An Investigation of the Influences on Decision-Making Algorithms in Allogeneic Stem Cell Transplantation in Different Groups of Pediatric Nonmalignant Diseases

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Received: 21 March 2020

Accepted:11 February 2021

Abstract:

Background: Haematopoietic stem cell transplantation (HSCT) represents the definitive treatment for many non-malignant diseases. Treosulfan is considered a safe and effective conditioning drug compared to other conventional myeloablative conditioning (MAC) regimens, especially in patients with comorbidities. **Aim of the work**: To evaluate the safety and efficacy of Fludarabine-Treosulfan-Thiotepa reduced toxicity conditioning in different paediatric nonmalignant disease. **Patients and methods**: 54 patients (55 transplants) were reviewed retrospectively, they had metabolic, immunodeficiency, BM failure, hemoglobinopathy and other nonmalignant diseases. All had the same conditioning. 96% received serotherapy (Alemtuzumab/ATG). post-transplant Graft-versus-Host disease (GVHD) prophylaxis was given in all patients, based mostly on ciclosporin. 90% of the patients were fully HLA-matched. **Results:** Median age at transplant was six years. No primary graft failure, 4%(n=2) had secondary graft failure. Overall survival at a median follow-up of 15months was 90.9%. Neutrophil engraftment occurred at a median of 12 days, Platelet engraftment occurred at a median of 19 days. immune reconstitution was achieved at a median time of nine Chimerism was full donor in 64%(n=35), high donor in 18%(n=10), and mixed donor in 6%(n=3). 60%(n=33) developed GVHD but only 4%(n=2) had acute severe GVHD, another 4%(n=2) had severe chronic GVHD. One patient had severe VOD.

Conclusion: This study demonstrates that Fludarabine-Treosulfan-Thiotepa regimen is a safe and effective conditioning that can achieve engraftment, with very low rates of graft failure, transplant-related mortality and morbidity, even if it is used twice in the same patient.

Key words: Bone marrow transplantation; nonmalignant; conditioning.

Introduction:

Haematopoietic stem cell transplantation (HSCT) is the definitive treatment for many paediatric non-malignant conditions, as metabolic disorders, primary immunodeficiency, inherited bone marrow failure syndromes (1, 2). Transplantation for these patients have two main challenges. Firstly, unlike patients with malignant diseases, these patients have not been exposed to chemotherapy before, so they usually necessitate myeloablative conditioning (MAC) to achieve engraftment. Secondly, these patients usually come to transplant with other comorbidities, so they are more vulnerable to the toxicity of the conditioning (3, 4).

Therefore, the use of reduced intensity conditioning (RIC) regimen in these patients with is associated with high risk of graft failure, on the other hand, the use of MAC regimens carries high risk of toxicities and organ damage. Thus, conditioning regimens that can achieve engraftment without increasing the toxicity risk are optimum for transplantation of these patients, these are called reduced toxicity conditioning (RTC) regimens(5). Treosulfan, a bifunctional alkylating agent with myeloablative and immunosuppressive effects, has been increasingly used as an RTC regimen especially for patients with non-malignant diseases. Treosulfan has a low toxicity profile with reported acute toxicities including mucosal, hepatic, skin, and neurological involvement. These toxicities are generally mild and reversible, and importantly, venocclusive disease (VOD) is very rare(1, 2, 4-6).

Thiotepa, is a poly-alkylating agent with potent functional antineoplastic abilities. The most common toxicities of thiotepa in high doses are myelosuppression and cutaneous toxicities(7).

Herein, we present the results of this reduced toxicity myeloablative conditioning (RTC) regimen consisted of Fludarabine, Treosulfan and Thiotepa (FTT) used in a series of patients with various paediatric non-malignant conditions. We assessed the efficacy and the safety of this regimen.

Patients and methods:

This retrospective case series study was conducted on 54 Patients with non-malignant diseases, who were indicated to have bone marrow transplantation (BMT), at Royal Manchester Children's Hospital,

Manchester, UK, in the period between 2012 and 2018.

The protocol of this study was approved by the Ethical Committee of the Faculty of Medicine, Benha University. Informed consent was taken from the patients' parents/guardians before participation in this study. BMT was performed according to the standard bone marrow transplant protocol(8). the transplantation process proceeded as follows:

A. Pre-transplant preparation

Pre-transplant consultation was done, obtaining the consent for transplantation and to data collection was gained.

B. Transplant phase

All types of donors have been used, 33 patients (60%) received the transplant from a matched related donor (MRDs), 20 Patients (36%) received a transplant from a matched unrelated donor (MUDs) and two patients (4%) received the transplant from Haploidentical donors. In vitro alpha-beta T cell depletion was carried in these haploidentical transplants.

Fifty patients (90%) were fully matched (10/10), while two patients (4%) had one point mismatch (9/10 and 7/8), only one patient (2%) had two points of HLA mismatch (8/10), and two patients (4%) were haploidentical (5/10).

Regarding stem cell sources, bone marrow (BM) was used in 41patients (75%), while peripheral blood stem cells (PBSCs) were used in 13 patients (23%), and umbilical cord blood (UCB) was used in one patient (2%).

The conditioning regimen was discussed and agreed with the team according to an individualized schedule. Ovarian biopsy or testicular biopsy were taken at the same time.

Conditioning:

In all patients a reduced toxicity myeloablative conditioning (RTC) was used:

- Treosulfan, as a myeloablative drug, was given at a dose 36-40 g/m2, divided into 3 doses.
- Fludarabine was used as an immunoablative conditioning at a dose of 150-160 mgs/m^2, given as either 40mgs/m2/day X 4 doses or 30mgs/m2/day X 5 doses.
- Thiotepa was added to boost the myeloablative effect of Treosulfan at a dose 10mgs/kg, on two divided doses on the same day.

Serotherapy:

It was used for in-vivo lymphodepletion (T-cell depletion) to decrease the incidence of graft versus host disease (GVHD). It was given in **53** patients (96%) as either

Alemtuzumab or Anti-thymocyte globulin (ATG). Alemtuzumab was used in most patients (n=48, 87%). Five patients (9%) received ATG, which is now preserved to umbilical cord transplant (UCT).

After graft infusion. Three major risks were anticipated:

1.Risks of conditioning therapy:

- Bone marrow suppression: Patients were supported by red blood cells or Platelet transfusions accordingly, Granulocyte colony-stimulating factor (GCSF) was commenced in some cases, mainly in UCT
- Mucositis: patients were usually supported with painkillers and parenteral nutrition.
- Veno-occlusive disease (VOD): Prophylactic Defibrotide was given to reduce the risk of the VOD in high-risk patients. VOD was diagnosed according to Seattle and Baltimore diagnostic criteria (9-11). Defibrotide was used in 20 high-risk patients (36%), these were patients with conditions causing high iron overload secondary to repeated red cell transfusions including haemoglobinopathy and DBA, or pre-existing liver disease including metabolic disorders (Wolman and MPS I), Osteopetrosis and HLH, or those having a second transplant.

2. Infections

Patients remained immunosuppressed post-transplant by the immune suppressive drugs to prevent GVHD, to minimise the risk of infections:

- Isolation throughout neutropenia stage in a double high-efficiency particulate air (HEPA) filtered cubicles.
- Patients' blood, urine and stool were screened weekly for viral reactivations.
- All patients received antifungal and antiviral prophylaxis, Trimethoprim-sulfamethoxazole and Phenoxymethylpenicillin were commenced after engraftment as prophylaxis for Pneumocystis Jiroveci (PCP) and encapsulated infections respectively.

3. Graft versus host disease (GVHD)

This risk was reduced by :

- Achieving the best donor match.
- Serotherapy: Lymphodepleting agents as Alemtuzumab or ATG.
- Immunosuppressive drugs like ciclosporin (CSA).

GVHD was classified according to the onset into acute GVHD (the first 100 days post-

transplant) and chronic GVHD (after 100 days), and was graded according to the European bone marrow transplant criteria (EBMT criteria) into grade I/II/III and IV(12).

The most used post-transplant GVHD prophylaxis was ciclosporin (CSA) alone in 39 patients (70%). Mycophenolate Mofetil (MMF) was given in addition to CSA in 12 patients (22%), it was usually used when unrelated PBSCs were used. Post-transplant methotrexate (MTX) was given in two patients (4%). Methylprednisolone was added to CSA in one patient (2%) and another patient (2%) received Tacrolimus alone.

C. Post-transplant phase

Neutrophil engraftment was recognized when the absolute neutrophil count exceeded 0.5 x 10^9/l for three days in a row. Platelet engraftment was recognized when unsupported platelet count exceeded 20 x 10^9/l for three days in a row, and red cell engraftment was considered when patients independent of red cell transfusion maintained their haemoglobin above 80 g/l.

Primary graft rejection was defined as the total white cell count of < $0.5x10^9$ at day +28. Secondary graft failure was considered when initial engraftment happened followed by a progressive decrease in the donor chimerism to <10%. Chimerism was performed at engraftment, two months, three months, six months and one year after transplant. The target high-level chimerism is ≥90%, and mixed chimerism when it was between 10% and 90%.

Immune reconstitution was considered when CD4 T-cells are >400 cell/mm3. In absence of GVHD, immune suppression was stopped, and prophylactic medications were also stopped, and patients remained on long-term prophylactic penicillin V. and referred for routine immunizations.

Statistical methods:

The SPSS 12.0 statistical software was used for statistical analysis (Spss Inc, Chicago, ILL Company). Categorical data were presented as number and percentages while quantitative data were expressed as median ± standard deviation and range. Qualitative data were expressed as frequency and percentage. The difference among 3 independent means was analyzed using Kruskal Wallis test (KW) for non-parametric ones. The accepted level of significance in this work was stated at 0.05.

Results:

There were 54 patients (55 transplants), Thirty-six patients (66%) were males and eighteen (34%) were females. Median age at

transplant was six years and seven months ± five years (Range, 4 months to 18 years). Ten patients (18%) were less than one year old when they received the transplant.

Fifty-three patients (96%) received a primary transplant, one (2%) received this as a second transplant after the failure of a first transplant procedure and one patient (2%) received two transplants with treosulfan-based conditioning. The indications for the transplantation were variable **(Table 1).**

Patients were admitted at the hospital for a median of 34 ± 19 days (Range, 18 to 98 days). Alive Patients were followed up for a median of 15 ± 19 months (Range, two to 77 months).

1. **The impact of the underlying disease on patient characteristics.**

The median age at transplant was significantly younger in Malignant infantile osteopetrosis (MIOP) group at six months followed by Metabolic disorder group at three years old (P 0.035), they needed the transplantation very early due to the life-threatening condition of the MIOP and due to the need to correct the metabolic condition before permanently damaging the patient's systems especially the central nervous system. Regarding the gender, males were more represented in most groups except for Inherited bone marrow failure syndrome (IBMFS) and Malignant infantile osteopetrosis (MIOP) (P 0.044).

2. **Graft versus host disease (GVHD).**

Overall, 33 patients (60%) developed GVHD, either skin, gut or lung. 14 patients (25%) developed acute GVHD at a median of 46 days ± 14 days (Range, 14 to 69 days). Out of them, 12 patients (22%) developed grade I/II acute GVHD. Two patients (4%) developed grade III/IV acute GVHD, one of them received well-matched unrelated BM transplant and developed grade IV Gut GVHD and died later due to multiorgan failure (MOF). The other patient received 7/8 mismatched UCB and developed grade IV skin, gut and lung GVHD, which was persistent.

On the other hand, 10 patients (18%) developed chronic GVHD at a median of 150 days ± 57 days (Range, 100 to 266 days), 8 patients (14%) were Grade I/II. Only two patients (4%) had Grade III/IV GVHD. All chronic GVHD were limited, non-extensive, and resolved completely with no need for long-term immunosuppression.

3. **Veno-occlusive disease (VOD).**

Six patients (11%) had VOD, four out of them were high risk and already received Defibrotide prophylaxis. Five patients (9%), had mild VOD, while one patient (2%) had severe VOD (osteopetrosis, despite

receiving Defibrotide, the transplant was complicated with severe VOD, which necessitated peritoneal drainage of gross ascites).

4. Infection.

CMV reactivation was found in nineteen patients (35%), third of them were high risk (where CMV status was mismatched between the donor and the recipient). EBV reactivation was found in thirteen patients (24%) and was successfully treated. Adenovirus reactivation happened in seven patients (13%). one of them had invasive Adenoviraemia that led to graft failure and died early before a chance for the second transplant.

5. Engraftment and Immune reconstitution.

Neutrophil engraftment happened at a median of twelve ± five days (Range, 10 to 33 days), while platelet engraftment was at a median of nineteen ± 16 days (Range, eight to 100 days). Full donor chimerism was achieved in thirty-five patients (64%), while ten patients (18%) had high donor chimerism (>90%), and only three patients (6%) had mixed donor chimerism (<90%) but was still enough to correct the condition. one patient had their follow up chimerism at other hospital and was not recorded in this data, and six patients either died or had graft failure. Patients who did not suffer from graft failure had immune reconstitution at a median time of nine ± five months from transplant (Range, four months (132 days) to 23 months (695 days)).

6. Graft failure (GF)

No primary graft failure happened, only two patients with osteopetrosis (4%) had secondary graft failure with autologous reconstitution at 13 and 26 months respectively. Both had a second transplant, one of them received myeloablative conditioning (MAC) with Fludarabine and Busulfan and the other received FTT. Both were successfully engrafted.

7.Survival

Overall survival was 90.9% **(Figure 1)**, five patients (9.26%) died at a median of 81 ± 60 days (Range, 40 to 194 days) **(Table 2).** The most common cause of death was MOF. 85.5% of the patients survived, were engrafted successfully and sustained their graft function.

8. The impact of the underlying condition on the outcomes

Graft failure was significantly higher in the Malignant infantile osteopetrosis (MIOP) group (P <0.000), otherwise, no other significant differences were found in any outcome (GVHD, VOD, infection, engraftment, immune reconstitution or survival) in the study (P >0.05)

Table (1): Underlying conditions in the study population.

Condition	Number of patients and %	Individual diagnosis
Metabolic disorder	11 (20%)	3 Mucopolysaccharidosis type I (MPS I)
		2 Wolman Syndrome
		2 Mitochondrial neuro-gastrointestinal encephalopathy (MNGIE)
		2 X-Adrenoleukodystrophy (Cerebral Inflammatory Disease)
		1 Glycogen storage disease type IB (GSD1B) with neutropenia
		1 congenital sideroblastic anaemia with immunodeficiency, fevers, and developmental delay (SIFD)
Primary immunodeficiency (PID)	10 (18%)	1 Leukocyte adhesion defect (LAD)
		1 Wiskott Aldrich syndrome (WAS)
		8 Variable immunodeficiency conditions
Inherited bone marrow failure syndrome (IBMFS)	14 (25%)	6 Diamond Blackfan anaemia (DBA)
		5 Constitutional neutropenia
		2 Amegakaryocytic Thrombocytopenia
		1 Bernard Soulier S
Haemoglobinopathy	12 (22%)	6 Thalassemia
		6 Sickle cell disease (SCD)
Hemophagocytic lymphohistiocytosis (HLH)	2 (4%)	
Malignant infantile osteopetrosis (MIOP)	4 (7%)	4 Transplants in three patients
Non- malignant Myelodysplastic syndrome (MDS)	2 (4%)	

Table (2): Diagnosis, protocol, progress and outcomes of the complicated patients.

Diagnosis and comorbidities	Transplant	Complications	Cause of death	Days to death
HLH (Severe HLH with lung and CNS disease) (Non-TRM)	FTT + Alem Defib CSA + MMF MRD BM	Brain atrophy, chemical dermatitis, Respiratory failure, Multi-resistant organism sepsis	Progressive CNS disease	73
SIFD congenital (Persistent pulmonary hypertension) (Non-TRM)	FTT + Alem CSA MRD BM	Idiopathic pneumonia, white matter CNS changes.	Respiratory failure + MOF	40
MDS (Bronchiectasis) (TRM)	FTT + Alem CSA MUD PBSC	Adenovirus and Herpes simplex viremia, Aspergillus and Pneumocystis pneumonia (PCP), Inflammatory Bowel and Intrahepatic Cholestasis	MOF + progressive Pneumonia	194
Hurler S (Tracheostomy for langeotracheomalacia) (TRM)	FTT + Alem CSA MRD BM	CMV reactivation, Adenovirus gut infection, respiratory deterioration	MOF + pseudomonas sepsis	81
Thalassemia major (TRM)	FTT + Alem Defib CSA MRD BM	EBV reactivation, transplant associated microangiopathy (TMA)	MOF TMA	134

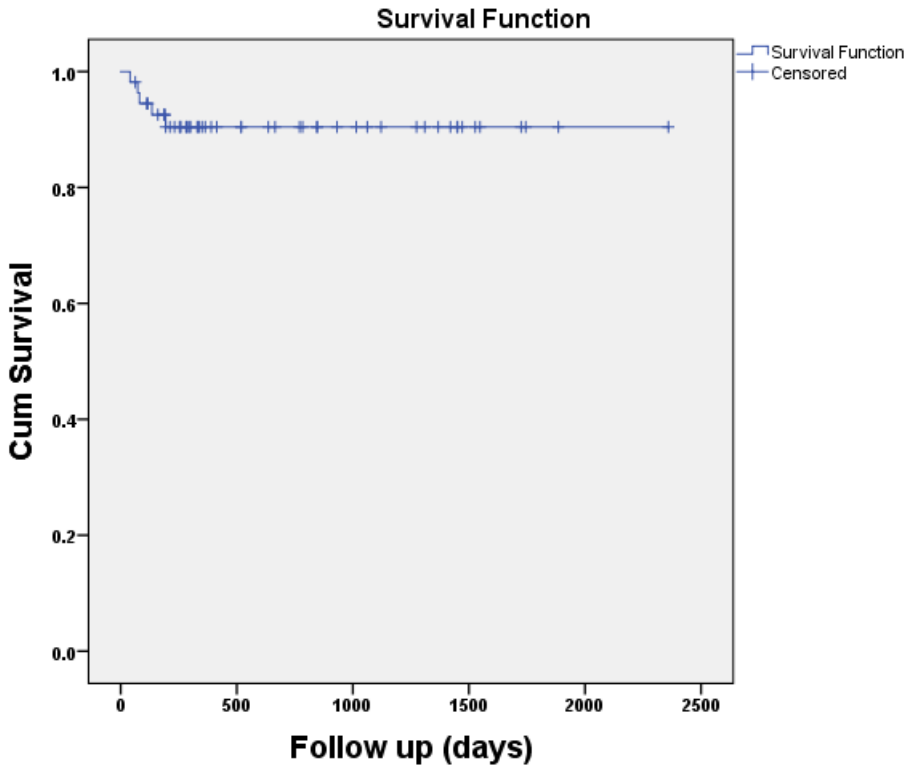

Figure (1): Overall survival.

Discussion:

This study demonstrates that the Fludarabine-Treosulfan-Thiotepa (FTT) conditioning regimen is a safe and effective regimen, it can achieve engraftment, with a low rate of graft failure, transplant-related mortality and morbidity. It is also suitable for all ages and conditions. It is proposed that such a regimen would reach the balance between efficacy and safety.

Few studies have examined the effectiveness and safety of Busulfan-based or Treosulfan-based conditioning regimens in a series of mixed non-malignant conditions (1-5), we compared the results to these studies. We did not compare this series' results to the studies that specified certain pathologies as this would tie the outcomes to the inherent characteristics related to these diseases(6, 13-18)

The outcomes in this study were comparable across the different groups except for Graft failure which correlated to the osteopetrosis diagnosis. We report the success and the safety of this conditioning regimen in infants

less than one year, additionally, it can be used twice in the same patient after a graft failure.

Engraftment

A high rate of engraftment was achieved, no primary graft failure happened, secondary GF occurred in 4% of the patients, which lies in the spectrum of the recorded range in other treosulfan-based conditioning studies (3.2% to 18.75%) (1-5).

Dinur et al. (1) reported primary graft failure in 6.6%, in addition to 4.5% who died before engraftment. Greystoke et al. (3) reported primary graft failure in 3%, an additional 3% also died before engraftment. Beier et al. (5) reported 3% of his patients who needed CD34 cell top-up. Furthermore, these studies reported secondary graft failure incidence (Range, 3 to 9%) (1-3, 5). Dinur et al. reported secondary graft failure in Fludarabine-Treosulfan group (6.6%), and no secondary graft failure in FTT group (0%) (1). Slatter et al. reported an overall graft rejection of 5% (4).

In Busulfan-based studies, the incidence of primary graft failure ranged from 6 to 24% (14, 19-22), while the incidence of secondary graft failure ranged from 1 to 10% (19, 22).

Survival

Overall survival (OS) in this series was 90.9%, and transplant-related mortality (TRM) was 5.5%, this is comparable to the other Treosulfan-based studies which reported OS ranged from 70.5% up to 90% (1-5). In Busulfan-based studies, OS was reported as 79 to 85% and TRM was reported as 9 to 19% (19-22)

Graft versus host disease (GVHD)

Acute GVHD grade I-IV developed in 14 patients (25%), grade III-IV developed in two patients (4%). This represents the lowest incidence in comparison to other Treosulfan-based studies (1-5), that reported acute GVHD grade I-IV (Range, 31 to 47%) and grade III-IV (Range 10 to 26%). While in different cohorts of Busulfan-based conditioning, acute GVHD was found to range from 7 to 25% (14, 19-22).

In this series, 10 patients (18%) developed chronic GVHD, in a agreement with the literature of Treosulfan-based conditioning (Range 7 to 21%) (1-5), and Busulfan-based conditioning (Range 3 to 25%) (14, 19-22). None of the patients died from GVHD in contrary to other reports, where (9%) and (3%) died of GVHD (1) (3).

Venocclusive disease (VOD)

The results show a low rate of VOD despite the risk, with a low rate of death from VOD. Severe VOD (Grade III/IV) was reported in one high-risk patient (2%), in comparison to other Treosulfan-based studies which reported VOD between 0 and 5% (1-5). In

comparison to Busulfan-based studies, the reported incidence ranged from 0 to 16%. (14, 19).

Infection

Viral reactivation in this series occurred in 30 patients (55%), which is comparable to other Treosulfan-based studies (Range 9 to 69%) (1-3). In a Busulfan-based study (19), viral reactivation occurred in 38 to 45% of patients. CMV reactivation occurred in 35% of the patients, compared to a range of 3 to 35% in these studies (1-3). Adenovirus reactivation was evident in 13% of the patients, compared to a range of 6 to 11% in the aforementioned studies (1-3). EBV reactivation in this study happened in 24%, compared to (Range, 11 to 13%) in two studies (1, 2). In the current study, viral reactivation was associated with low mortality, but with prolonged morbidity. Adenovirus was the most problematic one leading directly to the death of two patients in this study.

Conclusion:

This reduced toxicity myeloablative Fludarabine-Treosulfan-Thiotepa regimen is a safe and effective conditioning regimen, it can achieve high engraftment, with very low rates of graft failure, transplant-related mortality and morbidity. Its efficacy is consistent within different nonmalignant diseases.

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To cite this article: Samar Elbahy, Mohamed ElBakry, Sameh Abdulsamea, Robert F. Wynn. An Investigation of the Influences on Decision-Making Algorithms in Allogeneic Stem Cell Transplantation in Different Groups of Pediatric Nonmalignant Diseases. BMFJ 2021;38(1): 196-209. DOI: 10.21608/bmfj.2020.26296.1231