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The use of post-transplantation cyclophosphamide in peripheral blood HLA-matched stem cell transplantation as graft versus host disease prophylaxis in patients with malignant or non-malignant hematological disorders: A single center experience of 52 patients

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Abstract

Studies addressing the utilization of post-transplant cyclophosphamide as graft-versus-host disease (GVHD) prophylaxis in allogeneic hemopoietic stem cell transplantation from matched sibling donors are limited and with controversial results. Chronic GVHD incidence necessitating systemic treatment is around 35% in peripheral blood stem cell transplantation (PBSCT) from HLA-matched sibling donors. In this study high-dose cyclophosphamide was added to PBSCT aiming to reduce the incidence of GVHD to hit a desirable figure. Fifty two patients with either benign or malignant hematological disorders who underwent stem cell transplantation at Nasser Institute Hospital in Egypt from November 2017 to October 2018 were enrolled in this study. Fifty patients had fully HLA-matched siblings while the remaining two patients had one locus class I mismatched donors. Pre-transplant conditioning regimen consisted of fludarabine and busulfan in 73.1% of patients and fludarabine and cyclophosphamide were used for 26.9% of patients. For GVHD prophylaxis, cyclophosphamide was given at a dose of 50 mg/kg/day on days 3 and 4 post-transplantation, and cyclosporine starting day 5 in 96.1% of patients. For the one-locus mismatched, both CSA and MMF were administered starting day 5. The 1-year incidence of acute GVHD was 15.3% and for chronic GVHD was 13.4%.

Keywords: PTCY, aGVHD, cGVHD, HLA-matched and relapse
Introduction

Graft-versus-host disease (GVHD) remains the worst nightmare in the field of stem cell transplantation (SCT) [1]. Despite the progress achieved in supportive measures, and the emergence of many novel agents for the treatment of GVHD among which are JAK-2 inhibitors, rates of chronic GVHD (cGVHD) have remained high and showed insufficient treatment results partly due to incompliance to treatment of some patients [2-4]. The median duration of immunosuppressive therapy needed to control cGVHD varies according to the stem cell source. It ranges from 2 to 5 years after peripheral blood stem cell transplantation (PBSCT) [5]. Strategies to reduce cGVHD with its long term post-SCT morbidity and mortality without affecting the precious effect of graft-versus-tumor (GVT) are highly needed [6, 7].

The biological mechanism by which post-transplant cyclophosphamide (PTCY) helps in reducing GVHD after SCT includes; in vivo selective destruction of alloreactive T cells, induction of tolerance, and intra-thymic clonal deletion of alloreactive T lymphocytes [8, 9]. Early administration of PT-Cy after HSCT does not affect engraftment negatively, but rather decreases the risk of cGVHD. Luznik and colleagues (2012) reported that the cumulative incidence of grades III-IV GVHD was less than 10% after using cyclophosphamide (CY) at dose of 50 mg/kg/day on days 3 and 4, or only on day 3 followed by tacrolimus and mycophenolate mofetil (MMF) in HLA haploididentical bone marrow transplantation (BMT) with reduced intensity conditioning [10, 11]. Kanakry and coworkers (2014) have demonstrated that PT-Cy administration on days 3 and 4 after
HLA-matched related or unrelated BMT using fludarabine/busulfan (FLU/BU) conditioning resulted in a cumulative incidence of grades II-IV aGVHD, grades III-IV aGVHD, and cGVHD of 51%, 15%, and 14%, respectively [12]. Thus, the cumulative incidence of cGVHD is consistently about 15% with PT-Cy as the sole GVHD prophylaxis after HLA-matched related or unrelated BMT.

Meanwhile, it should be noted that PBSCT has superior features when compared to bone marrow graft. This is attributed to a faster neutrophil and platelet (PLT) engraftment [13], in addition to a higher safety profile for the healthy donors, thus helping them eschew the risk of general anesthesia [14, 15].

The current work is designed to address the leverage of using PT-Cy as a GVHD prophylaxis on the outcome of a fully HLA-matched sibling PBSCT, considering its higher safety profile and faster engraftment kinetics among patients [16].

Subjects and methods

1 Study design

This is a study of 52 patients with either malignant or non-malignant hematological disorders who underwent PBSCT at Nasser Institute Hospital in Egypt, in the period from November 2017 to October 2018 and still under follow up.
2 Eligibility criteria

Peripheral blood stem cell donors were either HLA-identical siblings, or mismatched donors at a single class I antigen. All patients and donors signed an informed pre-transplant consent.

3 Exclusion criteria

Patients with Eastern Cooperative Oncology Group performance (ECOG) status 2 or higher were excluded from this study. Other exclusion criteria were uncontrolled infections, pregnancy, or severe organs dysfunctions.

4 Pre-transplant conditioning regimens

Fifty patients were fully HLA-matched and two had one locus mismatch. Pre-transplant conditioning in 38 patients (73.1 %) included a total dose of 160 mg/m$^2$ of intravenous Fludarabine, in addition to 16 mg/kg of oral Busulfan, both of which were divided over 4 days. Diagnoses of those 38 cases were as follows: 30 patients were diagnosed with acute myeloid leukemia (AML), 21 of whom (70%) underwent the transplant in first complete remission CR-1, while the other 9 (30%) were transplanted in CR-2. Four patients were diagnosed with high risk myelodysplastic syndrome (MDS). Two patients were diagnosed
with chronic myeloid leukemia (CML); one of them was indicated for transplantation after failure to respond to all available tyrosine kinase inhibitors (TKIs), while the other one was in second chronic phase. One patient had Philadelphia positive acute lymphoblastic leukemia (ALL Ph+ve) and the last patient had non-Hodgkin lymphoma (NHL) that relapsed post auto-SCT. For the other 14 patients (26.9 %), the conditioning regimen consisted of a total dose of 120 mg/m² of intravenous fludarabine and 25 mg/kg/day intravenous cyclophosphamide both were divided over 4 days. All patients had severe aplastic anemia (SAA) except one who was diagnosed as hypocellular MDS.

5 GVHD prophylaxis

On days 3 and 4 post-transplantation, cyclophosphamide was administered at a dose of 50 mg/kg/day [17], and ciclosporine was started on day 5 onwards for the 50 fully HLA-matched transplants (96.1 %). Ciclosporine and mycophenolate mofetil were given on day 5 in the 2 patients with single HLA class I antigen mismatch (3.9 %).

6 Stem cells source and dose

All patients were transplanted using G-CSF mobilized donor peripheral blood stem cells. The median stem cells dose was $7 \times 10^6$/kg of recipient’s weight (range, 3-10.7) for all disease entities. Median stem cell doses for different diseases are shown in table (1).
7 End points

Primary end points of the current study are the incidence of aGVHD, cGVHD and overall survival (OS). Tempo of neutrophil and PLT engraftment, relapse rate (RR), non-relapse mortality (NRM), were all assessed as secondary end points.

Results

Statistical Analysis

Numerical data were expressed as median and range. Qualitative data were expressed as frequency and percentage. Survival analysis (OS and disease free survival (DFS) was performed using Kaplan-Meier method. Hazard ratio (HR) with it 95% confidence interval (CI) was used for risk estimation. All tests were two-tailed. A p-value < 0.05 was considered statistically significant. Data analysis was performed using IBM SPSS advanced statistics version 24 (SPSS Inc., Chicago, IL).

1 Patients characteristic

Fifty two patients were enrolled in this study. Males were 67.3 % and females were 32.7 %. Median age for all patients was 33 (range, 4-60). Patients’ characteristics and demographics are summarized in table (2).
2 Graft versus host disease

2.a Acute GVHD

Eight patients (15.3 %) developed aGVHD, all in the first 100 days post transplant. One patient had one locus mismatch. Twenty five percent of the aGVHD patients were classified grade I-II and presented with GIT symptoms. The other 75% had grade III-IV aGVHD, half of them had both skin and GIT symptoms, while the other half had GIT and hepatic symptoms as demonstrated in table (3). Patients diagnosed with aGVHD grades III-IV received methylprednisolone at a dose of 2 mg/kg daily dose.

The incidence of aGVHD was higher in the myeloablative conditioning (MAC) regimen compared to the non myeloablative conditioning regimen by about 2.5 folds, however, this difference did not achieve statistical significance (p-value= 0.9).

All patients who developed aGVHD received CD34+ cell count less than 7.1x10^6 /kg. Occurrence of aGVHD lead to a significant high risk of death (HR= 6.3, P-value= 0.001, CI= 95 %). In contrast to CMV reactivation which did not (HR= 2.9, P-value= 0.054, CI= 95 %) as demonstrated in figure (1).

2.b Chronic GVHD

Seven patients (13.4 %) developed cGVHD and all were graded as limited. They all showed complete response to prednisolone 1 mg/kg daily dose.

3 Engraftment details
The median times to neutrophil engraftment to reach \(0.5 \times 10^3/\text{mL}\) and PLT engraftment to reach \(20 \times 10^3/\text{mL}\) were 17 (range, 11-27) days and 14 (range, 10-30) days, respectively. Platelet engraftment has been without blood transfusion for several days. The median times to neutrophil engraftment to reach \(1.0 \times 10^3/\text{mL}\) and PLT engraftment to reach \(100 \times 10^3/\text{mL}\) were 18 (range, 12-32) days and 20 (range, 12-35) days, respectively. Table (4) summarizes engraftment details by diagnosis.

4 Disease-free survival and OS

The 1 year overall survival (OS) for the 52 patients was 73.1 %, while disease-free survival (DFS) was 69.5 % as shown in figure (2). The two main disease entities involved in this study were AML (30 cases (57.8 %) and SAA (13 cases (25 %). Regarding AML patients, DFS and OS were 66.7 % and 70 %, respectively as shown in figure (3). Meanwhile, DFS for SAA patients was 76.9 % as shown in figure (4).

5 Transplant related morbidity, relapse and non-relapse mortality

5.a Transplant related morbidity

All transplant related morbidities are demonstrated in table (5). The main transplant related morbidity was neutropenic sepsis that occurred in 15 cases (28.8 %), and was managed by broad spectrum antibiotics and antifungals. Thirteen patients had circulatory failure necessitating vasopressors administration and mechanical ventilation. Unfortunately, 11 of them (21.1 %) failed to achieve adequate response to treatment attempts and died due to
septic shock. CMV reactivation occurred in 10 cases (19.2 %), for which ganciclovir was initiated resulting in a response rate of 90%. Nine patients had hemorrhagic cystitis all of which responded to intra-venous hydration and hemostatic measures including irradiated single donor PLT transfusion. Seven patients (13.4 %) had pneumonia as evidenced by multi-slice CT scans. Among those 7 patients, 5 responded to adequate antibiotics and antifungals after a mean duration of 17 days [18]. After complete resolution of pneumonia, patients were kept on oral voriconazole as a secondary prophylaxis for 3 months post-transplant. Total relapse rate was 5.7 % (3 cases); two cases (3.8%) were originally diagnosed with AML and one case (1.9%) with CML. CSA toxicity was diagnosed in only two patients, either in the form of renal toxicity with elevated serum creatinine level or as microangiopathic hemolytic anemia (MAHA).

5.b Relapse and non-relapse mortality

Non-relapse mortality was 25 %, while Relapse rate was 1.9 %. Eleven patients died due to septic shock representing almost 80% of all mortalities. The other three causes of mortality were CMV pneumonitis, aGVHD and relapse in one of the AML patients, as presented in table (6).

Discussion

In this study post transplantation high-dose cyclophosphamide (PTCY) was administered in G-CSF–mobilized peripheral blood stem cells transplantation aiming to reduce the incidence of cGVHD as far as possible. The idea of using PTCY in HLA matched transplants came from the concept of its usage in haploidentical transplants. Raj and his
colleagues (2014) reported that using high-dose CY after HLA haploidentical transplantation of mobilized blood cells resulted in 18% incidence rate of cGVHD [19].

In our study, fifty two patients with either benign or malignant hematological disorders were enrolled. Pre-transplant conditioning regimens consisted mainly of FLU/BU for malignant disorders and FLU/CY for SAA [13, 16] and hypocellular MDS. The cumulative incidence of cGVHD was 13.4 % after 1 year of follow up.

Our rate is also comparable to that depicted by Luznik et al (2010) when high-dose CY was used after HLA-matched related or unrelated HSCT [20]. We also observed no cases of extensive cGVHD and the cGVHD cases reported hereby were limited. Acute GVHD incidence grades I-II and III-IV were 3.8% and 11.5 %, respectively. These figures are much lower relative to other studies using the same post-transplant CY dose after HLA matched transplants. In 2018, Shah and coworkers have reported a cumulative incidences of grades 2-4 and 3-4 acute GVHD (aGVHD) at day + 100 and 2-years were 32 and 4%, and 59 and 24%, respectively [21]. Mielcarek and colleagues added CSA starting day + 5 after PT-Cy infusion in an attempt to reduce the risk of severe GVHD in patients with hematological diseases receiving PBSCT from matched sibling donor (MSD) or unrelated donor (UD) [22]. Although a lower cumulative incidence of cGVHD and no grade III–IV aGVHD were reported, there was high incidence of grade II aGVHD that exceeded 70%

Our results only demonstrated incidence of grade II-IV aGVHD (11.5 %).

In HLA identical related and unrelated grafts, the addition of MMF and tacrolimus to PT-Cy allowed satisfactory control of aGVHD (about 17 %, with no grade IV) in a previous study performed by Carnevale-Schianca and colleagues in 2017 [23, 24]. Our results are in
accordance with those rates. The incidence of aGVHD was higher in myeloablative conditioning regimen than non-MAC regimen (18.4 % versus 7.1%, respectively) but was yet statistically insignificant.

All patients who developed aGVHD have received a CD34+ cell count less than $7 \times 10^6$/kg, so high CD34+ could not be responsible for its development. However, it should be noted that some previous researches have reported a positive impact on outcome after infusing high numbers of CD34+ cells in terms of a better engraftment and less susceptibility to sepsis in patients undergoing BMT [25-27]. On the other hand, other reports have shown an increased risk of aGVHD or cGVHD in patients receiving high doses of unmanipulated peripheral blood stem cells [28, 29]. Hence, the influence of the CD34+ cells dose on survival remains controversial.

Peripheral blood stem cell transplantation has a superior safety profile over bone marrow stem cells harvesting, and faster engraftment on the expenses of higher cGVHD incidence as previously reported [30-32]. The incidence of cGVHD in our study was only 13.4 %.

Mielcarek and his team have revealed two-year cumulative incidences of relapse rate (RR) and non-relapse mortality (NRM) of 17% and 14%, respectively [22]. The RR reported hereby was much lower (5.7%) than that reported by Mielcarek and colleagues, however, the NRM was notably higher (about 25 %). In our study, overall survival and disease-free survival were 73.1 % and 69.5 % respectively, compared to Mielcarek work that showed 2 years overall survival and disease-free survival 70% and 69% respectively.
Conclusion

The addition of high-dose CY after HLA-matched sibling PBSCT can reduce the risk of acute and chronic GVHD among patients undergoing peripheral blood stem cell transplantation. However our follow up is only one year and a longer follow up is warranted to judge the relapse rate.

Acknowledgement

The authors declare no competing financial interest.

Conflict of Interest

The authors have no conflicts of interest or financial or personal issues that could inappropriately affect the content of this article.

Ethical considerations

In accordance with the Declaration of Helsinki and the approval of the ethics committee at Nasser institute hospital for research and treatment, a signed informed consent was obtained from all adult patients and from the guardians of minor patients to participate in this study.
References


<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>AML</th>
<th>SAA</th>
<th>MDS</th>
<th>CML</th>
<th>NHL</th>
<th>ALL Ph+ve</th>
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<td>Number N= 52</td>
<td>30 (57.8 %)</td>
<td>13 (25 %)</td>
<td>5 (9.6 %)</td>
<td>2 (3.8 %)</td>
<td>1 (1.9 %)</td>
<td>1 (1.9 %)</td>
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<td>Sex (M= 35 (67.3 %) F= 17 (32.7 %)</td>
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<td>M= 8, F= 5</td>
<td>M= 2, F= 3</td>
<td>M= 2</td>
<td>M= 1</td>
<td>M= 1</td>
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<td>Age Median 33 (4-60)</td>
<td>Median= 34 (20-52)</td>
<td>Median= 24 (4-47)</td>
<td>Median= 44 (12-60)</td>
<td>Median= 20 (20-34)</td>
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<td>45</td>
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<td>Regular blood and PLT transfusion</td>
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<td>Very good partial remission</td>
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<td>MDS-RA= 1</td>
<td>DLBCL</td>
<td>B - ALL</td>
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<td>Conditioning Regimen</td>
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<td>Fludarabine/ Busulfan = 4</td>
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<td>GVHD Prophylaxis in addition to PTCY</td>
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<td>Score 2 = 8 Score 3 = 5</td>
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<td>Negative = 2 Positive = 1 Positive = 1</td>
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<td>HLA Fully matched</td>
<td>N=50 (96.1 %) One-locus</td>
<td>29</td>
<td>13</td>
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<td>Source of stem cells</td>
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<td>Peripheral blood</td>
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<td>7 (3.2-7)</td>
<td>6.6 (3.7-8)</td>
<td>4.4 (4.1-7)</td>
<td>5.9 (4.9-7)</td>
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<th>Neutrophils 0.5</th>
<th>Median= 17.5 (15-23)</th>
<th>Median= 15 (11-18)</th>
<th>Median= 16 (14-23)</th>
<th>Median= 21 (16-27)</th>
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| Age                  | Median= 30 (12-58) | Median= 32 (17-57) | Median= 27 (12-48) | Median= 40 (19-58) | Median= 23 (17-42) | 47 | 45 |

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<table>
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Table 1: Patients and donors characteristics and demographics
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<td>GIT</td>
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<tr>
<td>III-IV</td>
<td>Skin, GIT</td>
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<td>5.7%</td>
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<td>GIT, Liver</td>
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<td>3.9%</td>
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Table 2: Acute graft-versus host disease incidence rates
<table>
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<th>Diagnosis</th>
<th>CMV reactivation N=10 (19.2%)</th>
<th>Hemorrhagic cystitis N=9 (17.3%)</th>
<th>Neutopenic sepsis N=15 (28.8%)</th>
<th>Pneumonia N=7 (13.4%)</th>
<th>Relapse N=3 (5.7%)</th>
<th>CSA toxicity N=2 (3.8%)</th>
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<tr>
<td>AML</td>
<td>7</td>
<td>5</td>
<td>7</td>
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<td>SAA</td>
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Table 3: Transplant related morbidity by diagnosis.
Diagnosis | Mortality 14/52 (26.9 %)  
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<tbody>
<tr>
<td></td>
<td>Septic shock N= 11 (21.1 %)</td>
<td>CMV pneumonitis N= 1 (1.9 %)</td>
<td>aGVHD N= 1 (1.9 %)</td>
<td>Relapse N= 1 (1.9 %)</td>
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<td>AML</td>
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Table 4: Transplant-related mortality by diagnosis.
Table 5: Transplant related morbidity by diagnosis.

<table>
<thead>
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<th>Diagnosis</th>
<th>CMV reactivation</th>
<th>Hemorrhagic cystitis</th>
<th>Neutropenic sepsis</th>
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<tr>
<td></td>
<td>N=10 (19.2%)</td>
<td>N=9 (17.3%)</td>
<td>N=15 (28.8%)</td>
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<td>N=3 (5.7%)</td>
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<tr>
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<td>1</td>
<td>1</td>
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<tr>
<td>NHL</td>
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<td>1</td>
<td>1</td>
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</table>
Table 6: Transplant-related mortality by diagnosis.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Mortality 14/52 (26.9 %)</th>
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<tr>
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<td>Septic shock N= 11 (21.1 %)</td>
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<tr>
<td>AML</td>
<td>7</td>
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<tr>
<td>SAA</td>
<td>3</td>
</tr>
<tr>
<td>MDS</td>
<td>1</td>
</tr>
<tr>
<td>NHL</td>
<td></td>
</tr>
</tbody>
</table>
Figure (1): Cumulative incidence of grade II-III and III-IV aGVHD
Figure (2): Hazard function with aGVHD (Panel A) and CMV reactivation (Panel B)
Figure (3): CMV reactivation cumulative incidence

CMV

Cumulative incidence %

Days

CI = 19.2 %
Figure (4): Cumulative incidence of cGVHD
Figure (5): All patients overall and disease free survival
Figure 6: Hematological malignancies overall and disease free survivals
Figure 7: Aplastic anemia overall and disease free survivals
Figure (8): Cumulative incidence of NRM at 100 days and 1 year