitinib dose of 200 mg twice per day (b.i.d.).

Background: Ruxolitinib is a potent and specific JAK1/JAK2 inhibitor recently approved for the treatment of myelofibrosis. **Patients and Methods:** We conducted a single-center phase I/II clinical study testing 3 dose levels (50 mg b.i.d. [n = 4], 100 mg b.i.d. [n = 5], and 200 mg b.i.d. [n = 18]). We enrolled 27 patients older than 14 years with relapsed or refractory acute myeloid leukemia (n = 26) or acute lymphoid leukemia (n = 1). **Results:** The median age was 66 (range, 25-88) years. Thirteen patients were evaluable for dose-limiting toxicities. The most common Grade 3 or 4 nonhematologic event was infection (n = 26 events; most frequently pneumonia; 15 of 26; 58%). One patient with multiple relapses after 7 lines of therapy had a CRp at a ruxolitinib dose of 200 mg b.i.d. **Conclusion:** In this cohort of heavily pretreated patients with relapsed or refractory acute leukemias, ruxolitinib was overall reasonably well tolerated, with 1 patient achieving CRp.

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Introduction

Acute myeloid leukemia (AML) is an aggressive hematologic malignancy representing a diverse group of clonal hematopoietic cell disorders. Despite progress in leukemia therapy, most adult patients with acute leukemia still die from disease progression. Approximately 13,780 new cases of AML were estimated to be diagnosed in the United States in 2012, and an estimated 10,200 people died of this disease during that year.[1] Treatment outcomes in AML remain poor, particularly in the relapsed or refractory setting.[2]

This study is registered at www.clinicaltrials.gov (NCT01251965)

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Because of continued poor prognosis, predominance of older patients who are unable to tolerate intensive chemotherapy, and high relapse rates despite achieving complete remission (CR), novel therapies are urgently needed in the upfront and relapsed settings. Assorted molecular markers have been identified in AML that represent potential therapeutic targets. One example is FMS-like tyrosine kinase 3 (FLT3), which harbors a constitutively active mutation in approximately 25% to 30% of AML patients.[3] Consequently, several FLT3 inhibitors are in clinical trials in AML. Another set of molecular lesions that have received increasing attention and research focus are activating mutations in the genes encoding the Janus kinase (JAK) family of enzymes, which have been initially identified as the main drivers of pathogenesis for BCR–ABL1-negative 'classic' myeloproliferative neoplasms (MPNs).[4-7] In addition to its importance in MPNs, the JAK-STAT (signal transducer and activator of transcription) pathway has been found to be dysregulated in a number of different hematologic malignancies,[8] including AML[9] and acute lymphoid leukemia

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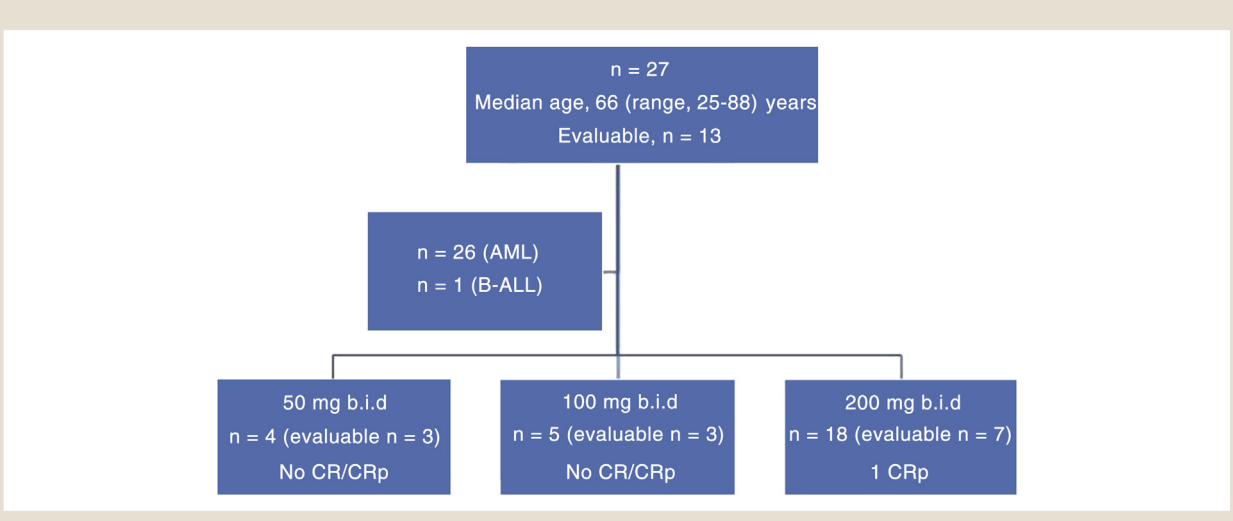
(ALL).[10-12] Further, JAKs have been identified as potential targets for development of novel therapies for AML on the basis of preclinical studies implicating abnormalities in JAK family kinases in progression/transformation to AML or ALL (either from antecedent MPN or de novo).[13-16] Ruxolitinib, a potent, selective JAK1 and JAK2 inhibitor was approved by the US Food and Drug Administration (FDA) for the treatment of intermediate- or high-risk myelofibrosis in 2011 and is being actively investigated as a treatment for patients with acute leukemia and other hematologic malignancies.[17-19] Notably, MPN patients derive clinically meaningful benefit, including enhanced survival, from ruxolitinib regardless of whether they harbor the *JAK2*V617F mutation, an important driver of pathogenesis in MPNs. The fact that the salutary effects of ruxolitinib are independent of the presence of a mutant clone in MPNs denotes that this drug inhibits the entire JAK-STAT pathway, which is universally overactive in these neoplasms, a situation distinct from most of the other kinase inhibitors (the activity of which is almost totally dependent on the presence of a mutated enzyme).

Recently, investigators from our group studied ruxolitinib in a phase II study[20] that enrolled patients with relapsed myeloid malignancies, including myelodysplastic syndrome (MDS) (n = 1), chronic myelomonocytic leukemia (n = 4), chronic myelogenous leukemia (n = 2), ALL (n = 3), and AML (n = 28) at a starting dose of 25 mg given orally twice daily (b.i.d.), with dose escalation up to 50 mg b.i.d.[20] In that study of 28 patients with AML (18 with AML secondary to MPN) who had received a median of 2 (range, 1-4) previous lines of therapy, 3 had a CR (1 with incomplete recovery of peripheral blood counts [CRp]). In all 3 responding patients, the response occurred in the absence of preceding myelosuppression, and disappearance of blasts from the bone marrow occurred slowly over a varying number of cycles. Responding patients also experienced a significant reduction in spleen size and improvement in their quality of life. Overall, ruxolitinib given at 25 and 50 mg b.i.d. was well tolerated, with only 4 patients developing Grade 3 or 4 toxicities. In the context of that phase II pilot trial, because ruxolitinib was overall well tolerated at these lower doses, we hypothesized that even higher doses of ruxolitinib might also be tolerated and potentially yield further clinical benefit in acute leukemia patients. In the present study, we sought to determine the safety, maximum tolerated dose (MTD), and dose-limiting toxicity (DLT) of ruxolitinib at doses of 50, 100, and 200 mg b.i.d. in patients with relapsed/refractory acute leukemia.

Patients and Methods

This phase I/II clinical trial enrolled patients with relapsed or refractory acute leukemia who were treated at The University of Texas M.D. Anderson Cancer Center (MDACC). The primary objectives were to determine safety, including DLT and MTD of ruxolitinib in patients with relapsed/refractory AML or ALL, and to describe the clinical activity of ruxolitinib in this patient population. Inclusion criteria included the following: age older than 14 years; diagnosis of relapsed or refractory AML or ALL; adequate organ function (alanine aminotransferase and/or aspartate aminotransferase $\leq$ 1.5 times the upper limit of normal and serum creatinine $\leq$ 2.5 mg/dL); Eastern Cooperative Oncology Group performance status (PS) $\leq$ 2; a period of at least 2 weeks having elapsed since the last specific antileukemic therapy (with the exception of hydroxyurea); and no other active malignancies (with the exception of basal cell or squamous cell carcinoma of the skin, or carcinoma "in situ" of the cervix or breast). Patients with known HIV positivity, active hepatitis A, B, or C infection, or a serious psychiatric illness that would prevent them from yielding informed consent were excluded. Also excluded were pregnant or lactating women and patients with acute promyelocytic leukemia. The study was approved by the MDACC institutional review board and was conducted according to the principles of the

Figure 1 Clinical Study Algorithm for Phase I/II Study of Ruxolitinib in Patients With Relapsed/Refractory Acute Leukemia



Abbreviations: AML = acute myeloid leukemia; B-ALL = B-cell acute lymphoblastic leukemia; b.i.d. = twice per day; CR = complete response; CRp = complete remission with incomplete recovery of platelet count.