International journal of clinical oncology. (2015.6) 20(3):423-430.

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Key Words;
multiple myeloma; autologous stem cell transplantation; immunomodulatory agents; proteasome inhibitors; histone deacetylase inhibitors.

Abstract

The introduction of novel molecular targeting agents against multiple myeloma has dramatically and rapidly changed the therapeutic strategies for this incurable hematologic disease. Novel agents such as thalidomide, bortezomib and lenalidomide have significantly improved the response rate, progression free survival, and overall survival as compared with conventional chemotherapies, and made it easy to control disease for a long time. Initial therapies for newly diagnosed myeloma patients are depend on the individual clinical conditions. Induction therapy with novel agents and high dose chemotherapy followed by autologous stem cell transplantation is a standard therapy for newly diagnosed younger myeloma patients. On the other hand, several combinations of novel agents and other drugs (melphalan, prednisone, dexamethasone, et al) are widely used for transplantation ineligible myeloma patients as initial therapy. Although clinical advantage of maintenance therapy after induction therapy has been reported, it is not recommend in routine practice. Maintenance therapy would be an option for some patients. Despite the great improvements of novel agents, the majority of patients eventually relapsed. A number of treatment options including novel agents, which demonstrated the marked clinical effects, are reported in salvage therapy setting. The appropriate therapy is considered by disease status or patient status in relapsed or refractory patients. Furthermore, new generation of novel agents such as pomalidomide, carfilzomib or panobinostat are recently available for relapsed or refractory myeloma. It is necessary to determine the optimal combination of drugs, administration timing and subjects to be treated in future clinical trials.

Introduction

The patients with multiple myeloma (MM) who need the systemic chemotherapy are symptomatic MM. The symptoms of MM are defined by CRAB criteria (elevated serum Calcium, Renal failure, Anemia and Bone disease) [1]. The therapy with MP (melphalan and prednisone) for MM started in 1960' and had been considered as a standard therapy for more than 40 years [2]. Several combined therapies had been developed to overcome MP and showed the superior effect of response rate. However, they could not demonstrate the prolongation of survival time [3, 4]. Clinical trials of high dose therapy (HDT) supported by autologous stem cell transplantation (ASCT) started in 1980' and showed the better results both in response rate and relapse free survival. HDT using high dose melphalan has been the standard therapy for younger adult less than 65 years at the moment [5, 6]. Recently, the development of novel molecular targeting agents such as thalidomide, lenalidomide and bortezomib has

demonstrated the significant survival advantage compared with conventional chemotherapies [7-9]. These new drugs make rapidly change the treatment strategies for MM and updated the guidelines used in USA, Europa and Japan [10-12].

Patients eligible for autologous stem cell transplantation

Retrospective study of the overall survival in MM patients at Mayo clinic showed that no significant change of median survival in the patients diagnosed during 1971 to 2000, but a significant improvement in survival was seen during 2001 to 2006 [9]. This improvement in survival was predominantly among newly diagnosed younger patients supposed to be treated with HDT-ASCT. In addition, the further improvement in survival was seen in the patients diagnosed during 2006 to 2010 [13]. Importantly, the improvement was primarily seen among patients over 65 years and closely linked to the use of new agents in initial therapy. The survival of younger patients did not change significantly despite the use of novel agents indicating the stronger impacts of the HDT-ASCT in survival for younger patients compared with novel agents. Therefore, the induction therapy followed by HDT-ASCT is considered as the primary therapy for the newly diagnosed symptomatic patients who are younger than 65 years and have no severe comorbidities.

Induction therapy and conditioning

The purpose of induction therapy is to reduce the myeloma cell burden and collect the hematopoietic stem cells for ASCT. Alkylating agents such as melphalan are thought to damage the healthy hematopoietic stem cells and disturb the stem cell collection. Induction therapy for the HDT eligible patients were VAD (vincristine, adriamycin and dexamethasone), which are not affect the stem cell collection and induces rapid myeloma cell reduction. However, VAD has not been used for induction therapy after the novel agents become clinically available. While, combination therapy containing thalidomide and dexamethasone (TD) or lenalidomide and dexamethasone (LD) showed good clinical response as induction therapy [14-18], combination therapy including bortezomib and dexamethasone (BD) is widely used instead of VAD [19-22]. Recently, addition of immunomodulatory drugs (IMiDs) such as thalidomide or lenalidomide to bortezomib-based induction therapy is also reported to be useful [23-26].

High-dose melphalan (200 mg/m^2) has been used as a standard conditioning regimen. Although total body irradiation (8 Gy) or bortezomib together with high-dose melphalan prior to ASCT was tried to improve the clinical outcome of HDT-ASCT, it is

not sufficient to conclude the standard regimen instead of high-dose melphalan alone [27, 28]. Combination of busulfan and melphalan or bendamustin and melphalan as a conditioning regimen is now under investigation [29, 30].

Consolidation and maintenance therapy

The consolidation therapy after ASCT including tandem ASCT has been reported. Tandem ASCT prolonged the event free survival (EFS) or overall survival (OS) especially for the patients who could not achieved more than very good partial response in the initial ASCT [31-33]. However, the effect of novel agents as consolidation or maintenance therapy has demonstrated that combination with bortezomib, thalidomide and dexamethasone improved the response rate in the molecular level [23, 34, 35] and bortezomib as consolidation therapy prolonged the progression free survival (PFS) [36].

The maintenance therapy after HDT-ASCT has been investigated in a number of trials. Six clinical trials with thalidomide as maintenance therapy showed a significant increase in PFS, and three of them also showed the prolongation of OS [37-39]. The maintenance therapy with thalidomide resulted in shorter OS in the patients with high risk cytogenetic abnormalities such as deletion of chromosome 13. Two clinical trials with lenalidomide as maintenance therapy after ASCT demonstrated the remarkable benefit of lenalidomide in PFS and one trial showed the significant increase in OS. However the cumulative incidence of second primary malignancies (SPM) was significantly increase in the patients treated with lenalidomide [40, 41]. The issue to be clarified is whether the lenalidomide maintenance induces the increase in SPM and whether the benefits of lenalidomide outweigh the risk of SPM in maintenance therapy after HDT-ASCT setting. Meta-analysis regarding this issue showed that 5-year cumulative risk of SPM in lenalidomide group was 6.9%, which is significantly higher than that of placebo group (4.8%, $p=0.037$), and this increased risk is closely related to oral melphalan exposure and advanced age [42]. Because the benefit of lenalidomide is obvious, it would be considerable to select this agent in maintenance therapy.

Novel and potent agents are under development and will become commercially available. These agents will result in deeper response and improve clinical outcomes. Therefore, it is not clear whether the standard therapy for younger patients is HDT-ASCT in future. Recently, randomized phase 3 study was performed to confirm the role of HDT-ASCT and maintenance therapy for newly diagnosed MM younger than 65 years. Standard high-dose melphalan followed by HDT-ASCT has significantly prolonged both PFS and OS compared with MPR (melphalan, prednisone and lenalidomide) (median PFS, 43 vs. 22.4 months, $p<0.001$; four-year OS, 81.6 vs. 65.3%,

p=0.02). In addition, maintenance therapy with lenalidomide showed a significant prolongation of PFS compared with no maintenance (41.9 vs. 21.6 months, p<0.001) [43]. This study demonstrated again the significance of deeper response and continuous maintenance therapy in younger MM patients.

Patients not eligible for autologous stem cell transplantation

Myeloma is most frequently diagnosed among people aged 65-74. Median age at diagnosis is reported 69 years old and 61.9% of the patients are more than 65 years [44]. Most elder patients over 65 years and younger patients with severe comorbidities are not eligible for HDT-ASCT. These patients are speculated about 70 % of the newly diagnosed MM.

MP was the standard therapy for these patients for 40 years until the introduction of novel agents. Currently, novel agents has been demonstrated to play the crucial role in treating ASCT ineligible patients and widely used as front line therapy for these patients. Although MP is not selected as the first choice for MM, MP is considered for the patients with poor performance status, more than 75-80 years, or some complications interrupting the use of novel agents.

Immunomodulatory agents (IMids) based therapy

The clinical studies comparing MPT (melphalan, prednisone and thalidomide) versus MP in previously untreated newly diagnosed elderly patients with MM has been reported [45-50] and meta-analysis was performed from these six randomized controlled trials. Although the patient baseline characteristics and thalidomide regimens were different in each trial, addition of thalidomide to MP significantly improved OS (median survival: MP 32.7 months vs. MPT 39.3 months, p=0.04) as well as PFS (median survival: MP 14.9 months vs. MPT 20.3 months, p<0.0001) and 1-year response rates [51]. Based on these evidences, MPT is considered one of the standard therapies for ASCT ineligible patients in Europe and America, but thalidomide is not approved for the initial therapy in Japan. Main adverse effects of thalidomide are peripheral neuropathy and deep venous thrombosis.

Lenalidomide, which is a derivative of thalidomide, is also reported to be effective for ASCT ineligible setting. The study comparing the MPR (melphalan, prednisone and lenalidomide) and MP to the patient not eligible for ASCT showed that MPR resulted in the superior effect on response rate and thought to be a promising first-line treatment for newly diagnosed elderly myeloma patients [52]. Randomized study compared MPR followed by lenalidomide maintenance (MPR-R) with MPR or MP in patients ineligible

for transplantation showed that MPR-R significantly prolonged PFS (median survival: MPR-R 31 months vs. MPR 14 months, P<0.001 or vs. MP 13 months, P<0.001) and response rates were significantly superior with MPR-R and MPR (77% and 68%, respectively, vs. 50% with MP) [53]. However, this study could not show the superiority of MPR in PFS compared with MP and the PFS benefit associated with MPR-R was not noted in patients older than 75 years of age.

Addition of lenalidomide to dexamethasone has also investigated. Lenalidomide plus high-dose dexamethasone (RD) showed to improve one-year PFS and overall response rate, whereas toxicities such as neutropenia and thromboembolic events despite aspirin prophylaxis were more pronounced compared with high-dose dexamethasone alone [18]. Non-inferiority trial of RD versus lenalidomide plus low-dose dexamethasone (Rd) as initial therapy including elder patients reported that Rd is associated with better short-term OS (one year OS: RD 87% vs. Rd 96%, p=0.0002) and with lower toxicity than RD [15]. Based on these results, large scale randomized study comparing Rd until disease progression (continuous Rd), Rd for 72 weeks (18 cycles), and MPT for 72 weeks for patients with myeloma who were ineligible for ASCT was conducted [54]. This study demonstrated that the continuous Rd significantly improved the PFS (median PFS: continuous Rd 25.5 months vs. Rd 20.7 months and MPT 21.2 months, P<0.001 for both comparisons) compared with both 18 cycles of Rd and MPT. In addition, continuous Rd reduced the risk of death at the interim analysis (4 year survival: continuous Rd 59% vs. MPT 51%, p=0.02) compared with MPT. The toxicities associated with continuous Rd (hematologic and neurologic toxic events, infections and second primary hematologic cancers) were acceptable as compared with MPT. These evidences indicate the continuous Rd will become one of the standard therapies for newly diagnosed myeloma patients ineligible for ASCT.

Bortezomib based therapy

Bortezomib, which is a proteasome inhibitor, is an only approved novel agent for initial therapy in Japan. Randomized study comparing VMP (bortezomib, melphalan and prednisone) versus MP for previously untreated HDT-ASCT ineligible patients with symptomatic myeloma showed that VMP resulted in a significant reduction in risk of death compared with MP (median OS: VMP 56.4 months vs. MP 43.1 months, p<0.001) after 5 years' follow-up despite subsequent therapy of novel-agent-based salvage therapies [55, 56]. In addition, although OS in younger patients (<75 years) was longer than elder patients (≥ 75 years), non-statistically significant differences in OS were seen among VMP treated patients with or without renal impairment and high-risk

cytogenetics such as t(4;14), t(14;16) or del(17q). However, discontinued or reduced treatment were frequently observer in this trial because of toxicities such as peripheral neuropathy in the patients received bortezomib twice per week until 4 cycles of VMP. In this regard, the efficacy and safety of modified VMP, which reduced the infusion of bortezomib from twice per week to once per week, were investigated to decrease neurologic toxicities [57]. This study showed that the PFS, OS and response rate of modified VMP were similar with those of conventional VMP. In addition, the incidence of grade 3/4 peripheral neuropathy was significantly reduced in the modified VMP (8% in the once per week vs. 28% in the twice per week, $p<0.001$) and the incidence of discontinued therapy because of peripheral neuropathy was also reduced in modified VMP (5% in the once per week vs. 15% in twice per week, $p<0.001$). Similarly, reduced intensity of bortezomib-based therapy was reported to result in effective and safe outcomes for elderly myeloma patients [58]. Subcutaneous injection of bortezomib instead of original intravenous injection is currently recommended to reduce the peripheral neuropathy without impairing the efficacy in myeloma patients [59]. Based on these results, VMP is widely used regimen in newly diagnosed patients not eligible for ASCT.

Maintenance therapy

Several maintenance therapies after the initial therapy with novel agents in patients ineligible for ASCT have been investigated. Most of these studies were performed in the sets of induction therapy followed by maintenance therapies. Maintenance therapy with thalidomide after MPT, MP or CTD (cyclophosphamide, thalidomide and dexamethasone) showed the significant improvement of PFS but the most of the studies could not confirm the prolongation of OS [45, 46, 60, 61]. Whereas thalidomide maintenance resulted in the obvious neurologic toxicities and therefore it is not generally recommended as standard therapy. Lenalidomide maintenance after MPR also improved the PFS especially in relatively younger HDT-ASCT ineligible patients but could not show the benefit in OS [53]. Continuous Rd as described above might be the option depending on the patient's condition [54]. VMPT-VT, which is combination of bortezomib, melphalan, prednisone and thalidomide (VMPT) followed by maintenance with bortezomib and thalidomide, showed the significant improvement of PFS, response rate and OS compared with VMP without maintenance therapy. However, adverse effects such as neutropenia, cardiac events and peripheral neuropathy were more frequent in the VMRT-VT patients than in the VMP patients [62, 63]. Maintenance therapy of VT (bortezomib and thalidomide) versus VP (bortezomib plus prednisone)

after VMP or VTP (bortezomib, thalidomide and prednisone) as induction therapy showed that the complete response in VT was better than that in VP but was not significantly different [58]. As described, the most effective drug combination, doses or duration of maintenance therapies for patients with not eligible for ASCT are not established as generally approved standard therapies at this moment. Maintenance therapies would be considered based on the individual patient condition such as age, performance status or comorbidity.

Relapsed or refractory patients for initial therapy

Despite the great improvements of novel agents, the majority of patients eventually relapsed or refractory for initial therapy due to drug resistance. The salvage therapies are practically very important issues to manage these patients. However, relapsed or refractory patients are quite heterogeneous populations, which contain the patients with relapse after stem cell transplantation, with primary resistant after initial therapy or with relapse after initial therapy in ASCT ineligible setting. A number of treatment options at relapse are reported and the appropriate therapy is selected by the disease status (e.g. short treatment-free interval form initial treatment, unfavorable cytogenetic factors, biochemical or clinical relapse), patients status (e.g. age, adverse effects of initial treatment, performance status, comorbidities, organ dysfunction), or the drug components used in initial therapy. The salvage therapies include HDT-ASCT, retreatment using previous chemotherapy regimens, and new regimens with different novel agents.

Second ASCT or retreatment with novel agents

Retrospective analysis on patients who underwent a second ASCT compared with conventional chemotherapy for relapsed MM after first ASCT was conducted and showed that a second ASCT significantly improved the OS and PFS, which was affected by the younger patient's age (<55 years) at second ASCT and a longer remission duration (>18 months) from first ASCT [64]. Thus, a second ASCT in relapsed MM could be a considerable option for selected patients [65]. Although allogeneic stem cell transplantation has been tried and the possibility of beneficial effects in the patients with relapsed/refractory myeloma was reported, it is not sufficient to conclude the established salvage therapy in the era of novel potent anti-myeloma agents [66, 67].

Retreatment with novel agents used in initial therapy is considered in relapsed/refractory myeloma. The meta-analysis of 23 bortezomib-based retreatment studies in relapsed/refractory myeloma has been reported that the bortezomib

retreatment is well tolerated and effective in relapsed patients [68]. Median time to progression (TTP) and OS were 7.5 and 16.6 months, respectively, and severe adverse events such as thrombocytopenia, neutropenia, and peripheral neuropathy were 35%, 15%, 3%, respectively. In addition, Patients with fewer previous therapies (≤ 4) and relapsed (not refractory) patients achieved higher improvement in TTP and OS. Retreatment with IMids especially with lenalidomide in relapsed/refractory myeloma has been also investigated. Patients who received either thalidomide-dexamethasone or lenalidomide-dexamethasone as initial therapy were retreated with IMiD (thalidomide or lenalidomide) as salvage regimens [69]. The response rate more than partial response was 44% and lenalidomide retreatment were more effective than thalidomide retreatment. Based on these evidences, retreatment would be considered for the patients who sufficiently responded to first-line novel therapy without persisting severer adverse effects at relapse.

Salvage therapy with novel agents

The novel agents make a marked progress of therapeutic strategies in relapsed/refractory myeloma in any situation of patients. Clinical evidences of many investigations revealed that the first generation of novel agents (thalidomide, lenalidomide and bortezomib) were crucial in relapsed/refractory myeloma after HDT/ASCT, or after the initial therapy with/without novel agents. Monotherapy with thalidomide, bortezomib or lenalidomide have demonstrated significant improvement in PFS, OS and response rate compared with dexamethasone alone in relapsed/refractory MM [67, 70, 71]. Furthermore, the addition of dexamethasone to these agents has resulted in further beneficial effects than monotherapy [70, 72, 73]. In addition, numerous studies have been investigated the efficacies and safeties in combination of one or two novel agents with other cytotoxic drugs such as cyclophosphamide, pegylated liposomal doxorubicin, bendamustine, vincristine or melphalan, in relapsed/refractory myeloma [10, 11].

Next generation of novel agents

The next generation of novel agents has been recently approved in USA and/or Europe for the treatment of patients with relapsed/refractory myeloma who have received at least two prior regimens, including bortezomib and IMids. Pomalidomide is a new IMids and the combination with low-dose dexamethasone resulted in the significant longer PFS (median; 4.0 months vs. 1.9 months, $p< 0.0001$) and OS (median; 12.7 months vs. 8.1 months, $p<0.0285$), and higher response rate (response rate after

median 10 months follow-up; 31% vs. 10%, $p<0.0001$) compared with high-dose dexamethasone [74]. The survival advantage of pomalidomide plus dexamethasone to high-dose dexamethasone in PFS was observed even in the patients refractory to both bortezomib and lenalidomide. The results of phase 3 clinical trial comparing the combination therapy with proteasome inhibitor carfilzomib, lenalidomide and dexamethasone (KRd) versus lenalidomide and dexamethasone (Rd) in relapsed MM have been reported [75]. The patients previously treated with bortezomib or lenalidomide were included in this trial unless they were refractory to these agents. This trial demonstrated that KRd significantly extended PFS (median; 26.3 month with KRd vs. 17.6 months with Rd, $p=0.0001$) and increased in the rate of overall response (87.1% with KRd vs. 66.7% with Rd, $p<0.001$). Furthermore, KRd is tolerable and superior health-related quality of life over 18 cycles of treatment. Finally, panobinostat, which is a potent oral pan-histone deacetylase inhibitor, was just recently approved by the U.S. Food and Drug Administration in combination with bortezomib and dexamethasone for the treatment of myeloma patients who have received at least two prior treatment regimens including bortezomib and IMids. The approval was based on the results of PFS in a subgroup of patients from a randomized, phase 3 trial comparing the combination with panobinostat, bortezomib and dexamethasone versus placebo, bortezomib and dexamethasone [76]. The median progression-free survival in all the patients was significantly longer in the panobinostat group than in the placebo group (12.0 months vs. 8.1 months, $p<0.0001$). In addition, the median PFS in the subgroup of patients who had received prior treatment with bortezomib and IMids were 10.6 months in the panobinostat group and 5.8 months in the placebo group. Grade 3-4 laboratory abnormalities and adverse events such as thrombocytopenia, neutropenia, diarrhea, asthenia or fatigue, and peripheral neuropathy were reported on the panobinostat group.

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