Stem Cell Sources for Allogeneic Stem Cell Transplantation

Essay

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ABSTRACT

HLA-matched related allogeneic stem cell transplantation (SCT) has been successfully used as the treatment of choice in selected high-risk or recurrent hematologic malignancies, marrow failure syndromes, severe congenital immunodeficiency states, and selected metabolic disorders. (28)

In the early 1990s, it was found that granulocyte colony-stimulating factor (G-CSF)-mobilized peripheral blood stem cells (PBSCs) led to speedier granulocyte and platelet recovery after autologous transplantation than seen with marrow. The use of PBSCs quickly became the community norm, despite the lack of randomized trials measuring the impact of PBSC use on survival in specific disease states. There was hesitation in applying this technology to the allogeneic setting, because unmodified growth factor-mobilized PBSC collections contain, on average, 1 log more T cells than a standard marrow collection and murine studies have demonstrated a close relationship between the number of T cells in a graft and the development of acute graft-versus-host disease (GVHD). (26,55,56,57)

Key workds:

- Stem cell trnusplantation
- Haplo-indentical transplantation
- Cord blood trausplantation
- Matched unreleted donon

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List of Abbreviations

6-MP	6-Mercaptopurine
AA	Aplastic Anaemia
aGVHD	Acute Graft versus Host disease
ALL	Acute Lymphoblastic Leukaemia
APC	Antigen presenting cells
ATG	Anti-thymocyte globulin
BM	Bone marrow
BMDW	Bone Marrow Donor Worldwide
BMT	Bone marrow transplantation
CB	Cord blood
CBT	Cord blood transplantation
CFU	Colony-forming units
cGVHD	Chronic Graft versus Host disease
CIBMTR	Center for international blood and marrow transplant research
CML	Chronic myeloid leukemia
CMV	Cytomegalovirus
CLL	Chronic lymphocytic leukemia
CSP	Cyclosporine
CTL	Cytotoxic T Lymphocyte
CY	Cyclophosphamide
DFS	Disease-free survival
DLI	Donor lymphocyte infusion
EBV	Epstein-Barr virus
FLU	Fludarabine
G-CSF	Granulocyte colony-stimulating factor
G-PBMCs	GCSF–mobilized Peripheral Blood Mononuclear Cells
GM-CSF	Granulocyte macrophage colony-stimulating factor
GVH	Graft versus Host
GVHD	Graft versus Host disease
GVL	Graft-versus-Leukemia
HCL	Hairy cell leukemia

HD	Hodgkin disease
HLA	Human leukocyte antigens
HSC	Haemopoietic Stem Cell
HSCT	Haemopoietic Stem Cell Transplantation
IBMTR	International Bone Marrow Transplantation Registry
IL	Interleukin
KIR	Killer Immunoglobulin-like Receptor
MDS	Myelodysplasia
MF	Myelofibrosis
MGH	Massachusetts General Hospital
MHC	Major histocompatibility complex
mHC	Minor histocompatibility complex
MM	Multiple myeloma
MMF	mycophenolate mofetil
MNC	MonoNuclear Cells
MTX	Methotrexate
MUD	Matched unrelated donor
NHL	Non-Hodgkin lymphoma
NK	Natural Killer
NMDP	National Marrow Donor Program
NYBC	New York Blood Center
OS	Overall survival
PB	Peripheral blood
PBSC	Peripheral blood stem cells
PBSCT	Peripheral blood stem cell transplantation
PCR	Polymerase Chain Reaction
PNH	Paroxysmal nocturnal hemoglobinuria
pre-DC1	Th1-inducing myeloid dendritic cell precursors
pre-DC2	Th2-inducing lymphoid dendritic cells
RD	Related donor
RR	Relapse rate
SCC	Sickle cell disease
SCID	Severe combined immune deficiency

SCT	Stem cell transplantation
TBI	Total body irradiation
TCD	T-cell depletion
TCR	T-cell receptors
Th	T-helper
UCB	Umbilical cord blood
UCBT	Umbilical cord blood Transplantation
URD	Unrelated donor
VLA	Very late antigen
VCAM	Vascular cell adhesion molecule
WAS	Wiskott-Aldrich syndrome
WBCs	White blood cells

CHAPTER I

Hematopoietic Stem Cell Transplantation Spotlights

HISTORICAL PERSPECTIVE

Early Preclinical Studies

After the effects of radiation on hematopoiesis became evident during World War II, Jacobson and colleagues reported in 1949 that mice could survive a lethal exposure to total body irradiation (TBI) if the spleen was shielded (1). Shortly after, Lorenz and colleagues reported that radiation protection could also be conferred by infusion of bone marrow (2). In 1956, Ford and associates showed that cytogenetic characteristics of the marrow in such mice were those of the donor and not the recipient (3).

A syndrome developed after recovery of hematopoiesis when the infused marrow was from a donor of a different strain (4). This syndrome was due to Graft versus Host (GVH) disease (GVHD), a complication that was soon recognized to limit the use of allogeneic marrow transplantation in humans. In further studies in mice, methotrexate (MTX) and 6-mercaptopurine (6-MP) were found to be effective in inducing immune tolerance or ameliorating GVH reaction (5,6,7).

The dog served as a random-bred model for studies of principles and techniques of bone marrow (BM) transplantation (BMT) applicable to humans. It was demonstrated that the results of in vitro histocompatibility typing could predict the outcome of BMT (8,9). Littermates genotypically identical to their donors for the major histocompatibility complex (MHC) survived longer after marrow transplantation than did those transplanted with marrow from MHC-non-identical siblings. Despite the MHC genotypic

identity, GVHD was still potentially severe in many but not all dogs. This indicated that minor histocompatibility complex (mHC) antigens were involved in the development of GVHD. Immunosuppression with cyclosporine (CSP) or MTX, given for prevention of GVHD, improved survival after allogeneic marrow grafting (10,11). It was then established that these two drugs are more effective when used in combination (12).

Early Clinical Studies

Following the demonstration in mice that marrow grafting could be accomplished after lethal irradiation, it seemed logical to apply this technique to the treatment of human hematological malignancy using intensive chemotherapy or irradiation followed by marrow aplasia. The first attempts, reported in 1957, were largely unsuccessful; only one transient graft was successful. Nevertheless those studies contributed one important discovery that relatively large amounts of marrow could be infused intravenously into human patients without ill effects provided that the marrow was anti-coagulated and screened to break up particles. (13)

The next important observation was made in 1959. Two patients with advanced acute lymphoblastic leukemia (ALL) were given supralethal TBI and marrow infusion from identical twin. Hematological recovery occurred in two weeks, showing clearly that a compatible marrow graft could protect against lethal marrow aplasia produced by irradiation. In those first two patients, leukemia recurred in few months, indicating that irradiation alone might not be sufficient to eradicate leukemia and that additional chemotherapy might be necessary (14).

Three other critical developments contributed to the success of human marrow transplantation: One was the development of the knowledge and technology needed to provide supportive care to patients without marrow functions. The second critical development was elucidation of the human histocompatibility system. In 1958 Dausset was the first to recognize human leukocyte antigens (HLA) and their importance in histocompatibility. In the 1960s, several brilliant investigators made great progress in the definition and recognition of the antigens controlled by loci of chromosome 6, the complex "super gene" that represents the MHC system in humans (15). The third critical development was demonstrating in an outbred species that matching at MHC would predict successful outcome of marrow graft (9).

Different sources of hematopoietic stem cells have been or are being used for the reconstitution of lympho-hematopoietic function after myeloablative, near-myeloablative, or non-myeloablative treatment. Bone marrow (BM)–derived stem cells, introduced by E. D. Thomas in 1963 are considered the classical stem cell source (16). Fetal liver stem cell transplantation has been performed on a limited number of patients with aplastic anemia or acute leukemia, but only transient engraftment has been demonstrated (17). Peripheral blood (PB) as a stem cell source was introduced in 1981 and umbilical cord blood (UCB) was introduced as a source in 1988 (18,19). The various stem cell sources differ in their reconstitutive and immunogenic characteristics, which are based on the proportion of early pluripotent and self-renewing stem cells to lineage-committed late progenitor cells and on the number and characteristics of accompanying "accessory cells" contained in stem cell allografts (20).

Bone marrow was the first commonly used source of Haemopoietic Stem Cells (HSC) for transplantation. Bone marrow transplantation from HLA-identical donors was first successfully used by two groups in 1968 to treat patients with immunologic deficiencies (21,22). After extensive preclinical studies of GVHD, the first report of a successful BMT for aplastic anemia (AA) from an HLA-identical sibling donor was published in 1972 (23). A report of 100 patients with end-stage leukemia treated with BMT was presented by a Seattle group in 1977 (24).

The effectiveness of peripheral blood (PB) cells to repopulate lethally irradiated animals was originally demonstrated in the dog model. The in vivo observation that cells from peripheral blood could provide long term engraftment after marrow lethal treatment was the strongest evidence that peripheral blood cell infusion as a source of repopulating cells was initially described for patients with aplastic anemia (25).

In the early 1990s, it was found that granulocyte colony-stimulating factor (G-CSF) or granulocyte macrophage colony-stimulating factor (GM-CSF), mobilized peripheral blood stem cells (PBSC) led to speedier granulocyte and platelet recovery after autologous transplantation than seen with marrow; given the practical and economic benefits of more rapid recovery, use of PBSC quickly became the community norm, despite the lack of randomized trials measuring the impact of PBCS use on survival in specific disease states. There was hesitation in applying this technology to allogeneic setting, because unmodified growth factor-mobilized PBCS collections contain, on average, 1 log more T cells than a standard marrow collection and murine studies have demonstrated a close relationship