Complication free survival long-term after hemopoietic cell transplantation in thalassemia

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Thalassemia patients have witnessed and have been the protagonists of two extraordinary events in the progress of their treatment during recent decades. Medical therapy (transfusion and regular chelation) has dramatically changed their prognosis from a fatal disease in childhood to a chronic disease into adulthood with an open, undefined prognosis. Hematopoietic cell transplant has changed the paradigm of thalassemia, introducing for the first time in medical history the notion of a cure for this congenital disease.

Allogeneic hematopoietic cell transplantation (HCT) has become a standard of care for the cure of transfusion-dependent thalassemia patients, with thousands undergoing this curative approach worldwide. Transplant has expanded from the industrialized countries and is now performed in several parts of the world, including those where the disease is most prevalent.[1]

As transplantation is a curative approach usually performed in childhood, with a limited but not absent risk in a non-neoplastic disease in which prolonged survival (decades) can be achieved with conventional medical therapy, data on long-term real-life complications are essential. In this issue of the Journal, Rahal *et al.*[2] and the French co-operative group[2] report on these much needed data.

Of the over 134 patients transplanted in the period 1984-2012 (median age at transplant 5.9 years, interquartile range 3-11 years) in 21 French centers, 107 were alive and well two years after HCT; 2 subsequently died from chronic graft-*versus*-host disease (GvHD) and 6 were later lost to follow up. The remaining 99 patients were part of these detailed analyses on long-term complications. Almost all patients had been transplanted in childhood after a myeloablative conditioning and almost all had received hematopoietic cells from an HLA identical sibling.

After a median follow up of 12 years (interquartile range 7-19 years) 11% of these patients presented thyroid dysfunction, 5% diabetes, and 2% cardiac failure. Hypogonadism was present in 56% of females and 14% of males. As expected, females who experienced normal puberty were younger at transplant compared to those who experienced delayed puberty. Almost half of the females aged 20 years or over had spontaneous and successful pregnancy after transplantation, confirming another single center report.[3]

Interestingly, no secondary cancer, delayed graft failure with thalassemia recurrence or transplant-related mortality were registered. As correctly reported by the Authors, and as also expressed in other recent reports,[4] the issue of secondary cancers probably requires a longer follow up to be confirmed. However, the limited incidence of chronic GvHD allows for some slight optimism in this setting. The data regarding absence of long-term thalassemia recurrence do not confirm recent isolated case reports (*EP Alessandrino and C Giardini, 2018, personal communications)*, but even in this case, longer follow up would probably be necessary.

Most patients have been successfully treated for iron overload even if the suggested target of normal transferrin saturation has not been completely reached in all of them.[5]

The great strength of this report is that it includes 73% of the transplanted patients and 93% of the patients who have survived for at least two years in the multi-center (21 transplant centers) experience of an entire large nation and, therefore, provides reliable real-life data on a population judged suitable for transplantation in the years indicated without other forms of selection. Moreover, conditioning, age at transplant, and follow-up methods were substantially uniform for almost all the patients. This report provides the most uniform world-wide long-term analyses from the entire transplant activity of one country.

Another great strength of this work is that the Authors successfully managed to separate iron overload thalassemia-related long-term complication from transplant-related complication. Because of the homogeneous donor selection, and the very limited incidence of chronic GvHD, the reported transplant-related complication could likely be related to the intensity of the conditioning regimen, and mainly to the use of high doses of the alkylating agent busulfan. This makes this analysis likely predictive for long-term complication in gene therapy programs in hemoglobinopathies[6] requiring myeloablative preparative regimens.

There are three unavoidable limitations to a general use of these data. One is that patients were transplanted at a very young age (following the indications of the Pesaro Group), and it is likely that patients transplanted at an older age would present many more long-term thalassemia-related complications.[7,8] Moreover, patients reported here were transplanted more than a decade ago with a standard myeloablative regimen. Today, less toxic preparative regimens have been developed,[9-11] and their long-term complications could be different and, hopefully, of a lower grade. Finally, 91% of patients transplanted in France were transplanted from an HLA identical sibling, and therefore long-term complications of transplants from different donor types could not be completely represented in this research.

Nevertheless, taking into account the above reported limitations, these data can be used to set up rational screening programs for patients transplanted in childhood.

There are several important considerations arising from this article.

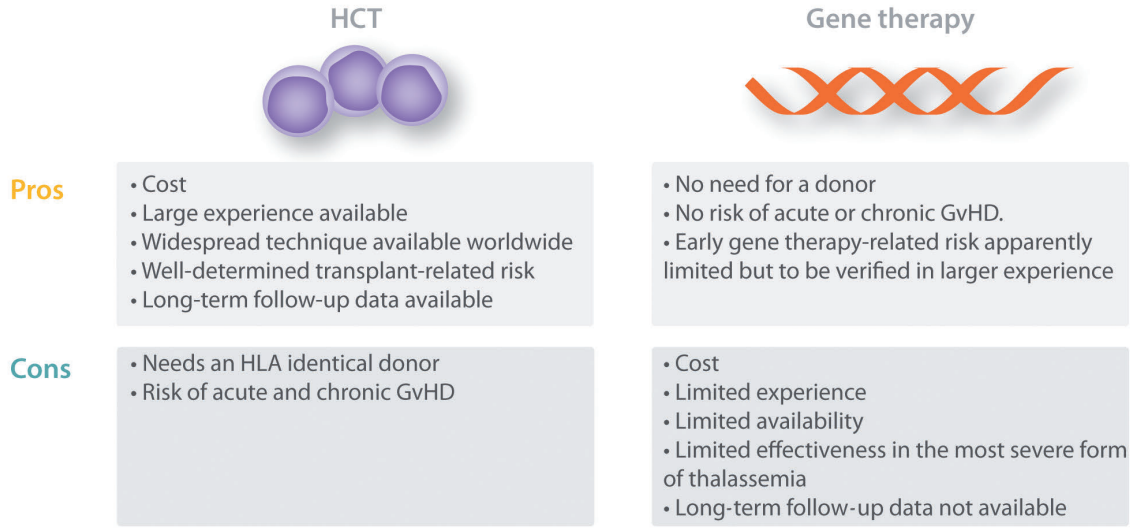

Figure 1. Factors to be considered in deciding hematopoietic cell transplant *versus* gene therapy. GvHD: graft-*versus*-host disease.

1) Once again it has been confirmed that transplantation in thalassemia should be performed as soon as possible, not only to maximize transplant outcome, but also to minimize long-term complications. The data on spontaneous puberty make this issue very clear.[2]

2) Long-term complications are less than those expected in medically-treated thalassemia[12] and, with the exception of hypogonadism, are of limited incidence with a quality of life similar to that of a matched normal population.[13]

3) Several reports of spontaneous maternities have been published, but this is the first report with epidemiology data including probability of maternity and paternity after an analysis of almost the entire transplanted population.

4) For the first time, the issue of adolescents being overweight is reported post transplant for a congenital disease. Clearly this observation requires more in-depth analysis and prospective dedicated studies with comparison to normal population data.

5) The problem of iron overload in the post-transplant setting has been resolved, and most patients can easily achieve normal iron burden[5] thus avoiding long-term iron toxicity complications.[14]

6) Like iron overload, other complications related to thalassemia can be treated after transplantation, such as hepatitis C and B virus infection, with the therapies available today.

7) Specific follow-up guidelines and screening recommendations can be proposed and can be used specifically for this category of patients in order to prevent / cure the complications that are known today.[15,16]

8) Recent data on the emerging gene therapy approach clearly indicate that a myeloablative preparative regime is necessary to allow gene-modified autologous stem cell engraftment. Therefore, if the long follow up confirms current safety data on the cellular product,[17] complications relating to the conditioning regimen, such as those reported here, can be foreseen and similar screening programs can be set up.

Lastly, this article provides a further contribution to the debate on the therapeutic decision-making process for thalassemia patients. This debate, which has so far been limited to medical therapy and transplantation, will soon be carried forward by another great innovation in the treatment of this disease: gene therapy.[17] Even if this approach has so far only demonstrated complete clinical effectiveness in non β^0/β^0 thalassemia, the door has been left ajar and will certainly be thrown wide open soon.

Regardless of the problem of gene therapy costs, which will probably significantly compromise its wide applicability, these data reporting long-term limited complication and no cancer after HCT can be of enormous help in establishing the correct therapeutic approach.

As discussed by many authors, transplantation, medical therapy, and now gene therapy, is an individual and highly personal decision.[18] Because of this, there have been no randomized prospective trials and it is likely that none will ever be performed. Several different medical, personal, and socio-economic aspects must be considered, taking into account the impressive epidemiology and the social conditions of countries were this disease is prevalent.[19] Figure 1 reports the factors to be considered today in approaching transplantation or gene therapy for the cure of transfusion-dependent thalassemia.

In my personal opinion, this report by Rahal *et al.*[2] reinforces the position of transplantation in this difficult decision-making process, particularly in the case of young children when an HLA identical sibling donor is available.

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Still a role for second-line chemoimmunotherapy in chronic lymphocytic leukemia?

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In this issue of the Journal, Cuneo *et al*. report a retrospective observational study of the efficacy of bendamustine rituximab (BR) given as first salvage therapy for chronic lymphocytic leukemia (CLL) patients within the GIMEMA and ERIC networks.[1] Among 237 patients, the median progression-free survival (PFS) was an excellent 25 months and the median time to next treatment 31.3 months. Predictors of shorter PFS in multivariable analysis included del(17p), unmutated *IGHV* and advanced stage. Cuneo *et al.* further performed a matched adjusted comparison of overall survival (OS) between the subset of BR-treated patients without del(17p) who had received front-line chemoimmunotherapy (CIT), and similar patients who had received ibrutinib second-line in named patient programs in the UK and Italy. Interestingly, there was no difference in OS, with 63% alive in the ibrutinib group at 36 months, as compared to 74.4% in the BR group.[1]

At first glance these data may seem surprising, as ibrutinib has had OS benefit in both the RESONATE trial,[2] comparing ibrutinib with ofatumumab in relapsed refractory CLL, and in the RESONATE-2 trial,[3] comparing ibrutinib with chlorambucil in previously untreated CLL. It is important to note that the control arms of both of these trials did not unfortunately represent particularly effective therapy, especially in comparison to the BR presented here; they were also both relatively small studies. A US Intergroup trial comparing ibrutinib to ibrutinib rituximab to BR for front-line therapy of CLL in older patients has completed accrual and results are awaited.

While these data from randomized trials are invaluable, they often do not capture the full picture of a new therapy, hence the value of observational studies like that of Cuneo *et al*.[1] Eligibility, particularly for phase III trials, is typically strict, resulting in a selected healthy patient population. This may be particularly true of the ibrutinib randomized studies. For example, although the median age of patients receiving ibrutinib in RESONATE-2 was 73 years, only 31% had a cumulative illness rating score (CIRS) over 6, indicating a very low level of comorbidity for their age.[3] Why does this matter? Although ibrutinib is often said to be well-tolerated among older patients with comorbidities, the data supporting this claim are actually quite limited, and a recent multicenter retrospective study has found that a CIRS score of over 6 was in fact associated with inferior event-free survival and OS, as well as increased risk of dose reduction or discontinuation, among ibrutinib-treated patients.[4]

Other real-world analyses with ibrutinib, as well as longer follow up of the prospective trials, have also made