Effect of Post Allogenic Stem Cell Transplant Cyclophosphamide on Recovery of some Haematologic Parameters Compared with Other Regimens of GVHD Prophylaxis

Thesis

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Islam M. Mostafa

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List of Abbreviations

Abbr.		Full term
aGvHD	:	Acute graft-versus-host disease
AIDS	:	Acquired immune-deficiency syndrome
AML	:	Acute myeloid leukemia
APC	:	Antigen-presenting cells
ATG	:	Anti-thymocyte globulin
BLPD	:	B-cell lymph proliferative disease
BM	:	Bone marrow
BMI	:	Body mass index
BU	:	Busulphan
CAMs	:	Cell adhesion molecules
CCI	:	Charlson Comorbidity Index
CD	:	Cluster of Differentiation
cGVHD	:	Chronic graft-versus-host disease
CLL	:	Chronic lymphocytic leukemia
CML	:	Chronic myelocytic leukemia
CMV	:	Cytomegalovirus
CRP	:	C-reactive protein
CSA	:	Cyclosporine A
CT	:	Computerized tomography
CTLs	:	Cytotoxic T lymphocytes
DMSO	:	Dimethyl sulfoxide
EBV	:	Epstein–Barr virus
ECOG	:	Eastern Cooperative Oncology Group
FHCRC	:	Fred Hutchinson Cancer Research Center
G-CSF	:	Granulocyte colony-stimulating factor
GvHD	:	Graft-versus-host disease
HSCT	:	Hematopoietic cell transplantation
HSCT-CI	:	Hematopoietic cell transplantation-specific comorbidity index
HL	:	Hodgkin lymphoma
HLA	:	Human leucocyte antigen
HSCs	:	Hematopoietic stem cells
HSCT	:	Hematopoietic stem cells Transplantation
Ig	:	Immunoglobulin

IL	:	Interleukin
IPA	:	Invasive pulmonary aspergillosis
KPS	:	Karnofsky Performance Score
MDACC	:	MD Anderson Cancer Center
MDS	:	Myelodysplasia
MDS	:	Myelodysplastic syndrome
MM	:	Multiple myeloma
MSC	:	Mesenchymal stromal cells
MTX	:	Methotrexate
NHL	:	Non Hodgkin lymphoma
NK	:	Natural killer
NMA	:	Non-myeloablative
NRM	:	Non-relapse mortality
OS	:	Overall survival
PBSC	:	Peripheral blood stem cells
PCP	:	Pneumocystis carinii pneumonia
PCR	:	Polymerase chain reaction
PFTs	:	Pulmonary function tests
PTLD	:	Post-transplantationlymphoprofilerativedisorder
RBCs	:	Red blood cells
RCTs	:	Randomized controlled trials
RIC	:	Reduced-intensity conditioning
RSV	:	Respiratory syncitial virus
SDF1	:	Stromal-derived factor 1
SF	:	Serum ferritin
TBI	:	Total body irradiation
TCD	:	T- cell depletion
TRM	:	Treatment-related mortality
UCB	:	Umbilical UCB
US	:	United States
VCAM-1	:	Vascular cell adhesion molecule-1
VOD	:	Veno-occlusive disease
VZV	:	Varicella zoster virus

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INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (HSCT) is a potentially curative therapy for many malignant and nonmalignant hematological disorders ***(Appelbaum et al., 2004).***

Although HLA-identical siblings or HLA-matched unrelated donors (MUD) are considered the ideal sources of hematopoietic stem cells, many patients lack timely access to a suitable matched donor, especially in the context of highly aggressive disease. A promising alternative stem cell source is the HLA-haploidentical mismatched family donor who is readily available for nearly all patients ***(Reisner et al., 2011).***

Despite the fact that outcomes for patients receiving reduced intensity conditioning (RIC) allogeneic matched related or unrelated donor HSCT have continued to improve over time owing to improvements in transplantation techniques and supportive care, graft versus host disease (GvHD) remains a major source of post-transplantation morbidity and mortality. Although advances in immunosuppressive regimens have had some impact on the incidence and severity of acute GvHD, they have had little

impact on the incidence and severity of chronic GvHD ***(Chao et al., 2000).***

In fact, chronic GvHD has become one of the most common and clinically significant problems affecting long-term HSCT survivors, occurring in up to 70% of patients surviving more than 100 days post-transplantation. Management of chronic GvHD remains a major challenge, and has become a significant health problem in HSCT survivors with the increasing use of mobilized peripheral blood stem cells ***(Flowers et al., 2002).***

The combination of calcineurin inhibitors (CNIs), such as tacrolimus or cyclosporine, with methotrexate was developed more than 3 decades ago and remains the most common regimen used for GvHD prophylaxis. Although CNI-based immunosuppression has resulted in satisfactory rates of acute GVHD and survival outcomes, these regimens are not uniformly effective, and many patients are still dying from GvHD and related complications. Furthermore, these regimens are associated with considerable toxicity ***(Edinger et al., 2003).***

Nephrotoxicity is the most common and clinically significant adverse effect of cyclosporine. The renal effects

of cyclosporine can manifest as acute azotemia, tubular dysfunction, or as chronic progressive renal disease, that is irreversible ***(Williams et al., 2005).***

Neurologic side effects have been reported in patients being treated with cyclosporine with symptoms such as headaches and visual abnormalities, resembling hypertensive encephalopathy, Psychosis, seizures, anxiety and sleep disturbances have been documented but are rare. Other potential side effects of cyclosporine include gastrointestinal symptoms such as anorexia, nausea, vomiting, diarrhea and abdominal discomfort. Thomson Micromedex Healthcare Series. Subsequent strategies focusing on stringent ex vivo T cell depletion of the graft, often coupled with intensive preparative regimens, proved effective in preventing GvHD but at the expense of delayed immune reconstitution and high rate of non-relapse mortality (NRM). In this setting, cell-based strategies to increase post-transplantation immune recovery could efficiently decrease infectious mortality but are, at present, difficult to perform outside highly specialized centers ***(Handgretinger et al., 2012).***

In recent years, several groups have devised successful approaches to perform T cell-replete transplantation, even in

the full haplotype-mismatched setting. Among other approaches, that has gained the most interest has been the use of high-dose post-transplantation cyclophosphamide (PTCy) as in vivo T cell allo-depleting agent ***(Peccatori et al., 2015).***

This approach has demonstrated promising results, includingacceptable rates of NRM and severe GVHD in single- and multi-institution phase II trials and achieving outcomes equivalent to those of HSCT performed using HLA-identical donors or MUD ***(Bashey et al., 2014).***

Cyclophosphamide has been used in many combinations in BMT for its antitumor and immunosuppressive properties. Uses of high-dose cyclophosphamide in the post-transplantation setting has successfully modulated GvHD in preclinical models, as well as in a variety of clinical trials using HLA-matched and haplo-identical donors, mostly in the adult population ***(Kanakry et al., 2014).***

High-dose post-transplantation cyclophosphamide (PTCy) targets all reactive donor T cells that are highly proliferative early after BMT, thus minimizing the risk of severe GvHD, while still enabling survival of resting

memory T cells that can offer protection against infection and aGVL effect ***(Ganguly et al., 2014).***

Promising clinical trial data using PTCy with or without additional immunosuppressive agents have been demonstrated in HLA-matched related, unrelated, and haploidentical transplantation settings ***(McCurdy et al., 2015).***

PTCy has been incorporated after myeloablative regimens, as well as after reduced-intensity regimens for both malignant and nonmalignant disorders Prior reports demonstrated the safety and feasibility of PTCy as single-agent GVHD prophylaxis after myeloablative HLA matched T cell replete BMT in adults, with rates of GvHD similar to that of HLA-matched BMT with conventional immunosuppression, including a calcineurin inhibitor (CNI) and methotrexate ***(Peccatori et al., 2015)***

AIM OF THE WORK

To assess the effects of using post-transplant cyclophosphamide as GvHD prophylaxis in allogeneic matched related stem cell transplant on recovery of blood counts compared with other regimens of GVHD prophylaxis

Chapter (1)

Hematopoietic Stem Cell Transplantation

More than 25,000 hematopoietic stem cell transplantations (HSCTs) are performed each year for the treatment of lymphoma, leukemia, immune-deficiency illnesses, congenital metabolic defects, hemoglobinopathies, and myelodysplastic and myeloproliferative syndromes. Before transplantation, patients receive intensive myeloablative chemoradiotherapy followed by stem cell "rescue." Autologous HSCT is performed using the patient's own hematopoietic stem cells, which are harvested before transplantation and reinfused after myeloablation. Allogeneic HSCT uses human leukocyte antigen (HLA)-matched stem cells derived from a donor. Survival after allogeneic transplantation depends on donor–recipient matching, the graft-versus-host response, and the development of a graft versus leukemia effect ***(Hatzimichael and Tuthill, 2010).***

HSCT was started more than half a century ago as a standard therapeutic modality for a variety of malignant and non-malignant diseases, it has evolved from experimental