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Review

Immunoselection techniques in hematopoietic stem cell transplantation

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ABSTRACT

Hematopoietic Stem Cells Transplantation (HSCT) is an effective treatment for hematological and non-hematological diseases. The main challenge in autologous HSCT is purging of malignant cells to prevent relapse. In allogeneic HSCT graft-versus-host disease (GvHD) and opportunistic infections are frequent complications. Two types of graft manipulation have been introduced: the first one in the autologous context aimed at separating malignant cells from hematopoietic stem cells (HSC), and the second one in allogeneic HSCT aimed at reducing the incidence of GvHD and at accelerating immune reconstitution. Here we describe the manipulations used for cell purging in autologous HSCT or for T Cell Depletion (TCD) and T cell selection in allogeneic HSCT. More complex manipulations, requiring a Good Manufacturing Practice (GMP) facility, are briefly mentioned.

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1. Introduction

Hematopoietic stem cell transplantation (HSCT) is the standard therapy for various hematological malignancies and for numerous inherited and autoimmune disorders. Autologous (auto) HSCT in malignant diseases has lower morbidity and mortality, but higher incidence of tumor relapse. Thus, manipulations attempt to eliminate tumor cell contamination. After use of auto-HSCT manipulation in clinical trials, nowadays this technology is rarely used and few trials have been recently conducted. In contrast, allogeneic (allo) HSCT shows higher incidence of morbidity and mortality with longer time of disease progression. Thus, graft manipulation focuses on reduction of graft-versus-host disease (GvHD) by reducing the number of T cells (negative selection) and/or on enrichment of CD34 hematopoietic stem cells (HSC) (positive selection) by using immunological techniques like paramagnetic microbeads conjugated with anti-CD34, anti-T or anti-B cell monoclonal antibodies (Moab).

2. Cell selection methods

The availability of high-quality Moabs led to effective positive and negative cell selection systems such as the Ceprate SC immunoaffinity column (CellPro, Bothell, WA) [1,2], the Isolex 300i magnetic cell selection system (Nexell/Baxter, Irvine, CA) and the CliniMACS CD34 reagent system (Miltenyi Biotech, Bergish-Gladbach, Germany). Only the magnetic isolation techniques are accepted for clinical use due to higher selection efficiency. The Ceprate SC and the Isolex 300i were the first instruments to receive Food and Drug Administration (FDA) approval for CD34 enrichment [3,4], but they are no longer available. The Isolex 300i system was approved for CD34 cell selection of auto-HSCT, but it was also used for T-cell depletion in allo-HSCT. This system consisted of an anti-CD34 Moab reagent and paramagnetic beads (Dynal) conjugated with anti-mouse IgG that were incubated with the apheresis product loaded on a magnetic column. Bound CD34 cells were released from the beads by chymopapain that competes for the CD34 antibody binding site.

At present, the only clinically approved device is the CliniMACS system, which employs superparamagnetic microbeads conjugated to an anti-CD34 Moab. When tagged CD34 cells pass through the paramagnetic column, they are retained. The cells detach from the column when the magnetic field is withdrawn. This procedure is summarized in Fig. 1. The CliniMACS system achieves a final product with a 3.5–5 log reduction of CD3 cells [5].

3. Graft manipulation in autologous HSCT

Auto-HSCT is a standard of care for numerous malignancies, but relapse is the primary cause of death. In addition to therapy-resistant cells, residual clonogenic tumor cells in the HSCT may contribute to disease relapse. Molecular studies can detect tumor cell contamination in the graft from patients, including those with multiple myeloma (MM) [6], non-Hodgkin lymphoma (NHL) [7], and acute myeloid leukemia (AML) [8]. In vivo purging attempts to improve malignancy control and to alter tumor cell kinetic mobilization using intensive chemotherapy and/or cytolytic Moabs. In ex vivo purging, HSCT are manipulated with chemotherapeutic agents [9], Moabs plus complement and cell selection devices to eliminate contaminating tumor cells (negative selection), or to enrich for HSC selected from the graft (positive selection).

3.1. Negative selection with monoclonal antibodies (Moabs)

Ex vivo manipulation of HSCT with anti-B cell Moab plus complement in follicular NHL has been the best studied negative selection method [10–12]. The course of patients with follicular NHL who underwent purged auto-HSCT was reported by Gribben et al. [13]. PCR detected disease-specific gene rearrangements in bone marrow (BM) samples from all patients prior to BM purging. Purged BM HSC from 57 patients remained PCR positive after purging, whereas products from 57 patients were PCR-negative. Fifty-three out of 57 patients who received PCR negative products remained disease free, compared with 21 out of 57 patients who received PCR-positive products. The difference was statistically significant. These data were updated [14] showing that the freedom from relapse was 89% for patients receiving PCR-negative products vs 19% for patients receiving PCR positive products. This difference was highly significant.

3.2. CD34 positive selection

Positive selection of autologous CD34 HSC has been used in hematological and non-hematological diseases such as multiple myeloma, chronic lymphocytic leukemia and systemic sclerosis.