# Effect Of Post Allogenic Stem Cell Transplant Cyclophosphamide On engraftment and relapse Compared with Other Regimen Of GVHD (graft versus host disease) Prophylaxis

Thesis

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# List of abbreviations

| | | |
|---|---|---|
| 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 |

# List of abbreviations *(Cont ..)*

| | | |
|---|---|---|
| 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 FR 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 Y 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 NJ 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 ME 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 M 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 D et al., 2005).***

Hypertension caused by renal vasoconstriction and sodium retention, is generally seen within the first few weeks of therapy. The blood pressure elevation induced by cyclosporine frequently responds to dose reduction ***(Taler Sj et al., 1999).***

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 R 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 J 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 A 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 CG et al., 2014).***

High-dose post-transplantation cyclophosphamide (PTCy) targets alloreactive donor T cells that are highly proliferative early after BMT, thus minimizingthe risk of severe GvHD, while still enabling survival of resting memory T cells that can offer protection against infection and aGVL effect ***(Ganguly S 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 S 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 J et al., 2015).***

# Aim of the Work

The aim of this study is to The assess clinical outcome of using post transplant cyclophosphamide as GvHD prophylaxis in allogeneic stem cell transplant as regard engraftment and relapse .

## Hematopoietic Stem Cell Transplantation

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 bone marrow transplantation for rare cases with refractory acute leukemia, combined immune deficiency, or aplastic anemia to standard of care for patients with many congenital or acquired severe disorders of the hematopoietic system ***(Gratwohl etal 2013).***

A Danish investigator, Capricious – Moeller, noted that when the legs of guinea pigs were shielded during exposure to total body irradiation (TBI), the usual depression of platelet counts and post irradiation hemorrhagic diathesis were prevented. These important observations were largely ignored or forgotten for 25 years, but in 1951, Jacobson and colleagues re-discovered these observations. They reported that mice exposed to doses of radiation that caused fatal marrow aplasia could be protected from death by shielding of the spleen, a hematopoietic organ in the mouse. With remarkable insight they also showed that protection from lethal effects could be accomplished by the intra-peritoneal

injection of spleen cells following TBI ***(Schmitz, Pfistner and Sextro, 2002).***

The attempts for BMT have been reported back to 1894, with the first successful allogenic bone marrow transplant done worldwide, using HLA identical sibling ***(Simultaneous transplants done in Minneapolis by Robert Good, et al., 1968) (Thomas, Buckner, Clift, 2009).***

In 1988, successful transplantation occurred in a young boy with Fanconi anemia using UCB collected at the birth of his sibling. In 1992 a patient was successfully transplanted with UCB instead of BM for treatment of leukemia. Over the past decade, the use UCB has expanded rapidly, and now more than 1000 transplants have been performed using UCB as a stem cell source, UCB has been used to transplant in patients for whom BM can't be used ***(Theodore, 2005).***

In addition to BM and UCB, PBSCs have gained popularity as source of stem cells since their initial introduction in 1980s ***(Theodore, 2005).***