Antithymocyte globulin and cyclosporin: standard of care also for older patients with aplastic anemia

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Treatment of aplastic anemia (AA) is challenging because cytopenia exposes patients to infectious and hemorrhagic complications, and immunosuppressive agents may further increase the risk in the short term: this is particularly true in older patients, in whom age, per se, is a risk factor. For this reason, I believe the study published in this issue on behalf of the French Cooperative Study Group for Aplastic Anemia,[1] on 88 patients over the age of 60 years, given immunosuppressive therapy (IST), is clinically relevant and useful on a practical level. The authors identified 184 treatments, including the standard combination of anti-thymocyte globulin and cyclosporine-A (ATG-CsA). Responses were significantly better in those that had followed an ATG-CsA regimen; overall response rate was 70% after first-line treatment and the overall 3-year survival was an excellent 74%. The Authors conclude that age, per se, is not a limiting factor for standard immunosuppressive treatment of patients with AA.

Treatment of severe aplastic anemia (SAA) patients over the age of 60 is problematic, and transplant studies claiming good results in older patients[2] contain only very few patients over the age of 60: in the study by Shin and coworkers, which suggests that transplant outcome is comparable in patients younger or older than 40 years, the maximum patient age was 63 years.[2] The cyclophosphamide (CY) dose-finding study by Anderlini and coworkers on patients receiving an alternative donor transplant, which showed over 90% one-year survival for the low dose CY group, had only a handful of patients over the age of 40, and the median age overall was 21 years.[3] More recently, a European Group for Blood and Marrow Transplantation (EBMT) study showed that the outcome of transplant for SAA patients over the age of 40 remains unsatisfactory[4] and has not improved in the past decade. Also, in patients with leukemia, age is a predictive factor, but transplant mortality is much lower than in SAA patients; a recent study in patients over the age of 70 years reported a transplant mortality of 20%.[5] Therefore, age has a stronger impact on survival after transplantation in SAA than leukemia, for reasons which are not clear. Currently, transplantation over the age of 60 is rarely taken into consideration by transplant centers: in the EBMT study 2010-2015, 95 grafts there performed on patients over the age of 60 (16 transplants/year in Europe).[4]

Immunosuppressive treatment is also strongly age-dependent: in a prospective randomized EBMT study, the 6-year survival was 100% for patients <20 years old, 92% for patients aged 20-40 years, 71% for those aged 40-60, and 56% for patients older than 60 years.[6] Two recent retrospective analyses have addressed the issue of first-line treatment in a large number of SAA patients with either horse ATG-CsA (in 465 patients)[7] or rabbit ATG-CsA (in 955 patients).[8] The one year cumulative incidence of response was 65% for both horse or rabbit ATG, but patients over 60 years of age had lower response rates.[7,8] As for survival, the horse ATG-CsA study shows a 5-year survival of 70% for patients over the age of 40, compared to 90% for young patients.[7] The rabbit ATG-CsA study shows a similar 5-year survival for patients aged 40-60 (80%), but over the age of 60, survival at 5 years is in the order of 50%, compared to 90% for younger patients.[8] Therefore, also after ATG-CsA, age remains one of the major predictors of response and survival.

The French study by Contejean and coworkers[1] compares

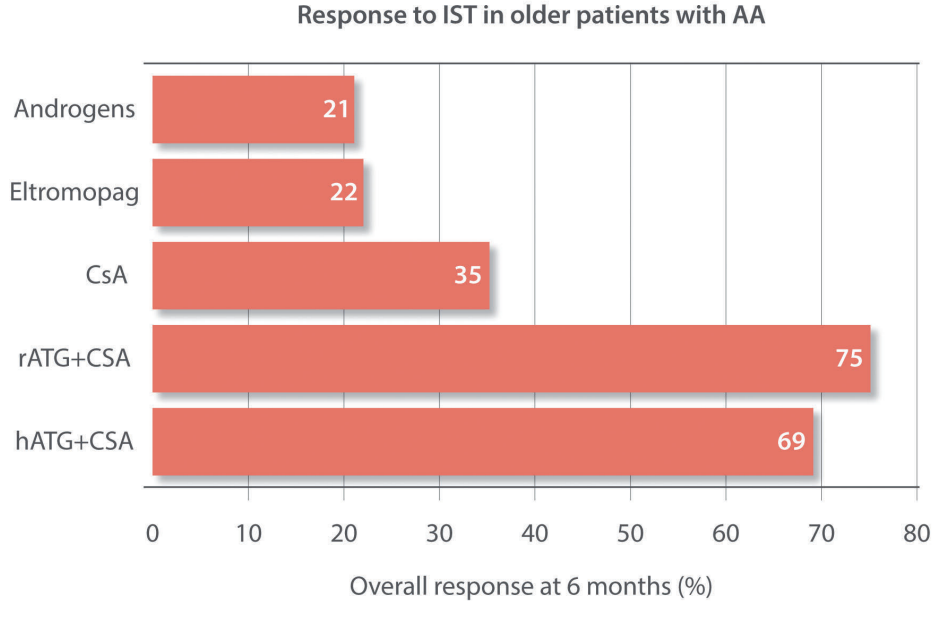

Figure 1. Proportion of patients responding to immunosuppressive therapy (IST). hATG: horse anti-thymocyte globulin; rATG: rabbit ATG; CsA : cyclosporine A.

favourably with these two large international reports: response rate to ATG+CsA at 6 months was 70% compared to 35% for patients receiving CsA alone, 22% for eltrombopag alone, and 21% for androgens alone (Figure 1). Overall response rates in patients receiving these different treatment options is outlined in Figure 1, which highlights a superior response rate with the ATG+CsA combination. Figure 1 also shows there was no difference in response for patients in this older patient population receiving horse (hATG) *versus* rabbit ATG (rATG), which is in keeping with two large recently published real-life studies.[7,8] Also, survival was comparable in patients receiving horse or rabbit ATG. The higher response rate of patients receiving ATG+CsA did not translate to a significantly improved survival compared to other regimens, as already shown in an EBMT study;[9] possibly due to second treatment or improved supportive care. Further support to long-term survival also for non-responders comes from the rabbit ATG study; it showed that the 10-year survival of AA patients, classified at 6 months as non-responders to a first course of rATG+CsA, was comparable whether patients were then allografted (64% survival) or not (60% survival).[8] Late responses, improved supportive care, and second treatments could possibly explain the outcome of non-allografted patients.

In conclusion, ATG+CsA remains the treatment of choice for patients with AA, also for those over the age of 60; it should be preferred over the administration of CsA with or without androgens or eltrombopag, with or without CsA. Whether the addition of eltrombopag to ATG-CsA first line will further improve the outcome, as recently suggested,[10] will be determined by an ongoing prospective randomized trial (RACE trial, EBMT). This study also confirms that in real-life analysis, horse or rabbit ATG produce almost identical response rates and survival, also in older AA patients.

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Milk and the "Grandmother Effect"– a new contribution to the legacy of Ray Owen

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The article by Schonewille *et al.*, in the September 2018 edition of Haematologica,[1] tests the theory originally proposed by Owen *et al.* [PNAS, 1954[2]] that a "Grandmother Effect" can protect the offspring from hemolytic disease of the fetus and newborn (HDFN) [see illustration, Figure 1]. This disease is caused by maternal antibodies formed against the baby's red blood cells (rbc). One should note here that, thanks to the research of Owen and others in the 1950s, anti-Rhesus D (RhD) antibody (aka "Rhogam") prophylaxis began to be practiced for all pregnant women who are RhD- bearing an RhD+ fetus. The absence of such therapy prior to 1954 enabled Owen and colleagues to determine that, when the grandmother had RhD, the mother who was RhD- and had thereby already been "naturally" exposed to this antigen *in utero* and as a newborn via breast-feeding, was rendered incapable (for the most part) of producing antibody to an RhD encountered in her adult life as the mother of a child sired by her RhD+ husband. Subsequent to the routine application of Rhogam (anti-RhD prophylaxis) in the 1960's, the incidence of hemolytic disease of the newborn was greatly decreased, although not completely eliminated. Briefly, Rh- mothers are given a bolus of Rhogam at 28 weeks of pregnancy. If the baby that is born is Rh+(a 50:50 chance, if her husband is RhD heterozyogous), she will receive a second dose, 72 hours after giving birth. This procedure has revolutionized obstetrics and made it possible for healthy Rh+ babies to be born from multiple pregnant Rh- women.

While a boon to Ob/Gyn medicine, this highly effective clinical practice made it nearly impossible for others to