ORIGINAL

International Journal of Myeloma 4(1): 7–12, 2014
©日本骨髄腫学会

Comparison of bortezomib, cyclophosphamide, and dexamethasone (VCD) induction with bortezomib and dexamethasone (BD) induction for newly diagnosed symptomatic multiple myeloma

Shuichiro TAKASHIMA[1], Toshihiro MIYAMOTO[1], Tomohiko KAMIMURA[2], Goichi YOSHIMOTO[1], Koji KATO[1], Yoshikiyo ITO[2], Tsuyoshi MUTA[1], Takamitsu MATSUSHIMA[3], Motoaki SHIRATSUCHI[3], Kazuki TANIMOTO[1], Katsuto TAKENAKA[1], Hiromi IWASAKI[4], Takanori TESHIMA[4] and Koichi AKASHI[1,4]

Bortezomib exerts a synergistic anti-myeloma effect in combination with other novel agents as well as cytotoxic drugs. In this study, we examined the efficacy and safety of the combination regimen bortezomib, cyclophosphamide, and dexamethasone (VCD) in comparison with the combination regimen bortezomib and dexamethasone (BD) in Japanese patients with multiple myeloma (MM). Twenty-two newly diagnosed MM patients treated with three cycles of either BD (n = 10) or VCD (n = 12) were enrolled in this study. We found no significant difference in cumulative dose (p = 0.29) for bortezomib between the two groups, indicating that the addition of cyclophosphamide did not require reduction of bortezomib dosage. There was no significant difference in overall response rate (90% vs 83%, respectively; p = 0.57) as well as very good partial response or better response rate (40% vs 17%, respectively; p = 0.23) after treatment between the BD and VCD groups. Grade 3–4 neutropenia as well as peripheral neuropathy was comparable between the two groups (p = 0.29 and 0.19, respectively). Thus, the addition of cyclophosphamide did not exacerbate adverse events. Modification of the regimen may be necessary for further validation of the efficacy of VCD.

Key words: multiple myeloma, bortezomib, cyclophophamide, induction therapy

Introduction

The treatment of multiple myeloma (MM) has been dramatically changed by the introduction of novel agents including thalidomide, bortezomib, and lenalidomide [1]. Among these new drugs, bortezomib can rapidly achieve a profound effect, and its value in induction therapy before autologous stem cell transplantation (ASCT) was clearly demonstrated in the IFM 2005-01 Phase III trial [2]. In this study, bortezomib + dexamethasone (BD) significantly improved post-induction and post-transplantation response rates compared with vincristine + doxorubicin + dexamethasone (VAD), which was previously the standard induction therapy. Other studies also demonstrated that BD yields high response rates post-induction and post-ASCT in newly diagnosed MM patients [3,4]. These results clearly revealed that the BD regimen would be one of the efficacious induction therapies prior to ASCT in the treatment of newly diagnosed MM.

In addition, experimental data showed that the combination of bortezomib and cytotoxic agents such as melphalan or doxorubicin delivers synergic anti-myeloma effects [5,6]. In fact, the addition of a third agent to BD has been associated with higher response rates in the treatment of MM [7–9]. The major combinations of bortezomib-containing regimens include bortezomib + dexamethasone + intravenous cyclophosphamide (VCD or CyBorD), bortezomib + adriamycin + dexamethasone (PAD), bortezomib + thalidomide + dexamethasone (VTD), and bortezomib + dexamethasone + lenalidomide (VRD), although

Received: October 9, 2013, accepted: January 7, 2014
[1] Department of Medicine and Biosystemic Science, Kyushu University Graduate School of Medical Sciences
[2] Department of Hematology, Harasanshin Hospital
[3] Department of Medicine and Bioregulatory Science, Kyushu University Graduate School of Medical Sciences
[4] Center for Cellular and Molecular Medicine, Kyushu University Hospital

Corresponding author: Toshihiro MIYAMOTO, MD, PhD
Department of Medicine and Biosystemic Science, Kyushu University Graduate School of Medical Sciences, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan
TEL: 81-92-642-5230, FAX: 81-92-642-5247
E-mail: toshmiya@intmed1.med.kyushu-u.ac.jp

the optimal combination of induction therapy before ASCT remains to be determined [7–10]. Because of the high cost of treatment regimens such as VTD and VRD, VCD represents a promising candidate for initial therapy, with a high response rate equivalent to that of VRD or VTD, and several ongoing clinical trials are now evaluating the efficacy and safety of this regimen in patients with both newly diagnosed and relapsed/refractory MM [8,11–15]. However, to our knowledge, only few reports have compared the efficacy and safety of the BD and VCD regimens [16].

In Japan, the combination therapy of bortezomib with other cytotoxic agents was sanctioned in September 2011, whereas the application for lenalidomide and thalidomide as the first line of treatment for newly diagnosed MM has not been accepted at the time of submission of this article. Thus, the use of bortezomib-containing regimens such as VCD has recently been introduced for the treatment of newly diagnosed MM, and the efficacy and safety of these regimens have not yet been established for Japanese patients. In this study, we evaluated the efficacy and safety of VCD induction in the treatment of Japanese patients with newly diagnosed MM, and compared our findings with those for the BD regimen.

Patients and Methods

Patients

This was a retrospective analysis of 12 patients with symptomatic MM who were treated with three cycles of VCD regimen at Kyushu University Hospital between September 2011 and April 2013. 10 patients receiving three cycles of BD regimen between April 2010 and August 2011 were selected for the historical control group. All patients provided informed consent, and this study was approved by the Institutional Review Board of Kyushu University Hospital.

Treatment regimens

In the BD group, after short-term administration of high-dose dexamethasone, bortezomib was administered at a dose of 1.3 mg/m^2 on days 1, 4, 8, and 11, with dexamethasone (20 mg) on days 1–2, 4–5, 8–9 and 11–12. In the VCD group, bortezomib dosage was identical to that in the BD group, with the addition of cyclophophamide (500 mg/m^2 on days 1 and 8), and dexamethasone (40 mg) on days 1, 4, 8, and 11, i.e. "twice weekly VCD". In another "once weekly VCD" regimen, bortezomib was administered at a dose of 1.3 mg/m^2, plus cyclophosphamide (300 mg/m^2), and dexamethasone (40 mg) on days 1, 8, 15, and 22. Cyclophophamide was all administered intravenously.

Patients received granulocyte colony-stimulating factor, bisphosphonates, and transfusions as necessary for amelioration of therapy-related toxicities. Prophylactic antibiotics for *Pneumocystis jirovecii* and valacyclovir for herpes zoster were also administered.

Statistical analysis

The aim of this study was to compare response rates and toxicity profiles between the BD and VCD regimens as induction therapy for newly diagnosed MM. All patients were assessed for responses using the International Myeloma Working Group criteria after three cycles of treatment [17], and therapy-related toxicity was graded according to the National Cancer Institute Common Toxicity Criteria (NCI CTC) version 4.0. Chi-square testing was used for univariate comparison to examine categorical variables, and the Mann-Whitney test was used to compare numerical variables. p-value < 0.05 were considered statistically significant.

Results

Patients

Patient characteristics are summarized in Table 1. Baseline parameters (age, sex, myeloma subtype, and International Staging System stage) were similar between the two groups. G-banding cytogenetic analysis of marrow aspirates revealed a complex karyotype in one patient of the BD group and two patients of the VCD group. t(4;14) and deletion 17p13, which are regarded as high-risk cytogenetic abnormalities [18], were detected by fluorescence in situ hybridization in each one

Table 1. Patients characteristics

	BD (n=10)	VCD (n=12)	P-value
Median age (years), range	59.5 (39–70)	53.5 (34–70)	0.28
Male sex, n (%)	6 (60)	6 (50)	0.48
Myeloma type, n (%)			0.82
IgG	5 (50)	8 (67)	
IgA	1 (10)	3 (25)	
IgD	1 (10)	0	
Bence Jones Protein	2 (20)	1 (8)	
non-secretary	1 (10)	0	
karyotype, n (%)			N.E.
normal	7 (70)	10 (83)	
complex	1 (10)	2 (17)	
N.E.	2 (20)	0	
FISH, n (%)			N.E.
t(4;14)	0	1 (8)	
–17p13	1 (10)	0	
International Staging System stage, n (%)			0.37
I	3 (30)	5 (42)	
II	3 (30)	4 (33)	
III	4 (40)	3 (25)	

Abbreviations; N.E.: not examined

Table 2. Treatment exposure and response

	BD (n=10)	VCD (n=12)	P-value
Median cumulative dose of bortezomib (mg/m^2), range	15.6 (10.4–15.6)	15.6 (14–15.6)	0.29
Mean dose of bortezomib per cycle (mg/m^2), range	4.9 (3.5–5.2)	5.2 (4.7–5.2)	0.29
Best response across all cycles, n (%)			
Complete response	1 (10)	1 (8)	0.71
VGPR or better	4 (40)	2 (17)	0.23
ORR (PR or better)	9 (90)	10 (83)	0.57
Stable disease	1 (10)	2 (17)	0.57
Progressive disease	0	0	N.E.

Abbreviations; VGPR: very good partial response, ORR: overall response rate, PR: partial response, N.E.: not

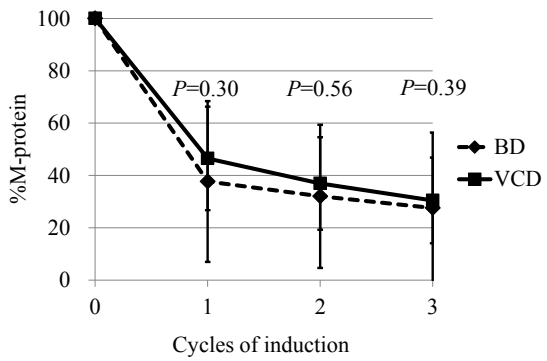

Figure 1. Reduction rates of serum M protein levels in the first three cycles. Serum levels of M protein were seriously measured after each cycle of BD or VCD regimen, and compared to that at diagnosis. Data are shown as means ± SD.

patient. Six out of 10 patients (60%) and ten out of 12 patients (83%) treated by BD and VCD regimen, respectively, underwent subsequent ASCT. Three patients received "twice weekly VCD" alone, while nine patients received "twice weekly VCD" followed by "once weekly VCD". Three out of nine patients changed the schedule from "twice weekly VCD" to "once weekly VCD" because of cytopenia, while the others changed the schedule due to the convenience in the outpatient department.

Treatment response

The median cumulative dose of bortezomib in three cycles was 15.6 mg/m^2 (range, 10.4–15.6) in the BD group and 15.6 mg/m^2 (range, 14.0–15.6) in the VCD group (p = 0.29), respectively. Complete response (CR) was achieved in one patient (10%) in the BD group and in one patient (8%) in the VCD group (p = 0.71). Of note, the patient who achieved CR in VCD group was one of the three patients received "twice weekly VCD" alone. Very good partial response (VGPR) or better response rate was 40% (4/10) in the BD group and 17% (2/12) in the VCD group (p = 0.23). Overall response rate (≥PR, ORR) was 90% (9/10) in the BD group and 83% (10/12) in the VCD group (p = 0.57). One patient remained stable disease (SD) in the BD group, while two patients remained SD in the VCD group (Table 2).

We also evaluated reduction rates per cycle for serum M-protein levels, as shown in Figure 1, to compare the parameters between the two regimens. Contrary to our expectations, there was no significant difference in reduction rates of M-protein levels between the groups.

Adverse events during VCD treatment

Adverse events observed during BD or VCD treatment are shown in Table 3. Although grade 1–4 neutropenia was more common in the VCD group than in the BD group (83% vs 30%; p = 0.02), the incidence of severe grade 3–4 neutropenia was similar between the groups (17% vs 0%; p = 0.29). No significant difference was observed in regard to thrombocytopenia and anemia between the groups (p = 0.42 and 0.45, respectively). No case in both groups required bortezomib dose reduction on account of severe cytopenia.

Peripheral neuropathy was the most common non-hematological toxicity in both groups, and the incidence and severity of peripheral neuropathy were similar between the groups (p = 0.22). Other adverse events included infection, liver dysfunction, and skin eruption, as shown in Table 3. One case in the BD group developed grade 3 bacterial pneumonia, which responded well to antibiotics, and three cycles of BD treatment were completed as scheduled. Elevated serum aspartate amino transferase (AST) and alanine amino transferase (ALT) levels were detected in two (20%) and five (42%) patients of the BD and VCD group, respectively (p = 0.27). Levels of AST

Table 3. Adverse events

	BD (n=10)	VCD (n=12)	P-value
Hematological AEs, n (%)			
Neutropenia (grade 1–4)	3 (30)	10 (83)	0.02
Neutropenia (grade 3–4)	0	2 (17)	0.29
Thrombocytopenia (grade 1–4)	8 (80)	8 (67)	0.42
Thrombocytopenia (grade 3–4)	3 (30)	2 (17)	0.41
Anemia (grade 1–4)	9 (90)	12 (100)	0.45
Anemia (grade 3–4)	1 (10)	0	0.45
Nonhematological AEs			
Peripheral neuropathy (grade 1–4)	9 (90)	8 (67)	0.22
Peripheral neuropathy (grade 3–4)	2 (20)	0	0.19
Infection (grade 1–4)	1 (10)	0	0.45
Infection (grade 3–4)	1 (10)	0	0.45
Liver dysfunction (grade 1–4)	2 (20)	5 (42)	0.27
Liver dysfunction (grade 3–4)	0	2 (17)	0.29
Skin eruption	3 (30)	1 (8)	0.23

Abbreviations; AE: adverse events

and ALT were quickly normalized with supportive care in most cases except two cases (one from each group), which required reduction of bortezomib dose. Skin eruption was documented in three patients in the BD group, and one in the VCD group ($p = 0.23$).

Concerning the difference in toxicity profiles between "twice weekly VCD" and "once weekly VCD", neutropenia and thrombocytopenia were significantly more common in the twice weekly schedule than in the once weekly schedule, although anemia and non-hematological adverse events were similar between the two schedules (data not shown).

The VCD regimen did not significantly increase the incidence and severity of hematological and non-hematological adverse events. In a total, although bortezomib dosage was reduced in two patients as mentioned above, treatment was not discontinued despite any adverse events.

Discussion

Bortezomib acts solely as a novel anti-myeloma agent [19], however, experimental studies have shown that bortezomib further augments the effects of cytotoxic agents including melphalan and doxorubicin [5,6]. On the basis of these results, the combination therapy of bortezomib and cytotoxic agents, as well as other novel agents, has been verified by several clinical trials [7–11,15,20]. In these trials, the VCD regimen was shown to provide marked response rates equivalent to those of VRD or VTD (post-induction ORR, 85%–100%) [7,9,11,20], and therefore, in terms of cost effectiveness, the VCD regimen would appear to have an advantage over VRD and VTD. Reeder et al. reported the efficacy of the CyBorD regimen as an induction therapy for 33 newly diagnosed MM patients, and demonstrated an ORR of 88% with VGPR and CR rates of 61% and 39%, respectively after four cycles of treatment [15]. In the EVOLUTION study, after a median six cycles, ORR was reportedly 75% and 100% for the original VCD (bortezomib at a dose of 1.3 mg/m^2 on days 1, 4, 8, and 11 + dexamethasone at a dose of 40 mg on days 1, 4, 8 and 11 + cyclophophamide at a dose of 500 mg/m^2 on days 1 and 8) and modified VCD (original VCD + cyclophosphamide at 500 mg/m^2 on day 15) arms, respectively, with VGPR or better response rates of 41% and 53%, respectively [11]. Considering that the usage of lenalidomide and thalidomide has not yet been sanctioned in the treatment of newly diagnosed MM in Japan, it is crucial to evaluate the efficacy and safety of the VCD regimen as an induction therapy for Japanese MM patients.

In this study, we retrospectively examined the efficacy and safety of the VCD regimen in the treatment of newly diagnosed MM patients, and compared this regimen with the BD regimen. Post-induction CR and ORR were similar between the two groups (Table 2), and the superiority of VCD over BD as shown in a previous study [16] was not demonstrated here. The relative small number of cases in our study might make it difficult to detect subtle differences in response rates between the two regimens, because the response rate in the BD group (ORR, 90%) was relatively high, as reported previously (47.0%–87.5%) [2–4,16]. To examine the effectiveness of induction therapy more precisely, we compared the reduction rates for serum M-protein levels in the first three cycles, but these were found again to be comparable between the two groups (Figure 1). In the EVOLUTION study, the increase of additional cyclophosphamide to BD enhanced treatment efficacy [11], suggesting that the amount of additional cyclophsophamide in our study might not be enough to augment the synergistic anti-myeloma effect of bortezomib. Alternatively, "once weekly VCD" regimen might have impaired the treatment efficacy of VCD in our study, because once weekly administration of bortezomib might be inferior to twice weekly administration in terms of dose intensity [21]. Thus, intensification of VCD by increase of additional cyclophosphamide to BD or intensification of bortezomib administration schedule (i.e. abolition of "once weekly VCD") might reveal the superiority of VCD over BD. "Modified VCD" employed in the EVOLUTION study might represent one of the efficacious protocols of VCD regimen.

Considering that achievement of VGPR or better response before ASCT is a strong prognostic factor for longer PFS [22], post induction VGPR or better response rates in our study (17–40%) were not satisfactory despite relative high ORR in both groups. This might be partially due to the relative small number of treatment cycles (three cycles in both groups). The maximum effect of VCD may be observed after four or more cycles of treatment, because several clinical trials with VMP therapy suggested that at least 16 bortezomib administrations were required to achieve CR [23–25]. Subcutaneous administration of bortezomib [26–28], which was sanctioned in December 2012 in Japan, might help to increase cumulative dose of bortezomib without exacerbating peripheral neuropathy.

Our study showed that the incidence of adverse events in the VCD regimen was comparable to those of the BD regimen. Neutropenia was more common in the VCD group than in the BD group, whereas the frequency of grade 3–4 severe neutropenia was similar between groups. The incidence and severity of thrombocytopenia and anemia was also comparable between the two groups. These results suggest that cyclophosphamide in combination with bortezomib and dexamethasone does not exacerbate myelosuppression. Nine out of ten patients in the BD group and eight out of 12 patients in VCD group developed peripheral neuropathy, which was the most common non-hematological adverse event in both groups. Peripheral neuropathy was tolerable and manage-

able with supportive therapy in most cases, and reduction of bortezomib dose was required in only one case. It should be emphasized that the addition of cyclophosphamide to the BD regimen did not exacerbate the incidence and severity of peripheral neuropathy as well as other non-hematological adverse events.

Despite small number of cases, the superiority of VCD over BD was not obvious in this study, and three cycles of VCD in the current form may be insufficient as an induction therapy prior to ASCT. On the other hand, when one examines the data for adverse events, induction therapy with VCD may be as safe as BD in Japanese patients. The efficacy of this regimen needs to be evaluated in an intensified fashion in combination with ASCT in the future.

Acknowledgement

We appreciate the medical and nursing staff working on Kyushu University Hospital. This work was supported by JSPS KAKENHI (24790977 to S.T.).

Conflict of Interest

The authors declare that they have no conflict of interest.

References

1) Stewart AK, Richardson PG, San-Miguel JF. How I treat multiple myeloma in younger patients. Blood. 2009; 114: 5436-43.
2) Harousseau JL, Attal M, Avet-Loiseau H, Marit G, Caillot D, Mohty M, et al. Bortezomib plus dexamethasone is superior to vincristine plus doxorubicin plus dexamethasone as induction treatment prior to autologous stem-cell transplantation in newly diagnosed multiple myeloma: results of the IFM 2005-01 phase III trial. J Clin Oncol. 2010; 28: 4621-9.
3) Harousseau JL, Attal M, Leleu X, Troncy J, Pegourie B, Stoppa AM, et al. Bortezomib plus dexamethasone as induction treatment prior to autologous stem cell transplantation in patients with newly diagnosed multiple myeloma: results of an IFM phase II study. Haematologica. 2006; 91: 1498-505.
4) Jagannath S, Durie BG, Wolf J, Camacho E, Irwin D, Lutzky J, et al. Bortezomib therapy alone and in combination with dexamethasone for previously untreated symptomatic multiple myeloma. Br J Haematol. 2005; 129: 776-83.
5) Mitsiades N, Mitsiades CS, Richardson PG, Poulaki V, Tai YT, Chauhan D, et al. The proteasome inhibitor PS-341 potentiates sensitivity of multiple myeloma cells to conventional chemotherapeutic agents: therapeutic applications. Blood. 2003; 101: 2377-80.
6) Ma MH, Yang HH, Parker K, Manyak S, Friedman JM, Altamirano C, et al. The proteasome inhibitor PS-341 markedly enhances sensitivity of multiple myeloma tumor cells to chemotherapeutic agents. Clin Cancer Res. 2003; 9: 1136-44.
7) Cavo M, Tacchetti P, Patriarca F, Petrucci MT, Pantani L, Galli M, et al. Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: a randomised phase 3 study. Lancet. 2010; 376: 2075-85.
8) Reeder CB, Reece DE, Kukreti V, Chen C, Trudel S, Hentz J, et al. Cyclophosphamide, bortezomib and dexamethasone induction for newly diagnosed multiple myeloma: high response rates in a phase II clinical trial. Leukemia. 2009; 23: 1337-41.
9) Richardson PG, Weller E, Lonial S, Jakubowiak AJ, Jagannath S, Raje NS, et al. Lenalidomide, bortezomib, and dexamethasone combination therapy in patients with newly diagnosed multiple myeloma. Blood. 2010; 116: 679-86.
10) Sonneveld P, Schmidt-Wolf IG, van der Holt B, El Jarari L, Bertsch U, Salwender H, et al. Bortezomib Induction and Maintenance Treatment in Patients With Newly Diagnosed Multiple Myeloma: Results of the Randomized Phase III HOVON-65/ GMMG-HD4 Trial. J Clin Oncol. 2012; 30: 2946-55.
11) Kumar S, Flinn I, Richardson PG, Hari P, Callander N, Noga SJ, et al. Randomized, multicenter, phase 2 study (EVOLUTION) of combinations of bortezomib, dexamethasone, cyclophosphamide, and lenalidomide in previously untreated multiple myeloma. Blood. 2012; 119: 4375-82.
12) Khan ML, Reeder CB, Kumar SK, Lacy MQ, Reece DE, Dispenzieri A, et al. A comparison of lenalidomide/dexamethasone versus cyclophosphamide/lenalidomide/dexamethasone versus cyclophosphamide/bortezomib/dexamethasone in newly diagnosed multiple myeloma. Br J Haematol. 2012; 156: 326-33.
13) Fu W, Delasalle K, Wang J, Song S, Hou J, Alexanian R, et al. Bortezomib-cyclophosphamide-dexamethasone for relapsing multiple myeloma. Am J Clin Oncol. 2012; 35: 562-5.
14) Ahn JS, Yang DH, Jung SH, Park HC, Moon JH, Sohn SK, et al. A comparison of bortezomib, cyclophosphamide, and dexamethasone (Vel-CD) chemotherapy without and with thalidomide (Vel-CTD) for the treatment of relapsed or refractory multiple myeloma. Ann Hematol. 2012; 91: 1023-30.
15) Reeder CB, Reece DE, Kukreti V, Chen C, Trudel S, Laumann K, et al. Once- versus twice-weekly bortezomib induction therapy with CyBorD in newly diagnosed multiple myeloma. Blood. 2010; 115: 3416-7.
16) Davies FE, Wu P, Jenner M, Srikanth M, Saso R, Morgan GJ. The combination of cyclophosphamide, velcade and dexamethasone induces high response rates with comparable toxicity to velcade alone and velcade plus dexamethasone. Haematologica. 2007; 92: 1149-50.
17) Durie BG, Harousseau JL, Miguel JS, Blade J, Barlogie B, Anderson K, et al. International uniform response criteria for multiple myeloma. Leukemia. 2006; 20: 1467-73.
18) Kumar SK, Mikhael JR, Buadi FK, Dingli D, Dispenzieri A, Fonseca R, et al. Management of newly diagnosed symptomatic multiple myeloma: updated Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) consensus guidelines. Mayo Clin Proc. 2009; 84: 1095-110.
19) Richardson PG, Hideshima T, Anderson KC. Bortezomib (PS-341): a novel, first-in-class proteasome inhibitor for the treatment of multiple myeloma and other cancers. Cancer Control. 2003; 10: 361-9.
20) Moreau P, Avet-Loiseau H, Facon T, Attal M, Tiab M, Hulin C,

et al. Bortezomib plus dexamethasone versus reduced-dose bortezomib, thalidomide plus dexamethasone as induction treatment before autologous stem cell transplantation in newly diagnosed multiple myeloma. Blood. 2011; 118: 5752-8; quiz 982.
21) Palumbo A, Bringhen S, Ludwig H, Dimopoulos MA, Blade J, Mateos MV, et al. Personalized therapy in multiple myeloma according to patient age and vulnerability: a report of the European Myeloma Network (EMN). Blood. 2011; 118: 4519-29.
22) Moreau P, Attal M, Pegourie B, Planche L, Hulin C, Facon T, et al. Achievement of VGPR to induction therapy is an important prognostic factor for longer PFS in the IFM 2005-01 trial. Blood. 2011; 117: 3041-4.
23) Mateos MV, Richardson PG, Schlag R, Khuageva NK, Dimopoulos MA, Shpilberg O, et al. Bortezomib plus melphalan and prednisone compared with melphalan and prednisone in previously untreated multiple myeloma: updated follow-up and impact of subsequent therapy in the phase III VISTA trial. J Clin Oncol. 2010; 28: 2259-66.
24) Palumbo A, Bringhen S, Rossi D, Cavalli M, Larocca A, Ria R, et al. Bortezomib-melphalan-prednisone-thalidomide followed by maintenance with bortezomib-thalidomide compared with bortezomib-melphalan-prednisone for initial treatment of multiple myeloma: a randomized controlled trial. J Clin Oncol. 2010; 28: 5101-9.
25) San Miguel JF, Schlag R, Khuageva NK, Dimopoulos MA, Shpilberg O, Kropff M, et al. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. N Engl J Med. 2008; 359: 906-17.
26) Kamimura T, Miyamoto T, Yokota N, Takashima S, Chong Y, Ito Y, et al. Higher incidence of injection site reactions after subcutaneous bortezomib administration on the thigh compared with the abdomen. Eur J Haematol. 2013; 52: 63-70.
27) Kamimura T, Miyamoto T, Takashima S, Yokota N, Chong Y, Ito Y, et al. Injection site reaction after subcutaneous administration of bortezomib in Japanese patients with multiple myeloma. Int J Hematol. 2012; 96: 525-7.
28) Moreau P, Pylypenko H, Grosicki S, Karamanesht I, Leleu X, Grishunina M, et al. Subcutaneous versus intravenous administration of bortezomib in patients with relapsed multiple myeloma: a randomised, phase 3, non-inferiority study. Lancet Oncol. 2011; 12: 431-40.