THE ROLE OF HEMATOPOIETIC STEM CELL TRANSPLANTATION IN THE TREATMENT OF NON MALIGNANT DISEASES

Essay
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ABSTRACT

For a long time, hematopoietic stem cell transplantation was an experimental procedure associated with high transplant related morbidity and mortality, so it was offered only for patients with terminal malignancies who had no other options for cure. However, with improved patient selection, advances in supportive, improved prevention of graft versus host disease, the introduction of mobilized peripheral blood progenitor cells, and the innovation of reduced intensity conditioning regimens; the results of hematopoietic stem cell transplantation have continued to improve. Thereby, bone marrow transplantation is now applied to a long list of non malignant diseases with a wide range of results depending on the disease, the type of transplant, and the stage of the disease. For some of the diseases HSCT has proven to be the most effective therapy, whereas for others it is the only curative treatment. The aim of this work is to thoroughly evaluate the role of HSCT in the treatment of different non malignant diseases and to place such an aggressive approach in the algorithm of their management.

Keywords:

- Allogeneic hematopoietic stem cell transplantation
- Autologous hematopoietic stem cell transplantation
- Reduced intensity regimens
- Non malignant diseases

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LIST OF ABBREVIATIONS

AA	Aplastic anemia
ACR	American College of Rheumatology score
ALD	Adrenoleukodystrophy
ALL	Acute lymphoblastic leukemia
Allo-HSCT	Allogeneic hematopoietic stem cell transplantation
ALP	Alkaline phosphatase
ALT	Alanine aminotransferas
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
APS	Antiphospholipid Syndrome
AST	Aspartate aminotransferase
ATG	Antithymocyte globulin
Auto-HSCT	Autologous hematopoietic stem cell transplantation
AVN	Avascular necrosis of bone
BM	Bone marrow
BMD	Bone mineral density
BMT	Bone marrow transplantation
BO	Bronchiolitis obliterans
Bu	Busulfan
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CGD	Chronic granulomatous disease
CIMF	Chronic idiopathic myelofibrosis
CLL	Chronic lymphocytic leukemia
CML	Chronic myeloid leukemia
CMV	Cytomegalovirus
CNS	Central nervous system
CR	Complete remission
CRVs	Community-Acquired Respiratory Viruses
CSP	Cyclosporine

CTLs	cytotoxic T- lymphocytes
CY	Cyclophosphamide
DBA	Diamond-Blackfan anemia
DC	Dyskeratosis congenital
DFS	Disease free survival
DLI	Donor lymphocyte infusion
DMARD	disease modifying antirheumatic drug
EBMT	European Group for Blood and Marrow Transplantation
EBV	Epstein Barr virus
ECP	Extracorporeal photochemotherapy
EDSS	Extended disability status score
EFS	Event free survival
EULAR	The European League against Rheumatism
FA	Fanconi anaemia
FL	Follicular lymphoma
G-CSF	Granulocyte colony-stimulating factor
GD	Gaucher's disease
GH	Growth hormone
GM-CSF	Granulocyte- macrophage colony-stimulating factor
GPI	Glycosylphosphatidylinositol
GVHD	Graft versus host disease
GVL	Graft versus leukaemia
GVT	Graft versus tumour
HbS	Haemoglobin S
HCT	Hematopoietic cell transplantation
HD	Hodgkin's disease
HDIT	High dose immunosuppressive therapy
HDT	High dose chemotherapy
HLA	human leukocyte antigens
HSCs	Hematopoietic stem cells
HSCT	Hematopoietic stem cells transplantation
HSV	Herpes simplex virus

HU	Hydroxyurea
IBTMR	International Bone Marrow Registry
Ig	Immunoglobulin
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
INF	Interferon
IPI	International Prognostic Index
IPS	Idiopathic pneumonia syndrome
IS	immunosuppressive
ITP	Immune thrombocytopenic purpura
IVIg	Intra venous immunoglobulin
JIA	Juvenile idiopathic arthritis
KIRs	killer immunoglobulin-like receptors
LDH	Lactate dehydrogenase
LVL	Large volume leukapharesis
MDS	Myelodysplastic syndromes
MHC	Major histocompatibility complex
MLD	Metachromatic leukodystrophy
MM	Multiple myeloma
MMF	Mycophenolate mofetil
MPS	Mucopolysaccharidoses
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MTX	Methotrexate
MUD	Matched unrelated donor
NHL	Non-Hodgkin's lymphomas
NK cells	Natural killer cells
OS	Overall survival
PBPCs	Peripheral blood progenitor cells
PBSCs	Peripheral blood stem cells
PCP	Pneumocystis carinii pneumonia

PFS	Progression free survival
PNH	Paroxysmal nocturnal hemoglobinuria
PTLD	Posttransplant lymphoproliferative disorders
RA	Rheumatoid arthritis
RF	Rheumatoid factor
RSV	Respiratory syncytial virus
SAA	Severe aplastic anemia
SCD	Sever combined immune deficiencies
SCN	Sever congenital neutropenia
SCT	Stem cell transplantation
SLE	Systemic lupus erythematosus
SOS	Sinusoidal obstruction syndrome
SSc	Systemic Sclerosis
TBI	Total body irradiation
TBV	Total blood volume
TCD	T cell depletion
TCR	T cell receptors
TNF-alpha	Tumour necrosis factor
TRM	Transplant related mortality
UCB	Umbilical cord blood
VOCs	Vaso-occlusive crisiss
VOD	Veno-occlusive disease
VZV	Varicella zoster virus
WAS	Wiskott-Aldrich syndrome

HISTORICAL BACKGROUND

At the end of World War II following the atomic bomb explosions, there was a great deal of interest of how radiation damages living organisms. It became recognized that the marrow is the organ most sensitive to radiation and that death following low-lethal exposures was due to marrow failure. Jacobson and associates made the observation that mice could withstand an otherwise lethal exposure to whole-body irradiation if the spleen was protected by a lead foil ***(Jacobson et al., 1949)***. Shortly thereafter, Lorenz and colleagues found that similar radiation protection could be conferred by infusion of bone marrow ***(Lorenz et al, 1951)***.

At first, it was thought that the radioprotective effect was due to a humoral factor derived from the spleen or marrow, which stimulated marrow recovery. In the mid-1950s, several reports offered a different explanation for the "radiation protection "effect. In 1955, Main and Prehn showed that a mouse given lethal irradiation and marrow infusion from a different strain would accept a subsequent skin graft from the donor ***(Main& Prehn, 1955)***, and in 1956, Trentin showed that the skin graft acceptance was specific for the donor strain ***(Trentin et al, 1956)***. Also in 1956, Ford and associates showed that the cytogenetic characteristics of the marrow in such mice were those of the donor and not the recipient, and Nowell and colleagues demonstrated the presence of rat granulocytes in mice protected with rat marrow ***(Nowell et al, 1956)***. These experiments made it clear that protection against radiation was due to the transfer of living cells and that a form of tolerance had been induced.

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 infusion to protect the recipient from otherwise lethal 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 properly anticoagulated and screened to break up particles ***(Thomas et al, 1957)***.

The next important observation was made in 1959. Two patients with advanced acute lymphoblastic leukemia were given supralethal total body irradiation (TBI) and marrow infusion from identical twin (syngeneic graft). Hematological recovery occurred in two weeks, showing clearly that a compatible marrow graft could protect against the 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 ***(Thomas et al, 1959)***.

Further observations demonstrated that more irradiation would be necessary to achieve engraftment in human patients and that successful engraftment depends on destroying not only the marrow to make “room” for the graft, but also the immune system of the recipient. Using a higher irradiation exposure, Mathe and associates achieved the first enduring human marrow graft, only to have the patient die of multiple complications

and infections that we now know as chronic graft versus host disease (GVHD) ***(Mathe et al, 1965)***.

Santos and Owens carried out studies in the mouse showing that cyclophosphamide (CY) alone was an effective immunosuppressant capable of allowing allogeneic engraftment. CY alone was effective in permitting engraftment and long term survival in patients with severe aplastic anemia ***(Storb et al, 1991)***. CY alone was also effective in securing engraftment in human patients with acute leukemia, but the antileukemic effect was inadequate and the disease recurred. To achieve the greatest immunosuppression and the greatest antileukemic effect, investigators decided to combine CY with TBI ***(Buckner et al, 1974)***.

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 function. 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 major histocombatibilty system in humans ***(Dausset, 1958)***. The third critical development was the demonstration in an outbred species that matching at major histocompatibility complex would predict a successful outcome of marrow graft ***(Storb et al 1971)***.

In November 1968, the Minneapolis team carried out the first marrow graft based on knowledge of HLA-typing in an infant with severe immunological deficiency ***(Gatti et al 1968)***.

Despite DLA genotypic identity, GVHD was severe in some animals, indicating the need for immunosuppresion after grafting**.** Presumably, GVHD in this setting is directed at minor histocompatibility antigens. A very effective prophylactic regimen in the dog was a combination of a short course of methotrexate (MTX) and long term cyclosporine (CSP) after BMT ***(Deeg et al, 1982)***. The equivalency of the two drugs was subsequently confirmed in randomized prospective human studies which showed that the combination is more effective than either drug alone ***(Ringden et al, 1993)***.

The effectiveness of peripheral blood 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 contained true stem cells. Introduction of the concept of peripheral blood cell infusions as a source of repopulating cells was initially described for patients with aplastic anemia ***(Storb et al, 1977)***.

HSCT has become the treatment of choice for a number of malignant and non malignant hematological disorders, and more recently for some solid tumors. Transplants are performed to reconstitute marrow function in patients with hematological and immunological deficiencies, to treat hematological malignancies, to correct genetic defects manifested in hematopoietic cells, and to permit wide field radiation and dose escalation of chemotherapy in the treatment of selected solid tumors.