ORIGINAL

International Journal of Myeloma 10(2): 21–25, 2020

Impact of high serum lactate dehydrogenase in multiple myeloma in upfront autologous stem cell transplantation in the era of new drugs: A single institute experience

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We retrospectively analyzed the clinical outcomes and prognostic factors of 26 newly-diagnosed multiple myeloma (MM) patients treated with bortezomib (BTZ)-containing induction therapy prior to HDT/ASCT (BTZ group). Twenty-six patients who were not treated with BTZ were used as a historical control (control group). Compared with the historical controls, median progression-free survival (PFS) of the BTZ group was significantly longer (48.5 M vs. 21.4 M), while the median overall survival (OS) was not (not achieved vs. 76.9 M). Both post-induction- and post-ASCT-response rates were significantly better in the BTZ group compared with the controls. Multivariate analyses revealed that a high serum LDH level at diagnosis was associated with both shorter PFS and OS. The introduction of new drugs before auto-SCT improved the clinical response and PFS but did not improve OS. High LDH at diagnosis is an independent poor prognostic factor in the setting of HDT/ASCT even in the era of new drugs.

Key words: multiple myeloma, autologous stem cell transplantation, bortezomib

Introduction

Multiple myeloma (MM) is a hematological malignancy that is characterized by abnormal proliferation of clonal plasma cells in bone marrow. While the treatment outcome of MM has been improved dramatically by the use of novel agents, i.e., proteasome inhibitors and immunomodulatory drugs (IMiDs), MM still remains difficult to treat and most patients eventually relapse. Induction chemotherapy, followed by high-dose chemotherapy with autologous stem cell transplantation (HDC/ASCT) as the first-line treatment, has shown promise in prolonging progression-free survival (PFS) in newly diagnosed MM (NDMM) patients who are eligible for myeloablative HDC [1, 2]. The achievement of a deeper response by induction therapy before HDC/ASCT is expected to produce longer disease control after ASCT [3].

The incorporation of bortezomib (BTZ) into the induction therapy has shown clinical benefit for MM patients in the setting of upfront HDC/ASCT [4]. BTZ-based regimens have been used as second-line induction therapy, in case the treatment response did not achieve a very good partial response (VGPR) [5] following first-line conventional chemotherapeutic induction, i.e., high-dose dexamethasone (DEX) or the combination of vincristine, adriamycin (ADR) and DEX (VAD) from 2008 to 2011, while was utilized as the first-line induction therapy since 2011 in our institute. To assess the clinical benefit of a novel agent-containing induction regimen, we retrospectively analyzed the treatment outcomes and prognostic factors of NDMM who received BTZ-containing induction regimen followed by HDT/ASCT in our institute.

Received May 7, 2020, accepted August 22, 2020
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Patients and Therapies

A total of 26 NDMM patients who were diagnosed and treated in our institute from January 2008 to May 2017 were analyzed retrospectively. BTZ and DEX regimen (BD: BTZ (1.3 mg/m^2/day) on days 1, 4, 8 and 11, and DEX (20 mg/day) on

days 1, 2, 4, 5, 8, 9, 11 and 12, every 21 days) were mainly used from Jan 2008 to 2012, as the second-line or the first-line induction therapy. Since 2013, cyclophosphamide (CY) was added to the induction regimen (CBD: CY (300 mg mg/m^2/day) on days 1, 8, 15 and 22, BTZ (1.3 mg/m^2/day) on days 1, 8, 15 and 22, and DEX (40 mg/day) on days 1, 8, 15, and 22, every 35 days). Fourteen and 11 patients received BD and CBD, respectively. One patient received both regimens (BTZ group). As a historical control group, 26 patients treated with conventional induction therapy from 2002 to 2010 were analyzed (control group, those included all patients who had received ASCT except clincal trials or those who received subsequent allogeneic transplantation). Principally, patients received four cycles of induction therapy and then proceeded to peripheral blood hematopoietic stem cell collection. Intermediate doses of cyclophosphamide (1.5–4 g/m^2) and granulocyte colony stimulating factor (G-CSF) were utilized in the collection [6]. Sufficient amounts of CD34 positive cells (range, 2.04–98.7 × 10^6 cells/kg) were harvested from all patients. Subsequently, patients received HDC with high-dose melphalan (100 mg/m^2/day) on days –3 and –2, followed by ASCT on day 0, and G-CSF was continued from day 1 to the day of neutrophil engraftment. BTZ (1.0 mg/m^2 on days –6, –3, 1, and 4) was combined with high dose melphalan in HDC in some patients. Levofloxacin, fluconazole and acyclovir were used prophylactically against infection. The treatment response was evaluated according to the criteria established by the International Myeloma Working Group [5]. Maintenance therapy with low dose lenalidomide was administered in case the treatment response rate after ASCT did not reach the VGPR. This study was conducted in accordance with the ethical principles of the Declaration of Helsinki, and was approved by our institutional review boards.

Statistical analysis

All analyses were performed with EZR version 1.36 [7]. Overall survival (OS) and PFS were calculated using the Kaplan-Meier method, and results were compared using log-rank statistics for univariate analysis and Cox proportional hazards model for multivariate analysis. Mann–Whitney U or Student's t-tests and Fisher exact test were used for comparison of continuous or qualitative variables, respectively. P-values below 0.05 were regarded as significant. Missing data were excluded from analysis.

Results

The patients' characteristics are summarized in Table 1. No statistically significant differences were observed between the BTZ group and the historical control group, in terms of gender, age, performance status (PS), paraprotein types, disease stage according to the International Staging System (ISS) [8], serum calcium, creatinine and lactate dehydrogenase (LDH) levels, hemoglobin levels, bone lesions, and the proportion of bone marrow myeloma cells before therapy. Since chromosomal abnormality (CA) was not routinely tested in all patients, data regarding high risk CA were excluded in subsequent analysis.

The response rates before/after HDC/ASCT are also shown in Table 1. Patients receiving the BTZ-containing regimen showed superior clinical responses compared with the control group; with the rate of better than VGPR before HDC/ASCT to 62% compared with 23% in the historical control group. Similarly, the rates of better than VGPR after HDC/ASCT in the BTZ group was increased to 86%, which was still superior to control group (43%). All patients were successfully engrafted and no therapy-related deaths were observed within two months from transplantation in either group.

With median follow-up periods from the day of transplantation of 48.3 months (M) in the BTZ group and 83.2 M in the control group, the median PFS of the BTZ-regimen group was significantly longer than that of the control group (50.0 M vs. 21.4 M; P = 0.01), while the median OS was not statistically different between the two group (88.0 M in the BTZ group vs. 76.9 M in the control group; P = 0.94) (Fig. 1). Those who received maintenance therapy was significantly higher in BTZ-group, but PFS or OS was not significantly different between patients who received or not received maintenance therapy (data not shown).

We next investigated the prognostic factors that were associated with the 26 myeloma patients treated with the BTZ-containing regimen followed by HDC/ASCT. Univariate analysis revealed that a higher proportion of bone marrow myeloma cells at diagnosis (≥60%) was associated with shorter OS (47.8 M vs. not reached, P = 0.03) and that a high serum LDH level at diagnosis was associated with both shorter PFS (12.5 M vs. 64.3 M, P < 0.01) and shorter OS (63.1 M vs. not reached, P = 0.02) (Table 2). Multivariate analyses revealed that older age was significantly associated with shorter OS (HR, 7.07; 95% CI, 1.03 to 48.3; P = 0.04), while high serum LDH level at diagnosis was associated with both shorter PFS (HR, 6.31; 95% CI, 1.42 to 28.0; P = 0.01) and OS (HR, 15.8; 95% CI, 1.52 to 163; P = 0.02) (Table 2). In this study, ISS was not related with either OS or PFS.

Discussion

Wherein, we described the clinical outcome and prognostic factors of NDMM treated with BTZ containing induction therapy followed by HDC/ASCT in our institute. Several studies have reported the superiority of the BTZ-containing regimen

Table 1. Patients' characteristics and disease status at diagnosis and treatment response to the induction therapy

		BTZ group	Control group	P value
Sex, n	Male/Female	12/14	13/13	0.79
Age, median (range)		56.5 (37–68)	57.5 (40–68)	0.78
Performance status, n	0–1	23	21	0.29
	≥2	3	0	
	Missing	0	5	
Type of M protein, n	IgG	13	11	0.51
	IgA	12	15	
	Missing	1	0	
Light chain, n	κ	15	13	0.81
	λ	10	10	
	Missing	1	3	
ISS, n	1	11	7	0.78
	2	8	9	
	3	7	7	
	Missing	0	3	
Ca (mg/dl) median (range)		10.0 (8.5–13.1)	9.4 (8–12.3)	0.46
Cre (mg/dl) median (range)		0.90 (0.34–4.77)	1.2 (0.45–4.59)	0.69
Hb (g/dl) median (range)		9.9 (5.6–15.8)	10.1 (4.3–17.6)	0.90
Bone lesions, n	+/–	20/6	22/4	0.73
LDH (IU/l) median (range)		197 (114–350)	199.5 (124–323)	0.74
BM myeloma cell ratio median (range)		40.3 (8–97.6)	28.1 (5–60.8)	0.08
Treatment response before ASCT, n	sCR, CR	2	0	<0.01
	VGPR	14	6	
	PR	10	12	
	SD	0	6	
	Missing	0	2	
Treatment response after ASCT, n	sCR, CR	12	5	0.06
	VGPR	8	6	
	PR	5	10	
	SD, PD	1	5	
High-risk chromosomal abnormality, n	del(17p)	1/11	1/6	
	t(4;14)	7/24	2/11	
	t(14;16)	0/9	0/6	
Maintenance therapy, n	+/–	11/15	3/23	0.03

Abbreviations. ASCT: autologous stem cell transplantation, BM: bone marrow, BTZ: bortezomib, Ca: serum calcium, Cre: serum creatinine, Hb: hemoglobin, Ig: immunoglobulin, ISS: International Staging System, LDH: serum lactate dehydrogenase, sCR: stringent complete response, CR: complete response, VGPR: very good partial response, PR: partial response, SD: stable disease.

as the induction strategy for NDMM patients who are candidates for upfront HDC/ASCT. In the IFM 2005-01 study, the BD regimen significantly improved the response rate during post-induction therapy and resulted in a trend towards PFS prolongation compared with the conventional VAD regimen [4]. Moreover, meta-analysis of the BTZ-based versus the non-BTZ-based induction regimens showed that the use of BTZ-based induction was associated with significant improvements in the clinical response and survival in the setting of upfront HDC/ASCT in transplant-eligible NDMM [9].

Consistent with previous studies, in our current cohort, incorporation of BTZ in induction therapy was shown to significantly improve the treatment response, both before and after ASCT, and the median PFS of the BTZ group was significantly prolonged compared with that of control group. However, the median OS did not improve significantly in the BTZ group, which was likely due to the effective salvage chemotherapies implemented in the control group between 2002 and 2010 [10–13].

Despite the improvement of treatment outcome by induc-

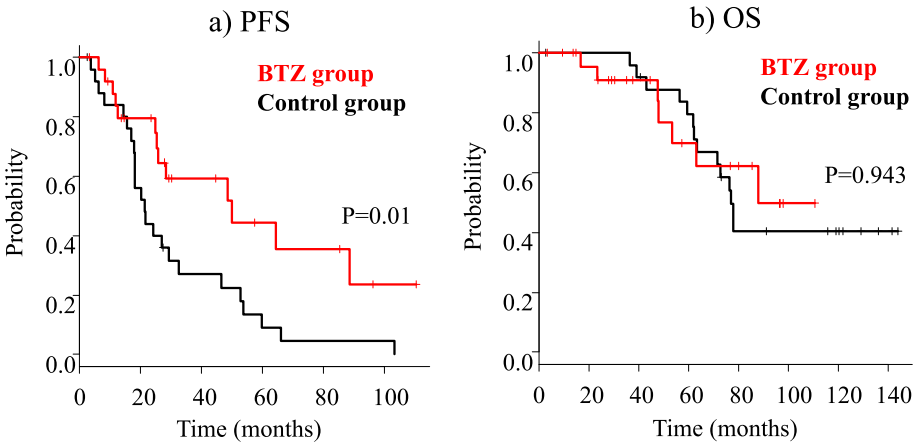

Figure 1. Survival period after autologous stem cell transplantation (ASCT). a) Progression-free survival (PFS) curves and b) Overall survival (OS) curves for the bortezomib (BTZ) and control groups.

Table 2. Univariate and multivariate analysis of factors associated with OS and PFS in MM patients in BTZ group

Univariate analysis

	OS (median, M)	P value	PFS (median, M)	P value
Age (≥61)	47.8 vs. NR	0.09	28.2 vs. 64.3	0.05
Sex (Male)	NR vs. 63.1	0.33	64.3 vs. 28.2	0.56
Performance status (≥2)	88.0 vs. NR	0.19	28.2 vs. 64.3	0.78
ISS (≥2)	NR vs. 88.0	0.58	48.5 vs. 49.9	0.51
Response before ASCT (≥VGPR)	NR vs. 63.1	0.44	48.5 vs. 49.9	0.98
Response after ASCT (≥CR)	NR vs. 88.0	0.89	48.5 vs. 49.9	0.82
BM myeloma cell ratio (≥60%)	47.8 vs. NR	0.03	18.8 vs. 49.9	0.17
Presence of bone lesions	NR vs. 88.0	0.37	48.5 vs. 88.4	0.61
Hypercalcemia (≥11mg/dl)	55.4 vs. NR	0.13	25.8 vs. 49.9	0.89
Renal dysfunction (Cre ≥1.0mg/dl)	53.3 vs. NR	0.11	25.8 vs. 49.9	0.41
Anemia (Hb < 10g/dl)	63.1 vs. NR	0.36	28.2 vs. 49.9	0.78
High LDH level (≥250 U/L)	63.1 vs. NR	0.02	12.5 vs. 64.3	<0.01
Maintenance (+)	NR vs. 88.0	0.41	49.9 vs. 48.5	0.67

Multivariate analysis

		Hazard ratio (95% CI)	P value
OS	**Age (≥61)**	**7.07 (1.03–48.3)**	**0.04**
	BM MM cell ratio (≥60%)	6.92 (0.87–55.3)	0.07
	High LDH level (≥250 U/L)	**15.8 (1.52–163)**	**0.02**
PFS	Age (≥61)	2.45 (0.72–8.37)	0.15
	High LDH level (≥250 U/L)	**6.31 (1.42–28.0)**	**0.01**

Abbreviations. OS: overall survival, PFS: progression free survival, MM: multiple myeloma, BTZ, bortezomib, ISS: international staging system, ASCT: autologous stem cell transplantation, BM: bone marrow, Cre: serum creatinine, Hb: hemoglobin, LDH: serum lactate dehydrogenase, M: months, NR: not reached.

tion therapy with novel drugs followed by HDC/ASCT, occasional early relapse and/or progression after HDC/ASCT still remains a critical problem. Among several factors that have been reported as poor prognostic factors in MM, this study revealed that high LDH level at diagnosis was an independent poor prognostic factor for PFS and OS in NDMM patients treated with the BTZ-containing induction regimen followed by HDC/ASCT. High serum LDH is suggested to reflect the aggressiveness of the disease and high tumor burden in MM and, indeed, has been incorporated as one of the risk factors in the Revised International Staging System (R-ISS) [14, 15]. This identifies an unmet need for the development of risk-

stratified therapeutic approach, i.e., more intensive induction, conditioning and/or post-ASCT treatments, for patients with high serum LDH level at diagnosis. Furthermore, it is expected that elucidating the molecular features of MM patients with high serum LDH will lead to the development of future molecular targeted therapeutics.

In conclusion, the introduction of new drugs before ASCT improved the clinical response and PFS but did not improve the OS. High serum LDH still remains as one of the poor prognostic factors, even in the era of novel agents in the setting of upfront HDC/ASCT, and the development of more effective therapeutic strategies, based on the proper identification of high-risk patients at diagnosis is necessary to improve the overall clinical outcome of MM.

Conflict of Interest

J.K. has received research funding from Celgene, Kyowa Kirin, Chugai Pharmaceutical, Ono Pharmaceutical, Sanofi, Eisai, Bristol-Myers Squibb, Sysmex, Astellas Pharma, Pfizer, Sumitomo Dainippon Pharma, Nippon Shinyaku, MSD, Fujimoto Pharmaceutical and Otsuka Pharmaceutical, has received honoraria from Janssen Pharmaceutical K.K., Celgene Corporation, Kyowa Kirin, Chugai Pharmaceutical, Ono Pharmaceutical, Sanofi, Eisai, Bristol-Myers Squibb, Astellas Pharma, Pfizer, Nippon Shinyaku, Sumitomo Dainippon Pharma, Fujimoto Pharmaceutical, AbbVie and Otsuka Pharmaceutical, and is a consultant for Janssen Pharmaceutical K.K., Celgene, Bristol-Myers Squibb, Sanofi and AbbVie. T.K. has received research funding from MSD, and has received honoraria from Chugai Pharmaceutical, Ono Pharmaceutical, Eisai, and Nippon Shinyaku.

References

1. Shinsuke I, Tadao I, Hirokazu M, Shuji O, Masahiro A, Hiroyuki H, et al. JSH practical guidelines for hematological malignancies, 2018: III. Myeloma-1. Multiple myeloma (MM). Int J Hematol 2019;109:509–38.
2. Mina R, Lonial S. Is there still a role for stem cell transplantation in multiple myeloma? Cancer 2019;183:2534–43.
3. Moreau P, Attal M, Pégourié 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.
4. 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.
5. Durie BG, Harousseau JL, Miguel JS, Bladé J, Barlogie B, Anderson K, et al. International uniform response criteria for multiple myeloma. Leukemia 2006;20:1467–73.
6. Shimura Y, Kuroda J, Uchiyama H, Kawata-Iida E, Tsutsumi Y, Nagoshi H, et al. Hematopoietic progenitor cell mobilization using low-dose cyclophosphamide and granulocyte colony-stimulating factor for multiple myeloma. J Clin Apher 2013;28: 368–73.
7. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant 2013;48:452–8.
8. Greipp PR, San Miguel J, Durie BG, Crowley JJ, Barlogie B, Bladé J, et al. International staging system for multiple myeloma. J Clin Oncol 2005;23:3412–20.
9. Sonneveld P, Goldschmidt H, Rosiñol L, Bladé J, Lahuerta JJ, Cavo M, et al. Bortezomib-based versus nonbortezomib-based induction treatment before autologous stem-cell transplantation in patients with previously untreated multiple myeloma: a meta-analysis of phase III randomized, controlled trials. J Clin Oncol 2013;31:3279–87.
10. Stewart AK, Rajkumar SV, Dimopoulos MA, Masszi T, Špička I, Oriol A, et al. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. N Engl J Med 2015;372:142–52.
11. Moreau P, Masszi T, Grzasko N, Bahlis NJ, Hansson M, Pour L, et al. Oral Ixazomib, lenalidomide, and dexamethasone for multiple myeloma. N Engl J Med 2016;374:1621–34.
12. Lonial S, Dimopoulos M, Palumbo A, White D, Grosicki S, Spicka I, et al. Elotuzumab therapy for relapsed or refractory multiple myeloma. N Engl J Med 2015;373:621–31.
13. Palumbo A, Chanan-Khan A, Weisel K, Nooka AK, Masszi T, Beksac M, et al. Daratumumab, Bortezomib, and Dexamethasone for Multiple Myeloma. N Engl J Med 2016;375:754–66.
14. Kiba T, Ito T, Nakashima T, Okikawa Y, Kido M, Kimura A, et al. Bortezomib and dexamethasone for multiple myeloma: higher AST and LDH levels associated with a worse prognosis on overall survival. BMC Cancer 2014;14:462.
15. Palumbo A, Avet-Loiseau H, Oliva S, Lokhorst HM, Goldschmidt H, Rosinol L, et al. Revised International Staging System for Multiple Myeloma: A Report From International Myeloma Working Group. J Clin Oncol 2015;33:2863–9.