ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Management of Chronic Graft-Versus-Host Disease by using memory T cells without depleted with Naive T-cell.

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ABSTRACT

"Graft-versus-host disease (GVHD)" is a serious risk that can develop after a transplant. Acute GVHD often shows up within 100 days, whereas chronic GVHD, which is similar to autoimmune illnesses, shows up later. Steroids are the mainstay of treatment, with alternative methods reserved for those who do not respond to steroids. Memory T cells are one of the investigational techniques that aim to reduce GVHD while also balancing immunological rebuilding. This study is focused on treatment for chronic GVHD by harnessing the potential of memory T cells while safeguarding naive T cells. A total of 150 patients from India, ranging in age from 1 to 60, were transplanted with allogeneic hematopoietic stem cells between 2022 and 2023 for the treatment of acute leukaemia and myelodysplastic syndrome. Aiming to manage chronic graft-versus-host disease while conserving naive T cells, the study centred on memory T cells. Optimal results were achieved through graft selection and individualised conditioning programmes that balanced the effects of graft-versus-leukemia and the avoidance of GVHD. An analysis of 150 patients of TN-depleted PBSC transplantation is presented in this work. The demographics, diagnoses, and treatment modalities of these individuals are diverse. This study's findings shed information on how recipient demographics affect outcomes like CMV serostatus and adverse occurrences. There was a high rate of overall and relapse-free survival at 5 years, demonstrating the procedure's efficacy despite the complications. This study concluded that using memory T cells without depleting naive T cells may reduce the incidence and severity of chronic graft-versus-host disease (cGVHD) after allogeneic hematopoietic stem cell transplantation.

Keywords: "Graft-versus-host disease (GVHD)", Post-transplantation memory T cells, Steroids, chronic graft-versus-host disease.

https://doi.org/10.33887/rjpbcs/2024.15.4.17

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ISSN: 0975-8585

INTRODUCTION

The most frequent side effect after donor stem cell transplant is graft-versus-host disease (GVHD), which presents a serious and perhaps fatal risk. This disease results from donor T cells attacking recipient cells, which sets off an immune response that attacks and destroys recipient organs. This immune-mediated attack, which can present as acute or chronic GVHD, has different clinical characteristics and temporal frames. The majority of the risks associated with GVHD arise in the first few months following transplantation, with early graft reaction being the most common. In contrast, long-term graft reactions pose a considerable long-term risk, increasing patient mortality, morbidity, and reduced quality of life [1].

GvHD is a major complication that can occur after receiving a stem cell transplant that can take two different forms: acute and chronic. The acute form, which manifests as fast alloreactivity, usually appears within the first 100 days after HSC. On the other hand, chronic GvHD presents with a complex multiorgan syndrome that is similar to autoimmune illnesses, but it appears later [2]. Skin tightening, liver problems, lung scarring, dry mouth, mouth sores, muscle inflammation, and tissue inflammation are all included in its clinical spectrum. In contrast to acute GvHD, the reason behind chronic GvHD remains uncertain. Some theories suggest it could stem from abnormal immune system recovery, leading to the emergence of T cells that attack the body's own tissues, or it may simply be an extension of acute GvHD [2].

Once HSCT is performed, acute GVHD usually occurs within the first 100 days, in contrast to long-term graft reactions, which appear later. Early graft reaction is mostly caused by donor T cells recognizing host antigens, which indicates an alloreactive response. On the other hand, chronic GVHD has characteristics similar to autoimmune disease and can occur either before or after acute GVHD. Chronic GVHD is typified by Th2 inflammation, while Th1 inflammation is primarily responsible for the understanding how acute GVHD develops. However, the inflammatory profiles of the two disorders are complex and overlap, making diagnosis difficult [3,4].

Handling chronic GVHD presents significant difficulties, especially in terms of treatment resistance and long-term consequences. There is a significant lack of standardization in the diagnosis and treatment of cGVHD, as evidenced by a survey conducted among transplantation programs [5]. Patients with modest or extensive disease symptoms have different prognoses; those with steroid-refractory cGVHD have an especially poor prognosis [6]. Therapeutic uncertainty is further compounded by the lack of widely accepted second-line therapy methods despite the disease's prevalence. In light of these complications, careful glucocorticoid treatment in conjunction with all-encompassing supportive care becomes essential for managing the complexity of cGVHD [5,6].

The current paradigm for treating cGVHD takes a multimodal approach. First, glucocorticoids—prednisone in particular—remain the main front-line treatment, to reduce immunological response and alleviate symptoms. A variety of second-line therapies, including Photopheresis outside the body, Rituximab treatment, Sirolimus therapy, Mycophenolate medication, Imatinib drug, Pentostatin treatment, Mesenchymal stem cell therapy, become available when persistent GVHD is shown to be unresponsive to steroids [7]. Additionally, new avenues for therapeutic study include boosting populations of regulatory T cells, specifically targeting B cells, or treating fibrotic processes linked to the pathophysiology of GVHD [8]. However the development of new treatment paradigms depends on how closely clinical trials are scrutinized, which means large-scale, painstakingly planned prospective studies are required to identify the best course of action. Simultaneously, a top aim is to carry out thorough correlative scientific studies, explaining the complex interaction between clinical results and systemic therapies, improving patient care and treatment algorithms in the field of managing chronic GVHD [7,8].

Because memory T cells can both protect vital immune system reconstruction and defensive responses against infections, they are being investigated as a potentially effective treatment for GVHD. Research demonstrates that retained T cells are less likely than naive T cells to induce GVHD while also promoting graft-versus-leukemia (GVL) responses without causing issues connected to GVHD. Studies on patients undergoing allogeneic hematopoietic stem cell transplantation (AHSCT) have shown that decreasing the count of inexperienced T cells from stem cell grafts can lower the occurrence of chronic GVHD while preserving the

transmission of functional T cell memory. However, a comprehensive investigation into the fundamental mechanisms and potential manipulation of memory T cells in the context of AHSCT is still required [9-11].
The aim of this study is to explore the effectiveness of memory T cells in the management of chronic graft-versus-host disease (cGVHD) following allogeneic hematopoietic stem cell transplantation. By harnessing the potential of memory T cells, the study seeks to address the limitations of current treatment approaches, particularly in patients who do not respond adequately to steroid therapy. Additionally, the research aims to assess the impact of memory T cell therapy on reducing the incidence and severity of cGVHD while preserving the function of naive T cells in transplant recipients. Through comprehensive investigation and evaluation, the study aims to contribute to the development of novel therapeutic strategies for improving outcomes in patients with cGVHD.

METHOD

Research Design

This study was conducted from December 2022 to November 2023 among 150 patients aged 1-60 with acute leukaemia or advanced myelodysplastic syndrome who participated in our hospital in India. This study employed a complete treatment approach to maximise patient outcomes after allogeneic hematopoietic stem (HCT) transplantation by managing chronic graft-versus-host disease (cGVHD) using memory T cells while maintaining naive T cells. Following a predefined protocol, every patient received pharmacologic immunosuppression and conditioning after hematopoietic cell transplantation (HCT). This treatment aimed to manage graft-versus-host reactivity and maintain favourable immune responses in a balanced manner. Also, participants received donor peripheral blood stem cell (PBSC) apheresis, which met strict cell selection requirements to assure graft quality and purity. The grafts underwent TN depletion to eliminate naive T cells while preserving memory T cells. They were thoroughly screened to satisfy the necessary criteria before being transplanted. The conditioning regimens employed in our study were tailored to accommodate the specific requirements and attributes of the recruited individuals. For example, the intense conditioning used in trials NCT00914940 and NCT01858740 included total body irradiation, thiotepa, and fludarabine. The purpose was to completely destroy the bone marrow and suppress the immune system as much as possible to promote successful transplantation and avoid the return of the disease. In contrast, trial NCT02220985 customised the conditioning method by considering the patient's age and comorbidities. It utilised an intermediate-intensity myeloablative conditioning regimen consisting of fludarabine, cyclophosphamide, thiotepa, and total-body irradiation. The customised conditioning regimens were designed to maximise the effectiveness of treatment while reducing the negative effects on health, especially in elderly individuals with preexisting health issues. This research also carefully selected the graft source and donor type. Participants in trial NCT00914940 were administered HLA-matched PBSC grafts from related donors (MRD) and were also given prophylactic tacrolimus to reduce the risk of graft-versus-host disease (GVHD). Trials NCT01858740 and NCT02220985 involved patients with either minimal residual disease (MRD) or HLA-matched unrelated donors (MUD). The patients were given graft-versus-host disease (GVHD) prophylaxis, which consisted of either tacrolimus plus methotrexate or tacrolimus plus mycophenolate mofetil. These tactics were designed to balance preventing graft-versus-host disease (GVHD) and retaining the beneficial effects of graft-versus-leukemia (GVL) to ensure the best possible outcomes for the recipients. Furthermore, our study followed institutional GVHD management norms by promptly starting systemic/topical corticosteroids, tacrolimus, and other drugs. Patient response and physician discretion defined systemic corticosteroid dose and tapering procedures, with constant monitoring to reduce treatment problems.

Inclusion and Exclusion Criteria

Inclusion

- The eligible patients were those who were referred for allogeneic hematopoietic cell transplantation (HCT) due to a high anticipated probability of relapse after receiving chemotherapy alone.
- Patients falling into 3 age groups patients aged as 14-55 years old, 0-21 years , and 0-60 years, respectively.

ISSN: 0975-8585

Exclusion

- Patients who cannot undergo allogeneic hematopoietic cell transplantation (HCT) due to significant organ failure or other medical issues judged incompatible by specialists.
- Prior allogeneic HCT patients may have specific medical considerations and consequences that could influence study results.
- Patients with acute leukemia or advanced myelodysplastic syndrome who did not satisfy their medical physicians' high expected chance of relapse after treatment alone.

Statistical analysis

Kaplan-Meier method for survival probability and cumulative incidence estimates with competing risks were used to examine associations such as acute GVHD and recurrence using a Cox proportional hazards model. The data were corrected for pertinent factors such as relapse-risk group and conditioning intensity. Statistical studies of clinical outcomes were conducted using R 3.6.0.

RESULTS

Table 1: Demographic characteristics of the Recipients studied

Characteristic	T_N-Depleted PBSC Recipients (n=150)
Median age, years (range)	36 (1-59)
Sex, No. (%)	
Male	70 (46.66%)
Female	80 (53.33%)
Performance status score, No. (%)b	
<_90	110 (73.33%)
< 90	40 (26.66%)

Table 2: Clinical details of PBSC Recipients

Characteristic	T_N-Depleted PBSC Recipients
Diagnosis, No. (%)	
Myeloid	70 (46.66%)
AML	70 (46.66%)
MDS with excess blasts	8 (5.33%)
Blastic plasmacytoid dendritic cell neoplasm	2 (1.33%)
CML with a history of myeloid blast crisis	3 (2.00%)
Mixed phenotype acute leukemia	7 (4.66%)
Lymphoid	70 (46.66%)
ALL	68 (45.33%)
CML with a history of lymphoid blast crisis	2 (1.33%)
Disease risk, No. (%)	
Standard-risk (CR1, no residual disease)	80 (53.33%)
High-risk (beyond CR1 and/or residual disease)	70 (46.66%)

Table 1 shows the demographic details of 150 Recipients who received “peripheral blood stem cells (PBSC)” that were depleted of TN. The beneficiaries' median age was 36, ranging from 1 to 59. There were 70

male recipients, which accounted for 46.66 % of the total, and 80 female recipients, which accounted for 53.33 % of the total. Performance status score was less than 90 for 110 (73.33%) and 40 (26.66%) awardees. Research participants' ages, sexes, and performance status scores were all varied, which may have been a significant confounding factor when assessing the efficacy of TN-depleted PBSC transplantation.

Table 2 outlines the diagnosis and illness risk of TN-depleted PBSC recipients. Most recipients had myeloid-related diseases, with 70 (46.66%) having acute myeloid leukemia (AML) and 8 (5.33%) having MDS with excess blasts. Blastic plasmacytoid dendritic cell neoplasm and CML with a history of myeloid or lymphoid blast crisis were other myeloid diagnoses. On the other hand, 68 recipients (45.33%) had acute lymphoblastic leukemia. 80 recipients (53.33%) were standard-risk, defined as first complete remission (CR1) with no residual disease, while 70 (46.66%) were high-risk, showing disease beyond CR1 and/or remaining disease. The range of diagnoses and illness risks in the study population may affect TN-depleted PBSC treatment techniques and results.

Table 3 shows donors, precondition regimens, and GVHD pharmacologic prophylaxis for TN-depleted PBSC transplantation. Donors included 80 receivers (53.33%) from matched related donors (HLA-MRD) and 70 recipients (46.66%) from matched unrelated donors. High-intensity conditioning was given to 100 participants (66.66%) and intermediate-intensity conditioning to 50 (33.33%). Participants received tacrolimus monotherapy, methotrexate, or mycophenolate mofetil for GVHD pharmacologic prophylaxis equally. This information highlights the range of donor sources, conditioning regimens, and GVHD prevention approaches that are utilised in TN-depleted PBSC transplantation. This variability is a reflection of the variation in treatment procedures that are utilised within the study population.

Table 3: T_N-depleted PBSC transplantation details

Characteristic	TN-Depleted PBSC Recipients
Donor, No. (%)	
HLA-MRD	80 (53.33%)
HLA-MUD	70 (46.66%)
Conditioning regimen, No. (%)	
High-intensity	100 (66.66%)
Intermediate-intensity	50 (33.33%)
GVHD pharmacologic prophylaxis, No. (%)	
Tacrolimus monotherapy	50 (33.33%)
Tacrolimus and methotrexate	50 (33.33%)
Tacrolimus and MMF	50 (33.33%)

HLA-MRD: Human Leukocyte Antigen - Matched Related Donor; HLA-MUD: Human Leukocyte Antigen - Matched Unrelated Donor; GVHD: Graft-Versus-Host Disease; PBSC: Peripheral Blood Stem Cell; MMF: Mycophenolate Mofetil

Table 4 shows TN-depleted peripheral blood stem cell (PBSC) transplanted graft parameters and CMV serostatus. The median number of CD34+ cells per kilogram of recipient body weight was 7.9 (range: 2.9-18.5), while the median number of CD3+ cells was 9 (range: 1.5-9.8). The median TN (CD31-CD45RA+CD45RO-) cell infusion per kilogram was 0.24 (range: 0.02-7.39). CMV-positive recipients were 100 (66.66%). These parameters reveal the infused transplantation's cellular cosmetics and recipients' CMV serostatus. Cell counts and TN cell percentages suggest that recipient graft potency and immune reconstitution may affect transplant outcomes and CMV reactivation.

ISSN: 0975-8585

Table 4: Graft characteristics and CMV serostatus in TN-depleted PBSC transplantation

Graft characteristics, No. of cells, median (range)	
CD341 3 106/kg	7.9 (2.9-18.5)
CD31 3 106 /kg	9 (1.5-9.8)
CD31CD45RA1 CD45RO2 (TN) 3 104 /kg	0.24 (0.02-7.39)
CMV serostatus, No. (%)	
CMV-seropositive	100 (66.66%)

Table 5 shows recipient-donor CMV, recipient EBV, and protocol-based recipient distribution. Most TN-depleted peripheral blood stem cell (PBSC) recipients were recipient-positive and donor-positive for CMV, but 40 (26.66%) were recipient-positive and donor-negative. CMV-seronegative recipients (40 [26.66%]) had never been infected. In addition, 15 recipients (10.00%) were recipient-negative and donor-positive for CMV, while 30 (20.00%) were both. Four recipients (2.66%) exhibited inconsistent CMV serostatus. One hundred thirty-three receivers (86.66 percent) were positive for EBV serostatus, while thirteen point three percent tested negative. The bulk, 80 beneficiaries (53.33%), were enrolled in procedure NCT02220985, followed by 45 (30.00%) in NCT00914940 and 25 (16.66%) in NCT01858740. These findings shed light on the recipients' immunological profiles, their risk for CMV and EBV-related problems, and how they were distributed among different clinical protocols. These factors could impact treatment outcomes and the overall conclusions drawn from the research.

Table 5: Recipient-donor CMV, recipient EBV, and protocol-based recipient distribution.

Characteristic	TN-Depleted PBSC Recipients
Recipient-positive, donor-positive	60 (40.00%)
Recipient-positive, donor-negative	40 (26.66%)
CMV-seronegative	40 (26.66%)
Recipient-negative, donor-positive	15 (10.00%)
Recipient-negative, donor-negative	30 (20.00%)
CMV serostatus equivocal (recipient)	4 (2.66%)
EBV serostatus, No. (%)	
Recipient-seropositive	130 (86.66%)
Recipient-seronegative	20 (13.33%)
Number of patients in each age group, No. (%)	
Age group 14-55 years	45 (30.00%)
Age group 0-21 years	25 (16.66%)
Age group 0-60 years	80 (53.33%)

Figure 1 has shown that the cumulative incidence of Grade 3 and Grade 4 events over a period of time. At the onset of observation, there were 2 instances of Grade 3 events recorded. As time progressed over the course of 1 year, the cumulative number of Grade 3 events increased to 3. However, throughout the entire duration of the observation period, spanning from 0 to 1 year, there were no reported Grade 4 events. This indicates a notable occurrence of Grade 3 events within the specified timeframe, with a modest cumulative

ISSN: 0975-8585

increase observed over the course of the year. Conversely, Grade 4 events remained absent throughout the observation period, suggesting a distinct pattern of incidence between Grade 3 and Grade 4 events.

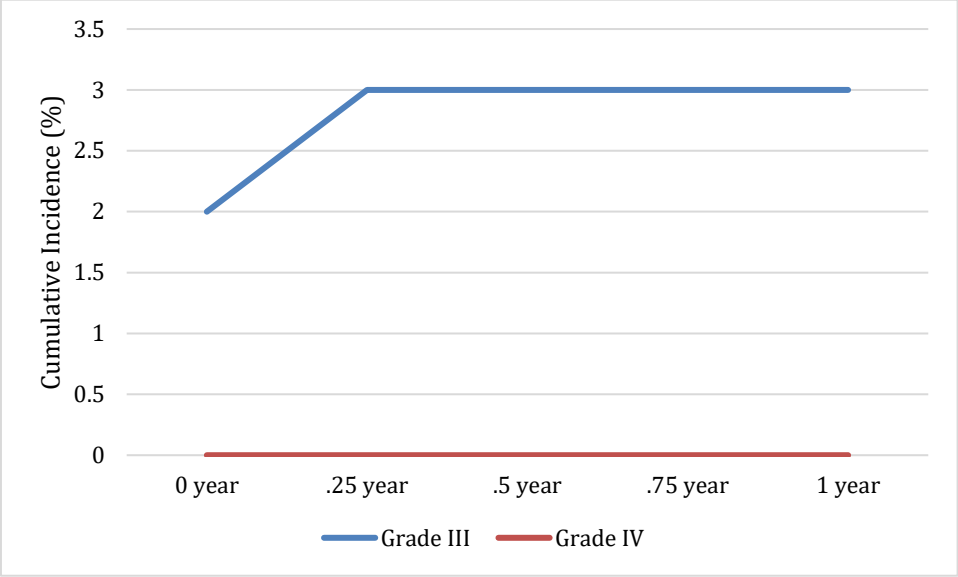


Figure 1: Cumulative Incidence of the Grade 3 and 4

Table 6 illustrates the average frequency of events and the probability of overall survival (OS) and relapse-free survival (RFS) during a 5-year period. The table shows that at the start of the period under scrutiny (time 0), the cumulative incidence of events and the possibility of both OS and RFS were 0%, the significance of no events had occurred, and the probability of survival was 100%. Event incidence grew gradually throughout the 5-year period, reaching 26%. Thus, OS ranged from 75% to 80%, while RFS stayed at 75% throughout the observation period despite this rise. This implies that while some events happened over time, the overall survival and relapse-free survival probability were relatively robust, indicating excellent outcomes for the observed group despite the prevalence of events.

Table 6: Cumulative incident frequency and 5-year OS and RFS probabilities.

Time (years)	Cumulative Incidence (%)	OS (probability)	RFS (probability
0	0	100	100
1	24.5	80	75
2	25	76	75
3	25.5	75	75
4	26	75	75
5	26	75	75

Table 7 shows the chance of CRFS, GVHD-free, GRFS, and aggregate event occurrence over five years. At time 0, the odds of CRFS and GRFS were 100%, indicating no occurrences, and these survival outcomes were 100%. The chances of CRFS and GRFS declined during the five years, reaching 72–75% at the study's conclusion. Also, by the end of the observation period, the total incidence of incidents had climbed to 6%. While CRFS and GRFS probability fell over time, showing some events happened, a large proportion of the studied

group maintained chronic relapse-free survival and GVHD-free, relapse-free survival status during the 5-year period.

Table 7: The chance of CRFS, GVHD-free, GRFS, and aggregate event occurrence over 5 years.

Time (years)	CRFS (probability	GRFS (probability)	Cumulative Incidence (%)
0	100	100	0
1	75	75	4
2	75	75	5
3	74	75	6
4	73	75	6
5	72	74	6

Table 8 shows the 6-year probability of chronic relapse-free survival (CRFS) by donor type and illness subtype. All groups had a 100% chance of CRFS at time 0, indicating no incidents. The probability of CRFS reduced across all groups as relapse and disease progression occurred. Recipients with linked donors had a 98%–75% chance of CRFS after six years throughout the same period. High-risk recipients had somewhat lower CRFS probability than intermediate-risk lymphoid or myeloid recipients. The probability of CRFS declined over time for all groups, but recipients with related donors had slightly higher probabilities than those with unrelated donors, and disease subtype influenced CRFS probabilities over the 6-year observation period.

Table 8: 6-year probability of chronic relapse-free survival (CRFS)

Year	Related	Unrelated	High	Intermediate	Lymphoid	Myeloid	Female	Male
1	100	100	100	100	100	100	82	56
2	98	97	97	94	97	94	63	39
3	75	75	80	75	80	75	48	35
4	75	75	74	71	73	70	39	31
5	75	73	75	73	74	72	30	22
6	75	73	75	72	74	71	17	17

Figure 2 showed the relative risks of relapse in naive T cell-depleted peripheral blood stem cell recipients who developed acute graft-versus-host disease (grade II-III) compared to those who did not. These risks are presented across various patient subgroups and donor types in the context of hematopoietic cell transplantation (HCT). Overall, the hazard ratio for relapse in all patients who developed acute graft-versus-host disease (GVHD) compared to those who did not is 0.27, indicating a substantially lower risk of relapse in this population.

When examining specific patient subsets, the hazard ratios vary:

- Myeloid recipients exhibit a hazard ratio of 0.35, indicating a slightly higher relative risk of relapse compared to the overall average.
- Lymphoid recipients have a hazard ratio of 0.45, suggesting a higher risk of relapse compared to myeloid recipients but still lower than the overall average.
- Patients receiving stem cells from matched related donors (MRD) have a hazard ratio of 0.36, indicating a lower risk of relapse compared to the overall average.

- Patients receiving stem cells from matched unrelated donors (MUD) have a hazard ratio of 0.41, suggesting a slightly higher relative risk of relapse compared to MRD recipients.

Furthermore, the data also consider additional factors such as conditioning regimen intensity and risk stratification:

- Patients receiving intermediate conditioning have a hazard ratio of 0.32, indicating a lower risk of relapse compared to those receiving high conditioning or standard risk conditioning.
- High conditioning and standard risk patients have similar hazard ratios of 0.33 and 0.3, respectively.
- Patients classified as high risk have a hazard ratio of 0.31, suggesting a lower risk of relapse compared to those classified as standard risk.
- Patients with no matched related donor (No MRD) have a hazard ratio of 0.39, indicating a slightly higher relative risk of relapse compared to MRD recipients.
- Patients with MRD pre-HCT have the lowest hazard ratio of 0.2, indicating the lowest risk of relapse among all subsets, suggesting that having a matched related donor before transplantation confers a protective effect against relapse. Overall, these hazard ratios provide valuable insights into the relative risks of relapse in various patient and donor subgroups, helping to inform clinical decision-making in the context of hematopoietic cell transplantation. Figure 2 has shown that the relative risks of death in naive T cell-depleted peripheral blood stem cell recipients who developed acute graft-versus-host disease (GVHD) grade II-III compared to those who did not. These risks are evaluated across various patient subgroups and donor types in the context of hematopoietic cell transplantation (HCT).

Overall, the hazard ratio for death in all patients who developed acute GVHD compared to those who did not is 0.25, indicating a substantially lower risk of mortality in this population.

When examining specific patient subsets, the hazard ratios vary:

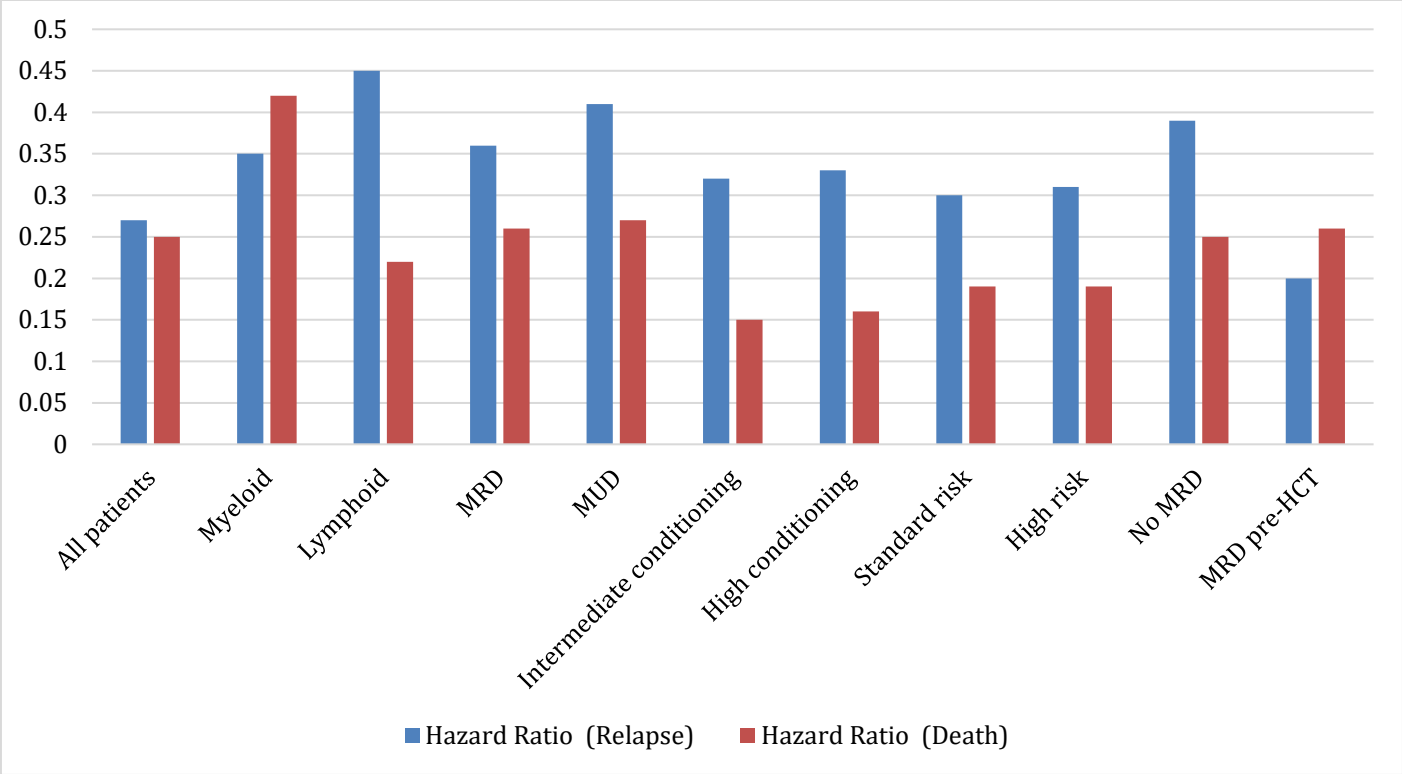
- Myeloid recipients exhibit a hazard ratio of 0.42, indicating a higher relative risk of death compared to the overall average. This suggests that myeloid recipients who develop acute GVHD may face a greater mortality risk.
- Lymphoid recipients have a hazard ratio of 0.22, indicating a significantly lower risk of death compared to myeloid recipients and even lower than the overall average. This suggests that lymphoid recipients who develop acute GVHD have a particularly favorable prognosis in terms of mortality.
- Patients receiving stem cells from matched related donors (MRD) have a hazard ratio of 0.26, indicating a lower risk of death compared to the overall average. This suggests that having a matched related donor may confer a protective effect against mortality.
- Patients receiving stem cells from matched unrelated donors (MUD) have a hazard ratio of 0.27, suggesting a slightly higher relative risk of death compared to MRD recipients but still lower than the overall average.

Furthermore, the data consider additional factors such as conditioning regimen intensity and risk stratification:

- Patients receiving intermediate conditioning have the lowest hazard ratio of 0.15, indicating a significantly lower risk of death compared to other conditioning regimens. This suggests that intermediate conditioning may be associated with better outcomes in terms of mortality.
- Patients receiving high conditioning and standard risk patients have similar hazard ratios of 0.16 and 0.19, respectively.
- Patients classified as high risk also have a hazard ratio of 0.19, indicating a lower risk of death compared to standard risk patients.
- Patients with no matched related donor (No MRD) have a hazard ratio of 0.25, indicating a slightly higher relative risk of death compared to MRD recipients.
- Patients with MRD pre-HCT have a hazard ratio of 0.26, indicating a similar risk of death compared to MRD recipients.

ISSN: 0975-8585

Overall, these hazard ratios provide valuable insights into the relative risks of mortality in various patient and donor subgroups, aiding in risk stratification and clinical decision-making in the context of hematopoietic cell transplantation.



MRD, Matched Related Donors; MUD, Matched Unrelated Donors; HCT, Hematopoietic Cell Transplantation

Figure 2: Comparing Relative Risks of Relapse and Mortality in patients with Naive T Cell-Depleted Peripheral Blood Stem Cell Recipients With Acute Graft-versus-Host Disease (Grade II-III) Versus Those Without

DISCUSSION

Research indicates that memory T cells may be able to help manage cGVHD, a potentially dangerous consequence. More specifically, research indicates that memory CD4+ T cells may be less likely to cause GVHD, which may be a potential target for therapeutic intervention [12]. This idea is further supported by clinical studies that show a significantly reduced incidence of chronic GVHD in patients transplanted with naive T cell-depleted stem cell transplants than in patients treated with traditional methods [10]. These results highlight memory T cells' capacity to lessen the effects of chronic GVHD after transplantation. Nevertheless, to fully realize their therapeutic potential, a thorough investigation and comprehension of the processes underpinning memory T cell-mediated effects in addressing long-term graft reactions are essential [10,12].

HSCT recipients face serious and frequently deadly consequences from GVHD. Acute GVHD post-HSCT is rare and affects a significant percentage of recipients, even with preventive measures such as immunosuppressive drugs. Similarly, a sizable fraction of cases develop chronic GVHD, which further exacerbates the complications associated with transplant outcomes. Standard therapy solutions remain elusive despite advances in pathology, diagnostic procedures, and predisposing factors awareness [13].

By reducing alloreactive T cell responses, new therapeutic approaches that target immune cells—such as suppressor T cells, tolerant dendritic cells, bone marrow-derived stromal cells—offer encouraging relief.

Furthermore, monoclonal antibodies that target signaling molecules or cytokines may be able to prevent GVHD, while further research is needed to confirm their clinical usefulness. The significance of customized care is important to pay attention to GVHD subtypes, underlying pathogenic processes, and disease phases. In the future, the discovery of new therapeutic targets and the application of methodical research techniques may lead to the creation of secure and efficient treatments, which would eventually improve management outcomes for GVHD [13].

Through a variety of ways, memory T cells could offer defense against cGVHD. Interestingly, memory stem cells—a subpopulation of Quiescent CD8(+) T cells with low CD44 and high CD62L expression—maintain many diverse T cell populations from a different source implicated in GVHD responses, these encompass effector memory, central memory, and effector CD8(+) T cells, with self-renewal capabilities [14]. Furthermore, Th17/Th1-mediated chronic GVHD is lessened by the host tissues' the PD-1 checkpoint pathway [15]. The beneficial role of memory T cells in this context is also underscored by the strong connection with the presence of T helper cells producing interleukin 2 specific to the host and active primary and secondary cGVHD. When taken as a whole, these complex processes highlight memory T cells' ability to slow the onset and course of cGVHD [16].

Studies emphasize how the GVL effect plays a critical role as an important immunological process that reduces the chance of leukemia returning after bone marrow transplant. Although GVL efficacy differs among hematological malignancies, GVL and GVHD are known to be associated [17]. Across a range of hematological malignancies, this phenomenon has been observed, with differing degrees of effectiveness: in acute lymphoblastic leukemia (ALL), it is notably absent or minimal; in acute myelogenous leukemia (AML), it is approximately 30% effective; and in chronic myelogenous leukemia (CML), it is approximately 40% effective [18,19].

In the management of cGVHD, using memory T cells while keeping naive T cells may improve long-term results. Research suggests that memory T cells are less prone to activation compared to naive T cells to cause GVHD, which lowers the chances of cGVHD while maintaining functioning T cell memory transfer. With no increased risk of GVHD induction, this strategy may help with post-transplant immune reconstitution. To completely understand the efficacy profile and long-term effects of this novel tactic, however, in-depth research is necessary [12,20].

The promise of memory T cell-based therapies to prevent and treat GVHD has drawn interest. These strategies show potential for enhancing clinical outcomes by specifically targeting T cells linked to GVHD while maintaining those specific to infections. To precisely define the lasting impacts of memory T cell-based treatments on the continuation of life, standard of life, and incidences of c GVHD recurrence, more research is nevertheless required. Notably, studies have shown that these strategies are efficient in reducing the number of novice T cells while preserving populations of immune cells with pathogen specificity [10].

Research on the best ways to optimize combination, timing, and dosage therapies for memory T cell-based tactics is still being done. Research has indicated that brief stimulation with anti-CD3/CD28 along with IL-21 can boost the generation of human memory stem cells, increasing their frequencies and proliferation for use in adoptive cell therapy for cancer treatment. Nevertheless, more research is required to identify the most effective scheduling schemes, dosage schedules, and synergistic combination treatments [21]. Further data highlights the importance of memory CD8(+) T cells in predicting outcomes for cancer patients receiving immunotherapy; higher levels are significantly linked with improved progression-free and overall survival rates [22].

This demonstrates how retained CD8(+) T cells may function as indicators of prognosis for memory T cell-based therapy response. However, there is still work to be done in developing tailored treatment plans and patient selection criteria for memory T cell-based therapies. Notably, the identification of memory CD8(+) T cells is promising in the context of clinical practice, indicating that these cells may be targets for individualized immunotherapy-based treatment plans for cancer patients. However, more investigation is needed to define precise patient selection standards and improve individualized treatment plans for memory T cell-based therapies [21,22].

Current efforts are being made to improve memory T cell-based therapy for GVHD by investigating new targets and approaches. Targeting immune cells that have the potential to prevent GVHD, such as uppressor T cells, immune-regulatory dendritic cells, and engineered antibodies, are promising approaches. Moreover, the incorporation of memory T cell-based tactics into traditional GVHD therapy methods is gaining traction. These methods have shown effectiveness in boosting immunological reconstitution and preventing GVHD at the same time. Still, more clarification through continued research projects is needed for the clinical use of these novel approaches [11-13].

CONCLUSION

This study concluded that using memory T cells without depleting naive T cells may reduce the incidence and severity of chronic graft-versus-host disease (cGVHD) after allogeneic hematopoietic stem cell transplantation. Single-arm phase II studies have limitations. However, our findings show a considerable reduction in cGVHD rates compared to standard techniques. The success of this technique suggests it could reduce post-transplant cGVHD problems. However, more study, particularly RCTs, is needed to confirm these findings, understand the effects on long-term outcomes, including recurrence and survival, and compare it to standard management. These studies will reveal the feasibility and efficacy of memory T cell-based cGVHD management techniques, improving allogeneic HCT patient care and outcomes. The study addresses a critical gap in the management of chronic graft-versus-host disease (cGVHD) after allogeneic hematopoietic stem cell transplantation. While steroids remain the mainstay of treatment for GVHD, alternative approaches are necessary for patients who do not respond adequately to steroid therapy. The investigation of memory T cells as a potential treatment modality for cGVHD represents an innovative approach to address this gap. However, the specific mechanisms underlying the efficacy of memory T cells in mitigating cGVHD and the long-term outcomes of this approach require further elucidation. The findings of this study pave the way for future research aimed at refining the use of memory T cells in the management of cGVHD. Further studies are needed to explore the optimal protocols for memory T cell therapy, including the selection and manipulation of memory T cells, dosing regimens, and timing of administration post-transplantation. Additionally, investigating the long-term safety and efficacy of memory T cell therapy in larger patient cohorts will be essential for establishing its role as a standard therapeutic approach for cGVHD. Moreover, understanding the interplay between memory T cells and other immune cells, as well as their impact on graft-versus-leukemia effects and overall immune reconstitution, will be crucial for maximizing the therapeutic potential of memory T cell-based interventions in the context of allogeneic hematopoietic stem cell transplantation.

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