AZA Plus LEN or VOR Do Not Improve Response Rates in MDS or CMML, Though DFS and OS Still an Open Question

Written by Lynne Lederman

Patients with higher-risk myelodysplastic syndrome (MDS) and chronic myelomonocytic leukemia (CMML) have a dismal prognosis; median survival in this patient population has been reported as ≤1.2 years, as cited in a 1997 study by Greenberg and colleagues. There is only one randomized study of azacitidine (AZA) in MDS showing a median survival of 24.5 months for AZA vs 15.1 months for conventional care regimens (HR, 0.58; CI, 0.43 to 0.77; log-rank $P = .0001$) [Fenaux P et al. *Lancet Oncology*. 2009].

Histone deacetylase inhibitors such as vorinostat (VOR) act synergistically with hypomethylating agents like AZA. A phase 1/2 study of VOR added to AZA in MDS in 33 evaluable patients showed a response of 70%, a complete response (CR) rate of 42%, and a median duration of response (DOR) of 16 months [Silverman LR et al. ASH 2013 (abstr 386)]. Lenalidomide (LEN) added to AZA in a phase 2 study in MDS (n = 36) resulted in an overall response rate (ORR) of 72%, a CR rate of 44%, and a DOR of >17 months [Sekeres MA et al. *Blood*. 2012]. AZA and LEN have nonoverlapping mechanisms of action.

Mikkael Sekeres, MD, Cleveland Clinic, Cleveland, Ohio, USA, reported on the Azacitidine With or Without Lenalidomide or Vorinostat in Treating Patients With Higher-Risk Myelodysplastic Syndromes or Chronic Myelomonocytic Leukemia study [Sekeres MA et al. ASH 2014 (abstr LBA-5)]. Groups participating in the study included the Southwest Oncology Group, Alliance, the Eastern Cooperative Oncology Group, and the National Cancer Institute of Canada.

Patients with higher-risk MDS or CMML were randomly assigned to AZA 75 mg/m^2/day days 1 to 7 (n = 92), AZA plus LEN 10 mg/day for 21 days (n = 93), or AZA plus VOR 300 mg BID days 3 to 9 (n = 91). The primary objective was 20% improvement of ORR. Secondary objectives were improvements in overall survival (OS), relapse-free survival, and leukemia-free survival.

The 3 study arms were similar in patient characteristics. The mean age was 70 years; about 18% of patients had CMML, and about 7% had therapy-related MDS. Grade 3 or higher toxicities for the safety population (n = 260) are summarized in Table 1.

Responses are summarized in Table 2.

Table 1. Grade ≥3 Toxicities Results

Toxicity	AZA	AZA + LEN (*P* Value vs AZA)	AZA + VOR (*P* Value vs AZA)	Total (n = 260)
Febrile neutropenia, n	10	13 (0.66)	13 (0.51)	36
GI, n	4	11 (0.10)	23 (< .001)	38
Rash, n	2	12 (.01)	1 (1)	15
Off treatment due to toxicity, side effect, or complication, %	9	23 (.04)	24 (.03)	19
Non-protocol-defined dose modifications, %	23	41 (.01)	36 (.05)	33

AZA, azacytidine; GI, gastrointestinal; LEN, lenalidomide; VOR, vorinostat.

Table 2. Responses to Treatment Results

Response Variable	AZA	AZA + LEN (*P* Value vs AZA)	AZA + VOR (*P* Value vs AZA)	Total (n = 260)
Median treatment duration, wk	25	24	20	23
ORR, %	37	39 (1.0)	24 (.07)	33
CR/PR/HI, %	24/0/13	18/1/19 (.66)	15/1/7 (.12)	19/1/13
CMML ORR, %	33 (n = 15)	59 (.15; n = 19)	13 (.41; n = 16)	34
RFS, median, mo	7	8 (.45)	11 (.29)	7
RFS on treatment > 6 mo, median, mo	7	7.5 (.74)	13 (.11)	8.5

AZA, azacytidine; CMML, chronic myelomonocytic leukemia; CR, complete response; HI, hematologic improvement; LEN, lenalidomide; ORR, overall response rate; PR, partial response; RFS, relapse-free survival; VOR, vorinostat.

There were no differences in ORR or other response criteria comparing AZA plus LEN or AZA plus VOR to AZA monotherapy. Dr Sekeres said that some subgroups may have benefitted from AZA-based combinations, as the hematologic improvement rates for neutrophils were higher for patients receiving the AZA plus LEN combination ($P = .05$), as were response rates for CMML patients compared to AZA monotherapy, although the limited number in this subgroup precluded adequate power to show a significant difference (59% vs 33%,

$P = .15$). 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

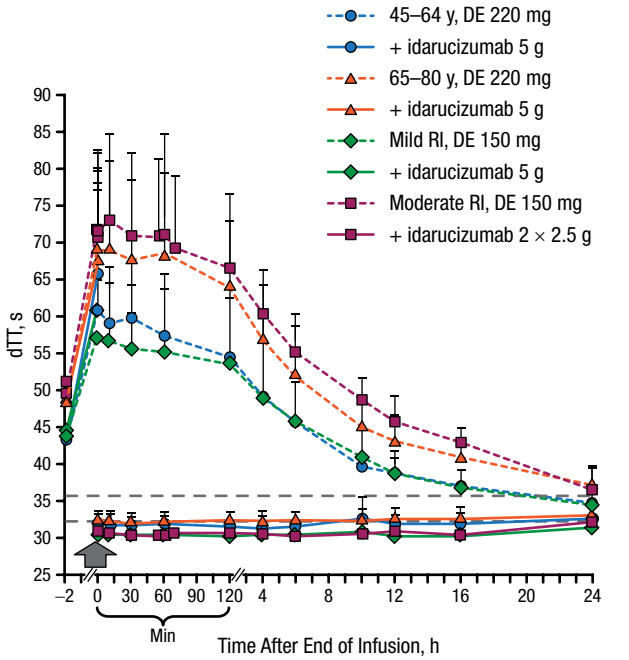
Written by Emma Hitt Nichols, PhD

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.

Reproduced with permission from J Stangier, PhD.

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