multivariable analysis incorporating time to transplantation for the patients with acute leukemia or myelodysplastic syndrome (MDS). In neither case did time to transplantation have an effect on posttransplantation survival (HR = 1.0, P = .4 for patients with acute myeloid leukemia [AML]/acute lymphoblastic leukemia [ALL], and HR = 1.0, P = .3 for patients with MDS). Moreover, the inclusion of this variable in the model had no effect on the hazard ratio associated with an elevated pretransplantation ferritin. Finally, one could argue that in patients with acute leukemia, time to transplantation is very closely related to disease stage (which we accounted for in our models). Therefore, we still submit that pretransplantation serum ferritin in our analysis reflects iron overload rather than disease stage.

We agree with Platzbecker and colleagues that, in the case of patients with low-risk MDS, earlier transplantation may diminish the impact of iron overload on transplantation outcome. However, it is worth pointing out that the decision analysis of Cutler et al1 used survival figures that presumably incorporate the effect of iron overload on patients who undergo transplantation in later stages of MDS. Moreover, if chelation therapy could be safely performed and could mitigate or even abrogate the detrimental impact of iron overload on transplantation outcome, the opposite may in fact happen: patients could undergo transplantation in later stages of MDS, which could improve quality-adjusted survival.

Philippe Armand

Conflict-of-interest disclosure: The author declares no competing financial interests.

Correspondence: Dana-Farber Cancer Institute, 44 Binney Street, Boston, MA 02115; e-mail: parmand@partners.org.

References


To the editor:

**Immunogenicity of factor VIII concentrates in patients with hemophilia: a randomized clinical trial is warranted**

The retrospective cohort study of Gouw et al1 deals with one of the most currently cogent issues in hemophilia: the immunogenicity of recombinant factor VIII (FVIII) and of plasma-derived FVIII containing von Willebrand factor (VWF) in patients more at risk of inhibitor (ie, those previously untreated) when exposed to a FVIII source.2 The authors found no difference in the rate of inhibitor development with the 2 different FVIII sources, at variance with other cohort studies3,4 that showed that VWF-containing FVIII products were less immunogenic than recombinant products. We believe that a number of problems in Gouw et al’s study make their demonstration of equivalent immunogenicity unsettled.

The first problem concerns the definition of VWF-containing products. The authors defined plasma-derived products with a high or low VWF content choosing the threshold of 0.01 IU of VWF antigen per IU of FVIII antigen. No information is provided on the rationale for the choice of the antigen content or of the threshold or on how the values of the antigen content were obtained for each concentrate. In addition, it is not clear why the authors did not choose to analyze subgroups within the group of concentrates defined as above with a high VWF content, considering the wide-ranging VWF content in these products.

The second problem is the assignment to product classes. It is not explained why patients were assigned to 1 of the 3 product classes (recombinant products, plasma-derived products with low and high VWF content) on the basis of the first product used and not on the prevalently used or last product used before inhibitor development. It appears that at least 50% of 104 patients who switched to a different product (more commonly from a plasma-derived to a recombinant one) did this within the first 5 exposure days (EDs), 75% of them within the first 15 EDs. Inhibitors developed in at least 50% of patients with inhibitors within the first 14 EDs, so that a relevant number of patients developed inhibitors after switching. Would the inhibitor incidence be different if patients had been differently assigned to product classes?

The third problem we would like to address is related to the role of prophylaxis. How were patients assigned to this mode of replacement therapy if the therapy was started on demand? Has the inhibitor developed during the on-demand treatment period or during the prophylaxis period? What were the reasons for starting or delaying prophylaxis in patients? A possible confounder was perhaps introduced if prophylaxis was differently prescribed to the patients of the 3 treatment groups (recombinant, monoclonal, and VWF-containing FVIII products). In fact, early prophylaxis might have played a protective role.5 This protective role was not found by Gouw et al1 because prophylaxis was started in at least 50% of the patients after 14 EDs, at the time when 50% of patients had already developed their inhibitor.

All of these issues emphasize the need for a randomized clinical trial in order to provide a definite answer on the different immunogenicity of FVIII products because the cohort studies published so far1,3,4 gave substantially different results.

Alessandro Gringeri and Pier Mannuccio Mannucci

Conflict-of-interest disclosure: The authors report receiving lecture fees from the majority of the manufacturers of recombinant and plasma-derived clotting factor products, and no other potential conflicts of interest relevant to this article.

Correspondence: Alessandro Gringeri, A. Bianchi Bonomi Haemophilia and Thrombosis Centre, Department of Medicine and Medical Specialties, University of Milan and IRCCS Maggiore Hospital, Mangiagalli and Regina Elena Foundation, Via Pace, 9 – 20122 Milan, Italy; e-mail: alessandro.gringeri@unimi.it.

References

Immunogenicity of factor VIII concentrates in patients with hemophilia: a randomized clinical trial is warranted

Alessandro Gringeri and Pier Mannuccio Mannucci