



Autologous hematopoietic stem cell transplantation conditioning regimens and chimeric antigen receptor T cell therapy in various diseases

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Abstract

Conditioning regimens employed in autologous stem cell transplantation have been proven useful in various hematological disorders and underlying malignancies; however, despite being efficacious in various instances, negative consequences have also been recorded. Multiple conditioning regimens were extracted from various literature searches from databases like PubMed, Google scholar, EMBASE, and Cochrane. Conditioning regimens for each disease were compared by using various end points such as overall survival (OS), progression free survival (PFS), and leukemia free survival (LFS). Variables were presented on graphs and analyzed to conclude a more efficacious conditioning regimen. In multiple myeloma, the most effective regimen was high dose melphalan (MEL) given at a dose of 200/mg/m². The comparative results of acute myeloid leukemia were presented and the regimens that proved to be at an admirable position were busulfan (BU) + MEL regarding OS and BU + VP16 regarding LFS. In case of acute lymphoblastic leukemia (ALL), BU, fludarabine, and etoposide (BuFluVP) conferred good disease control not only with a paramount improvement in survival rate but also low risk of recurrence. However, for ALL, chimeric antigen receptor (CAR) T cell therapy was preferred in the context of better OS and LFS. With respect to Hodgkin's lymphoma, mitoxantrone (MITO)/MEL overtook carmustine, VP16, cytarabine, and MEL in view of PFS and *vice versa* regarding

OS. Non-Hodgkin's lymphoma patients were administered MITO (60 mg/m²) and MEL (180 mg/m²) which showed promising results. Lastly, amyloidosis was considered, and the regimen that proved to be competent was MEL 200 (200 mg/m²). This review article demonstrates a comparison between various conditioning regimens employed in different diseases.

Key Words: Conditioning regimens; Multiple myeloma; Lymphoma; Hodgkin; Non-Hodgkin; Acute leukemia

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Core Tip: This literature review study is based on real-world data collected from various published research introducing multiple conditioning regimens for different disorders. Comparisons between regimens of an individual disorder were made using variables such as overall survival, progression free survival, complete remission, and leukemia free survival to conclude a laudable conditioning regimen having trivial adverse effects. The article is designed to discuss the conditioning regimens employed in autologous stem cell transplantation for various diseases. The primary objective of conducting this review is to highlight the various conditioning regimens, and discuss both the positive and the negative consequences along with proposing a treatment that is both efficacious and harmless.

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INTRODUCTION

Over the years, many treatment regimens have been crafted for multifarious diseases, and consequently, endorsement of hematopoietic stem cell (HSC) transplantation (HSCT) was a strategic approach for hematological disorders or underlying malignancy[1]. HSCs have the potential to develop into all types of blood cells, including white blood cells, red blood cells, and platelets, specifying them as an ideal choice[2]. The rationale behind the HSCT procedure is to replace the recipient's damaged cells with infused healthy stem cells and immune cells after exposure to a short course of chemotherapy or radiotherapy[3].

According to recent research, peripheral blood is 99% of the time used as a donor in autologous stem cell transplants [3]. In contrast, blood cells used in allogeneic stem cell transplantation (Allo-SCT) are taken from potential donors or cord blood units[4]. Today, more than 50000 HSCT procedures are performed annually worldwide. In Europe, are more than one-half of autologous transplants that are performed are autologous[5].

Conditioning regimens are devised in order to eradicate tumor cells and prevent graft rejection. In the 1970s, successful bone marrow transplantation (BMT) using cyclophosphamide (Cy) and total body irradiation (TBI) was reported[6]. Carmustine, etoposide, cytarabine, and melphalan (BEAM) is the most used conditioning regimen for Hodgkin's lymphoma, and it has a lower mortality rate when compared to other regimens[7]. Conditioning regimens with low toxicity are now generally preferred for patients with primary immunodeficiency[8]. To eliminate the damaged cells in the body, HSCT conditioning requires chemotherapy and/or radiation, but this procedure can have life-threatening side effects. Therefore, HSCT is primarily used to treat malignant illnesses where its advantages outweigh its potentially deadly hazards[9]. As an alternative to the traditional conditioning regimen, a reduced-intensity and non-myeloablative conditioning regimen has been presented[10]. According to research from the Fred Hutchinson Cancer Research Center, patients undergoing nonmyeloablative conditioning (grades III-IV acute graft-vs-host illness) had a considerably decreased incidence of severe acute graft-vs-host disease[11]. According to data from the Centre for International Blood and Bone Marrow Transplant Research, multiple myeloma (MM) and lymphoma are the most prevalent symptoms[3].

This article is designed to discuss the conditioning regimens employed in autologous stem cell transplantation (Auto-SCT) for various diseases. The primary objective of conducting this review is to highlight the various conditioning regimens, and discuss both the positive and the negative consequences along with proposing a treatment that is both efficacious and harmless.

HEMATOPOIESIS FROM HEMATOPOIETIC STEM CELLS

The discovery of induced pluripotent stem cells by the reprogramming of human and mouse fibroblasts in 2006 with traits like embryonic stem cells (ESCs) proved to be a landmark in the field of medicine[12]. This discovery ultimately paved the way for modern and significant contributions to drug discovery, cell therapy, basic research, and the widespread use of autologous cell-based therapy[13]. Since the isolation of human ESCs, valuable approaches have been made generally focused on directed differentiation to generate pluripotent hematopoietic stem and progenitor cells to be

manipulated in cellular therapy and to treat malignancies[14-16].

Since the very beginning, the stem cell concept has been crafted into a hierarchical tree-like model where the stem cells are sitting on the root of a branching family tree and the multipotent stem cells originate in an orderly branching fashion from their ancestral root[17]. To summarize, HSCs are immature ESCs that harbor the potential to differentiate into their lineage of cells including red blood cells, white blood cells, and platelets as shown in Figure 1[18].

HSCT

HSCT is the most widely used cellular immunotherapy, and is an indispensable treatment for many malignant, congenital, and acquired hematological ailments[19]. HSCT is a requisite after chemotherapy or radiotherapy to consolidate a patient's recovery and provide a lasting cure[20].

Auto-SCT

In autologous hematopoietic stem cell transplantation (ASCT), the stem cells are harvested from the recipient's own bone marrow, peripheral blood, or umbilical cord units. This mode of transplantation is effective since it reduces the occurrence of immunocompromise and transplant rejection[4].

Allo-SCT

Allogeneic transplantation uses fresh HSCs, so the collection from the donor as well as the conditioning of the patient occurs at the same time and reduces the risk of cell reduction *via* thawing or freezing[21]. Patients who undergo Allo-SCT require a longer period of immunosuppression in order to avert the likelihood of transplant rejection.

DISEASES TREATED BY AUTO-SCT

Owing to the great advancements in the field of medicine, Auto-SCT has now been regarded as an established therapeutic approach for many haemato-oncological, immunological, and hereditary conditions with the potential of cure. In 2012, the number of Auto-SCTs performed reached over one million[4]. There are following diseases for which the ASCT is being performed more frequently (Figure 2).

AUTO-SCT CONDITIONING REGIMENS IN VARIOUS DISEASES

Autologous HSCT conditioning regimens in MM

MM is an incurable, malignant B-cell neoplasm characterized by uncontrolled, destructive growth of mutated plasma cells along with the dissemination of multiple tumor cells throughout the bone marrow[22]. With the progress in the field of medical oncology, various drugs of paramount significance have been developed for the treatment of MM (*e.g.*, proteasome inhibitors and immunomodulatory drugs)[23].

The process of Auto-SCT is carried out in four basic steps: The mobilization, apheresis of mobilized stem cells, utilization of conditioning regimen and, finally, reinfusion[24]. According to a retrospective study by Brioli *et al*[25] involving 187 patients with MM and a comparison of high dose melphalan (MEL) 200 mg/m² (MEL 200) and low dose MEL 140 mg (MEL 140) conditioning regimens, the MEL 200 was used in 112 (60%) and MEL 140 in 75 (40%) of the patients. OS was found higher among patients treated with MEL 200 as compared to those who were given MEL 140 (66% *vs* 51% at 5 years) as mentioned in Figure 3.

A study by Nishihori *et al*[26] reviewing the effectiveness of various treatment modalities in MM also showed promising benefits by utilization of Bortezomib along with high dose MEL.

During the last decade, genetically engineered chimeric antigen receptor (CAR)-T cell therapy has been developed with the identification of several target antigens like CD19, CD38, CD138, and B-cell maturation antigen (BCMA)[27]. However, CAR-T cells targeting CD19 are the most identified CAR-T cells that are being used in hematological malignancies, and BCMA-targeted CAR-T cells are being evaluated to be used against MM. These new treatment strategies have brought a ray of hope to cure MM with reduced mortality rates and improved OS[28].

ASCT conditioning regimens in acute myeloid leukemia

In recent years, the therapeutic and prognostic profile of acute myeloid leukemia (AML) has been improved due to recent advances in chemotherapeutic agents and the rising trend of ASCT to consolidate adult patients with AML[29]. AML is a rare diagnosis. Due to high neoplasm potential, it is associated with a large number of leukemia-associated deaths with a reduced OS rate. The presence of balanced translocation between chromosome 8 and 21 [t(8;21)], inversion of chromosome 16, and translocation between chromosomes 15 and 17 [t(15;17)] has also been implicated in acute promyelocytic leukemia pathogenesis along with some genetic and epigenetic alterations[30]. Although recent advances have been paving an excellent pathway for halting the disease progression and improving OS rate, AML is still posing some serious therapeutic challenges to be overcome.

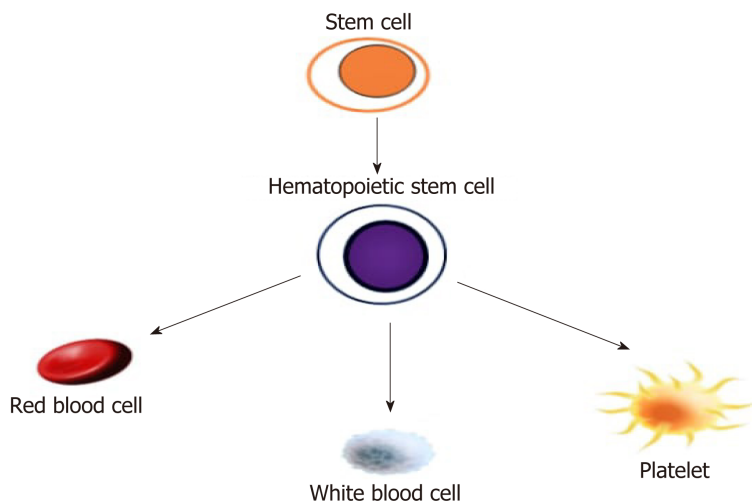


Figure 1 Differentiation of pluripotent embryonic stem cells into hematopoietic stem cells.

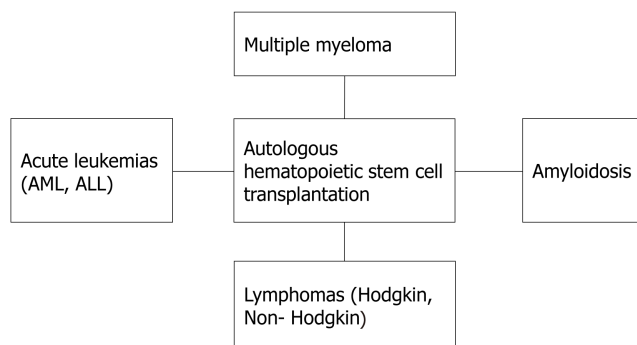


Figure 2 Pattern of various diseases treated by autologous hematopoietic stem cells transplantation. AML: Acute myeloid leukemia; ALL: Acute lymphoblastic leukemia.

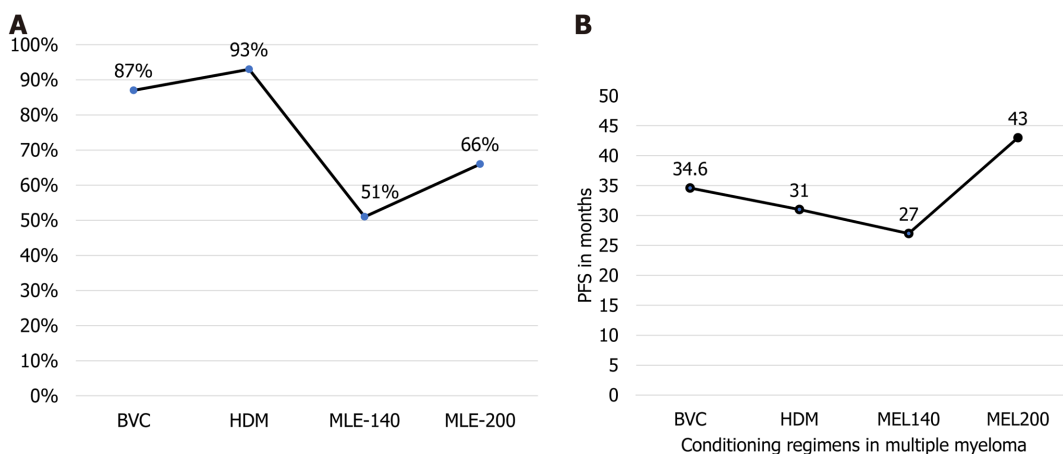


Figure 3 Comparison of various conditioning regimens in multiple myeloma. A: Comparison of overall survival between busulfan 0.8 mg/kg along with etoposide IV 400 mg/m² plus cyclophosphamide 50 mg/kg (BVC), melphalan (MEL) given at a dose of 100 mg/m²/d (HDM), high dose MEL 200 mg/m² (MEL 200), and low dose MEL given at a dose of 140 mg (MEL 140); B: Comparison of progression free survival between BVC, HDM, MEL 200, and MEL 140.

According to a retrospective analytical study involving 952 patients with AML by Nagler *et al*[31], the median age of patients was 50.5 years with 56% of the population ($n = 531$) consisting of the male population. The effectiveness of intravenous (IV) busulfan (BU) in ASCT was ascertained in this study and comparison was made with oral BU utilization in patients undergoing ASCT. IV conditioning regimens based mainly on BU (12.8 mg/kg) combined with Cy (120 mg/kg) were administered in about 517 patients, the combination of IV BU (12.8 mg/kg) and MEL (140 mg/kg) was given to 234 patients, a combination of IV BU and etoposide was tried in 82 patients, and the IV BU and idarubicin were

administered in 46 patients. Outcomes in terms of 2-year OS, leukemia free survival (LFS), and relapsed incidence were assessed. However, the effectiveness of all combinations was surprisingly higher in patients aged less than 50 as compared to older patients; OS was $67\% \pm 2\%$, LFS was $53\% \pm 2\%$, and relapse incidence (RI) was $40\% \pm 2\%$. Out of all the combinations discussed herein, the combination of IV BU (12.8 mg/kg) with MEL (140 mg/kg) was associated with significantly improved OS as compared to other three combinations, validating the effectiveness of IV BU and MEL as a regimen of choice when compared with other regimens used either IV or oral BUT that was actually showing the greater toxicity profile than IV BU administration with a low incidence of veno-occlusive disease[31].

The conditioning regimen is now considered the real estate of Auto-SCT success because it not only creates the space to transplant the HSCs but also eradicates the disease itself. A study conducted by Gorin *et al*[32] using the data from a registry of the European Society for Blood and Marrow Transplantation to compare the effectiveness of two standard conditioning regimens, *i.e.*, BU + MEL and BU + Cy, in Auto-SCT for AML patients. The first regimen consisted of BU (12.8 mg/kg) and MEL (140 mg/kg) combined (BUMEL) and the second consisted of BU (12.8 mg/kg) and Cy (120 mg/kg) (BUCY). This study involved 853 patients with available cytogenetics of AML and BUMEL therapy was used in 30% of the patients ($n = 257$), while 70% of the patients ($n = 596$) were administered with BUCY therapy and the outcomes were evaluated in terms of RI, LFS, and finally OS. The findings were truly mandating the utilization of the BUMEL regimen against BUCY due to reduced RI (39.5% vs 52.2% ; $P = 0.003$), better LFS (55.4% vs 44.6% ; $P = 0.005$), and finally better OS rate (73.8% vs 63% ; $P = 0.0007$), validating the higher effectiveness of BUMEL regimen in ASCT[32]. When the OS was compared between other conditioning regimens used vs BUMEL in ASCT for patients with AML, the BUMEL regimen was found to be highly effective on all grounds, making it the conditioning regimen of choice with excellent ultimate outcomes as shown in Figure 4.

The construction of a CD-70 CAR-T cell can prove to be a breakthrough in the field of oncology and medicine. CD70 is a type 2 transmembrane glycoprotein and a member of the tumor necrosis factor ligand family that is now increasingly being utilized as a therapeutic target for the treatment of AML; however, there is still very much to discover about this therapeutic approach. The antitumor activity of a CD70-specific monoclonal antibody along with hypomethylating agents for the treatment of patients with AML has been showing promising benefits[33]. Therefore, we can hope that in the future, designing of CAR-T cells will be conducive to the treatment of hematological malignancies with minimal myelotoxicity.

Autologous HSCT conditioning regimens in acute lymphoblastic leukemia

Acute lymphoblastic leukemia (ALL) is a familiar pediatric carcinoma marked by chromosomal translocations and somatic mutations[34].

Lee *et al*[35] carried out a retrospective study using myeloablative therapy. They inducted 44 patients from March 2009 to January 2014 and the efficacy was assessed by complete remission (CR). These patients underwent HSCT using a once-daily IV conditioning regimen. The regimen included BU (120 mg/m² for patients > 1 year of age and 80 mg/m² for patients < 1 year of age), fludarabine 40 mg/m², and etoposide 20 mg/kg. Results showed that 28 (63.6%), 12 (27.3%), and 1 (2.3%) patients achieved 1st, 2nd, and 3rd CR, respectively, while two (4.5%) patients had no remission at the time of HSCT. The complications reported in this study included elevated AST and/or ALT or total bilirubin[35].

To compare the efficacy of TBI plus etoposide and myeloablative regimen (including fludarabine, thiotepe, and IV BU/treosulfan), Peters *et al*[36] in 2021 conducted a multi-centre and randomized trial in high-risk ALL patients. Efficacy was measured in terms of treatment related mortality (TRM). They inducted 417 patients and randomly assigned them to two cohorts. Cohort 1 was given TBI and IV etoposide (60 mg/kg) while cohort 2 was administered with fludarabine (30 mg/m²) once daily, thiotepe (5 mg/kg) twice daily, and treosulfan (14 g/m²)/BU once daily. Following the TBI-based regimen and myeloablative regimen, the 2-year TRM was 0.02 [95% confidence interval (95%CI): 0.01 to 0.05] and 0.09 (95%CI: 0.05 to 0.14), respectively, thus showing that TBI plus etoposide regimen had good disease control.

For hematologic malignancies, CAR-T cell therapy has been unfolded as an efficacious therapeutic option. Its mechanism of action involves the patient's own T-cells that in turn express receptors modified to recognize specific epitopes of tumor-associated antigens on the target cell surface[37]. Numerous trials have been carried out to investigate the efficacy of this therapy. Subklewe *et al*[38] conducted "the pivotal global ELIANA trail" (NCT02435849) using genetically modified CD19-directed T-cell products, "Tisagenlecleucel". In another phase 1 trial (NCT01044069), Davila *et al*[39] pointed out the plausibility of CAR-T cell therapy. In this study, 16 patients were enrolled and given a 19-28z infusion of CAR-T cells after salvage chemotherapy. This blatantly boosted the overall complete response rate to 88%, which is higher than that expected with salvage chemotherapy alone.

To sum up, the introduction of CAR-T cell therapy has provided new directions to the field of oncology and medicine; however, ASCT is widely preferred because of being inexpensive. Moreover, CAR-T cell therapy needs further evolution by health professionals.

Autologous HSCT conditioning regimens in Hodgkin lymphoma

A retrospective, multi-center study by Yeral *et al*[42] involving 142 patients with HL undergoing ASCT showed the comparison of two conditioning regimens with end points represented by OS and progression free survival (PFS). The two conditioning regimens used were BEAM (carmustine 300 mg/m² given at day 6, etoposide 200 mg/m² and cytarabine 200 mg/m² between day 2 to day 5, MEL 140 mg/m² at day 1) was administered in 108 patients and 34 patients were administered with mitoxantrone (MITO) 60 mg/m² in three divided doses at day 5 along with MEL 180 mg/m² in three divided doses at day 2 constituting a group with MITO/MEL.

According to a study by Chen *et al*[43] involving 1012 patients with HL, BEAM and Cy, carmustine, and etoposide (CBV)-low or CBV-high were the most used regimens with a 3-year OS of 79% and PFS of 62% in the BEAM group, OS of 73% and PFS of 60% in the CBV-low, and OS of 68% and PFS of 57% in the CBV-high group. However, the BEAM-based

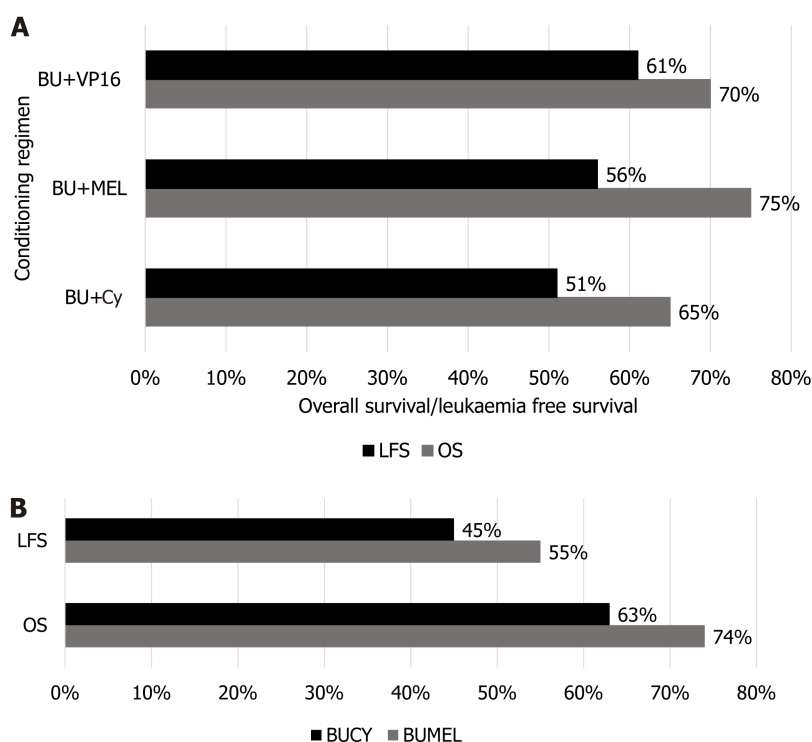


Figure 4 Comparison of various conditioning regimens in acute myeloid leukemia. A: Comparison of leukemia free survival (LFS) and over survival (OS) between intravenous busulfan (12.8 mg/kg) combined with cyclophosphamide (120 mg/kg), melphalan (140 mg/kg), and etoposide; B: Comparison of LFS and OS between busulfan (12.8 mg/kg) plus melphalan (140 mg/kg) and busulfan (12.8 mg/kg) plus cyclophosphamide (120 mg/kg). BU: Busulfan; MEL: Melphalan; Cy: Cyclophosphamide; LFS: Leukemia free survival; OS: Over survival; BUCY: Busulfan and cyclophosphamide; BUMEL: Busulfan and melphalan.

regimen was most effective in HL with better OS and PFS as compared to other regimens as shown in [Figure 5](#).

CAR T-cell therapy of B-cell malignancies has proved to be effective. Ramos *et al*[44] showed how the same approach of CAR-T cells specific for CD30 (CD30.CAR-Ts) can be used to treat HL.

Autologous HSCT conditioning regimens in non-HL

Non-HLs (NHLs) are a diverse collection of lymphoproliferative tumors with a greater propensity to expand to extranodal sites than HLs. Both nodal and extranodal regions are involved in the majority of NHL cases[45]. The mobilization of HSCs is followed by apheresis of the mobilized stem cells, use of a conditioning regimen, and finally reinfusion[46].

Between May 19, 2015 and September 15, 2016, Locke *et al*[47] carried out a single-arm, multicenter phase 1/2 study in which 119 patients were enrolled and 108 were given axicabtagene ciloleucel. Seven patients participated in phase 1, while the remaining 107 were enrolled in phase 2 studies. After receiving IV fludarabine and Cy as conditioning chemotherapy, participants received one dose of axicabtagene ciloleucel. Only pronounced adverse events, such as neurological events, hematological events, infections, autoimmune disorders, and secondary malignancies were documented after 3 mo.

Between February 25, 2011 and April 3, 2014, Okay *et al*[48] selected 1503 previously untreated patients for a randomized, open-label, phase 3 study. The forecasts for OS at 5 years, survival without disease, and survival without events were 81.9%, 46.5%, and 41.4%, respectively. All patients displayed neutropenia and thrombocytopenia. All individuals had nausea, mucositis, and vomiting. Hahn *et al*[49] assessed consecutive lymphoma patients who received BEAM HDCT and BeEAM followed by ASCT between 2015 and 2019. BEAM had a 3-year OS of 78.1% while BeEAM had a 3-year OS of 71.0%. BEAM had a 3-year PFS of 71.3% while BeEAM had a 3-year PFS of 74.1%.

CAR T-cell therapy has emerged as a standard of care for treating a number of disorders in recent years, overcoming any potential drawbacks associated with conventional therapies. Clinical trials of anti-CD19 CAR-T cell therapy for the treatment of refractory or relapsed B-NHL have produced encouraging effective outcomes[50].

Autologous HSCT conditioning regimens in amyloidosis

Amyloidosis (AL) is a clonal plasma cell dyscrasia characterized by the accumulation of misfolded fibrillar proteins in extracellular tissues, leading to organ failure and eventually death. Though associated with high treatment-related mortality, for nearly 20 years Auto-SCT has been used and demonstrated improved survival and a prolonged treatment-free interval[51].

According to a study by Tandon *et al*[52] involving 457 diagnosed cases of light chain AL undergoing AHSCT, two conditioning regimens, one with full dose MEL (200 mg/m²) and the other with low or reduced intensity MEL (100 mg/kg), were compared. Complete response was observed in high dose Mel group (53% *vs* 37%, *P* = 0.003), and the PFS was also validating the effectiveness of high dose Mel regimen when compared with low dose Mel group (55% *vs* 31%; *P* < 0.001) as shown in [Figure 6](#).

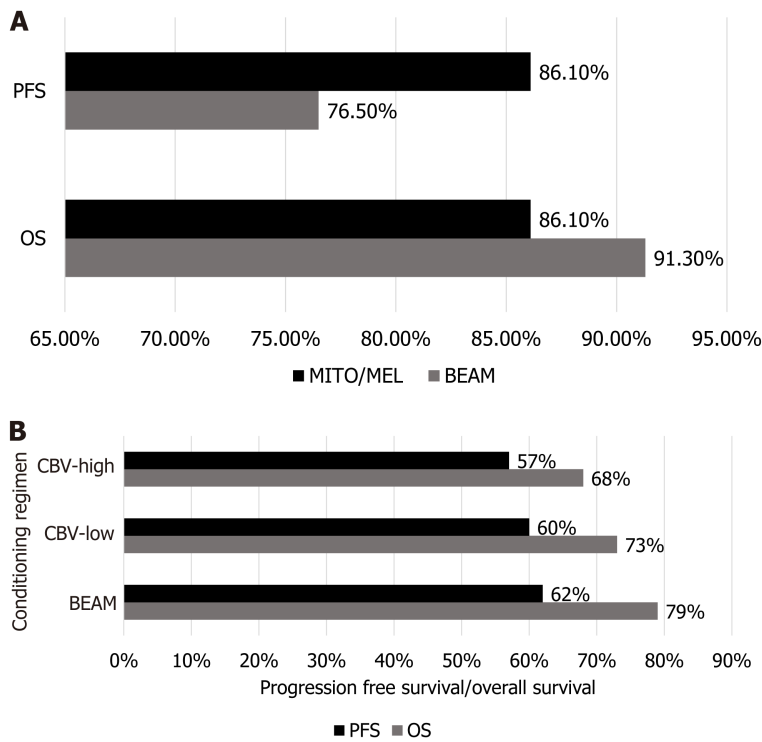


Figure 5 Comparison of various conditioning regimens in Hodgkin lymphoma. A: Comparison of progression free survival (PFS) and overall survival (OS) between carmustine, etoposide, cytarabine, and melphalan (BEAM) [carmustine 300 mg/m² given at day 6, etoposide 200 mg/m² and cytarabine 200 mg/m² between day 2 to day 5, melphalan (MEL) 140 mg/m² at day 1] and mitoxantrone (MITO) 60 mg/m² in three divided doses at day 5 along with MEL 180 mg/m² in three divided doses at day 2 constituting a group with MITO/MEL; B: Comparison of PFS and OS between BEAM (*n* = 313), CBV-low (cyclophosphamide, carmustine, and etoposide) (*n* = 279), and CBV-high (cyclophosphamide, carmustine, and etoposide) (*n* = 219). PFS: Progression free survival; OS: Over survival; BEAM: Carmustine, etoposide, cytarabine, and melphalan; MITO: Mitoxantrone; MEL: Melphalan.

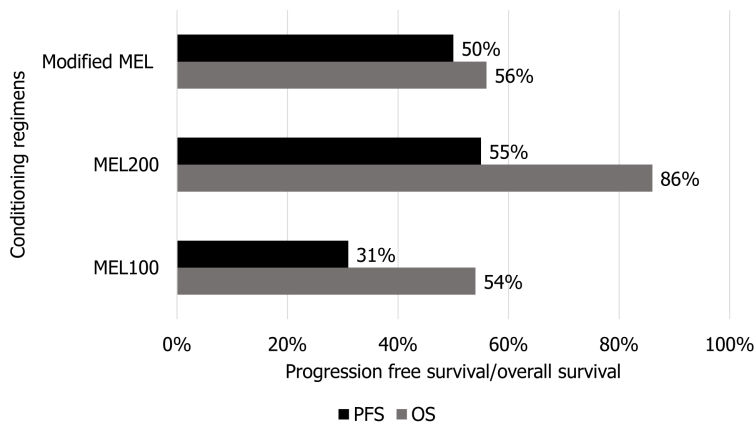


Figure 6 Comparison of progression free survival and overall survival between full dose melphalan (MEL) (200 mg/m²), low or reduced intensity MEL (100 mg/m²), and modified MEL (100 mg/m²). PFS: Progression free survival; OS: Over survival; MEL: Melphalan.

Similarly, a trial labeled SWOG (S0115) conducted by Sanchorawala *et al*[53] involved 93 patients diagnosed with high-chain amyloidosis (AL), AL with myeloma (AM), and host-based high-risk myeloma (hM), with 59, 9, and 25 patients in each group. The patients were treated with sequential doses of modified MEL (100 mg/m²). The estimated 2- and 5-year OS was 69%, 56%, and 80%, and 56%, 42%, and 55% for AL, AM, and hM, respectively. The estimated 5-year PFS was 50%, 30%, and 50% in AL, ALM, and hM, respectively. Skinner *et al*[54] evaluated 701 consecutive patients with AL between July 1994 and June 2002. Fifty-six percent (394) of the patients met the eligibility criteria for high dose MEL treatment. Overall median survival was 4.6 years and 56% of the patients remained alive. The estimated 5-year survival rate was 47%.

Strategies for the treatment of hematologic malignancies have evolved as the use of immunotherapy is an attractive approach. Rosenzweig *et al*[55] provided preclinical data evaluating bone marrow specimens for BCMA and CS1 expression in ten AL patients. All the AL samples expressed high levels of CS1 (76.5% ± 4.7%) but low levels of BCMA (4.9% ± 0.8%). The study reported the unique nature of plasma clonal cells in AL patients because of the scarcity of BCMA

expression.

CONCLUSION

This literature review study is based on real-world data collected from various published research introducing multiple conditioning regimens for different disorders. Comparisons between regimens for an individual disorder were made using variables such as OS, PFS, CR, and LFS to conclude a laudable conditioning regimen having trivial adverse effects. In MM, the most effective regimen was high dose MEL given at a dose of 200 mg/m²/d. However, for ALL, CAR-T cell therapy was preferred in the context of better OS and LFS. With respect to HL, MITO/MEL overtook BEAM in view of PFS and *vice versa* regarding OS. NHL patients were administered MITO (60 mg/m²) and MEL (180 mg/m²) which showed promising results. Lastly, AL is considered, and the regimen that proved to be competent was MEL 200 (200 mg/m²). This article presents a descriptive picture of diseases and the regimens employed in them along with mentioning the most successful regimen.

FOOTNOTES

Author contributions: Maqbool S, Baloch MF, Khan MAK, and Khalid A contributed significantly and equally to the preparation of the manuscript, including primary and final drafting; Maqbool S, Khalid A, and Naimat K conceived, designed, and performed the study; all authors read and approved the final manuscript.

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