Correspondence

Experience with obatoclax mesylate (GX15-070), a small molecule pan–Bcl-2 family antagonist in patients with relapsed or refractory classical Hodgkin lymphoma

Bcl-2 overexpression is frequently observed in classic Hodgkin lymphoma (cHL) and may confer poor prognosis. Obatoclax mesylate (GX15-070) is a small-molecule antagonist of the Bcl-2 family of proteins, which activates apoptosis in vitro and exhibits anti-tumor activity in animal models. The safety has been tested in human. We report the result of a phase 2 study of obatoclax in patients with relapsed or refractory cHL.

This study was supported by GeminX, registered at clinicaltrials.gov (NCT00359892) and approved by the institutional review board. Patients were eligible if they had relapsed or refractory cHL with a bidimensionally measurable disease, had received a minimal of 1 prior treatment and had progression of disease after stem cell transplant or were not a transplant candidate. They were required to have adequate major organ functions. Single-agent obatoclax was administered intravenously at 60 mg over 24 hours every 2 weeks.

Response was evaluated by CT after 4 cycles of treatment. Simon’s 2-stage model was used to evaluate the success rate (no progressive disease in 8 weeks) with α of 0.05 and a power of 0.8. We considered success rate ≥ 20% to be meaningful and ≤ 5% to be of no interest. If success was seen in ≥ 1 of first 10 patients, accrual was to continue to 29 patients.

Thirteen eligible patients received at least 1 dose of obatoclax (Table 1). Although the study met its first step end point, the lack of significant response decreased enthusiasm for continuing enrollment. The median number of prior treatment regimens was 6 (range 3-11). A total of 80 cycles of obatoclax was administered, with the median 4 cycles per patient (range 1-24). One patient withdrew consent after one treatment. Two patients were hospitalized for the management of fever with intravenous antibiotics before response evaluation and were taken off study. Otherwise the treatment was generally well tolerated. Toxicities that were considered to be definitely or probably related to the study drugs were dizziness (n = 5), euphoria (n = 3) and hypotension (n = 1), which were all grade 1.

There was no objective response observed. Five patients experienced a progression of disease within 8 weeks after initiation of treatment. Five patients had stable disease (38%) on evaluation after 8 weeks. One of them was taken off study at treating physicians discretion, because of lack of clinical benefit, and in other 4 patients with stable disease, the event free survival was 16, 16, 24, and 98 weeks.

Plasma concentrations of obatoclax were evaluated at 3, 23 and 25 hours after the first cycle of therapy in 11 patients. The median concentrations ± SEM were 6.25 ± 1.04 ng/mL, 4.96 ± 1.15 ng/mL, and 2.65 ± 0.44 ng/mL, respectively, consistent with a previous report.

In our study, obatoclax mesylate, a small-molecule BCL-2 antagonist, showed limited clinical activity in heavily pretreated patients with cHL. Future studies should investigate more potent Bcl-2 family inhibitors with pharmacodynamic studies to ensure target inhibition and biomarker analysis for possible patient selection.

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Table 1. Summary of obatoclax clinical activity in 13 patients with relapsed classical Hodgkin lymphoma

<table>
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<tr>
<th>Patient no.</th>
<th>Age, y</th>
<th>Sex</th>
<th>No. of prior regimen</th>
<th>Prior transplantation</th>
<th>Treatment duration, wk</th>
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</table>

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Conflict-of-interest disclosure: M.F. received research funding from Seattle Genetics, Novartis, MedImmune, Millennium, Genentech, and Onyx, received honoraria from Seattle Genetics and Novartis, and served on the advisory board for Seattle Genetics; J.R. received research funding from Millennium and Celgene; A.Y. received research funding from Genentech, Novartis, SBIO, Seattle Genetics, Syndax, and Sanofi-Aventis, and received honoraria from Novartis, Seattle Genetics, and Sanofi-Aventis. The remaining authors declare no competing financial interests.

Contribution: Y.O. collected and analyzed data and wrote the paper; A.C. collected and analyzed data and reviewed the paper; F.H. provided patient care and reviewed the paper; L.E.F. and M.F. provided patient care; J.R. provided patient care and edited paper; and A.Y. designed and supervised the clinical trial, provided patient care, analyzed data, and wrote the paper.

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References

To the editor:

Recombinant factor VIIa (rFVIIa) and hemodialysis to manage massive dabigatran-associated postcardiac surgery bleeding

Dabigatran is a new oral direct thrombin inhibitor approved to prevent stroke in atrial fibrillation. It has no antidote, and management of severe bleeding is uncertain. A participant in RE-LY (randomized trial that compared dabigatran with warfarin1) unintentionally underwent cardiac surgery with therapeutic dabigatran plasma levels, resulting in massive postoperative bleeding. We report the timeline of bleeding, hemostatic parameters, and dabigatran plasma levels (by HPLC) in response to emergency management with rFVIIa and hemodialysis.

Figure 1 summarizes blood product administration, coagulation parameters (aPTT, INR, fibrinogen, thrombin-clotting time [TCT]), dabigatran levels, and bleeding.

A 79-year-old, 80-kg male with non–insulin-dependent diabetes and chronic renal insufficiency (estimated creatinine clearance, 36 mL/min) was taking dabigatran 150 mg twice-daily. Two blood samples taken on chronic dabigatran therapy (obtained 1 and 2 months preoperatively) showed mild INR prolongation (1.3, 1.4 [normal, 0.8-1.2]), increased aPTT (49, 60 seconds [normal, 22-35 seconds]), prolonged TCT (128, > 150 seconds [normal, 20-30 seconds]), and normal fibrinogen (3.0, 3.1 g/L [normal, 1.6-4.2 g/L]). Dabigatran was discontinued 2 days (4 doses) before surgery.

The patient underwent tissue aortic valve replacement and single-vessel coronary artery bypass grafting using cardiopulmonary bypass performed with standard heparin anticoagulation (35 000 units of heparin; postoperative reversal with 400 mg of protamine). Preoperatively, severe bleeding (> 1500 mL/hr) persisted despite additional tranexamic acid (2 g) and protamine (200 mg), cryoprecipitate, plasma, and platelet transfusions (raising the platelet count from 86 to 131 × 10^9/L), preventing sternal closure. Three “cardiac” doses of rFVIIa (2.4 mg/dose) did not control the bleeding; at this time, testing showed INR = 1.2, PTT = 52, TCT = 129 (without in vitro correction by protamine); the platelet count was 127 × 10^9/L. After 2 “hemophilic” doses of rFVIIa (7.2 mg/dose), bleeding fell to ~ 800 mL/hr and the patient could be transferred to ICU for hemodialysis.

The patient was dialedyzed (without addition of anticoagulant) for 6 hours with a high-flux dialysis filter (Polyflux 210; Gambro). Dialysate flow was 700 mL/min; the average blood flow was 320 mL/min with 2 L net ultrafiltration. During hemodialysis, the bleeding subsided further. The first plasma dabigatran level (40 minutes after surgery, and after 3 liters of blood product/crystalloid) was 95 ng/mL—a concentration typically seen on dabigatran in the RE-LY study.2 Immediately before hemodialysis, the dabigatran level was 76 ng/mL, and after 6 hours of hemodialysis was 27 ng/mL. No additional blood products were required. The sternum was closed 4 days later.

The postoperative course was complicated by prolonged ventilatory/Enterobacter pneumonia, asymptomatic nonocclusive femoral DVT (by surveillance ultrasonography [postoperative day (POD 7)]), and acute-on-chronic renal failure. Discharge to a rehabilitation facility occurred on POD 56.

This patient developed massive postoperative bleeding resulting from elective cardiac surgery performed with therapeutic dabigatran levels. This illustrates the importance of adjusting the number of days “off” dabigatran before surgery according to current renal function. Based on experience with this case and other information, it is now recommended3 for a patient with creatinine clearance 30-50 mL/min that dabigatran be stopped 4 days before elective major surgery, and that a normal (or near-normal) TCT be documented presurgery. In our patient, the TCTs (measured postoperatively) were all greatly elevated, and preoperative measurement would have avoided surgery. We observed an excellent correlation between the TCT and dabigatran levels in our patient (Figure 1B).

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