New Directions In Mismatched Hematopoietic Stem Cell Transplantation In Hematological Diseases

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Essay

A protocol submitted for partial fulfillment of M. Sc. Degree in Clinical Hematology

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2012

الاتجاهات الجديدة في زراعة الخلايا الجذعية للنخاع من متبرع غير متوافق في علاج أمراض الدم

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Summary

Allogeneic hematopoietic stem cell transplantation (HSCT) has been successfully used to treat many highrisk hematologic malignancies and marrow failure syndromes. The best results with allogeneic HSCT have been obtained in patients receiving an allograft from a human leukocyte antigen (HLA) matched sibling. As the chance of finding an HLA genotypically identical sibling donor is only 25%, much attention has been focused on the use of alternative donors, either from unrelated volunteer adult donors, umbilical cord blood (UCB), or partially matched related donors. Despite the expansion of worldwide unrelated donor registries that have markedly improved the chances of finding a donor for many patients, the application of transplantation using unrelated adult volunteer donors remains limited by some major obstacles, including:

(1) The variable chance of finding a suitably genotypically matched unrelated donor, from 60%-70% for Caucasians to under 10% for ethnic minorities.

(2) The cumbersome process of identifying, typing, and harvestingan unrelated donor translating to the median time interval between initiation of a search and the donation of marrow of about 4 months, rendering this option less viable for patients who urgently need transplantation. Many such patients do not maintain a remission or survive the long waiting period until a donation is available.

(3) Ablative allogeneic transplant using a matched unrelated donor is still associated with a high transplantrelated mortality (TRM) (30%-40%) and high long-term morbidity.

UCB donations, On the other hand, overcome some of these limitations because of easy procurement, the absence of risk for donors, potential reduced risk of graft-versus-host

Acknowledgement

This essay would not have been possible without the support of many people. I wish to express my gratitude to my supervisors, ***Prof. Dr. Hoda Gad Allah*** who was abundantly helpful and offered invaluable assistance, support and guidance. Deepest gratitude are also due to the members of the supervisory committee, ***Assoc. Prof. Dr. Tamer Mohammed and Dr. Rasha Ibrahim*** without whose knowledge and assistance these papers would not have been successful.

Special thanks also to the head of hematology department in Maadi Armed Forces Medical Compound, ***Prof. Dr. Mohammed Khalaf,*** who learnt me the art of life, and gave me the power and energy to work and read.

I'd also like to convey thanks to my senior colleagues for their support and contineuos encouragement.

I also wish to express my love and gratitude to my beloved wife; for her understanding & endless love, through the duration of my studies.

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List of Abbreviations

ALL	Acute lymphoblastic leukemia
AML	Acute myeloid leukemia
APC	Antigen-presenting cells
ATG	Antilymphocyte globulin
BM	Bone marrow
BMT	Bone marrow transplants
BU	Busulfan
CFU	Colony forming unit
CI	Confidence interval
CIBMTR	Center for International Blood and Marrow Transplant Research
CLL	Chronic lymphocytic leukemia
CML	Chronic myeloid leukemia
CMV	Cytomegalovirus
COBLT	Cord blood transplantation
CSP	Cyclosporin
CT	Computerized tomography
CY	Cyclophosphamide
DMSO	Dimethyl sulfoxide
EBV	Epstein–Barr virus
G-CSF	Granulocyte colony-stimulating factor
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GvHD	Graft-versus-host disease
GVL	Graft-versus-leukemia
GVM	Graft-versus-Malignancy
HCT	Hematopoietic cell transplantation
HFD	Haplo-identical family donors
HLA	Human leucocyte antigen
HSC	Hematopoietic stem cells
HSCT	Hematopoietic stem cell transplantation
HSV	Herpes simplex virus
HTLV	Human T-lymphotropic virus

IBMTR	International Bone Marrow Transplant Registry
IPA	Invasive pulmonary aspergillosis
KIR	Killer immunoglobulin-like receptors
MDS	Myelodysplastic syndrome
mHAg	Minor histocompatibility antigen
MHCI	Major histocompatabilty complex class I
MHCII	Major histocompatabilty complex class II
MMF	Mycophenolate mofetil
MSC	Mesenchymal stromal cells
MTX	Methotrexate
NIMA	Noninherited maternal antigen
NK	Natural killer
NRM	Nonrelapse mortality
PBSC	Peripheral blood stem cells
PCR	Polymerase chain reaction
PTLD	Post-transplant lymphoproliferative disorder
RIC	Reduced-intensity conditioning
RR	Relative risk
RSV	Respiratory syncitial virus
SDF1	Stromal-derived factor 1
TBI	Total body irradiation
TCD	T-cell depletion
TNC	Total nucleated cell
TRM	Transplant related mortality
UCB	Umbilical cord blood
URD	Unrelated volunteer donors
VOD	Veno-occlusive disease
VZV	Varicella Zoster virus

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Introduction

Hematopoietic stem cell transplantation HSCT is considered the corner stone in the treatment of haematological, and some non hematological malignancies beside some other non malignant disorders, being a curative option of treatment ***[Kyoo-Hyung et al, 2009]***. Most of patients who suffer acute and chronic leukaemia, Hodgkin's and non Hodgkin's lymphoma, multiple myeloma, myelodysplastic syndromes, myeloproliferative disorders, pure red cell aplasia, paroxysmal nocturnal hemoglobinuria, aplastic anemia, thalassemia and sickle cell anemia will eventually require performing an allogenic hematopoietic stem cell transplantation ***[Mary, 2009]***.

As regard the hematological malignancies, high rate of relapse after autologous HSCT has in part been attributed to tumor contamination of the autograft. The distinctive characteristics of allogeneic HSCT are that the stem cell graft is free of contamination by malignant cells and contains T-cells that are capable of mediating an immunologic reaction against foreign antigens. This latter characteristic can be a major advantage if the immunologic response is directed against malignant cells, referred to as the graft-versus-leukemia GVL or graft-versus-tumor effect, thus potentially eradicating disease and reducing the chance of disease relapse ***[Effie, 2009]***.

Donor availability for Allogenic hematopoietic stem cell transplantation is the major obstacle to be faced with when deciding an allograft. The preferred human leucocyte antigen HLA-matched sibling donor is available for around only 25% of patients. However, there has been substantial progress over the last four decades in the use of alternative donors for those without a matched sibling, including adult unrelated volunteer donors URD, haplo-identical family donors HFD and, more recently, unrelated donor umbilical cord blood UCB, such that

it is now possible to find a donor for almost all patients requiring an allograft. At the present time, there is no international consensus regarding the optimal hierarchy to be used in donor choice ***[Dennis et al., 2009; Rachael et al., 2009;]***.

Haploidentical hematopoietic stem cell transplantation provides an opportunity for nearly all patients to benefit from HSCT when a human leukocyte antigen HLA genotypically matched sibling is not available. Initial results with the use of mismatched allografts led to limited enthusiasm because of graft-versus-host disease GVHD and infectious complications, resulting in an unacceptable treatment-related morbidity and mortality. Recent advances with effective T cell depletion, the use of a "megadose" of stem cells, earlier detection of severe infections, combined with better antimicrobial therapy and reduced-intensity conditioning RIC has significantly decreased the early transplant-related mortality and GVHD, whereas enabling prompt engraftment, hence advancing the therapeutic benefit of haploidentical transplantation. However, the cardinal problems related to delayed immune reconstitution allowing posttransplant infectious complications and relapse remain, limiting the efficacy of haploidentical HSCT. The encouraging reports from haploidentical transplant using noninherited maternal antigen NIMA-mismatched or natural killer NK alloreactive donors may greatly increase the donor availability and open the way to more appropriate donor selection in HLA-haploidentical HSCT. Future challenges remain in determining the safest approach for haploidentical transplant to be performed with minimal risk of GVHD, whereas preserving effective graft-versus-leukemia activity and promoting prompt immune reconstitution ***[Liang-Piu et al., 2007]***.

There are many issues that remain unresolved, including the role in certain diseases and timing of haploidentical HSCT.

The relative merits of a haploidentical family donor versus mismatched unrelated or umbilical cord blood donor remain to be defined. The data presented to date provide an important framework for future improvements via more appropriate patient selection, better donor selection, development of conditioning regimens that are safer yet result in reliable engraftment, and more effective strategies that eliminate the high risk of severe GVHD, whereas preserving antitumor and antimicrobial immunocompetence ***[Liang-Piu et al., 2007]***.

Aim of the work

Review of the new directions and the recent advances in the different options regarding mismatched allogenic hematopoietic stem cell transplantation.

Methods

Review of literature and recent publications, including journals relevant to our study.