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.

The clinical benefit of vosaroxin combination therapy may be underestimated in younger patients due to the high rate of SCT. All-cause mortality was similar for both groups at 30 and 60 days. The most common serious adverse events were febrile neutropenia, sepsis, pneumonia, bacteremia, and stomatitis, and were higher in the vosaroxin group but these did not translate to excess mortality. Serious and nonserious cardiac, renal, neurologic, and hepatic adverse events were comparable between treatment groups. Vosaroxin plus cytarabine provides patients with relapsed, refractory AML with a new option for salvage therapy.

FCR Superior in Treatment of Advanced CLL

Written by Brian Hoyle

Barbara Eichhorst, MD, Center of Integrated Oncology Cologne-Bonn, University Hospital Cologne, Cologne, Germany, described the confirmation of the superiority of a frontline chemotherapy with a regimen involving fludarabine plus cyclophosphamide plus rituximab (FCR) compared with bendamustine plus rituximab (BR) in previously untreated, physically fit patients with advanced chronic lymphocyte leukemia (CLL).

The study was prompted by results from the researchers' previous demonstration of significantly better overall survival in CLL patients treated with FCR compared with BR. Presently, 564 physically fit patients with untreated and active CLL, and no deletions in chromosome 17p were randomized to receive FCR intravenously (n = 284; fludarabine 25 mg/m^2, days 1–3; cyclophosphamide 250 mg/m^2, days 1–3; and rituximab 375 mg/m^2, day 0 in cycle 1 and 500 mg/m^2, day 1 during cycles 2-6) or BR intravenously (n = 280; bendamustine 90 mg/m^2, days 1–2; rituximab 375 mg/m^2, day 0 in cycle 1 and 500 mg/m^2, day 1 during cycles 2-6).

The study arms were comparable at baseline with the exceptions of a greater proportion of patients aged > 65 years (30.5% vs 38.7%; $P = .042$), greater mean number of cycles (5.27 vs 5.41; $P = .022$), and prevalence of immunoglobulin heavy chain variable (IGHV) mutations (55.3% vs 67.8%; $P = .003$) for the BR arm.

The intention-to-treat population received FCR (n = 282) and BR (n = 279). The primary end point of progression-free survival (PFS) in the intention-to-treat population during the follow-up observation time was reached, with a hazard ration of 1.6 that was statistically significant.

During a median observation time of 37.1 months (range, 0-59.9 months), complete response was observed in 39.7% and 30.8% of patients in the FCR and BR arms, respectively ($P = .034$). The overall response rate was comparable in the FCR and BR arms (95.4% and 95.7%, respectively; $P = 1.0$). Those treated with FCR achieved higher rates of minimal residual disease at all time points (Table 1).

Table 1. Minimal Disease Negativity

MRD Negativity	FCR, % (n/N) (n = 282)	BR, % (n/N) (n = 279)
BM at FR	26.6 (75/282)	11.1 (31/279)
PB at FR	48.6 (137/282)	38.4 (107/279)
PB 12 mo after FR	19.7 (47/238)	9.0 (20/222)
PB 18 mo after FR	18.0 (37/206)	8.5 (16/187)

BM, bone marrow; BR, bendamustine/rituximab; FCR, fludarabine/cyclophosphamide/rituximab; FR, final restaging; MRD, minimal disease negativity; PB, peripheral blood.

The FCR regimen produced significantly better PFS in patients treated with unmutated IGHV than the BR regimen (42.7 vs 33.6 months; $P = .017$), but not in patients with mutated IGHV (not reached vs 52.0 months; $P = .153$). The FCR regimen was significantly more beneficial than the BR regimen in terms of PFS in patients aged ≤ 65 years (53.6 vs 38.5 months; $P < .001$) but not in older patients (not reached vs 48.5 months; $P = .170$). Overall survival was similar (FCR, 90.6%; BR, 92.2%; $P = .897$).

Neutropenia was more frequent in the FCR arm (84.2% vs 59.0%; $P < .001$), as was thrombocytopenia (21.5% vs 14.4%; $P = .03$), all infections (39.1% vs 26.8%; $P < .001$), and infections during the first 5 months after therapy (11.8% vs 3.6%; $P < .001$). Those aged > 65 years treated with FCR were significantly more likely to experience infection (47.7% vs 20.6%; $P < .001$).

The data demonstrate the inferiority of BR vs FCR with respect to PFS and complete response rate and the association of FCR with higher rates of neutropenia and severe infection. The researchers concluded that FCR remains as the standard therapy in fit patients, with BR considered as alternative treatment in fit, but elderly, patients.

CKT Implicated in Worse Outcomes With Ibrutinib Therapy of CLL

Written by Brian Hoyle

Philip A. Thompson, MBBS, University of Texas MD Anderson Cancer Center, Houston, Texas, USA, reported that complex metaphase karyotype (CKT), defined as ≥ 3 unrelated abnormalities, rather than del(17p), is linked with inferior outcomes in patients with chronic lymphocytic leukemia (CLL) treated with ibrutinib who relapse or are fludarabine-refractory.