Brief report

MK-0457, a novel kinase inhibitor, is active in patients with chronic myeloid leukemia or acute lymphocytic leukemia with the T315I BCR-ABL mutation

Francis J. Giles,[1] Jorge Cortes,[1] Dan Jones,[1] Donald Bergstrom,[2] Hagop Kantarjian,[1] and Steven J. Freedman[2]

[1]Departments of Leukemia and Pathology, M. D. Anderson Cancer Center, Houston, TX; [2]Department of Clinical Oncology, Merck, Blue Bell, PA

MK-0457 (VX-680) is a small-molecule aurora kinase (AK) inhibitor with preclinical antileukemia activity. The T315I BCR-ABL mutation mediates resistance to imatinib, nilotinib, and dasatinib. MK-0457 has in vitro activity against cells expressing wild-type or mutated BCR-ABL, including the T315I BCR-ABL mutation. Three patients with T315I abl-mutated chronic myeloid leukemia (CML) or Philadelphia chromosome (Ph)–positive acute lymphocytic leukemia (ALL) have achieved clinical responses to doses of MK-04547 that are not associated with adverse events. Higher MK-0457 dose levels were associated with clinical responses and down-regulation of CrkL phosphorylation in leukemia cells. The possible role of AK inhibition in these clinical responses requires further investigation. The currently reported cases are the first observed clinical activity of a kinase inhibitor against the T315I phenotype. The observation of responses in 3 patients with T315I phenotype–refractory CML or Ph-positive ALL, at doses of MK-0457 associated with no significant extramedullary toxicity, is very encouraging. (Blood. 2007;109: 500-502)

Introduction

The aurora kinases (AKs) are essential for the regulation of mitotic chromosome segregation and cytokinesis. Aberrant AK activity occurs in many human tumors.[1] MK-0457 (VX-680) is a small-molecule AK and Janus kinase 2 (JAK-2) inhibitor that blocks cell-cycle progression and induces apoptosis in a diverse range of human tumor types.[2,3] It causes profound inhibition of tumor growth in xenograft leukemia models.[2] The T315I BCR-ABL mutation mediates clinical resistance to imatinib, nilotinib, and dasatinib.[4] MK-0457 has in vitro activity against cells expressing wild-type and mutated BCR-ABL, including the T315I BCR-ABL mutation.[5] To date, 3 patients with T315I abl-mutated chronic myeloid leukemia (CML) or Philadelphia chromosome (Ph)–positive acute lymphocytic leukemia (ALL) have been enrolled in an ongoing phase 1/2 study of MK-0457 for patients with refractory hematologic malignancies. We report here that MK-0457 is the first kinase inhibitor with clinical activity against this abl-mutated phenotype.

Patients, materials, and methods

Patients receive a 5-day continuous intravenous infusion (CIV) at 2- to 3-week intervals with dose escalation of MK-0457 in successive cohorts of 3 patients per dose level. Maximum tolerated dose (MTD) has not been reached with the 8, 12, 16, 20, 24, 28, and 32 mg/m^2/h dose levels. Intrapatient dose escalation is allowed. A nested polymerase chain reaction (PCR) strategy followed by direct DNA sequencing using the dideoxy-chain termination method was used to detect mutations in codons 221 to 500 of the BCR-ABL kinase domain. The protocol was approved by the MD Anderson Cancer Center (MDACC) Institutional Review Board and all patients provided written informed consent.

Results and discussion

The first patient with a T315I BCR-ABL mutation treated on study is a 53-year-old male diagnosed with CML in November 2001. Therapy was commenced with imatinib 400 mg per day resulting in a 15-month complete hematologic response (CHR). In May 2003, he lost CHR and commenced imatinib at 600 mg per day. In June 2003, the white blood cell (WBC) count was 430 $\times$ 10^9/L despite additional hydroxyurea, and the patient was referred to MDACC. He declined stem cell transplantation (SCT) and was treated with imatinib, hydroxyurea, and pegylated alpha interferon until March 2005 without hematologic response. The patient returned to MDACC with accelerated-phase (AP) CML and commenced therapy with nilotinib 600 mg twice a day in April 2005.[6] The patient had a transient response to nilotinib, which was discontinued in July 2005 when the T315I BCR-ABL mutation was detected. The patient was then treated with, and did not respond to, KOS-953 (17-allylamino-17-demethoxy-geldanamycin), an HSP-90 inhibitor.[7] He commenced therapy with MK-0457 at a dose of 12 mg/m^2/h in November 2005. By day 11 of cycle 1, the patient was pancytopenic with a WBC count of 0.4 $\times$ 10^9/L, hemoglobin (Hb) level of 76 g/L (7.6 g/dL), and platelet count of 31 $\times$ 10^9/L. These counts rapidly recovered, and 2 weeks later on day 1 of cycle 2 of therapy, the WBC count was 77 $\times$ 10^9/L, Hb level was 120 g/L (12 g/dL), and platelet count was 698 $\times$ 10^9/L. In the initial 4 cycles, this pattern was repeated (Figure 1) with an initial decrease in WBCs and a subsequent rise, with a steady increase, in platelet count to greater than 1000 $\times$ 10^9/L by end of cycle 4. Cycle 10 of therapy began in April 2006 at the 20 mg/m^2/h dose level at which time the patient was in chronic phase. The patient continues on

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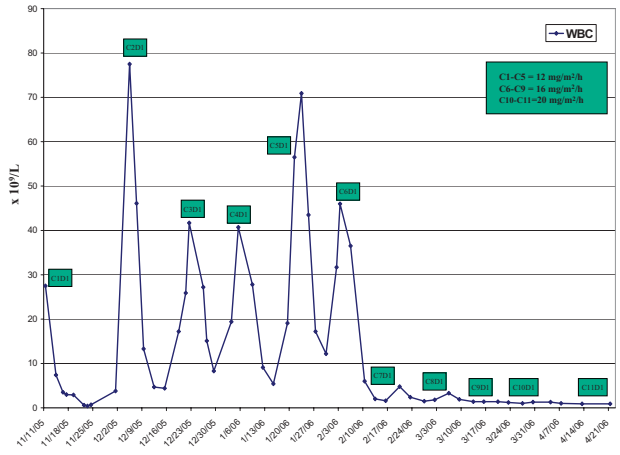

Figure 1. WBC response to MK-0457 therapy in a patient with imatinib- and nilotinib-resistant T315I BCR-ABL–positive CML.

MK-0457 therapy and has decreasing levels of T315I, with the latest result (July 2006) showing that 90% of PCR product is T315I.

The second patient with a T315I BCR-ABL mutation treated on study was a 33-year-old female diagnosed with CML in 1997. Following 6 months of hydroxyurea and alpha interferon therapy, she commenced imatinib, which she received at doses up to 800 mg daily until August 2005, at which time she had failed to achieve CHR and commenced dasatinib therapy.[8] After a transient response, she was taken off study in October 2005 secondary to lack of response. She was then referred to MDACC with refractory AP and was documented to have the T315I BCR-ABL mutation. The patient commenced therapy with MK-0457 at the 16 mg/m^2/h dose level in January 2006. Repeat PCR-based DNA sequencing of BCR-ABL no longer detected the presence of the T315I mutation after cycles 1 and 2 of therapy. The patient achieved hematologic response in June 2006 when receiving the 24 mg/m^2/h dose level and continues on MK-0457 single-agent therapy.

The third patient with the T315I BCR-ABL mutation is a 63-year-old male diagnosed with Ph-positive ALL in December 2003. He achieved CHR to standard induction therapy and received both systemic and intrathecal consolidation therapy. No cytogenetic response was achieved, and in September 2005 relapse was evident. He commenced dasatinib (70 mg twice a day) therapy. He achieved CHR and a diploid karyotype by November 2005. In January 2006, responses were lost and the dasatinib dose increased to 90 mg twice a day. The patient suffered recurrent lower nonthrombocytopenia-related gastrointestinal bleeding and dasatinib was discontinued in February 2006. The patient was then referred to MDACC and documented to have the T315I BCR-ABL mutation. The patient commenced therapy with MK-0457 at the 20 mg/m^2/h dose level in March 2006. At the time of study entry the patient had a WBC count of 15×10^9/L with 81% blasts. Following 2 cycles of therapy the patient had a CHR and stopped therapy to prepare for SCT, at which time the T315I was still dominant in the bone marrow.

BCR-ABL inhibition was monitored by performing peripheral blood flow cytometry for phosphorylation of CrkL, a BCR-ABL substrate,[9] at baseline and after the first MK-0457 cycle. In the CML patients treated initially at the 12 mg/m^2/h and 16 mg/m^2/h dose levels, the maximal plasma concentration of MK-0457 did not exceed 1 μM and no inhibition of pCrkL was detected. In the Ph-positive ALL patient dosed at 20 mg/m^2, the peak plasma concentration of MK-0457 exceeded 1 μM and pCrkL inhibition was detected. Both CML patients went on to achieve objective responses at dose levels of 20 mg/m^2/h and 24 mg/m^2/h, respectively, at which dose-level exposures exceed 1 μM. Carter et al[5] reported that with a 2-hour exposure to MK-0457, the 50% inhibitory concentration (IC_{50}) for inhibition of T315I BCR-ABL autophosphorylation in Ba/F3 cells was approximately 5 μM, which was significantly higher than their reported binding constant and IC_{50} for ABL enzymatic inhibition in vitro. On our analysis in T315I cell lines and leukemia cells, the IC_{50} for inhibition of BCR-ABL autophosphorylation with a 6-hour MK-0457 exposure is approximately 400 nM. Further data are needed on the relationship between MK-0457 pharmacokinetics and its clinical activity.

The only established therapeutic option for patients with the T315I BCR-ABL mutation is SCT.[4,10] Young et al[11] have presented a high-resolution crystal structure of the catalytic domain of a mutant form of Abl kinase (H396P), associated with imatinib resistance, in complex with MK-0457. MK-0457's binding to Abl accommodates the substitution of isoleucine for threonine at residue 315 (the "gatekeeper" position).[4,11] MK-0457's avoidance of the innermost Abl kinase domain cavity may explain its activity against mutant forms of Bcr-Abl, including T315.[11]The currently reported cases document the first observed clinical responses to a kinase inhibitor in the T315I phenotype. The relative contributions of AK, BCR-ABL, and JAK-2 inhibition have not been established. Responses in patients with refractory CML or Ph-positive ALL at doses of MK-0457 associated with no significant extramedullary toxicity are very encouraging.

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Authorship

Contribution: F.J.G. designed research, performed research, analyzed data, and wrote the paper; J.C., D.J., and H.K. performed research, analyzed data, and wrote the paper; and D.B. and S.J.F. designed research, analyzed data, and wrote the paper.

Conflict-of-interest disclosure: D.B. and S.J.F. are employed by Merck, whose product (MK-0457) was studied in the present work.

Correspondence: Francis J. Giles, The University of Texas M. D. Anderson Cancer Center, Department of Leukemia, 1400 Holcombe Blvd, Box 428, Houston, TX 77030; e-mail: frankgiles@aol.com.

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