Activity of the Aurora Kinase Inhibitor VX-680 against Bcr/Abl-Positive Acute Lymphoblastic Leukemias

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Abstract

The emergence of resistance to tyrosine kinase inhibitors due to point mutations in Bcr/Abl is a challenging problem for Philadelphia chromosome–positive (Ph-positive) acute lymphoblastic leukemia (ALL) patients, especially for those with the T315I mutation, against which neither nilotinib nor dasatinib shows significant activity. VX-680 is a pan-Aurora kinase inhibitor active against all Bcr/Abl proteins but has not been extensively examined in preclinical models of Ph-positive ALL. Here, we have tested VX-680 for the treatment of Bcr/Abl-positive ALL when leukemic cells are protected by the presence of stroma. Under these conditions, VX-680 showed significant effects on primary human Ph-positive ALL cells both with and without the T315I mutation, including ablation of tyrosine phosphorylation downstream of Bcr/Abl, decreased viability, and induction of apoptosis. However, drug treatment of human Ph-positive ALL cells for 3 days followed by drug removal allowed the outgrowth of abnormal cells 21 days later, and on culture of mouse Bcr/Abl ALL cells on stroma with lower concentrations of VX-680, drug-resistant cells emerged. Combined treatment of human ALL cells lacking the T315I mutation with both VX-680 and dasatinib caused significantly more cytotoxicity than each drug alone. We suggest that use of VX-680 together with a second effective drug as first-line treatment for Ph-positive ALL is likely to be safer and more useful than second-line treatment with VX-680 as monotherapy for drug-resistant T315I Ph-positive ALL. Mol Cancer Ther; 9(5); 1318–27. ©2010 AACR.

Introduction

Philadelphia chromosome–positive (Ph-positive) leukemias are characterized by the presence of a BCR-ABL fusion gene, resulting from a reciprocal translocation between chromosomes 9 and 22. The product of this gene, the Bcr/Abl oncoprotein, is a constitutively active tyrosine kinase that initiates chronic myeloid leukemia (CML) and ∼30% of acute lymphoblastic leukemia (ALL; refs. 1, 2). The tyrosine kinase inhibitor imatinib (formerly STI571), which relatively selectively interrupts Bcr/Abl oncogenic signaling, has become the new “gold standard” for the treatment of patients with CML (3). However, a subset of patients develops resistance to imatinib due to point mutations within the Abl kinase domain, which impair imatinib binding (4–6). The need for overcoming imatinib resistance has led to the development of a second generation of tyrosine kinase inhibitors, including nilotinib and dasatinib (7, 8). Although these bind to the majority of Abl mutants, neither has significant activity against leukemia cells with the Abl T315I mutation (9). This mutation has been reported to occur in ∼20% of imatinib-resistant CML patients that had been treated with this drug (7, 10). Leukemias carrying Abl point mutations seem to be rapidly selected out by treatment with such drugs, particularly in Ph-positive ALL: these were detected on average 10 months after initiation of kinase inhibitor treatment (11). Because of these reasons, the search for additional treatment for Ph-positive leukemias continues.

Serine/threonine kinases of the Aurora family, including Aurora A, Aurora B, and Aurora C, are essential for the control of mitotic processes during cell division (12). Abl mutant activation occurs in a variety of human tumor cells, indicating a role for this family in tumorigenesis (13, 14). VX-680 (MK-0457) is a pan-Aurora kinase inhibitor that induces apoptosis in many human tumor types by blocking cell cycle progression (14). Interestingly, Carter et al. (15), using a murine cell line transfected with different Bcr/Abl mutants, reported that VX-680 inhibits the activity of both wild-type and mutated Bcr/Abl proteins, including those with the T315I mutation. VX-680 is able to bind to Abl in a mode that accommodates the substitution of isoleucine for threonine at residue 315, the so-called gatekeeper position (16). Dai et al. (17) also showed that VX-680 is effective in imatinib-resistant CML cells and Ba/F3 cells expressing T315I Bcr/Abl. Similar results were observed by Fiskus et al. (18) who found that VX-680...
induces cell death in acute myeloid leukemia and CML cell lines.

Surprisingly, few other preclinical studies have been done with VX-680 on Ph-positive leukemias, and of these, most concentrated on CML or on cell line models for CML, such as K562. Moreover, studies with existing CML cell lines were done in the absence of stroma and those using primary patient materials used short-term treatment. However, the drug was used to treat three patients with two CML and one Ph-positive ALL with the T315I mutation in a small phase I study (19).

Because of the reported activity on the Bcr/Abl T315I mutant, drugs such as VX-680 may find increased use in the secondary treatment of relapsed Ph-positive ALL, in which drug resistance to imatinib, dasatinib, and nilotinib tends to rapidly evolve. However, it remains poorly characterized for this purpose. It is a reason for concern that mutant mice lacking one copy of the Aurora A kinase are more prone to develop malignancies than those who have the normal genetic complement, and treatment of mouse embryonic fibroblasts (MEF) with VX-680 caused the emergence of hyperdiploid cells (20). For these reasons, we have here explored the effects of long-term VX-680 treatment in both mouse and human Bcr/Abl-positive ALL cells in the presence of stroma to more closely approximate treatment with this drug in vivo.

Dasatinib (Sprycel, formerly BMS-354825; Bristol-Myers Squibb) is a potent, orally bioavailable dual Abl and Src kinase inhibitor that has been developed for overriding imatinib resistance (21). Dasatinib exhibits a 325-fold greater potency than imatinib in inhibiting the activity of nonmutated Bcr/Abl and is active against most imatinib-resistant Bcr/Abl mutations, except the T315I mutation (7, 22). We additionally report that relatively high VX-680 concentrations are needed to inhibit wild-type and T315I Bcr/Abl but that a combination with dasatinib in those ALL cells that respond to it is very effective in eradicating the ALL cells.

### Materials and Methods

**Drugs, reagents, and cells.** VX-680 (Selleck Chemicals LLC), dasatinib (Toronto Research Chemicals), AMN107 (nilotinib, Novartis), and vincristine (Hospira, Inc.) were diluted in DMSO.

The murine OP9 stromal cell line (CRL-2749) was obtained from the American Type Culture Collection. Human Ph-positive ALL cells (also see Table 1) include those expressing wild-type Bcr/Abl (UCSF02, TXL2, TXL3, and US9) and T315I mutants (BLQ1 and Pi2). TXL2 has been described and was from a Ph-positive ALL patient at diagnosis (23). US7 and US7R are Ph-negative ALL cells; however, US7R was isolated from the same patient in relapse phase. All human ALL samples expressed the Bcr/Abl P210 or P190 fusion protein (data not shown). The primary cells were passaged in (NOD/SCID/IL2Rγ−/−) mice (The Jackson Laboratory).

Leukemia cells harvested from the spleens of these mice were plated on irradiated OP9 feeder layers. The 8093 and Bin2 human Bcr/Abl P190-expressing transgenic mouse lymphoblastic leukemia cells have been previously described (24–26) and were grown in the presence of E13.5 irradiated MEFs. Mouse leukemia cells were grown in McCoy’s 5A medium including 15% fetal bovine serum (Invitrogen Corp.) supplemented with 110 mg/L sodium pyruvate, 1% L-glutamine, 1% penicillin/streptomycin, 10 ng/mL recombinant interleukin-3 (Invitrogen), and 50 μmol/L 6-mercaptoethanol. Human leukemia cells were grown in αMEM medium supplemented with 20% fetal bovine serum, 1% L-glutamine, and 1% penicillin/streptomycin.

**In vitro treatment with VX-680, dasatinib, AMN107, and vincristine.** Lymphoblastic leukemia cells were seeded in the wells of a 24-well plate or a 6-well plate at a density of 1 × 10⁶/mL in the presence of either irradiated OP9 cells or E13.5 MEFs. Cells were treated with drugs as indicated in triplicate wells, and viability of cells was measured by trypan blue exclusion. In experiments to make drug-resistant 8093 cells, VX-680 or nilotinib (AMN107) was added every 2nd day along with a fresh complete change of medium. Apoptotic cells were measured using Annexin V-FITC Apoptosis Detection Kit I (BD Pharmingen). Apoptotic cells were defined by double positivity for Annexin V and propidium iodide assessed by flow cytometry (FACScan, Becton Dickinson). For cell cycle distribution, cells were washed and fixed in 70% ethanol for 1 hour. Fixed cells were stained with propidium iodide and subjected to flow cytometry.

**Western blotting.** Human leukemia cells (BLQ1 and TXL2 cells) were treated with various concentrations of VX-680 with or without 100 nmol/L dasatinib for 24 hours and lysed in radioimmunoprecipitation assay buffer [50 mmol/L Tris-HCl (pH 8.0), 150 mmol/L NaCl, 1% Triton X-100, 0.5% deoxycholate, 0.1% SDS, 5 mmol/L EDTA] containing phenylmethylsulfonyl fluoride, aprotonin, leupeptin, pepstatin A, sodium fluoride, and...
sodium orthovanadate for 30 minutes on ice. Cell extracts were subjected to 8% to 15% SDS-PAGE. Membranes were reacted with PY20-horseradish peroxidase (BD Transduction Laboratories); phospho-Src family (Tyr416), Src, phospho—signal transducer and activator of transcription 5 (Stat5; Tyr694), and Aurora A (all from Cell Signaling Technology); Bcr (N-20) and Crkl (both from Santa Cruz Biotechnology); and glyceraldehyde-3-phosphate dehydrogenase (GAPDH; Chemicon International) antibodies using standard procedures.

**Giemsa staining.** For morphology analysis, cells were cytospun onto glass slides and fixed in methanol for 5 minutes, dried, and stained with Wright-Giemsa (Sigma). Cell images were acquired with an Axioplan 2 imaging upright microscope (Carl Zeiss).

**Statistical analysis.** Statistical analysis was done with SPSS software. Data are presented as mean ± SD. Statistical significance of differences between groups was evaluated using one-way-ANOVA (post hoc Scheffe test). *P* < 0.05 was considered to be statistically significant.

**Results**

**VX-680 is cytotoxic for Bcr/Abl-positive lymphoblastic leukemia cells, including those carrying the T315I mutation.** Aurora kinases have abnormally high levels of expression in several cancers (13). To investigate Aurora kinase expression in ALL, we did Western blotting using Aurora A antibodies on primary human ALL samples that had been passaged in nonobese diabetic/severe combined immunodeficient mice and subsequently grown on OP9 stromal support. As shown in Fig. 1, compared with controls, high levels of Aurora A were present in these leukemia samples. BLQ1, P12, TXL2, and UCSF02 (Table 1) are primary human Ph-positive ALLs. 8093 and Bin2 were isolated from the lymph nodes of BCR-ABL transgenic mice and are grown as cell lines in combined immunodeficient mice and subsequently treated with either drug alone, an increase in the numbers of cells with less than N DNA content was seen at 48 hours. Together, these results show that VX-680 and dasatinib synergize to induce cytotoxic activities in wild-type Bcr/Abl-positive ALL cells.

**VX-680 inhibits Bcr/Abl kinases in Bcr/Abl-positive ALL cells in coculture with stroma.** VX-680 was reported to inhibit both Aurora kinases and the Bcr/Abl kinase in vitro (16), whereas dasatinib targets Bcr/Abl as well as Src family kinases (27). To evaluate the effect of these drugs on Bcr/Abl when the ALL cells were grown in the presence of protective stroma, we treated BLQ1 and TXL2 cells with different concentrations of VX-680 with or without 100 nmol/L dasatinib for 24 hours. Figure 4 shows that treatment with 5 μmol/L VX-680 caused distinct inhibition in total phosphoryrosine, reflecting both direct and indirect substrates of the activated Bcr/Abl tyrosine kinase. We also evaluated the phosphorylation status of Crkl, a direct Bcr/Abl substrate, and that of Stat5, a well-known downstream target of Bcr/Abl. As shown in Fig. 4, without drug treatment, the majority of Crkl protein was phosphorylated in both BLQ1 and TXL2. After exposure to increasing concentrations of
Figure 2. VX-680 shows cytotoxic activity against human and mouse Bcr/Abl lymphoblastic leukemia cells. A, BLQ1 (T315I mutation), Pt2 (T315I mutation), TXL2 (no mutation), UCSF02 (no mutation), 8093, and Bin2 cells (1 × 10^6 per well) were grown in the presence of stroma. Viable cell counts were done in triplicate over a 24- to 72-hours period as indicated. Bars, SD. Results shown are one of two independently done experiments with similar results. B, BLQ1 and UCSF02 cells were treated with increasing concentrations of VX-680 for 48 hours. The percentage of apoptotic cells was determined by fluorescence-activated cell sorting analysis. C, BLQ1 cells were treated with 1 μmol/L VX-680 and cell cycle distribution was determined by flow cytometry at time points of 24 and 48 hours.
VX-680 for 24 hours, Crkl shifted to its nontyrosine phosphorylated, more rapidly migrating form but 10 μmol/L drug was required to inhibit all Crkl phosphorylation. Cotreatment with 1 μmol/L VX-680 and 100 nmol/L dasatinib in TXL2 cells (Fig. 4, right) induced a more significant reduction in phosphotyrosine, phospho-Crkl, phospho-Stat5, and phospho-Src than treatment with either VX-680 or dasatinib alone, whereas there was no significant effect of combining VX-680 with dasatinib in BLQ1 cells with the T315I mutation.

**Short-term response of leukemia cells to VX-680.** As mentioned above (Fig. 2A), after a 3-day treatment, VX-680 at a concentration of 1 μmol/L only killed ∼50% of the human ALL cells cocultured with stromal support. In the study reported by Giles et al. (19), two CML patients had a clinical response at doses of 20 and 24 mg/m²/h, reaching maximal plasma concentrations of 1 μmol/L or more, whereas levels of <1 μmol/L were reported at 12 and 16 mg/m²/h. Drug was administered continuously by i.v. infusion for a period of 5 days, followed by 14- to 21-day intervals without drug. We therefore wondered what the long-term effect could be of treatment with the drug followed by no treatment. To investigate this, BLQ1 cells were exposed to 1 μmol/L VX-680 for 3 days. After

Figure 3. VX-680 and dasatinib synergize to induce cytotoxic activity in wild-type Bcr/Abl-positive human ALL cells. A, TXL2 and UCSF02 cells were exposed to 1 μmol/L VX-680 with or without 100 nmol/L dasatinib for 24 to 72 hours as indicated, after which the percentage of viable cells was determined by trypan blue exclusion. B, TXL2 cells were treated with or without VX-680 and dasatinib for 48 hours in triplicate. **, P < 0.001, VX-680 and dasatinib cotreated TXL2 compared with VX-680–treated or dasatinib alone–treated TXL2 cells. Apoptotic cells were defined by flow cytometry as Annexin V and propidium iodide (PI) double-positive cells. C, TXL2 cells were exposed to VX-680 and/or dasatinib and cell cycle distribution was assessed by flow cytometry.
3 days, the drug was washed out and the cells were cultured without VX-680. From day 3 to day 21, we assessed their viability, numbers, and cell cycle distribution. As shown in Fig. 5A (top left), after 3 days of VX-680 exposure, viability of the cells decreased to 40%-50%. After removal of the drug, viability of the culture began to gradually increase. On day 15, viability of the culture had reached a level similar to that of the control group and the cells were able to proliferate again (Fig. 4A, bottom left). Cell cycle analysis indicated that although we removed VX-680, a subpopulation of BLQ1 cells was still arrested, with more than 4N DNA content (37%), compared with cells untreated with VX-680 (22.8%). On day 21, we compared BLQ1 cells that had never been VX-680 treated with those that had been exposed to the drug 21 days before (BLQ1-VX-Tx). Remarkably, compared with the control cells, a subpopulation of the VX-680–treated BLQ1 cells was much larger (Fig. 5B) than the original cells. Similar results were obtained with Pt2 cells (data not shown).

We then compared the sensitivity of BLQ1 and BLQ1-VX-Tx to treatment with VX-680. We found that BLQ1-VX-Tx cells were still sensitive to VX-680 (Fig. 5C). We also treated BLQ1 and BLQ1-VX-Tx cells with vincristine, a tubulin-depolymerizing agent. Interestingly, BLQ1-VX-Tx cells were more sensitive \( (P < 0.05) \) to vincristine than the original BLQ1 cells.

**Long-term treatment of leukemia cells with VX-680 in the presence of stroma.** We also wished to investigate the effect of long-term continuous treatment of Bcr/Abl-positive ALL cells with VX-680 to address the question if ALL cells would ever emerge that were able to proliferate in the presence of this drug. The relatively low proliferation rate of the human ALL cells precluded their use for this purpose. However, murine Bcr/Abl ALL cells proliferate rapidly on stroma and were therefore suitable to test this. We added VX-680 every second day along with a fresh change of medium to 8093 ALL cells. Consistent with the results in Fig. 2A, 75 nmol/L VX-680 decreased the viability of 8093 cells from 80%-90% to 25%-30% in the first 3-4 days. However, viability of 8093 cells began to increase gradually thereafter, and on the tenth day, viability of the culture recovered to a level similar to that of the control group. Thus, with the support of stroma, the cells were able to proliferate again even in the presence of concentrations of VX-680, which initially could kill \( \sim 70\% \) of cells within the first 2-3 days of treatment.

We next compared the sensitivity of the original 8093 cells and the VX-680–resistant 8093 cells (8093R) to treatment with 16 nmol/L nilotinib (AMN107) in the presence of stroma. As reported before (25), 8093 cells were sensitive to nilotinib and it caused a drop in viability to 20%-30% in the first 2-4 days. Similar to 8093 cells,

![Figure 4. VX-680 eliminates Bcr/Abl kinase activities. BLQ1 (T315I mutation) and TXL2 (no mutation) cells were treated with the indicated concentrations of VX-680 with or without 100 nmol/L dasatinib for 24 hours. Western blot analysis was done on total lysates with the antibodies indicated to the left. Blots were stripped and reprobed with Bcr (N-20), Src, and GAPDH antibodies as loading controls.](image-url)
8093R cells were initially sensitive to nilotinib (Fig. 6A) but both 8093 and 8093R cells were able to develop stroma-assisted resistance to nilotinib after more prolonged culture. In contrast to the BLQ1-VX-Tx cells (Fig. 5), we found that there was no difference in the cell cycle distribution and size between 8093 and 8093R cells (Fig. 6B and C). We also isolated RNA from VX-680–resistant 8093 cells to sequence the Abl ATP-binding domain of Bcr/Abl. However, the region of Abl encoding the ATP-binding pocket as well as the activation loop lacked point mutations in the VX-680–resistant cells (data not shown).

Discussion

In the present study, we have examined the activity of the Aurora kinase inhibitor VX-680 against Ph-positive ALL cells that were provided with the protective effect of stromal support, a clinically relevant model. Used as a monotherapy and at a concentration of 1 μmol/L, this drug compares quite favorably with dasatinib in terms of reducing overall ALL cell viability. Moreover, this is a concentration that was reported in the plasma of patients responding to and treated with this drug.

Using the CML cell lines K562 and BV-173 and two fresh CML patient samples but without stroma, Donato et al. (28) argued that inhibition of the Bcr/Abl T315I mutant is unlikely to be a major factor in the activity of VX-680 at clinically achievable (up to 5 μmol/L) levels. Our studies support this concept to some extent. We did notice a reduction in overall phosphoryrosine in the BLQ1 cells with T315I at 1 μmol/L concentrations. However, because of the nonquantitative nature of the assay used by ourselves and others (Western blotting), this is difficult to translate into clinical effects. The tyrosine phosphorylation of Crkl, a direct substrate of Bcr/Abl, was only blocked at high levels of VX-680. Nonetheless, VX-680 concentrations as low as 1 μmol/L generated

![Figure 5](image)

Figure 5. Responses of human ALL cells to short-term VX-680 treatment. A, BLQ1 cells were treated with 1 μmol/L VX-680 for 3 days. After 3 days, the drug was removed from the medium and cells were cultured without VX-680. During this period (days 3–21) without drug, viability (top left), cell numbers (bottom left), and cell cycle distribution (right) of BLQ1 cells were assessed. B, BLQ1 and BLQ1-VX-Tx cells were cytospun onto glass slides and fixed, dried, and stained with Wright-Giemsa on day 21. All images are at ×63 magnification. C, BLQ1 and BLQ1-VX-Tx cells were treated with 1.5 μmol/L VX-680 or 5 nmol/L vincristine for 72 hours. Cell viability was measured by trypan blue exclusion. *, P < 0.05, vincristine-treated BLQ1 compared with vincristine-treated BLQ1-VX-Tx.
a notable reduction in phospho-Stat5 levels, with a complete elimination of phospho-Stat5 at 5 μmol/L. We speculate that this is an effect of this drug on other kinase activities in these cells, albeit not of Src, of which the tyrosine phosphorylation was unaffected by VX-680.

We found that VX-680 reduced viability of the two human T315I-bearing ALL samples somewhat better than that of the two samples lacking the mutation. However, this is unlikely to be correlated with the mutation status. Because the two Ph-positive ALL samples lacking the T315I grow somewhat more slowly than those with the mutation, it seems that the different activity of VX-680...
on these cells may reflect the activity of the drug on Aurora kinases and cell cycle.

The only clinical trial published with this drug for the treatment of Ph-positive leukemias used a regimen of a 5-day treatment followed by a 14- to 21-day nontreatment. Dreier et al. (29) studied the long-term fate of colon cancer cell lines after short-term treatment with Aurora kinase inhibitors. After treatment with ZM447439 for 4 to 7 days, followed by removal of the drug, cells of different sizes with variable numbers of nuclei were recovered, which were able to proliferate. They hypothesized that such cells initially underwent multiple failed divisions in the presence of the Aurora kinase inhibitors and as a result became multinucleated giants. On removal of the drug, some of these giant cells were able to divide again in an asymmetrical way, producing giant cells as well as small cells. In our studies, after treatment of BLQ1 cells with 1 μmol/L VX-680 for 3 days, followed by the removal of the drug from the culture system, we observed the appearance of ALL cells that were clearly larger than the original cells. Alarming is, the cells we obtained were able to proliferate. In combination with the reports that VX-680 treatment of MEFs causes the emergence of hyperdiploid cells, we were concerned that these large ALL cells could represent a population with a greater degree of malignancy.

However, when we retreated these BLQ1 cells with VX-680, they were still sensitive to the drug and showed a greater sensitivity to vincristine. Dreier et al. (29) noted that the clones that emerged after removal of ZM447439 were not resistant to the drug, and in this study, the cells proliferated at similar rates to the parental cell line. Walsby et al. (30) indicated that after treatment of the NB4 acute myeloid leukemia cell line for 48 hours with AZD1152-HQPA or ZM447439, the cells showed a reduced clonal growth when replated as single cells, indicating that recovery from hyperploidy was impaired.

To examine the possibility of environmental-mediated drug resistance to VX-680, we determined the effects of long-term treatment with it on ALL cells in the presence of stroma. Consistent with our previous studies using other drugs (31), we observed the emergence of VX-680-resistant cells. Unlike the short-term–treated human ALL cells, these VX-680-resistant cells were similar in size to the parental cells. Similar to the parental cells, they could be made resistant to 16 nmol/L nilotinib, but reassuringly, the development of resistance to this drug was not accelerated. However, these in vitro results suggest that it will not be possible to eradicate all Ph-positive ALL cells when they are in the presence of stroma, regardless of whether in short-term or long-term treatment, if VX-680 is used as monotherapy.

Because VX-680 was reported to inhibit Ph-positive leukemias that have a T315I-mutant Bcr/Abl, the option to use this drug as a second-line monotherapy after the development of drug-resistant ALL is obvious. However, a drug that is specifically targeted to inhibit the Bcr/Abl T315I mutant has been recently reported (30). Based on the impressive cell killing noted in our study by the simultaneous use of VX-680 with dasatinib in Ph-positive ALL cells lacking T315I, as well as the useful effect of VX-680 on other kinases besides Bcr/Abl, we suggest that first-line therapy of Ph-positive ALL could include the use of Aurora kinase inhibitors together with a second drug. A combination of imatinib with intensive chemotherapy was recently reported to increase the event-free survival of children with Ph-positive ALL (30). Similarly, combinations of VX-680 with different kinase inhibitors, such as imatinib, dasatinib, nilotinib, or the newly reported AP24534, might be effective to definitively preclude the emergence of drug-resistant leukemia cells.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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