Opening Marrow Niches in Patients Undergoing Autologous Hematopoietic Stem Cell Gene Therapy

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KEYWORDS

• Marrow niches • Gene therapy • Pharmacokinetics • Conditioning
• Primary immune deficiency • Inborn errors of metabolism • Hemoglobinopathies

KEY POINTS

- Gene therapy for bone marrow disorders and inborn errors requires sufficient open marrow niches to allow gene-corrected autologous stem cells to engraft and correct all disease manifestations.
- In young children, the clearance of alkylating agents used for opening marrow niches can vary significantly, making it essential that pharmacokinetic studies be done to ensure optimal therapy.
- To minimize/eliminate late effects, nonchemotherapy approaches to opening marrow niches are being developed and may replace the need for chemotherapy as conditioning.

INTRODUCTION

The concept of opening marrow niches or "making space" for allogeneic hematopoietic stem cells (HSC) to engraft is well known. Hematopoietic cell transplants (HCT) for many patients with severe combined immunodeficiency (SCID) typically require no marrow ablative conditioning and result in at least T- and sometimes B-cell reconstitution, although rarely is multilineage engraftment seen.[1] A limited number of reports

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suggest that small numbers of donor HSC are engrafted; however, even this concept is controversial, because it is also thought that either some stem cells may engraft in the thymus or long-lived autonomous T- and B-lymphocytes may be able to reconstitute sufficient immunity in SCID patients to achieve long-term survival.[2] For malignant diseases, full donor chimerism is the goal, whereas for nonmalignant disorders, the degree of chimerism that is necessary, and whether multilineage engraftment is even required, depends on the specific disorder. With the exception of SCID, durable grafts generally require the achievement of some degree of multilineage engraftment involving donor T cells and the specific defective lineage or lineages. Donor T cells are needed to ensure tolerance of the graft by the recipient immune system.

For inborn errors of metabolism (in which marrow lineages are typically not involved) such as Hurlers mucopolysaccharidosis and adrenoleukodystrophy (ALD), the ultimate therapeutic goal is delivering the maximum amount of missing/defective enzyme to affected tissues. The rationale is that donor myeloid cells that are precursors of microglial cells can populate the brain and provide a source of enzyme.[3] Generally, this requires maximum engraftment of donor HSC. For the hemoglobinopathies, it is apparent that full allogeneic donor chimerism is not essential to correct the anemia and that even less than 50% donor chimerism will correct the disease manifestations in both thalassemia and sickle cell disease; whether this will be true for gene therapy remains to be determined and will be influenced by the transduction efficiency. For the primary immune deficiencies (PIDs) other than SCID, the degree of donor chimerism needed for disease correction varies. In Wiskott-Aldrich syndrome (WAS), it appears that mixed chimerism is adequate to correct the T-cell defect but that closer to full donor chimerism may be required to correct the thrombocytopenia and autoimmune manifestations, the latter likely mediated by abnormal B cells.[4] Studies in a mouse model of Chronic Granulomatous Disease (CGD) demonstrates as little as 20% donor chimerism is adequate to correct the disease with respect to infection and inflammation.[5] Even for some types of SCID-related disorders, in particular, Omenn syndrome, full donor chimerism may be needed in order to eliminate all disease manifestations.

The major chemotherapy agents that are used today for opening marrow niches for allogeneic HCT in patients with nonmalignant diseases are busulfan and melphalan. Treosulfan, an analogue of busulfan with both myeloablative and immunosuppressive activities, is also in use primarily in Europe. Finally, thiotepa has both myeloablative and immunosuppressive activities and has been used in combination with busulfan or melphalan. Because most of the diseases for which gene therapy is currently being used involve children, and drug clearance may change with age, it is critical that discussions regarding conditioning include what is known about the pharmacokinetics (PK) and pharmacodynamics (PD) of each agent.

Finally, at least for the nonmalignant disorders, the ideal approach to opening marrow niches would be to avoid or minimize the use of these drugs, all of which are alkylating agents associated with early and late side effects, especially in infants and young children. Significant progress has been made in understanding the biology of the marrow niche, in particular, the critical cells and their receptors. With this information, there has been a variety of approaches taken to use small molecules and monoclonal antibodies (mAbs) to either block homing receptors or specifically target HSC in order to open marrow niches without the need for alkylating therapy.

This article focuses on what is currently known about the need for opening marrow niches in recipients of gene-corrected autologous HSC, the PK of the currently available chemotherapy agents to minimize exposure, and the novel approaches that may be available in the future to eliminate the need for any chemotherapy-based conditioning before gene therapy.