Impact of Donor and Recipient Sex on Outcomes of HLA-Identical Sibling Allogeneic Hematopoietic Stem Cell Transplantation

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Introduction

Hematopoietic cell transplantation (HCT) is well established as therapy for hematologic malignancies as well as many non-malignant disorders. Over the last several years, the spectrum of diseases thatmay be treated with HCT has dramatically expanded, increasing the importance of this therapeutic modality and extending HCT beyond the traditional bounds of hematology and oncology***[Grouch et al.,2006].***

HCT is founded on the principle that hematopoietic stem cells (HSCs) infused, will home to and engraft in the stem cell niche within the bone marrow microenvironment, and will then proliferate and differentiate to repopulate all lineages of the blood***[Gratwohl et al., 2002].***

Donor selection is an importantway to decrease the risks after HSCS and is therefore akey component of the clinical practice of transplantation***[Remberger et al.,2002].***

In general, HLA-identical siblings are thepreferred donors, but some patients have more thanone HLA-matched sibling. Thus, it is important tounderstand the contribution of donor factors otherthan HLA matching to outcomes after SCT***[Kollmanet al.,2001].***

There are many criteriaproved or hypothesized to affect outcomes after SCT and one of these, sexis the most controversial***[James et al.,2003].***

Some investigatorshave found an increased risk of acute orchronic graft-versus-host disease (GVHD) associatedwith donor sexalthough it is uncertainwhether this risk applies just to male recipients or toall patients***[Randolph et al.,2004].***

Transplantation of stem cells from a female donor to a male recipient is a special circumstance in which donor T cells specificfor minor H antigens, encoded by genes on the recipientY-chromosomethat are polymorphic to their X-chromosome homologues, may make a contribution to GVHD and GVL activity***[Randolph et al.,2004].***

The role of previous pregnancies in recipients ofallogeneic SCT has never been evaluated, althoughthis also has the potential to influence outcomes andmay interact with donor parity***[Alison et al.,2006].***

Aim of the work

Investigate the effect of donor and recipient sex mis match on outcomes of HLA-identical sibling allogeneic stem cell transplantation.

Acknowledgement

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List of Abbreviation

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	Mycophenolatemofetil
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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Hematopoietic Stem Cell Transplantation

History of Hematopoietic Stem Cell Transplantation:

Hematopoietic stem cell transplantation HSCT is considered the corner stone in the treatment of haematological, and some non haematological malignancies beside some other non-malignant disorders, being a curative option of treatment ***[Kyoo-Hyung et al, 2009]***.

Every year, many hundreds of patients receive an autologous or allogeneic transplant procedure, and the numbers have increased vastly since the pool of allogeneic donors available worldwide widened, enabling a larger number of patients with no sibling donor to undergo an allogeneic transplant prodedure. Figure 1 shows the annual number of transplants reported in the International Bone Marrow Transplant Registry and how this increased as stem cell transplantation became a realistic treatment possibility. However, stem cell transplants have only become a therapeutic possibility since the late 1960s. Prior to this, understanding of such topics as human leukocyte antigen matching was rudimentary. The concepts of immunosuppression and graft-versus-host disease were entirely unexplored and little was known about preparative therapies. Early transplants thus invariably met with awoeful lack of success due to problems from regimen-related toxicity, graft-versus-host disease and lack of availability of support measures, including antibiotics and blood products.

As knowledge about these fundamental topics was acquired and methods of identifying a suitable donor improved along with support measures and knowledge about immunosuppression, so did the results of cell transplantation. Since the 1970s, steady progress has been made and stem cell transplantation is now regarded as a routine, rather than an experimental, approach in the treatment of a number of conditions which would have proven fatal earlier on. It is now possible to identify the risk factors which will predict a good or poor outcome in a particular clinical setting, thereby facilitating the decision of whether or not to proceed with the transplant. However, the problems which beset the early transplanters, in particular disease relapse, graft-versus-host disease and overwhelming infection, are still the major causes of treatment failure inspite of the improvements which have been made to support therapies and the immense amount of information now available regarding the cellular and humoral aspects of transplantation and our consequent ability to manipulate

and control the microenvironment in the transplant setting. Figure 2 depicts some of the milestones in the evolution of stem cell transplantation and therapeutic interventions which have become available in the context of the diseases for which transplantation was attempted early on ***[TáinBóCúailnge, 1967].***

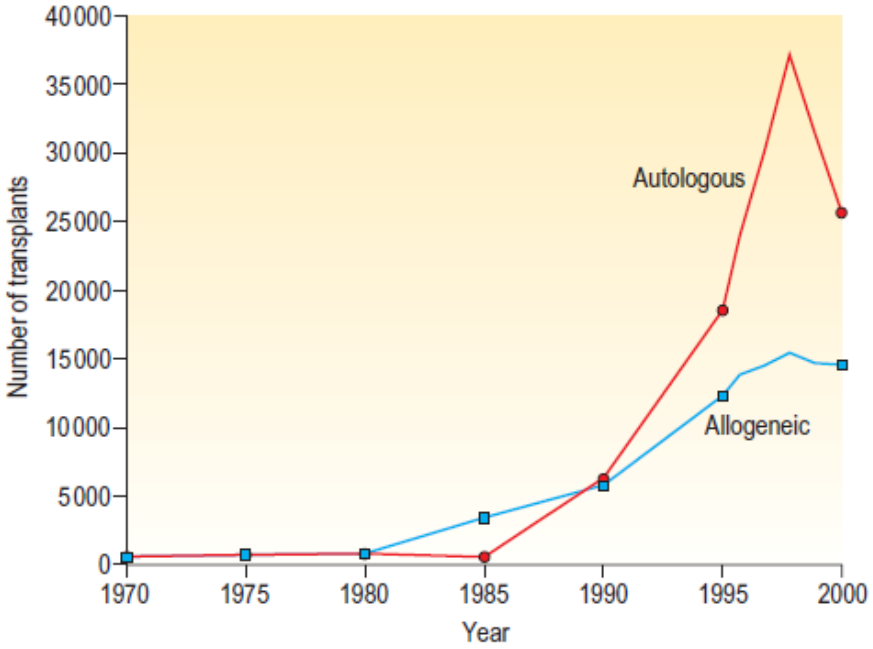

*Figure1:*Annual numbers of blood and marrow transplants worldwide, 1970–2000, from theCIBMTR***[Treleaven& Barrett, 2009]***.

As early as 1956, the idea that allogeneic bone marrow transplants (BMT) might exert a therapeutic immunologic effect against malignancies was proposed by Barnes &Loutit, who observed an antileukemia effect of transplanted spleen cells in experimental murine models. They also observed that animals who had been given allogeneic rather than syngeneic marrow cells died of a 'wasting disease' which would now be recognized as being graft-versus-host disease (GvHD) ***[Barnes et al., 1962].***

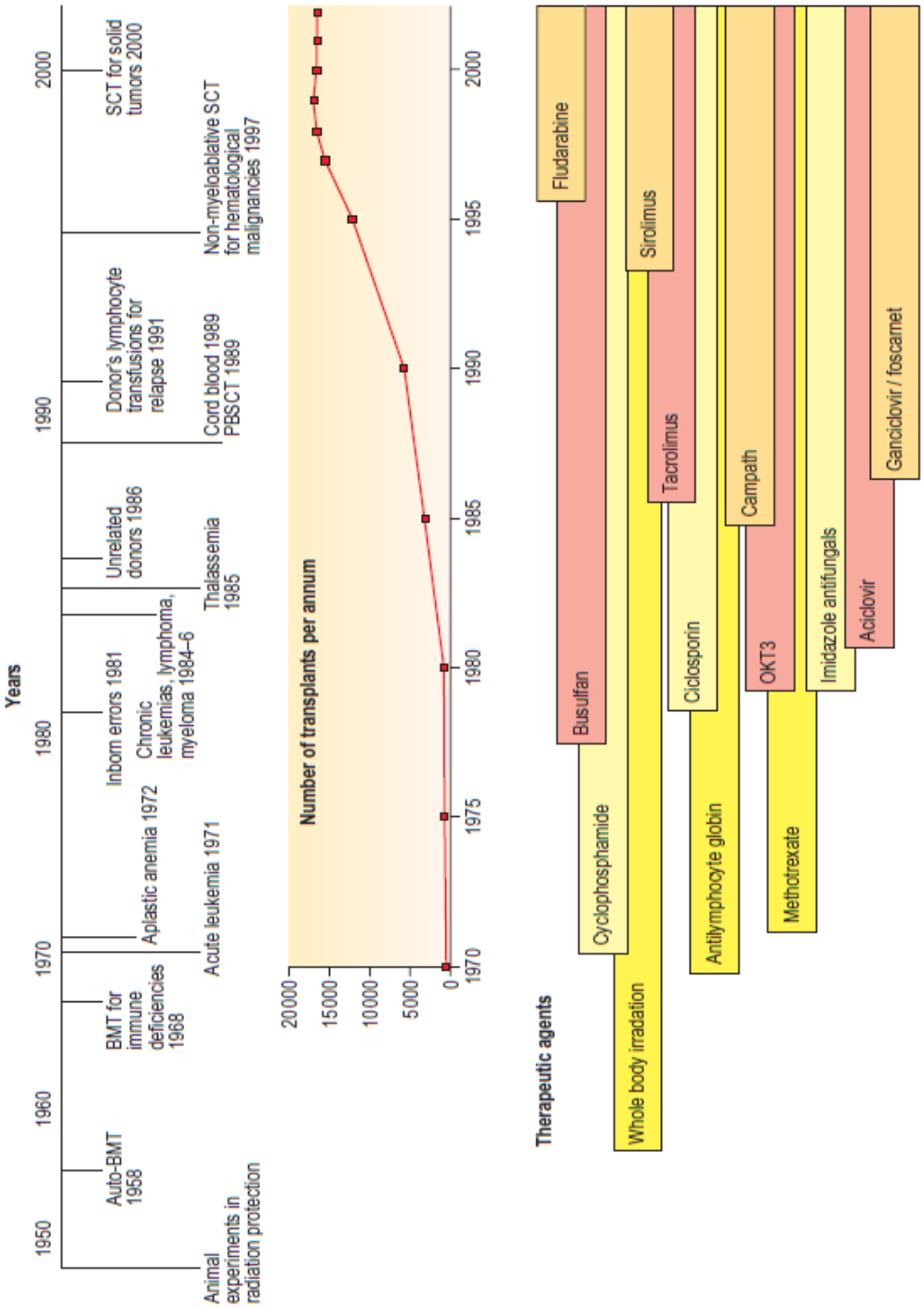

Figure 2: Some developmental steps in blood and marrow stem cell transplantation and the introduction of significant therapeutic agents, 1950–2000***[Treleaven& Barrett, 2009]***.