Documenta Haematologica -
Revista Romana de Hematologie | 2024, Vol. 2, Nr. 1

https://doi.org/10.59854/dhrrh.2024.2.1.13

– ORIGINAL PAPERS –

Allogeneic Stem Cell Transplantation in Treatment of Refractory/Relapsed Lymphomas

Valeria BERESTEANU[2*], Elizabeta LUPU[2], Roxana DUMITRU[2], Elena PELIN-DOLACHI[2], Ion ANTOHE[1,2], Angela DASCALESCU[1,2]

Abstract

Aim: *To assess the outcome of allogeneic stem cell transplantation in patients with refractory/relapsed lymphoma.*

Methods: *Between 2021 and 2023, 6 patients with refractory/relapsed (R/R) lymphoma underwent allogeneic stem cell transplantation at the Bone Marrow Transplant Department of Regional Institute of Oncology Iasi- 4 with Hodgkin lymphoma (HL), 1 with primary mediastinal large B-cell lymphoma (PMBCL) and 1 with Mycosis fungoides (MF). All patients received reduced intensity conditioning chemotherapy, combining Fludarabine, Busulfan or Melphalan. The prophylaxis of graft-versus-host-disease (GVHD) was made with Cyclophosphamide (n=4), Tacrolimus and Mycophenolate mofetil (n=5), Cyclosporine (n=1).*

Results: *The post-transplant evolution of the patients was marked by infectious complications (n=5), digestive mucositis (n=4) and viral reactivations (n=4). One patient with HL had acute cutaneous and hepatic graft-versus-host disease(GVHD) and two had chronic hepatic and intestinal GVHD. Imaging evaluation by PET-CT on day +100 shows a complete response in three patients with HL and progressive disease in the patient with PMBCL and one patient with HL.*

Conclusion: *Despite the introduction of increasingly effective treatment options for R/R lymphoma, transplantation continues to play an important role in the management of these patients. Allogeneic transplantation is an effective therapy for advanced aggressive lymphoma, limited by treatment-related toxicity and mortality.*

Keywords: *Lymphoma, allogeneic stem cell transplantation, graft-versus-host-disease, infectious complications, outcome.*

[1]Department of Hematology, "Grigore T. Popa" University of Medicine and Pharmacy, Iasi, Romania

[2]Department of Hematology, Regional Institute of Oncology, Iasi, Romania

Corresponding author:
***Valeria Beresteanu,** MD, Resident Doctor, Hematology Clinic, Regional Institute of Oncology, 2-4 General Berthelot street, Iasi, Romania
email: valeriaevtodiev@gmail.com

Introduction

Allogeneic hematopoietic stem cell transplantation (alloHSCT) is a known curative therapeutic option for a variety of hematologic and immunologic conditions [1]. The role of allogeneic transplantation for lymphoma is continually redefined as a result of advances in conventional treatments, in transplant technology, in diagnostic methods and in prognostic tools. The use of alloHSCT to treat lymphoma is increasing in patients with high-risk and relapsed/refractory disease and is usually

considered in the salvage setting, as an alternative to autologous stem cell transplantation or after failure of autologous transplantation [1,2]. The growing interest in alloHSCT arises from its possible benefit to induce an immune-mediated graft vs lymphoma effect (GVL). This effect has been confirmed by lower relapse rates in patients who have developed graft vs host disease (GVHD) after alloSCT. In recent years, new strategies using haploidentical donor (HID) have also reinforced this hypothesis [3]. However, a similar effect where graft acting against the recipient's cells, such as graft versus host disease, leads to an undesirable outcome. Graft versus host disease still remains a predominant cause of morbidity and mortality in patients following hematopoietic stem cell transplantation [4].

Methods

T We conducted a retrospective analysis of 6 patients (2 women, 4 men) with a median age at diagnosis of 32 years (20-39), with refractory or relapsed (R/R) classic Hodgkin lymphoma (HL) (n=4) and non-Hodgkin lymphoma (NHL)- Mycosis Fungoides (MF) (n=1) and primary mediastinal B cell lymphoma (PMBCL) (n=1), who received alloHSCT between 2021 and 2023 in the Bone marrow transplant Department from Regional Institute of Oncology, Iasi, Romania.

We analyzed patients' variables, such as age, gender, performance status (PS), previous treatment (including numbers of chemotherapy lines and previous autologous transplant), and disease status at the time of transplant. Variables related to the transplant procedure were the year of transplant, stem cell source, type of donor, GVHD prophylaxis, and conditioning regimen. Variables related to the transplant complications were acute and chronic GVHD and infectious complications. The disease status at the time of alloHSCT was evaluated by positron emission tomography (PET) and by clinical criteria in the patient with Mycosis Fungoides.

First-line chemotherapy consisted of ABVD (adriamycin, bleomycin, vinblastine, dacarbazine) in patients with Hodgkin lymphoma, Gemcitabine in patients with MF and RCHOP (rituximab, cyclophosphamide, doxorubicine, prednisolone) in a patient with PMBCL. Subsequent salvage lines included different combined regimens. Three patients received adjuvant-involved field radiotherapy. Autologous stem cell transplantation (ASCT) was performed in three patients after a median of 19 months from diagnosis (range 17–41). The median number of treatment lines before ASCT was 4 (range 3–4). The conditioning consisted of LEAM (lomustine, cytarabine, etoposide, melphalan).

Results

Pre-transplant data

Our case series included young patients with a median age before alloHSCT of 38 years (range 22-42), with good PS. All the patients were assessed for EBMT and HCT-CI score. According to EBMT score, 5 of the patients were included in the high risk, with an estimated 5-year overall survival (OS) of 33% and transplant-related mortality (TRM) of 41%. At the time of alloHSCT all 6 patients achieved partial response (PR) – 5 based on PET images and 1 patient by clinical evaluation.

Transplant data

The median time from diagnosis to alloSCT was 43 months (range 30–135). The patients exhibited the following lymphoma status at transplant: complete response (CR) (n = 1), partial response (n = 5). All six patients were transplanted with peripheral blood stem cells. Five patients received grafts from identical siblings (MRD, 12/12) and one from an unrelated donor (MUD, 12/12). All transplanted patients were given reduced-intensity chemotherapy (RIC), usually fludarabine-based: FluBu2 (n=2), FluMel100 (n=3) and FluMel140 (n=1). Graft versus host disease prophylaxis consisted of cyclosporine (n=1), tacrolimus (TAC) + mycophenolate mofetil (MMF) (n=1), post-transplant cyclophosphamide (PTCy) + TAC + MMF (n=4). The complications that appeared in the immediate post-transplant period were manageable, with a favorable response to specific treatment. Almost all patients had febrile neutropenia (n=5) which required broad-spectrum antibiotic therapy, and orodigestive mucositis (n=5) requiring parenteral nutrition, hydro-electrolyte rebalancing and analgesic treatment, including opioids. And one patient presented the moderate form of hepatic veno-occlusive disease. The following infectious complications were demonstrated in the early post-transplant period: enterocolitis with clostridium difficile (n = 2), sepsis with Escherichia coli (n = 1), urosepsis with Klebsiella oxytoca (n = 1). No deaths were noted up to day +100 after alloHSCT. Details on transplant data are presented in Table 1

Parameter	N=6
Median age of recipient at transplant; years, range	38 years (22-42)
Disease status at alloHSCT, n CR PR	 1 5
Type of donor, n MRD MUD	 5 1
Donor-recipient sex matching, n, Donor male-recipient female Donor female-recipient male Sex matching	 2 0 4
ABO-blood group matching, n, Matched Minor mismatch Major mismatch Bi-directional	 4 0 2 0
Type of conditioning, n FluBu2 FluMel100 FluMel140	 2 3 1
GVHD prophylaxis, n Cyclosporine TAC + MMF PTCy + TAC + MMF	 1 1 4
Median ANC>0.5 (x10^9/L), days, range	18 days (14–21)
Median PLT >20 (x10^9/L), days, range	21 days (14–30)

Table 1. Transplant details.

Post-transplant Outcome

All the patients were engrafted after a median of 18 days (range 14–21). Platelet count of >20 × 109/L was demonstrated after a median of 21 days (range 14–30). A total of four transplanted patients developed acute and chronic GVHD, respectively. Two subjects demonstrated acute GVHD grade I-II whereas late-onset acute GVHD was observed in two. The real challenge in the post-transplant period consists in maintaining the balance between the effect of graft versus host disease and graft versus lymphoma, so as to minimize the risk of relapse of the disease through immunosuppression of T lymphocytes (Figure 1).

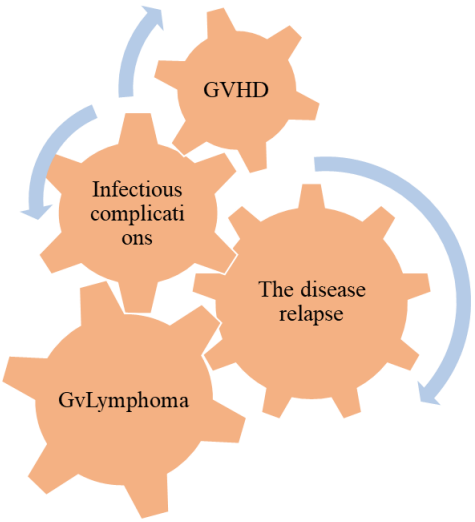

Figure 1. The interdependence between the infectious complications, graft versus host disease and the need for prolonged and combined immunosuppressive treatment, which increases the risk of losing the effect of the graft against lymphoma with the relapse of the disease.

Post-allograft disease assessment on day +100 was performed and CR was achieved in 4 patients, and 2 patients demonstrated disease progression. Median follow-up for the entire cohort was 9 months (range 5–31). In total 3 patients died – the patient with PMBCL and one patient with HL died from lymphoma progression, and the patient with MF died from severe infections. At the last follow-up, three patients were alive and maintained CR at 26 months, 24 months and 5 months from alloHSCT. All these patients had full donor chimerism at day +30 and day +100. The main post-transplant complications after day +30 and the applied treatment are presented in Figure 2.

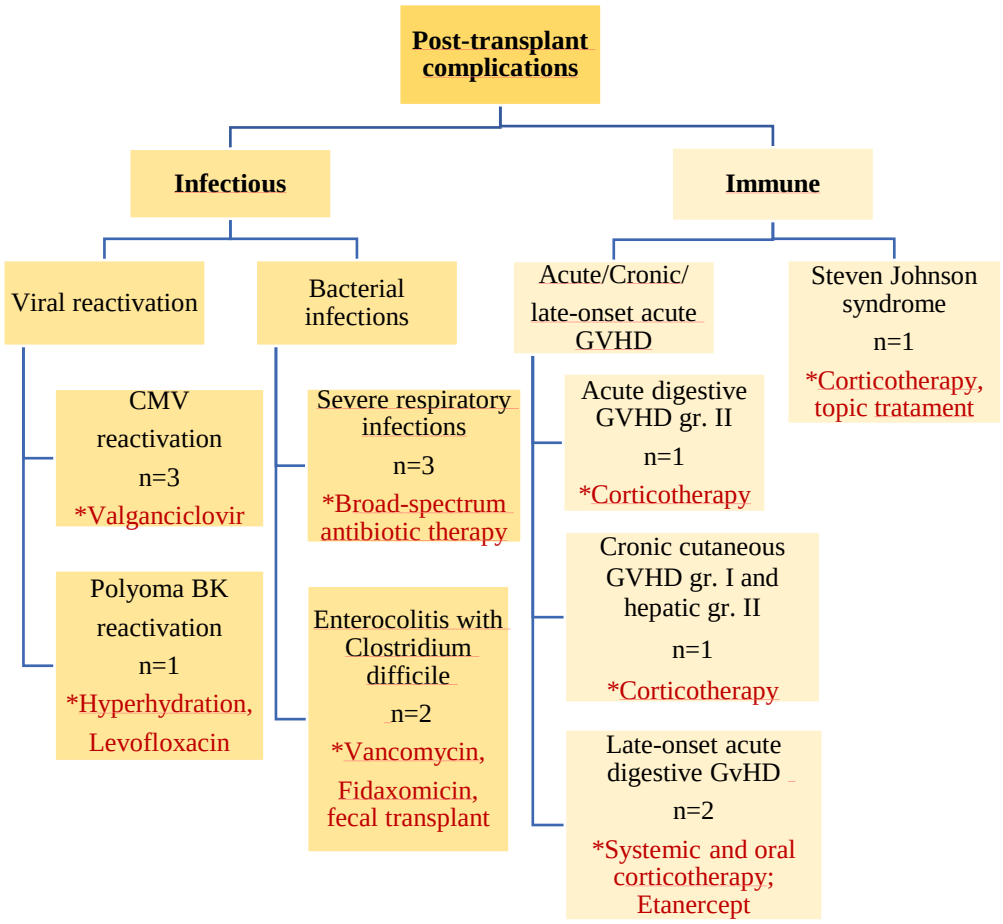

Figure 2. Post-transplant complications.

Discussion

The prognosis of patients who relapse after ASCT is poor [5]. A study of outcomes in 756 relapsed patients receiving ASCT before 2007 demonstrated a median post-progression survival of 1.3 years; the majority of patients had poor long-term outcomes, with approximately 10% surviving at 10 years [7]. The development of new drugs for relapsed/refractory lymphomas as monoclonal antibodies, checkpoint inhibitors, chimeric-antigen-receptor (CAR)-T cells for specific histological subtypes, has challenged the role of allogeneic transplant in this setting. Despite the high overall response rates achieved with new drugs, long-term outcome is still a matter of debate due to the short follow-up of these studies and the lack of principle of representing a curative procedure. So alloHSCT still represents the most powerful curative tool for patients with R/R lymphomas, even if the rates of non-relapse mortality (NRM) remain high. Therefore, choosing the right timing and integrating new therapeutic options with alloHSCT is a matter of debate [6].

Myeloablative conditioning (MAC) has historically been the preferred conditioning intensity for aggressive

hematologic malignancies, but it showed a high rate of NRM with a low probability of 3-year OS. A retrospective EBMT study on 168 HL patients compared the outcomes of RIC vs. MAC and it was found that the latter was associated with significantly higher NRM which translated into lower OS [5,8]. This is partially related to the idea of overcoming chemoresistance by increasing the total systemic dose to the highest possible amount while avoiding significant damage to organs other than the marrow. This practice in turn restricted the utilization of alloHSCT to fit and young patients, as high morbidity and mortality are associated with this approach. The development of RIC is a major landmark in the progress of the transplant field. It expanded the eligibility to many more patients and highlighted the anticancer properties of a healthy donor immune system [5]. There may be differences in outcome due to more or less intensive regimens, but overall outcome is affected considerably more by patient and disease related characteristics [2].

AlloHSCT is associated with significant toxicities, including graft-versus-host disease, which could increase non-relapse mortality risk by causing chronic morbidity and late deaths. GVHD, and especially chronic GVHD, has been shown to be associated with a lower risk of relapse, which may reflect the benefits of graft-mediated immune surveillance in the prevention of lymphoma relapse [5]. But chronic GVHD and/or its treatment are the major risk factors for many late complications including infertility, early menopause, osteonecrosis, chronic pulmonary and cardiac problems and increased risk for skin cancer. Transplant patients in remission face an ongoing risk of death that well exceeds that of an age-matched population and chronic GVHD is a major risk factor for late death after transplant [5, 7].

In the pathogenesis of acute GVHD, it has been established that donor-derived T-cells activated in the recipient play a major role in GVHD initiation and maintenance within a complex inflammatory cascade. To reduce the risk of GVHD, intensification of GVHD prophylaxis such as profound T-cell depletion is effective, but it inevitably increases the risk of infectious diseases and abrogates beneficial GVL effects [13]. Patients who develop aGVHD experienced ~60% more infections than patients who never develop aGVHD [12]. Infectious diseases can theoretically contribute to an elevation of inflammatory cytokines after alloHSCT. Possible interactions between viral infections and graft rejections of transplanted organ or GVHD are thought to be mediated by the alloreactivity of virus-specific T-cells. Bacterial infection can also induce GVHD rather non-specifically, considering the induction of systemic proinflammatory cytokines [13].

Similar to the graft-versus-leukemia effects seen in myeloid neoplasms, a graft-versus-lymphoma effect was described by several groups [5]. The most definitive evidence of graft vs lymphoma effects remains the clinical observation of lymphoma regression after withdrawal of immunosuppression or after infusion of donor lymphocytes. The existence of a GVL effect is also supported by the evidence of a reduced incidence of relapse for patients with Hodgkin and non-Hodgkin lymphoma after alloHSCT (ranging between 6% and 29%) relative to autologous transplant (ranging between 35% and 69%) [6]. In one retrospective study by the EBMTR, a lower recurrence rate was found for patients with chronic GVHD vs those without cGVHD (0% vs 35%, p=0.02) [5]. Besides the presence of GVL effects, the lack of involvement by lymphoma cells in the graft, may also contribute to a decreased recurrence rate after allogeneic transplantation [2]. Moreover, the fact that reduced-intensity conditioning transplants can induce remissions in relapsed or refractory disease is a good illustration of the strength of GVL [5].

Haplo-SCT with PTCy as GVHD prophylaxis is a promising platform to cure patients with R/R lymphoma when a HLA identical donor, either matched related or matched unrelated, is not available. Moreover, compared with a MUD transplant, Haplo-SCT has important advantages such as better timing to find a donor and increased chances of post-transplant immune-modulation [10]. Risk factors affecting the outcome of this category of patients are similar to the well-known variables identified in the setting of allogeneic transplant from other donor types. The two large studies by Ghosh and Kanate found that both disease-related factors, such as pre-transplant disease status (being not in CR), intermediate or high disease-risk index, histology different from follicular lymphoma, bulky or extranodal disease and patient-related factors, such as age, Karnofsky performance status, HCT-CI score, were the main independent variables affecting OS, PFS and NRM [6]. Post-transplantation cyclophosphamide–based haplotransplantation results in similar survival outcomes compared with MRD and MUD, which confirms its suitability when no conventional donor is available and also is associated with a lower risk of chronic GVHD than MUD transplantation [10, 11].

Approximately 10 to 20% of lymphomas are of T-or NK-cell lineage and constitute considerable challenges because of their complexity and in general their worse prognosis. Emerging data suggest a considerable role for allogeneic transplantation in these disorders. Advanced mycosis fungoides can be an aggressive disease at times impossible to control with conventional chemotherapy. Several reports indicate that allogeneic transplantation, in contrast to autologous, can be curative, sometimes even in patients with very refractory disease [2].
Disease status at HCT, but not histological subtype, was associated with worse NRM, relapse, PFS, and OS. Even for patients aged≥55 years, OS still approached 40% at 3 years, suggesting that HCT affects long-term remission and remains underused in qualified older patients with NHL [9].

Conclusions

Allogeneic Stem Cell Transplantation is a curative treatment for various subtypes of aggressive lymphoma and allows for long-term survival, limited by treatment-related toxicity and mortality. The attainment of chemosensitivity before transplantation provides better survival. New post-HCT strategies are needed to further augment GVL with minimal to no acute or chronic GVHD.

Patient consent for publication

The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the studyNo funding for this study.

Conflicts of interest

The authors declare no conflict of interest regarding this article.

References

1. McClune B. L., Woo Ahn K. et al. Allotransplantation for Patients Age ≥40 Years with Non-Hodgkin Lymphoma: Encouraging Progression-Free Survival. Biology of Blood and Marrow Transplantation, 2014. 20: 960-968.

2. Van Besien K. Current status of allogeneic transplantation for aggressive non-Hodgkin lymphoma. Current Opinion in Oncology 23(6):p 681-691, November 2011. doi: 10.1097/CCO.0b013e32834bb88e

3. Rivas M. M., Berro M., Prates M.V., Yantorno S., Fiad L., Arbelbide J.A. et al. Allogeneic stem cell transplantation improves survival in relapsed Hodgkin lymphoma patients achieving complete remission after salvage treatment. Bone Marrow Transplantation, 2019. doi:10.1038/s41409-019-0640-z.

4. Balakrishnan U., Kulkarni U. P., Pai A. A., Illangeswaran R. S. S., Mohanan E. et al. Biomarkers for early complications post hematopoietic cell transplantation: Insights and challenges. Frontiers in Immunology, 2023; 14: 1100306. doi: 10.3389/fimmu.2023.1100306.

5. Al-Juhaishi T., Borogovac A., Ibrahimi S., Wieduwilt M., Ahmed S. Reappraising the Role of Allogeneic Hematopoietic Stem Cell Transplantation in Relapsed and Refractory Hodgkin's Lymphoma: Recent Advances and Outcomes. J. Pers. Med. 2022, 12(2), 125; https://doi.org/10.3390/jpm12020125.

6. Mariotti J., Bramanti S., Santoro A., Castagna L. Haploidentical Stem Cell Transplantation in Lymphomas—Expectations and Pitfalls. J Clin Med. 2020 Nov; 9(11): 3589. Doi: 10.3390/jcm9113589.

7. Peggs K. S. Should all patients with Hodgkin lymphoma who relapse after autologous SCT be considered for allogeneic SCT? Blood Adv (2018) 2 (7): 817–820.
https://doi.org/10.1182/bloodadvances.2017011122.

8. Kopińska A., Koclęga A., Wieczorkiewicz-Kabut A., Woźniczka K., Kata D., Włodarczyk M., and Helbig G. Allogeneic Stem Cell Transplantation for Relapsed and Refractory Hodgkin Lymphoma: Real World Experience of a Single Center. Pathol Oncol Res. 2021; 27: 1609867. Doi: 10.3389/pore.2021.1609867.

9. McClune B. L., Woo Ahn K., Wang H., Antin J. H., Artz A., S., Cahn J. et al. Allotransplantation for

Patients Age ≥40 Years with Non-Hodgkin Lymphoma: Encouraging Progression-Free Survival. Biology of Blood and Marrow Transplantation, 2014 July; 20 (7): 960-968. https://doi.org/10.1016/j.bbmt.2014.03.013.

10. Mart´ınez C., Gayoso J., Canals C., Finel H., Peggs K., Dominietto A. et al. Post-Transplantation Cyclophosphamide-BasedHaploidentical Transplantation as Alternative to Matched Sibling or Unrelated Donor Transplantation for Hodgkin Lymphoma: A Registry Study of the Lymphoma Working Party of the European Society for Blood and Marrow Transplantation. Journal of clinical oncology. 2017, Oct. 35(30):3425-3432. http://ascopubs.org/doi/full/10.1200/JCO.2017.72.6869.

11. Ghosh N., Karmali R., Rocha V., Ahn K. W., DiGilio A., Hari P. N. et al. Reduced-Intensity Transplantation for Lymphomas Using Haploidentical Related Donors Versus HLA-Matched Sibling Donors: A Center for International Blood and Marrow Transplant Research Analysis. Journal of clinical oncology. 2016, June. http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2015.66.3476.

12. Miller H. K., Braun T. M., Stillwell T., Harris A. C., MD1, Choi S., Connelly J. et al. Infectious Risk Following Allogeneic Hematopoietic Cell Transplant Complicated by Acute Graft-Versus-Host Disease. Biol Blood Marrow Transplant, 2017 Mar; 23(3):522-528. doi: 10.1016/j.bbmt.2016.12.630.

13. Fuji S., Kapp M., Einsele H. Possible Implication of Bacterial Infection in Acute Graft-Versus-Host Disease after Allogeneic Hematopoietic Stem Cell Transplantation. Front Oncol., Apr. 2014; 4: 89. doi: 10.3389/fonc.2014.00089.