$P = .15$). Analyses by cytogenetic subgroups are pending. A strong signal for improved disease-free survival (DFS) was seen for the AZA plus VOR combination compared to AZA monotherapy (median 13 months vs 7 months, $P = .11$).

An open question is whether combination therapies in MDS are too toxic or whether toxicities need to be managed better. In this study, the investigators thought the toxicities were more severe than was reported by patients. It is possible that DOR and OS may be better end points for large MDS trials. In this trial, time to response was not assessed.

Idarucizumab Reverses Dabigatran in Elderly or Renally Impaired

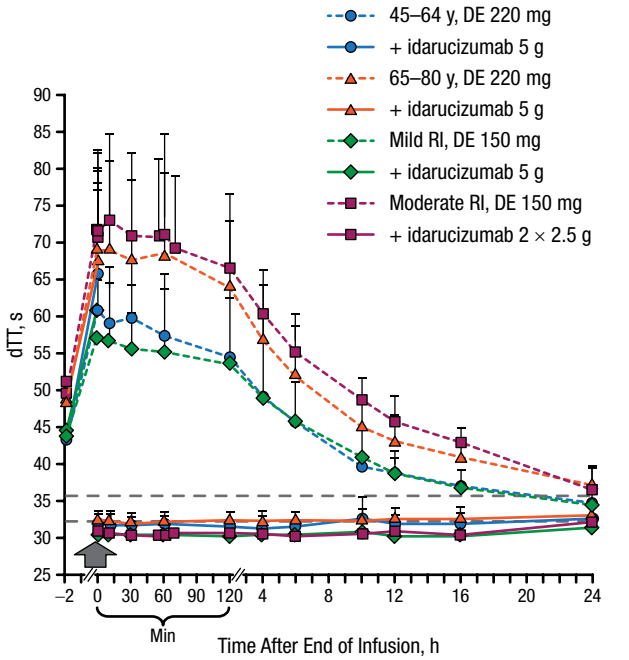
Written by Emma Hitt Nichols, PhD

The dabigatran antidote, idarucizumab, immediately and completely reversed anticoagulation by dabigatran in elderly and renally impaired volunteers, an effect that lasted for at least 24 hours. Joachim Stangier, PhD, Boehringer Ingelheim Pharma GmBH & Co KG, Biberach, Germany, presented data from the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of BI 655075 and Establishment of BI 655075 Dose(s) Effective to Reverse Prolongation of Blood Coagulation Time by Dabigatran study [NCT01955720].

Idarucizumab is the antigen-binding fragment of a humanized antibody that specifically targets dabigatran, a non-warfarin oral anticoagulant. Developed as an antidote to dabigatran, idarucizumab restored coagulation after easy and rapid intravenous administration. Key characteristics of idarucizumab are its initial short half-life of about 45 minutes and terminal half-life of 4.5 to 9 hours and that it is eliminated primarily renally through renal excretion and catabolism. A previous study in heathy male volunteers demonstrated that idarucizumab immediately and completely reversed the anticoagulation effect of dabigatran based on clotting times measured by diluted thrombin time (dTT), ecarin clotting time (ECT), activated partial thromboplastin time (aPTT), and thrombin time (TT) [Glund S et al. *Circulation.* 2013]. The purpose of the current study was to further evaluate the effect of idarucizumab on anticoagulation reversal in elderly and renally impaired volunteers treated with dabigatran etexilate (DE).

In this double-blind, randomized, 2-way crossover trial, 46 volunteers underwent 2 treatment periods, with a 6-day washout in between. During the first treatment period, patients received DE (220 mg, or 150 mg in the renally impaired) for 3 days, followed by a 5-minute infusion of idarucizumab or placebo about 2 hours after the last dose of dabigatran. A subset group of volunteers were re-treated with dabigatran 24 hours after the idarucizumab infusion. The study protocol was completed by all volunteers. The median peak dabigatran concentration was similar to that typically experienced by patients with atrial fibrillation.

Figure 1. Effect of Idarucizumab on the Anticoagulation Effect of Dabigatran



DE, dabigatran etexilate; dTT, diluted thrombin time; RI, renal impairment (CLcr: mild RI ≥60 to <90 mL/min; moderate RI ≥30 to <60 mL/min); TT, thrombin time.

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In both age groups (45 to 64 and 65 to 80 years) and in patients with mild or moderate renal impairment, idarucizumab immediately reversed clotting times to baseline levels, as measured by dTT, ECT, aPTT, and TT, which was sustained for at least 24 hours (Figure 1). Anticoagulation was restored to initial levels when dabigatran was readministered 24 hours after the idarucizumab infusion.

There were no clinically relevant drug-related adverse events in the study, and the rates of adverse events and local reactions were similar between the idarucizumab and placebo arms. In patients who received idarucizumab, there was a dose-dependent elevation in urine protein and low-weight proteins that returned to normal values within 24 hours.

Dr Stangier concluded that the data from this and other studies that have evaluated idarucizumab show that it is a

specific antidote for anticoagulation caused by dabigatran and that it is well tolerated. In addition, the multicenter, phase 3 RE-VERSE AD trial [NCT02104947] was initiated in May 2014 and will evaluate the efficacy and safety of dabigatran reversal by idarucizumab in patients who are taking dabigatran and present with a major bleeding event or require emergency surgery for other conditions.

Vosaroxin in Combination With Cytarabine Provides a New Salvage Option for AML

Written by Lynne Lederman

New safe and effective treatments are urgently needed for patients with relapsed or refractory (RR) acute myeloid leukemia (AML). Vosaroxin, a first-in-class anticancer quinolone derivative, plus cytarabine has been previously investigated in a phase 1/2 trial in patients (n = 69) with first relapsed or primary refractory AML [Lancet JE et al. *Haematologica*. 2014]. Median overall survival (OS) was 6.9 months, the complete remission (CR) rate was 25%, the median leukemia-free survival (LFS) was 25.2 months, and 60-day all-cause mortality was 8.7%.

Farhad Ravandi, MD, University of Texas MD Anderson Cancer Center, Houston, Texas, USA, presented results of the Study of Vosaroxin or Placebo in Combination With Cytarabine in Patients With First Relapsed or Refractory Acute Myeloid Leukemia [VALOR; Ravandi F et al. ASH 2014 (abstr LBA-6)]. VALOR was a phase 3, double-blind, randomized, placebo-controlled study. Patients with first RR AML were randomly assigned to vosaroxin (n = 356) 90 mg/m^2 days 1 and 4 of the first cycle and 70 mg/m^2 for the second cycle plus cytarabine 1 g/m^2 days 1 through 5 or to placebo (n = 355) days 1 and 4 plus cytarabine for 1 to 2 cycles of induction.

If the response was CR or complete remission with incomplete platelet recovery (CRp) patients received consolidation with 1 to 2 cycles. For complete remission with insufficient hematologic recovery (CRi), partial remission (PR), or treatment failure, there was no further treatment. The primary end point was OS; secondary end points were CR, safety, and tolerability. Tertiary end points included CR + CRp + CRi, event-free survival (EFS), LFS, and stem cell transplant (SCT) rate.

Patients in both groups were well matched for characteristics. The median age was 63 years; 42% had refractory AML, 36% were in early relapse, and 22% were in late relapse.

OS was 7.5 months for the combination vs 6.1 months for cytarabine monotherapy ($P = .06$; HR 0.87; 95% CI, 0.73 to 1.02); by stratified log-rank analysis $P = .02$. CR rates are shown in Table 1, and rates of CR + CRp + CRi are shown in Table 2.

Table 1. Complete Remission Rates

Patient Population	Vosaroxin/ Cytarabine, %	Placebo/ Cytarabine, %	*P* Value
Overall	30.1	16.3	< .0001
Age < 60 y	26.9	20.8	.24
Age ≥ 60 y	31.9	13.8	< .0001
Refractory	20.4	10.7	.02
Early relapse	27.6	12.4	.002
Late relapse	53.2	33.8	.01

Table 2. Rates of CR + CRp + CRi

Patient Population	Vosaroxin/ Cytarabine, %	Placebo/ Cytarabine, %	*P* Value
Overall	37.1	18.6	< .0001
Age < 60 y	34.6	23.1	.04
Age ≥ 60 y	38.5	16.0	< .0001
Refractory	27.6	12.1	.001
Early relapse	34.6	15.5	.0004
Late relapse	59.7	36.4	.004

CR, complete remission; CRi, complete remission with insufficient hematologic recovery; CRp, complete remission with incomplete platelet recovery.

Overall, 30.1% of patients in the combination group had allogeneic SCT vs 29% in the placebo group. The percentages of patients aged < 60 years receiving SCT were higher (46.2% vs 45.4% for the combination and control arms, respectively) than those of patients aged ≥ 60 years (20.8% vs 19.6% for the combination and control arms, respectively). A higher proportion of patients in the vosaroxin arm underwent an allogeneic SCT after achieving CR on the initial prescribed therapy. In a preplanned analysis of OS censored for allogeneic SCT, OS in the vosaroxin arm was a median 6.7 months vs 5.3 months in the placebo arm (HR, 0.83; $P = .02$). In an analysis of OS by subgroup, the vosaroxin combination was favored in patients aged ≥ 60 years and with early relapse. EFS was significantly better for patients treated with vosaroxin and cytarabine ($P < .0001$). LFS was not significantly different between groups.