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.