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Immune mediated marrow failure in very young children: horse ATG once again out of the magician's hat

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Immune mediated marrow failure in very young children: horse ATG once again out of the magician's hat.

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Aplastic anemia in children has an elaborate differential diagnosis. In general, inborn marrow failure syndromes involving DNA damage repair, ribosomal protein synthesis, telomere length maintenance and stem cell dysfunction are rare but important diagnoses to consider.

Several of these diagnoses can be identified by gene panel screening, but for others functional assays remain important since not all genes are known.

Most of these marrow failure syndrome diagnoses have clinical consequences, including adapting conditioning regimens for allogeneic hematopoietic stem cell transplantation (HSCT) as well as for follow-up, counseling and screening of families.

Other etiologies involve infectious diseases and auto-immunity. It is generally believed that autoimmunity is rare in very young children. In this edition of the journal, Whitmann et al[1] report intriguing data that this may need reconsideration: 30 patients, aged 16-35 months were treated with - mainly horse ATG based - immune suppressive treatment (IST) and the response was unexpectedly impressive: not only CR rates of 80% leading to transfusion independency and an overall survival of 100%, these responses were durable with no relapses with prolonged follow-up.

Many issues with a registry-based evaluation as presented here, can (and will) be raised, but to cut a long story short: these excellent results clearly indicate that IST remains a valuable option in young children with aplastic anemia.

This is of even greater importance since haplo-identical HSCT, using post-transplantation cyclophosphamide, has revolutionized the access to transplant in many parts of the world.

Let us be clear: If a healthy, matched sibling donor, willing to donate marrow (avoiding chronic graft-versus-host disease) is available, no time should be lost to

avoid dangerous or even lethal infections or bleeding complications. In large parts of the world well matched unrelated marrow donors are also considered an excellent option.

Even then the differential diagnosis should be evaluated carefully, to adapt condtioning regimens if appropriate, eg in Fanconi anemia. So, several weeks are needed to come to a plan for appropriate therapy. However, in the absence of a well matched donor, IST still deserves consideration.

HSCT has become safer, but it inherently carries risks of mainly graft-versus-host disease and graft failure. This can potentially affect quality of health and even survival.

IST has a long history of unexpected findings if not surprises: the classical study comparing horse with rabbit ATG[2] is a true hallmark: horse ATG was unexpectedly superior to rabbit. Later, studying the effect of adding eltrombopag to IST in adults, again: findings were unexpectedly beneficial for the addition of eltrombopag[3].

Let us now dive deeper in the paper presented in this volume of the journal. The data stem from North American registries. The diagnostic testing was not complete in all included subjects. However, it is unexpected for IST to be effective in cases of inherited marrow failure. Thus, missed diagnoses of inherited marrow failure would lead to lower response rates. Response evaluation and complication registration was not done in a systematic, prospective manner. But still, the unexpected high response rates remain remarkable. Some patients were treated decades ago, with now unusual approaches such as high dose cyclophosphamide, as immunosuppressive agent.

For clinical practice it would be of great value, not only to predict upfront who will respond to IST, but also when failure can be concluded. This will prevent unnecessary loss of time to proceed to salvage HSCT. This small retrospective series seems too limited to draw firm conclusions for such a clear timepoint to decide IST has failed. Having to wait 6 months before deciding HSCT can not be avoided, is too long for many patients. But after 4-6 months, only half of all patients ultimately responding to IST (defined as transfusion-independent) had done so. This clearly is challenging. Only the clinical situation (complications, side effects of ciclosporin, donor availability, shared decision making) can then lead the way.

A major potential risk of IST is the prolonged need of ciclosporin treatment or even dependency. This is hardly acceptable in children. The median duration of this drug in responding patients was 24 months, which seems tolerable, although the registry study is not the ideal setting to evaluate long term side effects.

The study presented here again challenges therapy decisions in young children with aplastic anemia. Our therapeutic toolkit is never static: post transplantation cyclophosphamide continues to change HSCT availability. Eltrombopag might be of additional value but is at this point in time not considered beneficial in young children

with aplastic anemia[4], but based on the data presented here ATG-based IST should not be erased.

References

1. Whitmann T, Willis L, Arnold S, et al. Immunosuppressive therapy for severe aplastic anemia in children under the age of 3 years yield a high response rate: a North American collaborative study. Haematologica. xxx

2. Scheinberg P, Nunez O, Weinstein B, et al. Horse versus rabbit antithymocyte globulin in acquired aplastic anemia. N Engl J Med. 2011;365(5):430-438.

3. Peffault de Latour R, Kulasekararaj A, Iacobelli S, et al. Eltrombopag added to immunosuppression in severe aplastic anemia. N Engl J Med. 2022;386(1):11-23.

4. Groarke EM, Patel BA, Gutierrez-Rodrigues, et al. Eltrombopag added to immunosuppression for children with treatment-naive severe aplastic anemia. Br J Haematol. 2021;192(3):605-614.