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THROMBOSIS AND HEMOSTASIS

*Comment on Doyle et al, page 285*

# iTTP: more long-term consequences

**Ara Metjian** | University of Colorado

**Immune thrombocytopenic purpura (iTTP) is a near-fatal disease unless immediate treatment is initiated with the current recommended therapies of therapeutic plasma exchange, immune suppression, and caplacizumab.[1,2] With this regimen, the mortality of iTTP in high-volume centers has been markedly reduced, transforming it instead into a chronic disease, where relapse and recurrent episodes of thrombotic microangiopathy (TMA) can occur. However, aside from ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) deficiency, factors that increase the risk for relapse are not well understood. To address these questions, in this issue of *Blood*, Doyle et al used a large and well-established national cohort of patients with iTTP in the United Kingdom, reviewing the incidence and potential risk factors of relapse in patients with iTTP, with special attention paid to the use of anti-CD20 therapies.[3]**

The authors identified 443 patients with at least 3 years of follow-up (specifically, a median follow-up of 8.6 years). Of these patients, 30% had at least 1 relapse during the study period, which was defined as either a decline in ADAMTS13 activity to <20% (ie, "ADAMTS13 relapse") or a "clinical relapse," which was a recurrence of TMA. Given the follow-up that was available, a relapse rate of 4% within the first year, reaching 40% within 5 years, was observed. The authors compared ADAMTS13 with clinical TMA relapses before and after 2012, noting that clinical relapses decreased from 23% to 11%, whereas ADAMTS13 relapses increased from 8% to 16%.

More than 50% of patients received anti-CD20 therapies. with most receiving rituximab. Remission of ADAMTS13 inhibition, defined as reaching an activity level of >20%, occurred in a median time of 21 days, with peak activity seen at 3 months. For those patients with iTTP who were followed up to 10 years, no difference was seen between those who had or had not received anti-CD20 therapy with time to first relapse, as immune reconstitution leads to relapse. As in earlier reports on preemptive therapy, Doyle et al observed that in those patients with iTTP who responded to anti-CD20 therapy initially, the patients did so again at time of relapse on retreatment with anti-CD20 therapy. And although standard initial therapies were effective for most patients with iTTP, Doyle et al observed that 28 of 443 (6%) had "frequent" relapses, defined as ≥0.5/year, requiring frequent retreatment.

As to risk factors for relapse, patients with iTTP with a "reversible" cause, such as medication or infection induced, had a lower rate of relapse vs those who did not (8% vs 16%). Most important, the authors also observed that Black-Caribbean race (ie, African descent) was associated with a higher risk of relapse (17% vs 7%), a finding that mirrors those initially reported in *Blood*.[4]

Many of these findings are known to experts within the field of thrombocytopenic purpura and reaffirm current practices. However, as would be expected with the retrospective nature of this study, significant changes occurred over the course of this study in the diagnosis, treatment, and management of iTTP. As a result, some of these findings are limited and will require prospective confirmation.

So, what does this study tell us? The findings reported by Doyle et al support the following observations: (1) an "immunologic" relapse can occur in patients with iTTP years after achieving remission, leading to ADAMTS13 deficiency; (2) ADAMTS13 deficiency leads to recurrent episodes of TMA; (3) regular surveillance and "preemptive" rituximab can raise the ADAMTS13 activity level and prevent TMA; and (4) patients with iTTP of African descent had an increased risk of relapse. Again, these observations support the assertion that iTTP should be considered a long-term disease, with a significant proportion at risk for relapse. This long-term risk of relapse in iTTP, be it an ADAMTS13 or clinical relapse, is also associated with higher rates of depression, cardiovascular disease, neurocognitive decline, and posttraumatic stress disorder.[5-7]

As with any good study, more questions requiring study have been raised. It is still unclear what factor(s) cause the emergence, let alone the recurrence, of the ADAMTS13 antibody. Although the current treatment of plasma exchange, immune suppression with anti-CD20 therapy, and caplacizumab is effective in reducing the risks of exacerbation, relapse, thrombosis, and death, the best treatment for ADAMTS13 inhibitor eradication remains unknown for those patients who do not respond to anti-CD20 treatment. Likewise, recommendations for ADAMTS13 testing are unclear, with International Society on Thrombosis and Haemostasis guidelines offering no explicit time frame,[1] but the US Thrombotic Microangiopathy Alliance recommending testing every 3 months

once in remission.[8] Still, with the use large national databases, it is hoped that continued progress will be made in understanding the long-term implications of this disease.

*Conflict-of-interest disclosure: A.M. is on the advisory boards of Sanofi, Genentech, and Takeda.* ■

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**TRANSPLANTATION**

*Comment on Sorror et al, page 295*

# Role of allotransplantation in older patients with AML

**Arnold Ganser** | Hannover Medical School

**In this issue of *Blood*, Sorror et al[1] present data showing no benefit of allogeneic hematopoietic cell transplantation (HCT) in older and medically infirm patients with acute myeloid leukemia (AML). In their large prospective multi-institutional observational study, they not only looked at the influence of age, comorbidities, genetic risk, and remission status on outcome but also paid special attention to frailty, impaired quality of life, depression, and diminished functional status.**

There were 692 evaluable patients, with 43% of the patients aged ≥65 years. For the entire cohort, 46% underwent HCT with 4-year survival of 54%, which was better than in the nontransplant arm. However, after adjusting for AML- and patient-specific variables, no benefit of HCT in all, older, and medically infirm patients was seen apart from patients with European LeukemiaNet–adverse risk and those never in first complete remission (CR1). Even more concerning, although fitter patients were selected for HCT, this superior quality of life and fitness were lost after transplantation, thereby questioning the current way of selection for HCT and strongly arguing in favor of randomized trials to identify those patients who benefit most from HCT. The authors conclude that our present approach to offer HCT to older and medically infirm patients with AML is not evidence based and that randomized trials are needed. They propose 3 different types of randomized trials depending on the biology of the disease as well as on comorbidities, quality of life, and functions.

Is this conclusion by Sorror et al in conflict with the most recent treatment recommendations by the international expert panel on behalf of the European LeukemiaNet? Actually not. There, HCT is proposed for patients, with an estimated relapse risk above 35% to 40%, which includes patients with adverse-risk AML and nonadverse risk disease with persistent minimally detectable disease.[2] For patients aged ≥60 years, HCT in CR1 is recommended at diagnosis for patients with intermediate- and adverse-risk disease able and willing to undergo remission-inducing therapy. This recommendation is based on large prospective but nonrandomized US and British studies in which patients received conventional induction chemotherapy.[3,4] This recommendation is also supported by the only prospective randomized phase 3 trial initiated by the European Blood and Marrow Transplantation Group (EudraCT-Number 2007-003514-34).[5] Here, patients older than 60 years with AML in CR1 after conventional induction and early consolidation chemotherapy received either reduced-intensity conditioning with 2 Gy total body irradiation and fludarabine (RIC) HCT or additional consolidation chemotherapy, with a superior leukemia-free survival in the HCT arm.[5] Up to now, all these recommendations have been category 2A only owing to the lack of fully published prospective randomized trials.

The present data, therefore, remain not only conflicting but actually do not address the major limitations in the therapy of older patients with AML, as only a minority of patients for whom HCT might be curative can be treated intensively before proceeding to transplantation.[6] In most studies, be it the trial by Sorror et al but also those by Ustun et al,[3] Russell et al,[4] and Niederwieser et al,[5] the patients had to be fit for intensive induction chemotherapy, which includes only a minority of older patients with AML. The latest developments with new effective drug combinations, like the use of additional FLT3 inhibitors[7] or combinations of hypomethylating agents with venetoclax,[8] now standard in the less fit AML patient, have not even been tested yet in conjunction with HCT.

These newer treatment modalities, especially in the less fit patients with AML, might alter the game, since patients unfit at the time of AML diagnosis because of the leukemia burden might become fit for RIC HCT upon entering complete remission with restoration of normal hematopoietic function. As suggested by Sorror et al, it is therefore time now for