

Bone marrow failure on steroids: when to use androgens?

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In this issue of *Haematologica*, Pagliuca *et al.* report on the European Society of Blood and Marrow Transplantation (EBMT) retrospective analysis on the use of androgens to treat bone marrow failure syndromes.¹

Androgens have been an option in the treatment of aplastic anemia since the 1960s with variable response rates.² Different steroids with androgenic or anabolic effects have been applied, from danazol and oxymetholone to nandrolone decanoate and oxandrolone.³ These formulations vary in administration, pharmacokinetics, anabolic effects, and toxicity. The mechanisms of action on the bone marrow are multiple and at least two pathways have been described. It stimulates erythropoiesis by activating the erythropoietin (EPO) receptor and increasing EPO production in the kidneys. It also stimulates the telomerase (*TERT*) gene expression in the hematopoietic tissue.⁴

Androgens have been used to treat acquired immune and inherited aplastic anemias, including Fanconi anemia and dyskeratosis congenita, but the success of immunosuppression (anti-thymocyte globulin and cyclosporine) and, more recently, eltrombopag to treat immune aplastic anemia have meant that androgens are now very unlikely to be a therapeutic choice for acquired cases.

For inherited bone marrow failure, the collective experience supports its use in certain circumstances. Several retrospective studies in Fanconi anemia with a relatively limited number of young patients showed good responses varying from 68% to 87% with a median duration of 2-3 years but with consistent adverse events, such as virilization, liver toxicity, and myelodysplasia.⁵⁻⁷ In telomere diseases, including dyskeratosis congenita, prospective studies showed good hematologic responses in approximately 80% of cases associated with telomere elongation.^{8,9} Again, liver toxicity (elevated liver enzymes in 41-88% of cases), virilization (in up to 59%), and edema (in 26%) are common adverse events. Severe adverse events are infrequent. However, virilization may have significant physical and psychological negative impacts in younger patients, especially in girls.

The study by Pagliuca *et al.* is the largest retrospective cohort with 274 aplastic anemia patients treated with an-

drogens in 82 EBMT centers. In total, 193 patients were diagnosed with acquired and 81 with inherited aplastic anemia with a median treatment duration of 5.6 and 20 months, respectively. Surprisingly, response rates were very similar between the two groups (acquired and inherited) with approximately one-third of patients responding at three months. Androgens as third-line therapy (or more) for acquired or after one-year post diagnosis for inherited cases were associated with improved failure-free survival. This is an important observation because inherited etiology was not comprehensively addressed in this retrospective cohort and many patients in the acquired group may have had a cryptic genetic etiology, including, for example, telomere-biology gene mutation, GATA2 deficiency, or *SAMD9/9L* mutation. That a genetic component is likely in this group is also supported by the late response to androgens after two or more immunosuppressive cycles. Conversely, the inherited group was mainly composed of Fanconi anemia, further suggesting that other inherited cases were allocated in the “acquired” group. The discrepancy in hematologic response between the current analysis and previous reports may be due to the response timepoint (3 months in the current analysis), as Fanconi anemia patients usually respond after six months when treated with oxymetholone and one year when danazol is administered.³ Toxicity was mainly associated with the liver, gastrointestinal tract, and kidneys, and appeared early, similar to previous analyses. The study by Pagliuca *et al.* reinforces the specific situations in which androgens may be a good option and those in which it should be avoided (Figure 1). First, androgens should not be considered as an option to treat acquired immune aplastic anemia, at least as first- or second-line therapy.¹⁰ On the one hand, immunosuppression combined with eltrombopag produces excellent response rates as front-line for older patients or those lacking a suitable sibling donor.^{11,12} On the other hand, alternative source hematopoietic stem cell transplant (HSCT) modalities may have very good results either as front-line or to rescue the minority of patients who fail eltrombopag added to immunosuppression.^{10,13,14} Excep-

Aplastic anemia

Etiology

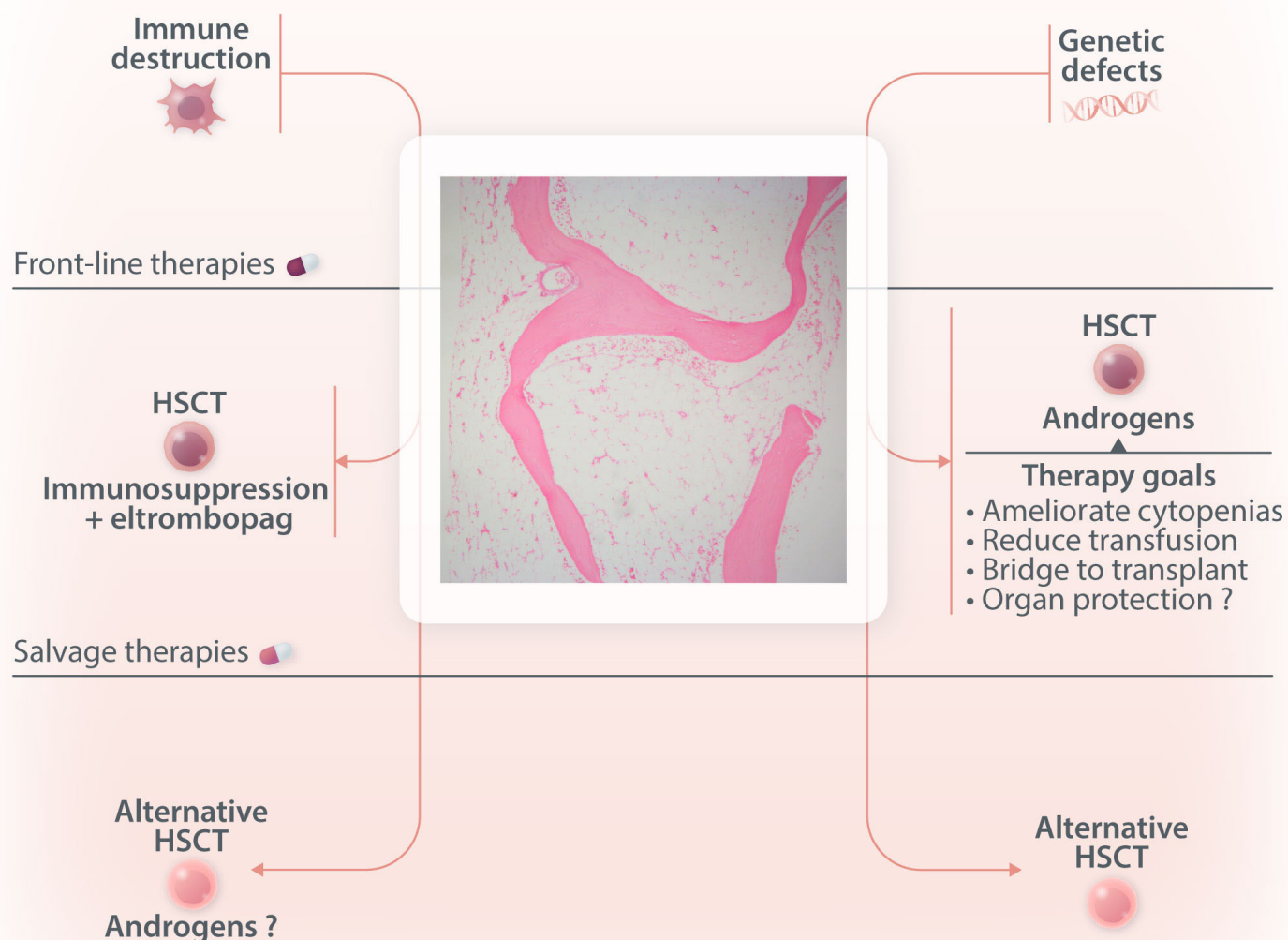


Figure 1. Different etiologies (immune-destruction, genetic defects) cause hematopoietic stem cell failure, clinically translating into aplastic anemia (empty bone marrow). Genetic defects causing marrow failure usually are related to impaired DNA repair (Fanconi anemia), defective telomere maintenance (telomeropathies), ribosomal deficiency (Shwachman-Diamond syndrome), or differentiation defect (GATA2 deficiency).^{10,15} Immune aplastic anemia may be effectively treated with related-matched hematopoietic stem cell transplant (HSCT) or intensive immunosuppression (anti-thymocyte globulin and cyclosporine) combined with eltrombopag, a TPO-agonist that stimulates hematopoietic progenitors.^{11,12,16} Inherited aplastic anemia may also be treated with HSCT but androgens may also be effective in alleviating cytopenias, reducing transfusion dependence, serving as a bridge to HSCT, and potentially protecting other organs.^{3,9,17,18} Exceptionally, androgens may be used as salvage therapy for patients with immune aplastic anemia who failed to respond to previous immunosuppression or HSCT.

tionally, androgens may be considered for patients with “acquired” aplastic anemia who failed multiple courses of immunosuppression, eltrombopag, and who are not eligible for HSCT.

For Fanconi anemia, telomeropathies, and other inherited cases, androgens may be an option under certain circumstances.³ First, these may be beneficial for patients with cytopenias not severe enough to justify a HSCT. Second, androgens may be an option for patients with severe cytopenias lacking a suitable donor. Third, androgens may be used as a bridge to HSCT to ameliorate cytopenias or transfusion dependence. Although the prevention of extra-

hematologic manifestations should be a goal, it is still unclear whether androgens can modulate liver or lung involvement.⁹ Finally, the androgen formulation should be based on the adverse event profile, availability, gender, and administration route. For example, oxymetholone appears to produce faster responses than danazol, but it more frequently results in virilization and should be avoided for girls.³ Nandrolone may cause less severe liver toxicity but administration is intramuscular.⁹

In summary, the study by Pagliuca *et al.* updates and summarizes the potential benefit of treating aplastic anemia patients with androgens. The benefits may be limited but

effective when appropriately used, especially in inherited cases. It may also serve as a bridge to HSCT when an appropriate donor is not readily available, or blood counts are not low enough to satisfy transplant criteria.

Disclosures

No conflicts of interests to disclose.

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