Costs and consequences of immunosuppressive therapy in children with aplastic anemia

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Acquired aplastic anemia (AA) is the most common form of bone marrow failure, generally defined by the effective mismatch between blood cell production in the bone marrow and peripheral demand. While an occasional association with exposure to environmental factors and drugs, or hepatitis is well documented, patient-specific etiologies of marrow aplasia are mostly elusive. Pathophysiologically, idiopathic AA is considered to arise from immune dysregulation, a notion supported by reports of disease remission after autologous recovery following bone marrow stem cell transplantation and inferential laboratory evidence.[1] Population-based studies reveal bimodal incidence peaks in late childhood and among older adults, although treatment strategies are not generally age-specific. Thus, the treatment algorithm for patients diagnosed with AA generally prioritizes matched sibling donor hematopoietic stem cell transplantation, when possible and economically feasible, over immunosuppressive treatment, most often using horse-derived anti-thymocyte globulin and cyclosporine A (CSA) (Figure 1). With similar long-term treatment outcomes of matched sibling donor hematopoietic stem cell transplantation and immunosuppressive treatment, some have argued vigorously that given the excellent tolerability of anti-thymocyte globulin and CSA, preference, especially in older patients, should be given to universal up-front immunosuppressive treatment to avoid the excess transplant-related toxicities that can compromise survival.[2] However, the shortcomings of the 'one-size-fits-all' approach are also apparent in the youngest patients, some of whom are later found to suffer from syndromic and heritable, rather than acquired marrow failure. Here, stem cell transplantation, including matched unrelated donor hematopoietic stem cell transplantation, would be the indicated treatment, even though misdiagnosis often becomes apparent only after sustained failure to respond to conventional immunosuppressive treatment.[3] On the backdrop of these and other issues, the study of long-term outcomes after immunosuppressive treatment by Kamio *et al.*, published in this issue of the journal reveals some expected age-independent commonalities, but also provides surprising insight into important problems unique to children.[4]

"Primum, non nocere" - *the case for not treating patients with non-severe disease*

Advocates of immunosuppressive therapy correctly emphasize its comparatively low cost, high tolerability and outpatient feasibility. Perhaps on that basis, the investigators in the study reported by Kamio *et al.* made a decision to treat children with non-severe disease using anti-thymocyte globulin-based combination immunosuppressive treatment.[4] According to a prior report by the same investigators, some patients in their study population (AA-92) with non-severe AA were actually randomized to receive granulocyte colony-stimulating factor to boost neutrophil recovery.[5] Three of the 27 patients with non-severe AA assigned granulocyte colony-stimulating factor subsequently developed myelodysplasia. It is important to remember that patients with non-severe AA are, by definition, transfusion-independent with one third of them expected to recover without specific treatment.[6] While causality remains questionable, there is currently no convincing evidence that granulocyte colony-stimulating factor improves outcomes in AA and the mere possibility that the development of myelodysplasia in patients with non-severe AA was related to treatment raises concerns.[7]

Is there benefit from withholding treatment for non-severe AA until disease progression? One recent study of children with AA who received immunosuppressive treatment seems to suggest just that, showing a better response to immunosuppressive treatment in children with very severe disease.[8] Indeed, the data presented by Kamio could be interpreted this way. The authors show that the risk of relapse 10 years after the first immunosuppressive treatment was higher in patients with non-severe AA (35.3%) than in patients with severe AA (12.9%) or very severe AA (12.0%).[4] They speculate that some cases of non-severe disease were misdiagnosed and relapse simply revealed the innate defect of the hematopoietic progenitor cell that is characteristic of heritable marrow failure. Of course, patients with inherited bone marrow failure have no benefit from immunosuppressive treatment. Finally, if the treatment intent in non-

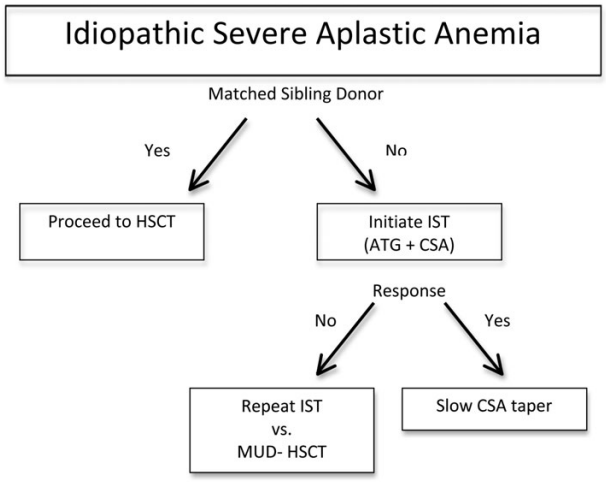

Figure 1. Treatment algorithm for idiopathic severe aplastic anemia. HSCT- hematopoietic stem cell transplantation; IST- immunosuppressive treatment; ATG- anti-thymocyte globulin; CSA- cyclosporine A; MUD- matched unrelated donor

severe AA is curative and if matched sibling donor transplantation is the best available treatment for patients with AA in general, why would these patients be excluded from what is perceived to be the standard of care?

Immunosuppressive treatment for non-severe AA would appear to be far from innocuous and the associated infections, electrolyte imbalances, hypertension, cyclosporine dependency and relapses all incur costs beyond those of watchful waiting.[4,9,10] As long as the benefit is unproven of treating those patients with non-severe AA early whose disease will ultimately evolve into severe AA, clinical equipoise would suggest that monitoring at intervals and family education might present a better course of action, thereby reserving treatment for patients whose disease progresses.[6]

Unrelated donor stem cell transplantation as universal first-line treatment in children – now an economic choice?

The thorough long-term evaluation of relapse after immunosuppressive treatment and retreatment in the report by Kamio *et al.* should also rekindle the well-worn discussion about the role of unrelated donor marrow grafting as first-line therapy for children with AA. The group at the US-National Institutes of Health reported an overall response rate of 74% after anti-thymocyte globulin-based combination immunosuppressive treatment for severe AA with a cumulative relapse rate of 33% at 10 years.[10] Although potentially explained by differences in the duration of tapering CSA, this would substantially exceed the 10-year relapse rate of 11.9% reported here after the same regimen. Not unexpectedly, in both studies a majority of patients had only partial responses to immunosuppressive treatment, but more worryingly among 264 of the 441 patients who responded to treatment in the study by Kamio *et al.*, 42 subsequently relapsed. This implies that 49.7% (n=219) of children treated with immunosuppressive treatment ultimately required a second-line treatment, not dissimilar to results reported by Scheinberg *et al.*[10] Moreover, responses to immunosuppression are notoriously slow and relapse or clonal disease can occur late. That general uncertainty for patients about durability of response and potential evolution is further compounded by supportive care needs and associated side effects, making for all the adversity of a chronic disease in a developing child.

Unlike stem cell transplantation using related donors, the success of unrelated marrow grafting in AA is more recent and directly attributable to improvements in HLA-matching, supportive care and elimination of radiation from the conditioning regimen.[11,12] Two recent retrospective studies in children revealed non-significant differences in overall survival when comparing outcomes after matched unrelated donor *versus* matched sibling donor hematopoietic stem cell transplantation.[13,14] Incidentally, an earlier study by Kobayashi showed that delaying hematopoietic stem cell transplantation until after immunosuppressive treatment has failed actually increases graft rejection and adversely affects outcomes.[15] Is it time to consider bone marrow transplantation as general first-line treatment for children with SAA, irrespective of related *versus* unrelated graft source? In reconciling the indisputable success of stem cell transplantation in children with AA and the emerging long-term consequences of immunosuppressive treatment, it will be important to consider childhood development, adolescent socialization and long-term quality-of-life issues.

'The immunoprivilege'

Stem cell transplantation is a complex and costly procedure that requires considerable financial resources and experience. However, a recent study serves as a reminder that access to anti-thymocyte globulin or other immunosuppressive drugs may also present an economic privilege. Jaime-Perez and colleagues demonstrated that in patients without access to anti-thymocyte globulin/ CSA, single-agent danazol treatment can result in an overall response rate of 45.9% with 5-year overall survival of 59%.[16] These are impressive results for an agent that by comparison is cheap, readily available and has a wide therapeutic index. Indeed, androgenic steroids have long been a mainstay of therapy in other countries.[17,18] Now, Kamio *et al.* report that up-front androgen treatment improves response rates to immunosuppressive treatment in children (67.9% *versus* 57%), albeit with an increased relapse rate of 29% at 10 years (RR: 3.1). As for high relapse rates in patients with non-severe AA, the loss of response could be attributed to uniform androgen cessation after 6 months in children with syndromic bone marrow failure who were inadvertently treated as having idiopathic AA. Androgen use has fallen out of favor in most western countries because of its virilizing side effects, inconsistent efficacy and the prolific pipeline of alternative immunosuppressive drugs.[19,20] Although the mechanism underlying androgen activity was long unclear, Calado recently reported that aromatase catalyzed its conversion to estradiol thereby mediating the up-regulation of lymphocyte telomerase activity.[21,22] If corroborated in hematopoietic stem and progenitor cells, these exciting studies may explain how androgens alleviate bone marrow failure. The observations, along with the anecdotal success of non-androgenic steroids in AA patients refractory to immunosuppressive treatment, and the potential benefit in response time reported by Kamio *et al.*, should motivate further exploration of these compounds. Not least, progress in this area may benefit those without ready access to costly treatment and provide alternative options for patients suffering from heritable marrow failure who lack a suitable stem cell donor, or access to marrow transplantation.

Conclusion

"The obstacle to discovery is the illusion of knowledge", (Daniel Boorstin; 1914-2004). Over 100 years have passed since Paul Ehrlich prescribed broth and a subcutaneous injection of unmatched whole blood in an, ultimately futile, attempt to treat a young patient with the ailment subsequently termed 'Aplastic Anemia'.[23] Even as the hard work of many has successively led to improved survival in patients with AA, our understanding of the disease remains frustratingly narrow. In children especially, neither diagnostic evaluation nor, it would seem, treatment is without room for improvement. There is no better illustration of the scope of the remaining challenge

than the nuanced presentation of outcomes by Kamio *et al.* in this issue of the journal.

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