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Hematopoietic Stem Cell Transplantation in Multiple Myeloma in the Era of Novel Agents and Targeted Therapies

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Abstract

Multiple myeloma, the second commonest hematologic malignancy, is characterized by neoplastic proliferation of a single clone of plasma cells in the bone marrow producing a monoclonal immunoglobulin and ultimately causing various complications and organ dysfunction.

Over the last 10 years, management of multiple myeloma has dramatically changed due to the introduction of several novel therapies that have improved the disease outcome and prognosis. Also; these agents have improved the quality of life of patients with myeloma due to their safety, tolerability and efficacy. The utilization of autologous hematopoietic stem cell transplantation, which is still the standard of care for transplant eligible patients, as well as the implementation of new therapeutic strategies such as drug combinations in addition to consolidation and maintenance therapies have resulted in further improvements in response rates and survival in patients with multiple myeloma.

Keywords: Multiple myeloma; Hematopoietic stem cell transplantation; Novel agents; Maintenance therapy

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Introduction

Multiple myeloma (MM) is a plasma cell neoplasm characterized by neoplastic proliferation of a single clone of plasma cells in the BM producing a monoclonal immunoglobulin and causing anemia, renal failure, bone destruction and infectious complications [1-3]. MM is the 2nd most commonly diagnosed hematologic malignancy (HM) and it accounts for approximately 10% of all HMs [2]. The median age of MM at diagnosis is 70 years in the United States of America (USA) and 72 years in Europe [3].

Diagnosis, Staging, Genetics and Risk Stratification

The diagnostic criteria for MM are: (1) clonal bone marrow (BM) plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma and (2) at least one of the following: (a) evidence of end-organ damage such as: hypercalcemia, anemia, lytic bone lesions and renal insufficiency, (b) clonal BM plasma cells ≥60%, (c) involved: uninvolved serum free light chain ratio ≥100, and (d) >1 focal lesion on magnetic resonance imaging [4-10].

MM is usually classified into 3 stages: (1) stage I; all the following: serum albunin ≥3.5 g/dL, serum beta 2 microglobulin (B2M) <3.5 mg/L, normal serum lactic dehydrogenase (LDH) and no high-risk (HR) cytogenetics; (2) stage II: not fitting stages I and III with serum B2M: 3.5-5.5 mg/L, and (3) stage III; all the following: serum B2M >3.5 mg/L and HR cytogenetics or elevated serum LDH level [2,6,8].

The following cytogenetic abnormalities have been reported in patients with MM: trisomies; monosomies; 17 p deletion; amp 1q20; t 14,16; t 14,20; t 4,14; t 6,14; and t 11,14 [2,6,8,11]. Also, the following molecular mutations have been reported in MM patients: NRAS, KRAS, TP53, BRAF, CCND1, FAM46C, MYC, XBP1 and CHST15 [12-15]. Recently, the following laboratory techniques have been utilized in the diagnosis and follow-up of patients with MM: (1) next generation sequencing (NGS), (2) genomic and epigenetic studies, (3) micro-RNA, and (4) minimal residual disease evaluation by flow cytometry, polymerase chain reaction, NGS [12-16].

The HR features in MM include: (1) cytogenetic abnormalities that include: 17 p deletion, t(14,16) and t(14,20); (2) international

scoring system stage II or III; (3) presence of comorbid medical conditions that limit therapy; and (4) renal failure, high serum lactic dehydrogenase and plasma cell leukemia [8]. MM patients are stratified into 3 risk groups based on their cytogenetic profiles as follows: (1) HR that includes 17 p deletion, t 14,16 or t 14,20; (2) intermediate risk that includes: t 4,14 and amp 1q20 (gain 1q); and (3) standard risk that includes: trisomies, t 11,14 and t 6,14 [2,6,8,11].

Management of MM

Over the last 10 years, management of multiple myeloma has dramatically changed due to the introduction of several novel therapies that have improved the disease outcome and prognosis [4,8,11,17,18]. The recent development of novel therapies has improved the depth of responses and has prolonged survival in patients with MM for many years [11,18]. The widespread use of autologous HSCT and the introduction of several novel agents into clinical practice have significantly contributed to major advances in the therapy and prognosis of MM [18].

Cytotoxic agents that have been used in the treatment of MM include: (1) corticosteroids such as prednisolone and dexamethasone, (2) conventional chemotherapeutic agents and regimens including: melphalan, cyclophosphamide, liposomal doxorubicin, bendamustine, carmustine (BCNU), D-PACE (dexamethasone, cisplatin, doxorubicin, cyclophosphamide, etoposide) and DCEP (dexamethasone, cyclophosphamide, etoposide, cisplatin) [19]. However, remarkable improvements in survival of patients with MM have been achieved following the introduction of thalidomide, bortezomib and lenalidomide as well as the recent introduction and approval of the following novel therapeutic agents: (1) newer proteasome inhibitors such as carfilzomib and ixazomib; (2) histone deacetylase inhibitors such as panobinostat and vorinostat; (3) new immunomodulatory drugs such as pomalidomide; (4) monoclonal antibodies such as daratumomab and elutuzumab; (5) Bruton tyrosine kinase inhibitors such as ibrutinib; (6) alkylating agents such as bendamustine; (7) interleukin (IL)-6 inhibitors such as situximab; (8) phosphoinositide 3-kinase inhibitors; and (9) various immunotherapies including CAR T-cells [4,8,10,19-21].

Frontline and Induction Therapies in MM

Several studies have shown that VRD (bortezomib, lenalidomide, dexamethasone) regimen is well tolerated and highly effective in the treatment of newly diagnosed MM patients [22-27]. Once used as first line therapy for MM, VRD has been shown to be superior to the doublet regimen of lenalidomide plus dexamethasone as well as the triplet regimens VCD (bortezomib, cyclophosphamide, dexamethasone) and VTD (bortezomib, thalidomide, dexamethasone) [25]. Carfilzomib, lenalidomide, dexamethasone (KRD) is an alternative promising regimen but has only been evaluated in small phase II studies in the frontline setting [25].

HSCT in Patients with MM

Autologous HSCT

Autologous HSCT, performed at the time of initial diagnosis or at relapse, is considered the standard of care for patients with newly diagnosed MM who are younger than 70 years [6,28,29]. However, autologous HSCT is not curative for MM [6,28]. Allogeneic HSCT is the only curative therapy for MM but at the expense of increased treatment-related mortality (TRM), so candidates for allografts should be carefully selected from the pool of young patients with relapsed and refractory (R/R) MM [30]. Several randomized clinical trials have shown that, compared with conventional chemotherapy alone, high-dose chemotherapy followed by stem cell rescue is associated with prolonged event free survival (EFS) and overall survival (OS) [6,28,29]. The recent widespread implementation of autologous HSCT in conjunction with novel therapies has revolutionized the management of MM and has markedly altered the natural history of the disease by improving disease responses and response duration ultimately leading to significant improvement in OS [28].

Eligibility for autologous HSCT is determined by: age, performance status, presence and severity of comorbid medical conditions, and frailty score as frailty has been shown to be a predictor of short survival and is considered an exclusion criterion for autologous HSCT [6].

Cryopreservation versus non-cryopreservation of stem cells

For most types of transplants, cryopreservation of HSCs is necessary and is an essential component of the clinical protocol [31]. Dimethyl sulfoxide (DMSO) is widely used as a cryopreservant for various types of stem cells and other body tissues. It has the following adverse effects: skin irritation, garlic breath or body odor; abdominal pain, nausea, vomiting and diarrhea; bronchospasm, chest tightness and dyspnea; altered heart rate and blood pressure, arrhythmias, heart block and myocardial ischemia; as well as various degrees of neurotoxicity, renal and hepatic dysfunction and death [31,32]. Additionally, DMSO has in vitro toxicity in the form of induction of red blood cell hemolysis and reduction in platelet aggregation and activity [32].

Several studies and 1 meta-analysis have shown that: non-cryopreserved autologous HSCT for MM is simple, safe and cost-effective and gives results that are equivalent to auto-HSCT with cryopreservation [33-38]. TRM at day 100 post-HSCT has ranged between 0.0% and 3.4 % [34,36-38]. Non-cryopreserved stem cells can be infused till day 5 post-apheresis without viability loss provided they are stored at + 4 ^{o}C in conventional blood bank refrigerator [33,35,36,38]. In a systematic review that included 16 studies having 560 patients with various HMs including MM, hematopoietic engraftment was universal and only 1 graft failure was reported [33,35]. The median times for engraftment following non-cryopreserved autografts were: 9-14 days for neutrophils and 14-25 days for platelets [33,35]. Other recent

studies on non-cryopreserved autologous HSCT in patients with MM have shown the following results: neutrophil engraftment between days 10 and 14 days and platelet engraftment between days 13 and 25 days post-autologous HSCT [39-46].

Melphalan is the standard chemotherapeutic agent that is used in the conditioning therapy prior to autologous HSCT in MM. The dose ranges between 140 and 200 mg/m2, given intravenously (IV) [33,35,36]. It is cleared from plasma and urine in 1 and 6 hours respectively. Stem cells can be safely infused as early as 8-24 hours following melphalan administration [33,35].

HSCT without cryopreservation has several advantages including: (1) simplicity of implementation, (2) allowing autologous HSCT to be performed entirely as outpatient, (3) reduction of transplantation costs, (4) reducing the time between the last induction therapy and high-dose chemotherapy, (5) prevention of DMSO toxicity, (6) expansion of the number of medical institutions performing stem cell therapies, (7) no significant loss of viability of the collected HSCs provided stem cell infusion is made within 5 days of apheresis, and (8) potent engraftment syndrome and autologous graft versus host disease (GVHD) [33-38]. HSCT without cryopreservation has the following disadvantages: (1) limitation of the use of standard high dose schedules such as BEAM (BCNU, etoposide, cytarabine and melphalan) employed in autologous HSCT for lymphoma, (2) plenty of coordination needed between various teams regarding timing of: stem cell mobilization, apheresis, administration of conditioning therapy, and infusion of stem cells, and (3) inability to store part of the collection and reserving it for a second autologous HSCT in case a rich product is obtained [33-38]

Outpatient HSCT

MM is the leading indication for autologous HSCT worldwide. Patients with MM are ideal candidates for outpatient autologous HSCT because of the following reasons: the ease of administering high-dose melphalan, the relatively low extra-hematological toxicity and the short period of neutropenia [39].

Several studies have shown: safety, feasibility and cost-effectiveness of outpatient autologous HSCT for MM [40-44]. Selection criteria for outpatient autologous HSCT include: expected compliance, proximity to the HSCT center for daily visits, 24-hour caregiver support, favorable performance status, and favorable comorbidity profile [45]. Lack of caregiver is a limiting factor for outpatient autologous HSCT [46].

Tandem and second AHSCT

Even before the era of novel therapies, tandem autologous HSCT had been performed in patients with MM and the results of tendem transplants showed superior outcomes compared to single autologous HSCTs [47,48]. Later on, two single center retrospective analyses showed higher rates of progression free survival (PFS) and OS in patients subjected to tandem autologous HSCT compared to recipients of single autologous HSCT [49,50]. A meta-analysis that included 6 studies comparing tandem to single autologous HSCT in patients with MM showed: (1) no difference between the 2 forms of autologous HSCT with respect to OS, EFS; and (2) although tandem autologous HSCT was associated with improved response rates but at the expense of increased TRM [51]. However, this meta-analysis was described as flawed and was criticized as it included a study with significant statistical errors [52].

Several studies have shown that a second autologous HSCT used as part of salvage therapy in patients with MM relapsing after the first autologous HSCT has been found to be safe and feasible particularly in carefully selected patients [53-57]. Factors associated with success of second autologous HSCT include: younger age, B2M < 2.5 mg/L at diagnosis, remission duration > 9 months from first autologous HSCT, > partial response achieved in response to the first autologous HSCT, and performance of second autologous HSCT before relapse and within 6-12 months from the first autologous HSCT [58,59].

Allogeneic HSCT in MM

Although allogeneic HSCT represents the only potentially curative therapeutic modality in patients with MM, it is associated with relatively high TRM [30,60,61]. In patients with HR disease or those relapsing after autologous HSCT, salvage therapy with novel agents followed by reduced intensity conditioning allogeneic HSCT have been shown to provide significant PFS benefit [30,62,63]. In patients lacking human leukocyte antigen (HLA)-matching sibling donors, alternate donors such as matched unrelated donors, cord blood transplantation and haploidentical forms of allogeneic have been employed and they have shown feasibility and effectiveness [60,64-66].

Consolidation and Maintenance Therapies in MM

Nearly all patients with MM relapse after autologous HSCT. Treatment given in the post-autologous HSCT period is aimed at suppression of residual disease in order to prolong duration of response, OS and PFS while minimizing toxicity [67].

The use of novel therapies in the consolidation therapy following single or tandem autologous HSCT has been shown to enhance the rate as well as the quality of response thus contributing to improvements in clinical outcomes including prolongation of PFS [68]. Bortezomib-based regimens used as consolidation therapy after autologous HSCT in patients with MM have been shown to be effective in the improvement of PFS and response rates [69].

Maintenance therapy represents an important therapeutic strategy to delay disease progression and relapse [67]. The following drugs have been used in post-autologous HSCT maintenance: interferon, thalidomide, bortezomib and carfilzomib [67,70-72]. Bortezomib is safe, well tolerated and efficacious and it can be used with no risk of second malignancy till disease progression [72].

In February 2017, the food and drug administration in the USA approved the use of lenalidomide as maintenance therapy following autologous HSCT for patients with MM, after showing efficacy and safety in several studies [73]. Lenalidomide has tumoricidal and immunomodulatory activities against MM

[74]. Several studies have shown the efficacy of lenalidomide maintenance after autologous HSCT as this therapy has been shown to be associated with significant improvements in OS, PFS and longer time to disease progression [75-78]. A multicenter, randomized double blind study that included 306 patients with newly diagnosed MM ≥ 65 years of age and ineligible for autologous HSCT treated initially with melphalan, prednisolone and lenalidomide induction followed by lenalidomide versus placebo maintenance showed the following results: (1) significant prolongation of PFS, (2) maximum benefit was achieved in patients 65-75 years of age, and (3) three year second primary tumor of 7% in the lenalidomide arm versus 3 % in the placebo arm [74]. Other studies on lenalidomide maintenance have shown more toxicity and low rate of development of second tumors [75,76]. Lenalidomide maintenance can be initiated as early as day 100 post-autologous HSCT [75]. Duration of lenalidomide maintenance longer than 3 years has been associated with further improvement in survival [76].

Novel Therapies in MM

The novel therapies that have recently been introduced into the treatment of MM include: (1) proteasome inhibitors such as bortezomib, carfilzomib and ixazomib, (2) immunomodulatory agents such as thalidomide, lenalidomide and pomalidomide, (3) monoclonal antibodies such as daratumomab and elotuzumab, and (4) histone deacetylase inhibitors such as panobinostat, in addition to other classes of medications that can also be used in the treatment of MM such as: glucocorticoids, DNA alkylating agents, as well as doxorubicin, cisplatinum and etoposide [4,8,10,19-21].

Daratumumab

Daratumumab is a human IgG_k monoclonal antibody that targets CD38 which is a cell surface protein that is overexpressed in m MM cells. It is given IV at dose of 16mg/kg weekly [79-82]. It induces death of MM cells by several mechanisms including: (1) complement-dependent cytotoxicity, (2) antibody-dependent cell-mediated cytotoxicity, (3) antibody-dependent cellular phagocytosis, and (4) apoptosis [79-82].

Daratumumab has shown substantial efficacy as monotherapy in heavily pretreated patients with MM as well as in combination with bortezomib in patients with newly diagnosed MM [80]. Two phase III randomized clinical trials in R/R MM using daratumumab in combination with either bortezomib and dexamethasone or lenalidomide and dexamethasone showed significantly longer PFS with manageable toxicity [80,82]. In a phase III randomized clinical trial performed in patients with newly diagnosed MM, not eligible for autologous HSCT, the addition of daratumumab to bortezomib, melphalan and prednisolone decreased the risk of death and disease progression but was also associated with higher rates of infections [81]. The adverse effects of daratumumab include: infusion-related reactions, hematologic toxicity in the form of neutropenia and thrombocytopenia and infectious complications [79-82].

Elotuzumab

Elotuzumab is an immunostimulatory monoclonal antibody targeting signaling lymphocyte activation molecule F7 (SLAMF7) [83]. In a phase III randomized clinical trial in patients with R/R MM, the combination of elotuzumab, lenalidomide and dexamethasone decreased the risks of death and disease progression by 30% [83].

Pomalidomide

Pomalidomide is a third generation immunomodulatory agent that has been approved for patients with progressive MM or those who have received at least 2 lines of therapy [84]. It has shown to be effective in combination with dexamethasone ± carfilzomib or other agents in patients with R/R MM or in those with HR cytogenetics [84-87].

Carfilzomib

Carfilzomib is a second generation proteasome inhibitor [88]. It is well tolerated and causes minimal neurotoxicity. It has demonstrated promising activity in patients with MM who are R/R to bortezomib or immunomodulatory agents [88-90]. It can be combined with dexamethasone or other agents [89-91]. It is under evaluation for patients with newly diagnosed MM [91].

CAR T-cells

CAR is a hybrid antigen receptor that is composed of an extracellular antigen-binding domain and an intracellular signaling domain. T-cells genetically targeted with a CAR to B-cell malignancies have demonstrated tremendous clinical outcome [92]. Immunotherapy using CAR-mediated T-cells has demonstrated high response rates in patients with B-cell malignancies. CAR T-cell therapy is a cellular therapy that redirects a patient's T-cells to specifically target and destroy tumor cells [93]. CARs are genetically engineered fusion proteins composed of antigen recognition domain derived from a monoclonal antibody and an intracellular T-cell signaling domain and co-stimulatory domain [93].

There are multiple steps in the production of CAR T-cells and these include: (1) leukapheresis to separate leukocytes, (2) enrichment of leukapheresis product with T-cells, (3) separation of T-cell subsets at the level of CD4/CD8 composition using specific antibody-based conjugates or markers, (4) T-cell selection or activation, gene transfer or genetic modification and viral transduction, (5) volume expansion of T-cells, isolation, washing and culture followed by cryopreservation, and (6) infusion of CAR T-cells [93,94].

Adverse effects of CAR T-cell therapy include: cytokine release syndrome (CRS), neurotoxicity, on target/off tumor recognition and anaphylaxis. Additionally, theoretical toxicities of CAR T-cells include clonal expansion secondary to insertional oncogenesis, GVHD and off-target antigen recognition [95]. Management of CAR T-cell toxicity includes: supportive measures, immunosuppression with tocilizumab (IL-6) receptor blockade for CRS], and suicide or elimination genes to allow for selective depletion of CAR T-cells [95].

CAR expressing T-cells have demonstrated success in the treatment of B-cell lymphoid malignancies particularly CD19+ ALL and CLL [96]. Cell surface glycoprotein (CS1) is highly expressed on MM cells and is an ideal target for the treatment of MM i.e. CS1 can be targeted by CAR natural killer cells to treat MM [96]. A patient with advanced and refractory MM received myeloablative treatment with melphalan 140mg/m^2, followed by autologous HSCT then infusion of CTL019 CAR resulted in complete response (CR) with no disease progression for 12 months after CAR T-cell infusion [97]. CAR T-cells can target the following antigens in patients with MM: B-cell maturation antigen (BCMA), CD138, CD19 and kappa-light chain [98]. A bispecific T-cell engager (BiTE) targeting BCMA and $CD3_E$ (BI 836909) has been developed and it has been shown to be highly potent and efficacious to selectively deplete BCMA-positive MM cells thus it represents a novel immunotherapeutic approach in the treatment of MM [99]. BCMA is only expressed on: some B-cells, normal plasma cells and malignant plasma cells. The first clinical trial using CAR T-cells targeting BCMA which is expressed in most cases of MM included 12 patients [100]. Dose escalation in infusion of CAR-BCMA cells was used and the trial showed remarkable success and impressive activity against MM cells. BM plasma cells became undetectable by flowcytometry and patients entered stringent CR lasting for 17 weeks before relapse [100].

CARs are proteins that incorporate: antigen domain, co-stimulatory domains and T-cell activation domains [100]. Only a limited number of patients with MM received CAR T-cell therapy but preliminary results are encouraging [98].

Relapsed and Refractory MM

The course of MM progression is highly variable as almost all patients with MM who respond to initial therapy will eventually relapse and require further treatment [101]. The introduction of novel agents over the last 15 years, the implementation of new therapeutic strategies as well as the adoption of drug combinations that include highly effective and tolerable drugs have improved: (1) the clinical outcome dramatically as response rates have increased from approximately 30% with single agents to about 90% with combination therapies, and (2) the quality of life even in heavily pretreated patients. However, determining the optimal sequence and combination as well as timing of each agent is necessary [101]. In a retrospective analysis of 628 patients with newly diagnosed MM who developed relapse after initial therapy it was found that prolonged duration of treatment was associated with improved survival [102]. Unfortunately, secondary plasma cell leukemia and extramedullary myeloma still present difficult therapeutic challenges [11].

There is no standard of care for MM relapse after autologous HSCT [103]. Regimens that are composed of combination therapy with: (1) drugs having synergistic effect and no cross-resistance and (2) one or two novel therapies are generally preferred as they lead to deeper and longer responses that are translated into improved survival [11,103,104]. However, treatment should be individualized based on toxicity as well as patient and disease characteristics [103]. A meta-analysis of phase III randomized controlled trials showed that, compared to doublet regimens, triplets resulted in improved OS, PFS, very good partial response and CR although the risk of having grade III/IV drug adverse effects were higher with triplet regimens [104].

Mechanisms of drug resistance in MM include: (1) multidrug resistance gene polymorphism, (2) P-glycoprotein overexpression in MM cells, (3) microenvironmental changes, (4) clonal evolution, (5) cancer stem cells, (6) upregulation and downregulation of various micro-RNAs, and (7) selected CD34+, CD 138+, B7-, H1+, CD19- plasma cell accumulation after treatment [105].

Therapeutic options for patients with R/R MM include: (1) salvage therapy; combination of old and new therapies such as: (a) bortezomib, thalidomide, cisplatin, cyclophosphamide, etoposide and doxorubicin (VTD-PACE); (b) KRD/carfilzomib, pomalidomide and dexamethasone (KPD) ± PACE or (c) daratumumab based therapy, (2) second autologous HSCT, (3) allogeneic HSCT, and (4) clinical trials [5,6,8,11]. Specific agents that are used in the treatment of R/R MM include: (1) immonomodulatory agents such as thalidomide, lenalidomide and pomalidomide, (2) proteasome inhibitors such as bortezomib, carfilzomib and ixazomib, (3) monoclonal antibodies such as daratumumab, (4) monoclonal antibodies targeting SLAMF7 such as elotuzumab, and (5) histone deacetylase inhibitors such as panobinostat [83,89,101,106].

Conclusions and Future Directions

The introduction of several novel agents and targeted therapies over the last 10 years has revolutionized the management of MM and has produced unprecedented outcomes in terms of disease control and OS. Currently, novel agents and targeted therapies are used: (1) prior to HSCT to reduce tumor burden and to optimally control MM, (2) following HSCT as consolidation and maintenance therapy to allow long-term disease control, and (3) as salvage therapy in case of relapse of MM after HSCT.

However, novel agents and targeted therapies should not be considered as a form of replacement to HSCT, but instead these two valuable therapeutic interventions should be considered complimentary to each other. The smart combination of novel agents and targeted therapies with various forms of HSCT in the new treatment paradigm of MM will ultimately lead to higher cure rates and longer disease controls.

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