Table 1. Best 5-Year Responses by Molecular Response at 3 Months

Response	Dasatinib 100 mg QD (n = 259)		Imatinib 400 mg QD (n = 260)	
BCR-ABL at 3 mo	≤10 (84)	>10 (16)	≤10 (64)	>10 (36)
CCyR	94	41	92	59
MMR	87	38	81	41
MR[4.5]	54	5	48	12

Response is given in percentages.

CCyR, complete cytogenic response; MMR, major molecular response; MR molecular response.

Table 2. Five-Year Outcomes by Molecular Response at 3 Months

Outcome	Dasatinib 100 mg QD (n = 259)		*P* Value	Imatinib 400 mg QD (n = 260)		*P* Value
BCR-ABL at 3 mo	≤10 (84)	>10 (16)		≤10 (64)	>10 (36)	
Estimated 5-y OS	94	81	.0028	95	81	.0003
Estimated 5-y PFS	89	72	.0014	93	72	<.0001
Estimated 5-y TFS	97	83	.0004	97	80	<.0001

Data are for on-study treatment and in follow-up after discontinuation of randomized treatment. Response is given in percentages.

OS, overall survival; PFS, progression-free survival; TFS, transformation-free survival.

study compared with patients whose BCR-ABL levels were >10% (Table 2).

Treatment failure occurred in 10 patients in the dasatinib arm and 14 patients in the imatinib arm, and disease progressed in 18 patients in the dasatinib arm and 23 patients in the imatinib arm. Mutations were identified in some patients whose treatment failed or disease progressed, and most of these patients discontinued the study early.

Important adverse events included pleural effusion, which occurred in 28% of patients who received dasatinib and only 1% of patients who received imatinib. In addition, arterial ischemic events such as myocardial infarction, angina pectoris, coronary artery disease, acute coronary syndromes, and transient ischemic attack occurred more frequently in the dasatinib arm. Other adverse events reported more frequently in the dasatinib arm included abdominal pain and headache, whereas facial edema, muscle spasms, myalgia, nausea, and vomiting occurred more frequently in the imatinib arm.

In conclusion, Dr Cortes stated that the 5-year data from the DASISION trial support the data from earlier analyses showing that dasatinib treatment resulted in higher rates of MMR and MR, faster time to MR, and less frequent transformation to accelerated or blastic CML. No new safety signals occurred. Although arterial ischemic events were more frequent with dasatinib treatment, they were uncommon.

Reduced-Dose Conditioning Comparable to Standard Dose Prior to ASCT in MDS

Written by Emma Hitt Nichols, PhD

Reduced-dose conditioning prior to allogenic stem cell transplantation (ASCT) in patients with myelodysplastic syndrome (MDS) or secondary acute myeloid leukemia (sAML) resulted in similar outcomes including nonrelapse mortality, incidence of relapse, and relapse-free survival compared with standard-dose conditioning. Nicolaus Kröger, MD, University Cancer Center Hamburg, Hamburg, Germany, presented data from the Dose-Reduced Versus Standard Conditioning in MDS/sAML trial [RICMAC; NCT01203228].

Currently, the most effective, potentially curative, treatment for MDS is ASCT. In favor of reducing toxicity, dose-reduced conditioning is being increasingly used; however, some retrospective data suggest that dose-reduced conditioning may lead to higher rates of relapse. The purpose of the RICMAC trial was to evaluate the effect of reduced-dose conditioning on the outcomes of patients with MDS or sAML after ASCT.

In the prospective, open-label, phase 3 RICMAC trial, patients (n = 129) with MDS or sAML were randomly assigned to receive standard-dose busulfan (12.8 mg/kg ideal body weight [IBW] intravenously [IV] or 16 mg/kg body weight [BW] orally) plus cyclophosphamide (120 mg/kg BW IV) or reduced-dose busulfan (6.4 mg/kg IBW IV or 8 mg/kg BW orally) plus fludarabine (5×30 mg/m^2 IV). Patients were considered to have cytologically proven MDS based on refractory anemia or refractory anemia with ring sideroblasts, excess blasts, or excess of blast in transformation. Patients with chronic myelomonocytic leukemia and sAML were also included. All patients had a blast count <20% regardless of chemotherapy at the time of ASCT. Other eligibility criteria included human leukocyte antigen (HLA)–matched related donors aged 18 to 65 years or unrelated donors aged 18 to 60 years

and no major organ dysfunction. One HLA antigen mismatch was also allowed. Patients were excluded if there was central nervous system involvement, a life expectancy < 6 months owing to comorbidities, serious psychiatric or psychological disorder, pregnancy or lactation, or positive serology for HIV.

The primary end point of the study was nonrelapse mortality at 1 year after ASCT. Secondary end points included incidence of acute and chronic graft-vs-host disease, overall survival (OS) at 2 years, event-free survival at 2 years, and incidence of relapse at 2 years. Slow recruitment led to early termination of the study.

There was no significant difference in nonrelapse mortality at 24 months ($P = .17$). Similarly, there was no significant difference in relapse incidence or relapse-free survival in both arms. There was a higher percentage in survival in the reduced-dose arm compared with the standard-dose arm, but results did not achieve significance ($P = .06$).

In a subanalysis, patients aged > 51 years had significantly lower rates of relapse-free survival compared with younger patients (HR, 1.93; $P = .03$). In addition, prior chemotherapy increased the risk of relapse (HR, 3.36; $P = .01$) and OS was significantly lower in patients with a performance status of 1 to 3 compared with 0 (HR, 2.58; $P = .04$). Interestingly, patients with a low cytogenetic risk who receive reduced-dose conditioning had significantly higher rates of OS compared with patients who received standard-dose conditioning (HR, 0.14; $P = .002$). However, there was no benefit in patients with intermediate risk and patients with high risk demonstrated greater rates of OS when treated with standard-dose conditioning (HR, 1.70; $P = .39$).

In conclusion, Dr Kröger indicated that the data from the RICMAC trial suggest that reduced-dose conditioning results in similar outcomes as standard-dose conditioning; however, he indicated that a longer follow-up period is required to confirm these results.

4F-PCC Reverses Apixaban Anticoagulation in Healthy Volunteers

Written by Emma Hitt Nichols, PhD

Infusion of 4 factor–prothrombin complex concentrate (4F-PCC) reversed the anticoagulation effect of apixaban in healthy volunteers, with no signs of thrombosis or serious adverse events. Charles Frost, PharmD, Bristol-Myers Squibb, Princeton, New Jersey, USA, presented data from the Reversibility of Apixaban Anticoagulation With the Four Factor Prothrombin Complex Concentrate Kcentra study [4PAR; NCT02270918].

Apixaban is a nonwarfarin oral anticoagulant that is approved for the treatment of venous thromboembolic events, but lacks evidence-based methods to reverse its anticoagulation effect. The purpose of this study was to determine if the administration of 4F-PCC could reverse apixaban anticoagulation in healthy volunteers.

In the open-label, 3-period crossover 4PAR study, 15 patients received 10 mg BID of apixaban for 3 days, and then were randomized to receive a 30-minute infusion of placebo, the 4F-PCC Cofact, or the 4F-PCC Beriplex 3 hours after the last dose of apixaban. After an 11-day washout period, patients received an alternative treatment, followed by another 11-day washout and another alternative treatment. The primary end point of the study was change in endogenous thrombin potential (ETP), including time points from baseline (prior to 4F-PCC or apixaban administration) to 30 minutes after 4F-PCC or placebo administration, as measured by the thrombin generation assay (TGA). The secondary end points included TGA parameters, results from other coagulation tests including prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (aPTT), and anti-factor Xa activity, as well as apixaban pharmacokinetics and safety measures such as vital signs, echocardiograms, physical examinations, and adverse events, with and without 4F-PCC administration.

Administration of 4F-PCCs resulted in a rapid reversal of the anticoagulation caused by apixaban compared with placebo, as measured by ETP, which was sustained over 72 hours. The adjusted mean change in ETP from baseline was 389 nM/min in patients who received Cofact compared with saline ($P = .001$); however, the change in ETP from baseline was not significant in patients who received Beriplex compared with placebo ($P = .135$). 4F-PCC infusion resulted in a significant improvement in other coagulation tests, including PT, INR, and aPTT compared with placebo ($P < .001$ for all measurements regardless of 4F-PCC brand).

Adverse events occurred in 7% of patients in the placebo arm and 33% and 13% of patients in the Cofact and Beriplex arms, respectively. The most common adverse events were nasopharyngitis and abdominal pain, which occurred in 2 patients each in the Cofact and Beriplex arms. In addition, 1 patient experienced drug-related mild dizziness in the Cofact arm. There were no serious adverse events.

According to Dr Frost, the data from the 4PAR trial suggest that infusion reduced anticoagulation by apixaban as measured by ETP, which reached significance for Cofact. In addition, 4F-PCC treatment was well tolerated and did not affect apixaban pharmacokinetics. He commented that these data support the need for additional studies to determine the most efficacious and safe dose of 4F-PCC to reduce apixaban anticoagulation.