Frontline therapy for newly diagnosed patients with multiple myeloma

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Abstract

Since the introduction of an alkylator to the treatment of multiple myeloma (MM), new effective agents have been developed, such as immunomodulatory drugs including thalidomide, lenalidomide, and pomalidomide; proteasome inhibitors including bortezomib, carfilzomib, and ixazomib; monoclonal antibodies including daratumumab and elotuzumab; and deacetylase inhibitors including panobinostat. Numerous regimens with these new agents have been developed and they have contributed in improving survival outcomes in MM patients. In addition, the recommended therapies for newly diagnosed MM change every year based on the results of clinical trials. This review will discusses the appropriate induction therapies based on recent clinical trials for patients with newly diagnosed MM.

Key Words   Multiple myeloma, Induction therapy, Prognosis

INTRODUCTION

Multiple myeloma (MM) is a clonal B-cell malignancy characterized by anemia, hypercalcemia, renal insufficiency, osteolytic bone lesions, and decreased immune function due to aberrant proliferation of malignant plasma cells in the bone marrow [1]. MM is the second-most common hematologic malignancy and it accounts for 10% of all hematologic malignancies in the United States [2]. In Korea, the incidence of MM is lower than that in Western countries, but is increasing rapidly over the last three decades. According to the 2012 Korean data on national cancer statistics, the age-standardized incidence rate of MM in 2012 was 10 times higher than that 20 years ago [3, 4]. This increase in MM incidence in Korea is presumed to be due to aging, exposure to environmental risk and improved early detection by the expansion of health insurance, relevant education of health providers, and public awareness of this disease.

Treatment options for MM have rapidly expanded in the recent decades. In the 1980s, induction therapy with alkylating agents, such as anthracyclines and corticosteroids, as well as high-dose chemotherapy followed by autologous stem cell transplantation (HDT/ASCT) were the main treatment approaches for MM [5, 6]. However, these treatment approaches have markedly changed since the introduction of several more effective novel agents, such as proteasome inhibitors, including bortezomib, carfilzomib, and ixazomib, and immunomodulatory drugs, including thalidomide, lenalidomide, and pomalidomide. Treatment with these agents improves response rates in relapsed or refractory MM. Furthermore, their use in induction therapy resulted in considerable improvement of outcomes and extended overall survival (OS) times [7, 8]. Numerous regimens with these agents have been developed and the result of clinical trials with new regimens are reported each year. Furthermore, the recent development of monoclonal antibodies and histone deacetylase inhibitor for MM have further expanded the treatment landscape by improving deep response rate and response duration.

The purpose of this review was to suggest the optimal combination for induction therapy based on recent clinical data for newly diagnosed patients with MM.

GENERAL APPROACH FOR SELECTING INITIAL THERAPY

Risk stratification

After being diagnosed with MM, patients must be evaluated for risk classification. Although the introduction of effective new agents for MM has improved survival outcomes, response to treatment is highly variable. Some patients may survive for more than 10 years, whereas others with an aggressive course may survive for less than 2 years. In general, high-risk MM is defined as the disease subgroup with a median OS of less than 3 years in transplant-eligible patients and less than 2 years in transplant-ineligible patients [9]. Identification of this subgroup at diagnosis would be beneficial to the personalized and intensive treatment approach from the time of induction therapy.

There have been numerous studies of accurate prognostic classification, and various prognostic staging systems have been proposed. Among them, the International Staging System (ISS) proposed by Greipp *et al.* [10] in 2005 was a preferred staging system. The ISS was developed using survival data from 10,750 patients from 1981 to 2002. However, several data of patients treated with novel agents were included in the analysis for ISS, and there was a debate for the prognosis value of ISS in the era of novel agents. In 2015, the Revised ISS (R-ISS) was suggested by the International Myeloma Working Group to improve risk stratification by adding cytogenetic abnormalities and serum lactate dehydrogenase (LDH) to the original ISS [11]. Cytogenetic abnormalities in R-ISS included del(17p), t(4;14), and/or t(14;16). Using these parameters, the prognostic power of the R-ISS was improved compared to that of the ISS, and showed predictive value independent of patients' age, performance of ASCT, and treatment received. In addition to the cytogenetic abnormalities included in the R-ISS, t(14;20), gains/amplification of 1q21, and del(1p) are also considered high-risk features [9, 12]. Accumulation of these cytogenetic abnormalities is associated with poor prognosis. The study of 1,069 MM patients treated in the Medical Research Council (MRC) Myeloma IX trial firstly showed the poor prognosis of patients who had had any two of the following abnormalities: 1) adverse translocations t(4;14), t(14;16), and t(14;20); 2) gain(1q); 3) del(17p) [13]. In addition, recent genome-wide analysis of the large data set of molecular and clinical data from newly diagnosed MM, 'double hit' myeloma was defined as the presence of ≥1 of the following two adverse genetic factors: a) bi-allelic TP53 inactivation and b) amplification (≥4 copies) of CKS1B (1Q21). It constituted 6.1% of the patients and was associated with median progression-free survival (PFS) of 15.4 months and median OS of 20.7 months despite modern therapies [14]. Analysis of molecular subtype by gene expression profiling (GEP) for MM is expected to provide additional prognostic information and to help making therapeutic decisions. Several studies have reported that 15-gene, 70-gene, or 92-gene models based on GEP had prognostic significance in MM [15-17].

Imaging at diagnosis, such as MRI and ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT), has been shown to be associated with prognosis. The diffuse pattern of marrow infiltration in MRI was associated with inferior survival than that with other MRI patterns, such as focal, variegated, and normal MRI patterns [18]. In addition, the number of FDG-avid focal lesions, presence of extramedullary disease, and maximum standardized uptake value have been reported as reliable prognostic ^{18}F-FDG PET/CT parameters in MM [19-21].

Assessment of eligibility for ASCT

The Intergroupe Francophone du Myelome (IFM) study was the first randomized trial showing the superiority of high-dose melphalan and total body irradiation followed by ASCT over the conventional chemotherapy in terms of response rate, event-free survival, and OS [22]. Subsequent randomized trials have also shown that HDT/ASCT, compare to conventional chemotherapy, improved response rates and survival [6, 23]. Although there are some debates regarding the role of HDT/ASCT in MM with the emergence of new and more effective agents, upfront ASCT did lead to better response and longer PFS in a recent randomized phase 3 EMN02/HO95 trial [HR, 0.76; 95% confidence interval (CI), 0.64–0.91; *P*=0.002] [24]. In addition, a meta-analysis of three large phase 3 randomized controlled trials showed the superiority of upfront ASCT over novel agents [25]. Therefore, assessment of eligibility for ASCT at diagnosis is important to decide treatment strategy for MM. Transplant-eligible patients typically receive four to six cycles of induction therapy, followed by HDT/ASCT and then maintenance therapy until progression.

Age, generally age of 65 years, was considered a main factor in determining ASCT. However, recently, HDT/ASCT has been extended to older patients and has shown comparable outcome to that in younger patients [26, 27]. It is necessary to determine whether ASCT will proceed by evaluating frailty parameters, including performance status, organ function, and comorbidities, rather than age alone.

OPTIMAL INDUCTION THERAPY

Transplant-eligible patients

The main result of recent clinical trials in transplant-eligible patients with newly diagnosed MM are summarized in Table 1. A combination regimen of three drugs including a proteasome inhibitor is preferred for induction therapy in MM. Bortezomib, thalidomide, and dexamethasone (VTD) regimen is a preferred regimen and has been evaluated in three randomized phase III trials [28-30]. Although the dose intensity and treatment cycle of VTD were different in three randomized trials, six cycles of VTD prior to ASCT showed superior CR rate than that shown by three cycles of VTD (35% vs. 19%). In the IFM trial, patients received four cycles of VTD with lower bortezomib dose of 1.0 mg/m^2 and CR rates prior to ASCT of only 13%. However, the

Table 1. Summary of major recent clinical trials in transplant-eligible patients with newly diagnosed multiple myeloma.

Ref.	Regimen	Cycle of induction	N	CR rate prior to transplant	Median PFS	Median OS
Cavo *et al.* [28]	VTD vs.	3	236	19%	3-year PFS; 68%	3-year OS; 86%
	TD		238	5%	vs. 56%	vs. 84%
Rosiñol *et al.* [29]	VTD vs.	6	130	35%	56.2 mo	4-year OS; 74%
	TD vs.		127	14%	28.2 mo	vs. 70%
	VBMCP/VBAD/B		129	21%	35.3 mo	vs. 65%
Moreau *et al.* [31]	VTD vs.	4	169	13%	NA	NA
	VCD		169	8.9%		
Rosiñol *et al.* [33]	VRD	6	458	33.4%	NA	NA
Moreau *et al.* [37]	D-VTD vs.	4	543	39%	18 mo PFS; 93%	NA
	VTD		542	26%	vs. 85%	

Abbreviations: CR, complete response; D-VTD; daratumumab, bortezomib, thalidomide, and dexamethasone; NA, not evaluable; OS, overall survival; PFS, progression-free survival; Ref, reference; TD, thalidomide and dexamethasone; VBMCP/VBAD, vincristine, VCD, bortezomib, cyclophosphamide, and dexamethasone; VRD, bortezomib, lenalidomide, and dexamethasone; VTD, bortezomib, thalidomide, and dexamethasone.

incidence of grade 3 or 4 peripheral neuropathy was lower with reduced VTD than with four cycles of VTD or six cycles of VTD (3% vs. 10% vs. 14%). Therefore, the dose intensity and treatment duration of VTD regimen were important to achieve deep response, but increased dosing and treatment cycle were also associated with the occurrence of peripheral neuropathy.

Another effective regimen was bortezomib, cyclophosphamide, and dexamethasone (VCD). A randomized trial comparing VTD with VCD as an induction therapy was conducted in patients with newly diagnosed MM. The overall response rate after four cycles of VCD was inferior to that after four cycles of VTD (83.4% vs. 92.3%, *P*=0.01). The incidence of grade 3–4 peripheral neuropathy was higher after VTD regimen than after VCD regimen (7.7% vs. 2.9%, *P*=0.05), but hematologic adverse events was frequent in VCD regimen [31]. In a matched-pair analysis by Cavo *et al.* [32], VTD, compared to VCD, showed a threefold or higher increase in CR rate in patients with newly diagnosed MM, but resulted in higher rates of grade 3 or 4 peripheral neuropathy. Therefore, VTD regimen was superior to VCD in terms of response rate, but had a problem of high incidence of peripheral neuropathy.

Substitution of lenalidomide for thalidomide in VTD regimen may decrease peripheral neuropathy and increase response rate. The phase 3 PETHEMA/GEM2012 study evaluated the efficacy and safety of six cycles of bortezomib, lenalidomide, and dexamethasone (VRD) in 458 patients aged ≤65 years with newly diagnosed MM [33]. The CR rate after VRD induction therapy was 33.4%, and the rate of VGPR or better was 66.6%. Responses deepened throughout VRD induction therapy. Furthermore, grade 3 or 4 peripheral neuropathy occurred in only 3.9% of patients. Therefore, VRD regimen is currently being considered as a standard induction therapy.

Carfilzomib and ixazomib are promising second-generation proteasome inhibitors and have been evaluated as an induction therapy with lenalidomide and dexamethasone

for patients with newly diagnosed MM. In the FORTE trial, 158 patients received four cycles of carfilzomib, lenalidomide, and dexamethasone (KRd) induction followed by HDT/ASCT, and the rate of VGPR or better prior to maintenance was 89% in all patients and 86% in patients with R-ISS II and III [34]. Ixazomib, lenalidomide, and dexamethasone (IRd) regimen has been evaluated in a phase 2 study by IFM. Following three cycles of IRd, the rate of VGPR or better was 36%, with 12% CR. No development of grade 3 or 4 peripheral neuropathy was observed [35].

The addition of an agent to a three-drug regimen was expected to improve efficacy prior to ASCT. However, the result of the randomized EVOLUTION trial, which compared VRD plus cyclophosphamide (VDCR), VRD, and VCD, was disappointing. VDCR did not improve response rate, and its toxicities appeared to be higher than that of the other regimens, especially hematologic toxicity [36]. However, the development of monoclonal antibodies, such as daratumumab or elotuzumab, has revived our hope for four-drug regimens. In the CASSIOPEIA trial, which compared daratumumab plus VTD (D-VTD) with VTD for transplant-eligible patients, the addition of daratumumab resulted in deep response after four cycles of induction (the rate of VGPR or better, 64.9% vs. 56.1%) and improved the median PFS. Furthermore, discontinuation rate during induction was slightly lower in the D-VTD group than in the VTD group (4% vs. 6%), and the occurrence of serious adverse events, including infection, was not different in both groups [37]. Therefore, the addition of daratumumab in an induction therapy may be considered for patients who are expected to show inadequate response to three-drug regimens, such as VTD or VRD.

Transplant-ineligible patients

The main result of recent clinical trials in transplant-ineligible patients for newly diagnosed MM are summerized in Table 2.

Generally, transplant-ineligible patients receive 8 or 12

Table 2. Summary of major recent clinical trials in transplant-ineligible patients with newly diagnosed multiple myeloma.

Ref.	Regimen	Cycle of induction	N	CR rate	Median PFS	Median OS
San Miguel *et al.* [38]	VMP vs.	9	344	30%	19.9 mo	Not reached
	MP		338	4%	13.1 mo	43.1 mo
Facon *et al.* [40]	KMP vs.	9	478	25.9%	22.3 mo	NA
	VMP		477	23.1%	22.1 mo	
Facon *et al.* [41]	Rd continuous vs.	Continuous	535	22%	26.0 mo	59.1 mo
	MPT18 vs.	18	541	12%	21.9 mo	49.1 mo
	Rd18	18	547	20%	21.0 mo	62.3 mo
O'Donnell *et al.* [43]	VRD lite	9	50	44%	35.1 mo	NA
Facon *et al.* [44]	DRd vs.		368	47.6%	Not reached	NA
	Rd		369	24.9%	31.9 months	
Mateos *et al.* [45]	D-VMP vs.	9	350	42.6%	Not reached	NA
	VMP		356	24.4%	18.1 mo	

Abbreviations: CR, complete response; DRd, daratumumab, lenalidomide, and dexamethasone; D-VMP, daratumumab, bortezomib, melphalan, and prednisone; MP, melphalan and prednisone; MPT, melphalan, prednisone, and thalidomide; NA, not available; OS, overall survival; PFS, progression-free survival; Rd, lenalidomide and dexamethasone; Ref, reference; VMP, bortezomib, melphalan, and prednisone; VRD, bortezomib, lenalidomide, and dexamethasone.

cycles of induction therapy followed by maintenance therapy until progression. Melphalan-containing regimens, such as melphalan, prednisone, and thalidomide (MPT) regimen or bortezomib, melphalan, and prednisone (VMP) regimen, were the main induction therapies for transplant-ineligible patients. In the phase 3 VISTA trial, which compared VMP with MP, CR rate was higher in the VMP group than in the MP group (30% vs. 4%). In addition, the median PFS was significantly higher in the VMP group than in the MP group (24.0 mo vs. 16.6 mo, $P<0.001$). However, addition of bortezomib to MP resulted in high incidence of peripheral neuropathy and gastrointestinal toxicity [38]. In real-world practice, especially in Asian countries, VMP was also an effective induction therapy, but it caused intolerance to the original treatment schedule. Serious adverse events developed in 68.4% of patients, 14.7% of which resulted in death. Development of peripheral neuropathy was the leading cause of discontinuation [39]. Therefore, bortezomib must be injected subcutaneously to decrease peripheral neuropathy, and early dose adjustment including weekly injection of bortezomib is essential according to frailty status and adverse events. Recently, the results of the phase III CLARION study, which compared carfilzomib, melphalan, and prednisone (KMP) regimen with VMP regimen in transplant-eligible newly diagnosed MM patients, were reported [40]. The patients received nine cycles of induction therapy. Substitution of carfilzomib for bortezomib in VMP regimen did not improve outcomes in terms of CR rate, median PFS, and OS. Although grade ≥ 2 peripheral neuropathy was lower in the KMP group than in the VMP group (2.5% vs. 35.1%), acute renal failure and cardiac failure frequently developed in the KMP group.

Recently, non-alkylator-containing regimens have emerged as effective induction therapies for transplant-eligible patients. The FIRST trial evaluated survival outcomes in patients with transplant-ineligible newly diagnosed MM treated with continuous treatment of lenalidomide and dex-amethasone (Rd), 18 cycles of MPT, and 18 cycles of Rd. Continuous Rd significantly improved median PFS, compared to MPT and fixed duration of Rd (26.0 vs. 21.9 vs. 21.0 mo, respectively). Median OS with continuous Rd was superior to that with MPT, but not to that with fixed Rd (59.1 vs. 49.1 vs. 62.3 mo, respectively) [41]. Therefore, based on the FIRST trial, Rd was considered a preferred regimen for induction in transplant-ineligible patients. In addition, Rd is used as a backbone of various induction regimens for transplant-ineligible patients. In a subgroup analysis of the SWOG-S0777 trial, compared to Rd, VRD showed significantly improved survival benefits in patients aged ≥ 65 years [42]. However, there was a concern regarding the dosing schedule of VRD in elderly patients. Reduced intensity of VRD (VRD lite) with lenalidomide 15 mg at days 1–21 was evaluated in 50 elderly patients in a phase II trial [43]. Thirty-seven (74%) of patients completed nine cycles of VRD lite induction therapy, whereas 4% of patients discontinued treatment owing to adverse events. The overall response rate was 86%, including 44% CR or better. Therefore, VRD was also accepted as a standard regimen for transplant-ineligible patients, and dose adjustment according to age and frailty was also needed. The interim analysis results of a randomized phase III trial (MAIA) comparing daratumumab, lenalidomide, and dexamethasone (DRd) with Rd in transplant-ineligible patients have been reported [44]. Patients received DRd or Rd until progression. The rate of CR or better was significantly higher in the DRd group than in the Rd group (47.6% vs. 24.9%, $P<0.001$), and the median PFS in the DRd group was significantly improved compared to that in the Rd group (not reached vs. 31.9 mo, $P<0.001$). Compared to Rd, infusion of daratumumab resulted in 2.7% of grade 3 or 4 infusion-related reaction and increased infection rates. Therefore, DRd induction therapy was very effective and tolerable and expected to become a standard induction therapy for transplant-ineligible patients in the near future.

A four-drug regimen was also investigated in transplant-ineligible patients with newly diagnosed MM. A combination of daratumumab, bortezomib, melphalan, and prednisone (D-VMP) was compared with VMP in a randomized phase 3 trial (ALCYONE trial) [45]. D-VMP, compared with VMP, resulted in significantly higher rate of CR after induction therapy (42.6% vs. 24.4%, $P < 0.001$) and reduced risk of progression to 50% (HR, 0.50; 95% CI, 0.38–0.65; $P < 0.001$). In addition, compared with VMP, D-VMP showed acceptable safety profile, but more frequent development of grade 3 or 4 infections. Therefore, four-drug regimens with daratumumab were considered promising induction therapies for transplant-eligible patients.

CONCLUSION

Three-drug regimens with proteasome inhibitors or immunomodulatory drugs are currently accepted as standard induction therapies for patients with newly diagnosed MM. Substitution of a second-generation inhibitor for bortezomib increased tolerability with high efficacy in transplant-eligible patients. Addition of monoclonal antibodies led to the availability of a four-drug regimen for transplant-eligible patients, and DRd and D-VMP are emerging as promising induction therapies for transplant-ineligible patients. To date, individualized and optimized therapies according to risk status are not possible; however, selection of an induction therapy should at least be determined with considerations of the efficacy and toxicity of the regimen and the patients' frailty.

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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