Hematopoietic Stem Cell Approaches to Cancer

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KEYWORDS

• Hematopoietic stem cells • In vivo selection and chemoprotection
• Methylguanine methyltransferase • Glioblastoma • CAR T cells
• Engineered TCRs

KEY POINTS

- Cancers with high expression of methlylguanine methyltransferase (MGMT) have a worse prognosis owing to resistance to temozolomide (TMZ) treatment, especially for glioblastoma.
- O^6-benzylguanine (O^6BG) is effective in reversing MGMT-mediated chemotherapy resistance but renders hematopoietic cells highly susceptible to TMZ-associated toxicities.
- The P140K mutant MGMT does not bind O^6BG and thus when expressed in blood cells can make them resistant to the combination therapy O^6BG and temozolomide.
- Combination O^6BG and TMZ treatment improves survival in glioblastoma and potentially other cancers with high expression of MGMT.
- Hematopoietic stem cells (HSCs) can also be targeted to produce T cells expressing engineered T-cell receptors and chimeric antigen receptors for immunotherapy.

INTRODUCTION

Hematopoietic Stem Cells

Hematopoietic stem cells (HSCs) and progenitor cells are particularly attractive for gene therapy. The ability to make all different kinds of blood cells for the life of a recipient is unique and could treat many diseases affecting the blood system from genetic disorders to human immunodeficiency virus and cancer. There are many different ways to genetically engineer HSCs, although lentiviral vectors are currently the most common method for gene transfer and gene modification

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systems used owing to their versatility and ability to stably integrate into the genome. One critical limitation of HSC gene therapy has been the low level of engraftment of genetically modified HSCs. Engraftment of genetically modified HSCs and multilineage repopulating cells depends mainly on the number of genetically modified HSCs infused into patients and the level of conditioning and reduction of endogenous HSC competition. Herein we discuss how the number of gene-modified cells can be increased for use in HSC gene therapy for cancer. Once the cells are infused, the only other mechanism for increasing the level of gene marking is with in vivo selection. This selection can be accomplished 2 ways, either if the therapeutic transgene confers a natural, constitutive selective advantage on the genetic correction relative to the unmodified cells or if a conditionally selectable gene is introduced and an in vivo selection step can be applied

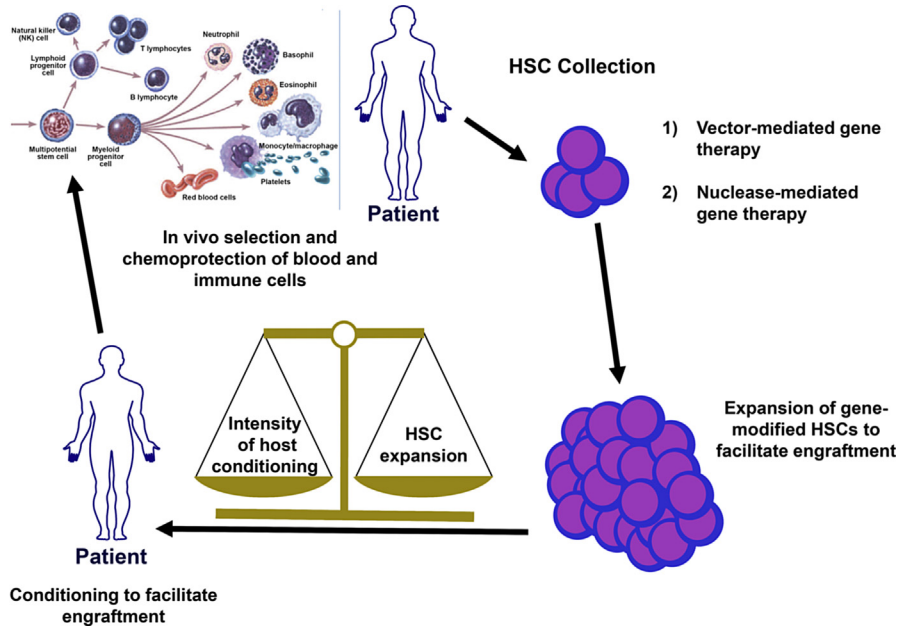

Fig. 1. Hematopoietic stem cell (HSC) therapy for cancer. HSCs are enriched from marrow or mobilized peripheral blood, usually using CD34 expression for the enrichment. $CD34^+$ cells can then be modified either with gammaretroviral or lentiviral vectors or with gene editing technology. The next step can include HSC expansion to increase cell numbers to facilitate engraftment. The balance indicates the relationship between the number of gene-modified HSCs available for transplant and the level of conditioning required to create space for the infused gene-modified cells. The more gene-modified HSCs are available for transplantation, the less host or patient conditioning will be required. Once infused, the cells will contribute to the reconstitution of the entire hematopoietic system. In genetic diseases, the disease phenotype can be corrected; human immunodeficiency virus (HIV) cells can be protected against HIV infection and, in the setting of cancer therapy, HSCs and the resulting gene-modified blood and immune cells can be rendered resistant to the chemotherapy used for the treatment of a particular cancer (eg, MGMTP140K) to protect blood and immune cells from the combination of O^6BG and N,N′-bis(2-chloroethyl)-N-nitroso-urea or temozolomide. (*Adapted from* Kiem HP, Jerome KR, Deeks SG, et al. Hematopoietic-stem-cell-based gene therapy for HIV disease [review]. Cell Stem Cell 2012;10(2):138; with permission.)