inside blood commentary

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CLINICAL TRIALS AND OBSERVATIONS

Comment on Scully et al, page 2055

Recombinant ADAMTS-13: goodbye, allergic reactions!

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In this issue of *Blood*, Scully et al describe very promising results of a phase 1 study of recombinant ADAMTS-13 (rADAMTS-13; a disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13) in patients with congenital thrombotic thrombocytopenic purpura (cTTP) that is likely to make these patients' lives allergy free.[1]

TTP, caused by a severe ADAMTS-13 deficiency (activity <10%), is a medical emergency because patients can die of microthromboses in multiple organs.[2] ADAMTS-13 deficiency results in the persistence of ultralarge von Willebrand factor (VWF) multimers that form platelet-rich microthrombi. ADAMTS-13 deficiency is mostly acquired (aTTP) as a result of an autoantibody that requires emergent plasma exchange (PLEX). PLEX has reversed mortality from almost 100% to less than 20% because it removes the antibody and replaces the missing enzyme from donor plasma. Rarely, severe ADAMTS-13 deficiency is caused by a defect in a gene that regulates this enzyme, resulting in cTTP. The diagnosis of cTTP in adolescents and young adults is not easy, and often these patients are initially treated with PLEX and glucocorticoids. Documentation of persistent severe ADAMTS-13 deficiency during remission (in the absence of an inhibitor) establishes a diagnosis of cTTP. This is confirmed by family studies and/or genetic analysis. Subsequently, these patients may develop recurring disease, often triggered by an infection, trauma, surgery, pregnancy, or other stressful conditions. A small subset of patients with cTTP, diagnosed in early infancy/childhood with very low ADAMTS-13 levels (<3%), requires life-long plasma infusions at 2- to 4-week intervals.[3]

Currently, simple plasma infusion is used to treat episodes of cTTP because only a small amount of ADAMTS-13 is required to obtain clinical response. In fact, mouse TTP models with ADAMTS-13$^{-/-}$ do not develop a TTP-like picture unless they are exposed to some trigger such as Shiga toxin.[4] The exact plasma dose required is not known; however, 10 to 20 mL/kg of plasma (including pathogen-reduced plasma) is empirically given to treat an acute episode or prophylactically transfused to prevent frequent recurrences in some patients. Because of the long half-life (2-4 days), plasma infusions are needed every 2 to 4 weeks in patients with persistent disease. Unfortunately, plasma infusion can cause many adverse effects, including mild to severe allergic reactions, volume overload, and transmission of unknown pathogens despite rigorous testing for known infectious agents. Plasma infusions can also have an impact on the quality of life for children and adults with cTTP, requiring a hospital clinic visit that can take up to several hours.

The rADAMTS-13 used in the Scully et al study provides an excellent treatment option for cTTP that avoids plasma-related adverse effects and can be used as a home therapy for controlling persistent disease. The drug has a long half-life similar to that of plasma-derived ADAMTS-13. Because the trial used only a single dose of rADAMTS-13 for pharmacokinetics study and tolerability, a longitudinal study of multiple exposures to assess the development of an inhibitor is warranted. Hundreds of cTTP patients have been successfully treated with plasma infusions for years without documented development of an inhibitor.[5] It is likely that these patients produce some ADAMTS-13 and therefore, when exposed to ADAMTS-13 from plasma, do not recognize it as a foreign protein. However, rADAMTS-13 developed in Chinese hamster ovary cells does not have a structure identical to human ADAMTS-13 and may induce an antibody response. Current functional assays generally do not accurately detect activity of <5%, so there is a need for more sensitive assays to detect lower levels of activity. Similarly, a knowledge of the discrepancy between ADAMTS-13 antigen and activity may help predict the development of an inhibitor.

Acquired autoimmune TTP still has an unacceptably high mortality rate of 10% to 20%. Most of these deaths occur within the hospital while arrangements are being made for initiation of PLEX. The rADAMTS-13 may reduce this mortality because most patients with aTTP do not have a very high titer inhibitor, and higher doses of rADAMTS-13 could potentially overcome antibody, at least transiently, to buy time for the initiation of PLEX. Caplacizumab, a humanized nanobody against VWF A1 domain that blocks interaction with GPIb/IX/V on platelets to prevent VWF-platelet microthrombosis, has shown promising early response in aTTP.[6] A combination of rADAMTS-13 and caplacizumab would be an ideal life-saving

cocktail for patients with aTTP when they present with severe disease. Even then, PLEX would remain standard of care therapy to remove the offending antibody and provide the large amount of ADAMTS-13 needed to neutralize autoantibody and replenish the enzyme. Early use of rituximab (anti-CD20) has already shown significant decrease in length of stay, number of PLEXs required to achieve clinical remission, exacerbation, and relapses, and it is being incorporated more often into clinical practice.[7] With the availability of rADAMTS-13 in the future, treatment options for both cTTP and aTTP will be broadened with the potential to decrease adverse events related to plasma and to further decrease mortality by expediting initiation of treatment.

Conflict-of-interest disclosure: R.S. is a consultant for Ablynx and is chairing the data and safety monitoring board for the ongoing clinical trial using caplacizumab. ■

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● ● ● MYELOID NEOPLASIA

Comment on Issa et al, page 2084

Prognostic relevance of CCAs/Ph$^-$ in CML settled

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In this issue of *Blood*, Issa et al[1] report that patients with chronic-phase chronic myeloid leukemia (CML) in remission after treatment with tyrosine kinase inhibitors (TKIs) with clonal chromosomal aberrations (CCAs) in Philadelphia chromosome–negative (Ph$^-$) metaphases had a significantly worse survival than similar patients without CCAs. This study is notable for the large number of patients with CCAs (n = 58) and the length of follow up (median, 7.6 years) (see figure).

Fifteen years after the initial report of CCAs in Ph$^-$ metaphases in imatinib responders with CML,[2] the report by Issa et al addresses the question of the prognostic relevance of CCAs/Ph$^-$. Up to now, most studies have included only a few patients, with limited observation time, and have not provided convincing prognostic data.[2-6] The frequency of transition to myelodysplastic syndromes (MDSs) have also remained unclear, as has the impact of age on CCAs. The study by Issa et al is the first with sufficient patients and long enough follow-up to address these questions.

Although the 58 patients with CCAs/Ph$^-$ were 12 years older than patients without ACAs, presence of CCAs/Ph$^-$ remained a significant independent prognostic factor in multivariate analysis. In 23 patients, loss of the Y chromosome (−Y) was the only abnormality, which has uncertain prognostic significance. The remaining 35 patients with CCAs/Ph$^-$ were analyzed separately and were found to have a worse prognosis.

What accounts for this inferior prognosis? The incidence of transformation to advanced phases of CML was similar to that among patients with ACAs in Ph$^+$ cells. This finding was due to inclusion of early response in the multivariate analysis (<10% *BCR-ABL1:ABL1* ratio after 3 months); exclusion of patients not meeting the 3-month milestone negated the adverse impact of CCAs/Ph$^-$ on prognosis.

CCAs/Ph$^-$ were observed in ~10% of 598 patients with Ph$^+$ CML in chronic phase. This is a higher percentage than reported in an earlier 2004 series of 1001 patients, of whom only 34 (3.4%) had CCAs/Ph$^-$.[3] The reason for the higher incidence of CCAs/Ph$^-$ might be more systematic cytogenetic analyses in the study by Issa et al. The type of TKI did not seem to play a role. The incidence of ACAs in Ph$^-$ metaphases (clonal and nonclonal) was similar in patients receiving imatinib (16%) and dasatinib (14%), with a slightly higher incidence in those receiving nilotinib (25%) and ponatinib (22%). The most commonly detected CCAs/Ph$^-$ were −Y in 25 patients, trisomy 8 in 7 patients, and complex CCAs/Ph$^-$ and monosomy 7 in 4 patients each. This is not much different from the data reported by Terre et al,[3] who found trisomy 8 in 12 patients, monosomy 7 in 7 patients, and −Y and other deletions in 5 patients each. Trisomy 8 and monosomy 7 are the aberrations most frequently reported by others.[4-6] Not all CCAs/Ph$^-$ were equally adverse in their effects; −7 and complex (≥3) aberrations carried the worst prognosis, whereas trisomy 8 as the only aberration had a prognosis similar to that of no ACAs.

Only 2 patients, both with monosomy 7, experienced progression to MDSs or acute myeloid leukemia, demonstrating that progression of patients with CCAs/Ph$^-$ to MDSs is a rare event in the absence of monosomy 7. A third patient with monosomy 7 died as a result of blast crisis. Dysplastic features, mostly cytopenias and macrocytosis, as described in early reports, could in part also be explained as treatment effects during a prolonged recovery phase of normal hematopoiesis. The biologic determinants of why −7 is associated with a risk of developing MDSs should be the subject of additional studies.