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Haploidentical transplantation in sickle cell disease: toward donor availability for all patients

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Until now, the management of sickle cell disease (SCD) has relied largely on hydroxycarbamide and transfusion therapy, while curative opportunities have been represented almost exclusively by allogeneic hemopoietic cell transplantation (HCT) with overall survival exceeding 90% when an HLA identical sibling was available[1-2]. Nonetheless, the field continues to be constrained by the persistent challenge of donor availability. It is a matter of fact that although matched unrelated donor transplantation has proven comparable to HLA-identical sibling HCT in transfusion dependent thalassemia, no similar results have been reported in SCD with the premature termination of the NIH study for low rate of success.[3-5] Graft failure remains the principal barrier when HLA-identical unrelated donor is used.[6]

In this issue of Haematologica, Dhedin and colleagues present the final report of the DREP-HAPLO phase 2 multicenter study evaluating reduced-intensity haploidentical transplantation incorporating thiotepa in both pediatric and adult patients (median age: 17 years; range: 12–40) with severe SCD, confirming the critical role of thiotepa in optimizing engraftment.[7] Authors reported a 4-years overall survival and rejection-free survival of 90.15% and 85.56%, respectively.

Several results from this trial deserve to be highlighted. Although the number of patients is limited (N=22), the follow-up is remarkable (median follow up was 4.25 years). The rejection- free survival is truly impressive, even when compared to the two previous haploidentical trials[8-9], with only one case of secondary graft failure. However, this result is partly "paid for" by a higher incidence of chronic graft versus host disease (the 2-year incidence of moderate to severe chronic GvHD was 27%). Noteworthy is also the significant improvement of quality of life parameters, particularly among adolescents despite of chronic GvHD.

From a clinical perspective, none of the patients in follow-up showed symptoms related to SCD, and from a biological standpoint, hemoglobin and hemolytic parameters normalized. This occurred even despite mixed chimerism: hemolytic markers remained normal, with HbS level <40% in those who received a heterozygous donor. This is an important finding that adds to the ongoing debate with gene therapy, where hemolysis persists in about 50% of cases after beti-cell or exa-cell therapy[10-11], and where vaso-occlusive crises, although not severe, have been reported after infusion[11].

Furthermore, with this procedure it was possible to offer curative treatment even to patients with cerebral complications such as moya-moya, who currently would not have access to gene therapy or patients that cannot tolerate a myeloablative regimen.

The data reported here, together with additional published experiences (Table 1), demonstrate the feasibility of haploidentical transplantation in this hemoglobinopathy and suggest that it can be made readily accessible to the majority of children and adults. In the absence of an HLA-identical sibling, haploidentical transplantation represents a viable clinical option. This consideration is particularly relevant in resource-limited settings, where treatment costs can constitute a major barrier to care. The possibility of offering transplantation to patients with sickle cell disease—both children and adults—without an HLA-identical donor, even in the presence of advanced disease and organ damage, and at a relatively limited cost, substantially expands the therapeutic landscape. Under these conditions, nearly all patients with sickle cell disease, including those who have historically had limited or no access to curative treatments, may now be offered a realistic and tangible opportunity for cure.
This study also highlights two important issues: how to reduce the incidence of chronic GvHD and how to improve anti-infective prophylaxis, bearing in mind that this patient population is functionally asplenic and therefore requires targeted prophylaxis.

Within the rapidly evolving therapeutic landscape of sickle cell disease, recent breakthroughs in gene therapy, alongside significant improvements in transplantation outcomes, have markedly broadened the spectrum of available treatment options. Gene therapy is currently substantially much more costly than transplantation and still relies on myeloablative conditioning. The debate also concerns the curative potential of transplantation compared with gene therapy, where the disease appears to be *transformed* rather than truly cured. While these developments represent a major step forward, they also introduce increasing complexity in clinical decision-making, highlighting the need to identify the most appropriate treatment for the right patient at the right time. This will constitute a central challenge in the years ahead, particularly given the large number of affected individuals, most of whom reside in low- and middle-income countries.

Last but not least, the authors are to be commended for this academic work, conducted with resources that were presumably more limited than those available to large, industry-sponsored gene therapy trials. While direct comparison or competition between academic research and profit-driven organizations is not realistic, it remains essential that academia continues to generate independent, methodologically robust clinical studies. Such investigations provide an important scientific context and reference framework, within which the results of more extensively funded for-profit-trials should be interpreted by the medical community.

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Table 1

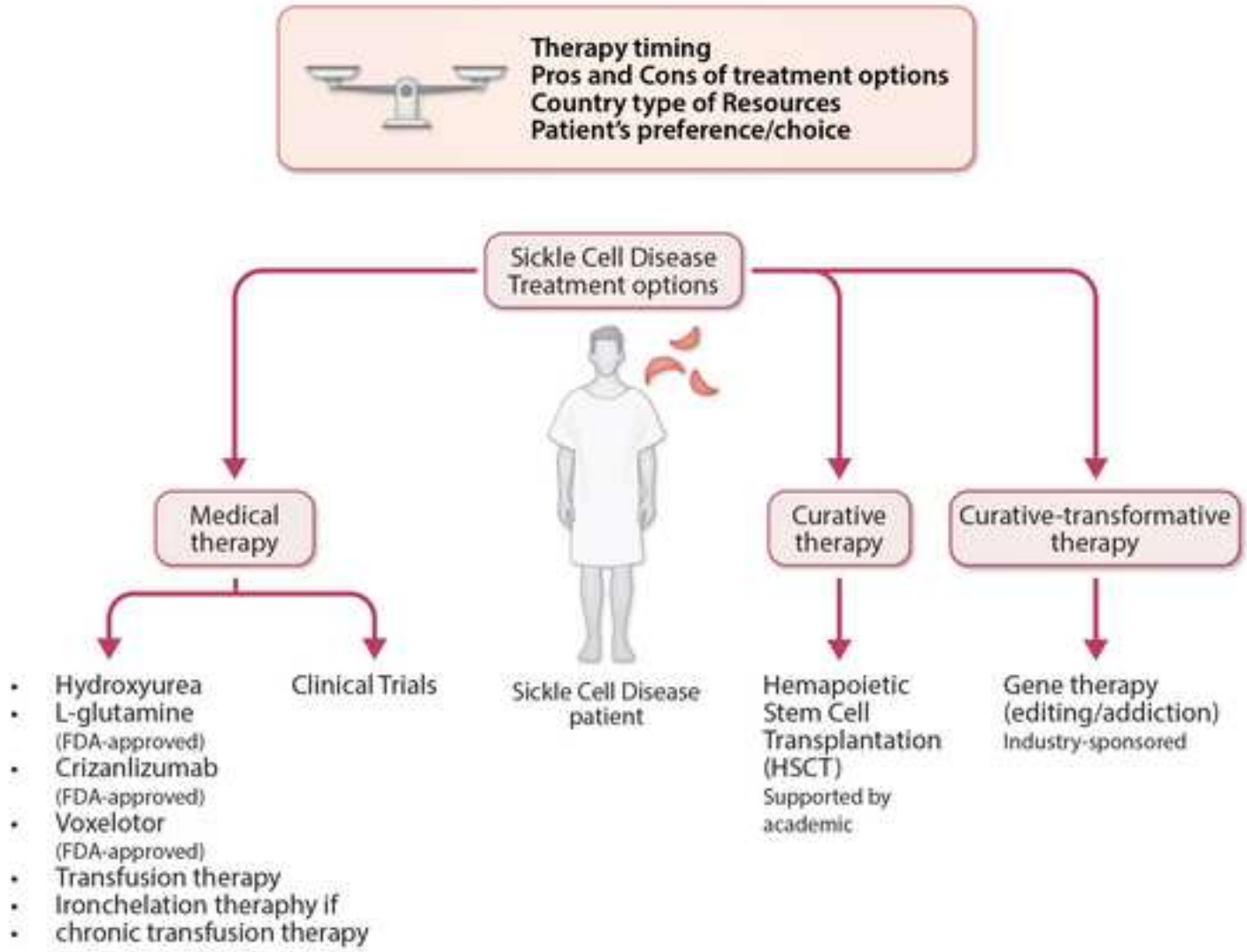
Report	N pts	Age	Source	Follow up	Overall survival	Event free survival	Graft failure	TRM
Kassim AA[8] NCT 01850108	70	19.1 (14.1-25.0 IQR)	9 G-CSF mobilized BM, 61 BM	2.4 years (1.5-3.9 IQR)	At 2 years for children 93.6% (95% CI: 76.9-98.3) At 2 years for adults 94.7% (95% CI: 80.6-98.7)	At 2 years for children 68.4% (95% CI: 49.1-81.6) At 2 years for adults 94.7% (95% CI: 80.6-98.7)	8/70 (11.4%)	5/70 (7.1%) (2 < 18y)
Kassim AA[9] NCT 03263559	42	22.8 (15.5-43.2 range)	42/42 BM	37.2 months (20-4-56.4 range)	At 2y 95% (95% CI, 81.5% to 98.7%)	At 2y 88% (95% CI, 73.5% to 94.8%)	3/42 (7.1%)	2/42 (<5%)
Alasbali R[12]	22	26.5 (15-41 IQR)	12/22 PBSC (54.5%) 10/22BM (45.5%)	14.6 months (0.5-44 IQR)	100%	100%	0	0

The conditioning regimen consisted of thymoglobulin 4.5 mg/Kg −9 to −7; thiotepa 10 mg/Kg on day −7; cyclophosphamide 29 mg/kg total day −6 and day −5; fludarabine 30 mg/m2 from day −6 to day −2 or 150 mg/m2 total; 200-cGy total-body irradiation on day −1. For Kassim AA[8] the conditioning regimen included also hydroxyurea 30 mg/Kg −70 to −10 day.

GvHD prophylaxis consisted of cyclophosphamide 50 mg/Kg on days +3 and +4; mycophenolate mofetil 15 mg/kg +5 through day +35; sirolimus day +5 through 1 year.

N: number; IQR: interquartile range; G-CSF: Granulocyte Colony-Stimulating Factor; BM: bone marrow; PBSC: peripheral blood stem cell; CI: confidence interval; TRM: transplant-related mortality

Figure legend: Representation of the therapeutic pathway of patients with sickle cell disease, including conventional medical therapy and clinical trials, the available curative treatment options, and the factors that may influence the choice among these options.


Therapy timing
Pros and Cons of treatment options
Country type of Resources
Patient's preference/choice
Sickle Cell Disease Treatment options
Medical therapy
Curative therapy
Curative-transformative therapy
Hydroxyurea
L-glutamine (FDA-approved)
Crizanlizumab (FDA-approved)
Voxelotor (FDA-approved)
Transfusion therapy
Ironchelation theraphy if chronic transfusion therapy
Clinical Trials
Sickle Cell Disease patient
Hemapoietic Stem Cell Transplantation (HSCT)
Supported by academic
Gene therapy (editing/addiction)
Industry-sponsored