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Original Article

Bortezomib in combination with chemotherapy and autologous hematopoietic stem cell transplantation in the treatment of newly diagnosed multiple myeloma patients: single-center study results

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Abstract: To evaluate the effectiveness, safety and prognosis related factors of the inductive therapy combined with autologous hematopoietic stem cell transplantation therapy as well as the initial overall scheme treatment of post-transplantation consolidation and maintenance therapy for myeloma patients suitable for autotransplantation. After the pre-treatment with intravenous melphalan and joint bortezombib, the ASCT is carried out. The one to two years of maintenance/consolidation treatment has to be done after the hematopoiesis is steady. For 17 cases receiving the traditional inducing chemotherapy and having the initial therapy of autotransplantation, the effectiveness before the general transplantation and the release depth after transplantation can be summarized, thus facilitating the analysis on the long-term existence and adverse effect on it. All of the 137 cases with the ASCT disease could obtain the hematopoietic reconstitution again, among whom, the pre-treatment is of 29 (56.9%) cases was in combination with bortezomib. The early-stage treatment reaction rate of ASCT was 100%, which could realize partial remission positively. The complete remission rate was 43.6%. The meso-position follow-up visit was 40.0 (13.2~87.1) months. The overall survival (OS) among the patients and the progressive-free survival time was 69.5 and 54.2 months respectively. The meso-position PFS time among the high-risk group and standard-risk group was 28.1 and 56.2 months respectively (P=0.016). The meso-position OS time was 43.7 and 63.0 months (P=0.032). The difference shows statistical significance. Relevant adverse effects of the treatment mainly include the oral mucosa anabrosis or erosion (89.1%), diarrhea (83.6%), peripheral nervous lesion (41.8%), herpes zoster virus infection (10.9%), and the liver function lesion (9.1%). The recovery can be realized after the hematopoietic reconstruction and symptomatic treatment. No deep venous thrombosis and lung damage are shown for patients, nor is there any infectious related death. The inducing therapy combined with ASCT taking bortezomib as the basis is considered a first-tier whole treatment scheme for patients with the multiple myeloma in accordance with the initial treatment. The scheme is safe and effective, and the curative effect can further be improved by the patients, thus getting the in-depth relief, prolonging the PFS and OS of patients, and enhancing the overall survival. In the new drug age, partial cellular genetic abnormality is still the main adverse prognostic factor affecting the survival of patients.

Keywords: Multiple myeloma, autologous peripheral blood hematopoietic stem cell, transplantation

Introduction

Multiple myeloma (MM) patients have been improved significantly due to treatment development in the recent 10 years. The high-dose chemotherapy (HDT) and autologous stem cell transplantation (ASCT), beginning from 1980s, have become a standard first-line treatment regimen [1-3] for MM patients. New medicine has been included into induction therapy to improve treatment response prior to ASCT and the consolidate and maintenance therapy are applied after transplant to further improve ease depth and extend the ease time, and more essentially, enhance the overall survival [4]. Therefore, our center has explored a lot of overall MM treatment regimen in recent years and has designed an overall regimen acceptable for patients suitable to MM transplant which took new medicine as basic induction treatment,

combined with ASCT and provided new medicine for maintenance/consolidate treatment after transplant. We observed the effect on autologous peripheral blood stem cell (PBSC) and implantation Kinetics of transplant by new medicine in combination with chemotherapy, and at the same time, summarized the efficacy before transplant and ease depth after transplant, analyze the degree and incidence of overall survival (OS), progression-free survival (PFS) and adverse reactions and determine how overall treatment efficacy effected by known adverse prognostic factors. The results of 137 MM patients who have been treated with above overall treatment regimen after newly diagnosed are reported as follows:

Patients and methods

Cases

137 MM patients suitable for transplantation after newly diagnosed and consistent with involving conditions within the period from March 1996 to August 2014 were non-randomly selected into the study. The diagnosis was in accordance with diagnosis and classification criteria [5] of hematopoietic and lymphoid tissue from WHO, and the staging used conventional Durie-Salmon (D-S) staging and international staging system (ISS) [6]. The prognosis grouping used the multiple myeloma prognostic stratification criteria [15] recommended by the Mayo Clinic study team in 2012. Since 2005, our center has carried out IFE detection and in 2007, detected the IgH rearrangement, p53 loss, 13q14 loss and 1q21 PCR by using interphase fluorescence immunoblotting (iFISH) , if IgH rearrangement turned out to be positive by FISH detection, then we need to further detect t(4,14), t(11,14) and t(14,16).

Induction treatment

The 17 MM patients were treated with an induction regimen based on conventional chemotherapy VAD (Vincristine + doxorubicin + dexamethasone). While the rest 120 were treated with an induction regimen based on new medicine, of which 10 with regimen B(/T)D (Bortezomib/Thalidomide + Dexamethasone) combined with two kinds of medicine, 25 with regimen B(/T)C(/A)D (Bortezomib/thalidomide + Cyclophosphamide/Doxorubicin + dexamethasone) combined with three kinds of medicine and 20 with regimen DPACE (±V/T) (Dexamethasone + Cisplatin + Doxorubicin + Cyclophosphamide + Etoposide ± Bortezomib/Thalidomide) combined with four or more kinds of medicine.

PBSC mobilizing collection and reinfusion: All patients were treated with HD-CTX (High-dose cyclophosphamide)/original regimen combined granulocyte colony stimulating factor (G-CSF) mobilizing PBSC. In the study, except 1 patient with poor mobilizing of bone marrow collection, the rest 136 were successfully collected with autogenous PBSC, of which 1.8 (1~4) times of median collection, 9.73 (5.35-16.85) × 10^8/kg accumulated with median collection of Mononuclear Cells (MNC), 3.78 (1.16~11.18) × 10^6/kg of CD34+ cells. The median reinfusion of MNC was 5.29 (1.20~14.50) × 10^8/kg and 2.30 (0.85-8.36) × 10^6/kg for CD34+ cells.

Transplant conditioning regimen

The conditioning regimen provides HD-Mel-200/CBV (200 mg/m^2 of Vein high-dose melphalan, -2 days, with intravenous drip) or combined with bortezomib (1 mg/m^2, -6 days, -3 days or +1 day, with intravenous injection or subcutaneous injection), patients applied with bortezomib will be combined with Dexamethasone (10~20 mg, -6 days, -5 days, -3 days, -2 days, +1 day and +2 days, with intravenous drip). We offered a melphalan or CVB regimen for conditioning (Cyclophosphamide + Vepeside + Busulfan).

Hematopoietic reconstitution

Reinfusion PBSC 0 day after transplant and record median time for the account of neutrophils (ANC) >0.5 × 10^9/L and platelet account >20 × 10^9/L.

Maintenance therapy after transplantation

The patients were provided with maintenance/consolidate treatment after transplantation, the maintenance therapy mainly use the regimen combined with Thalidomide and Dexamethasone (DT), patients with deep vein thrombosis or peripheral neuritis of 2-grade or greater will be provided maintenance therapy with Interferon or Lenalidomide, if possible,

Table 1. Detailed basic feature for patients in induction therapy group respectively based on new medicine and conventional chemotherapy

	New drug induction group n (%)	Conventional chemotherapy induction group n (%)	*P* value
Age (years)	50 (32-65)	48 (28-54)	0.056
Male vs Female	80 vs 40	12 vs 5	0.747
M protein subtype			0.357
IgA	36 (30.2)	2	
IgG	55 (46.2)	10	
IgD	7 (5.9)	1	
Light chain	19 (15.9)	2	
Oilg-secreting type	2 (1.7)	2	
D-S			0.495
I	0	0	
II	10 (8.5)	0	
III	108 (91.5)	16	
ISS			
I	30 (27.2)	1	
II	37 (33.6)	ND	
III	43 (39.1)	ND	

Table 2. Cell genetic characteristics for all patients

FISH	n	Karyotype	n (%)
IgH rearrangement	49	Normal	108 (87.8)
Del(17p)	12	Complex	7 (5.7)
1q21 amplification	34	Hypodiploid	7 (5.7)
Del(13q)	38	Hyperdiploid	2 (1.6)
t(11,14)	11	Others	4 (3.3)
t(4,14)	15		
t(11,16)	2		

patients within 1 year of transplant should be at least 2 consolidate therapy with BD regimen.

Efficacy evaluation

The efficacy evaluation should refer to MM efficacy criteria established by International Myeloma Working Group (IMWG) which was classified to Completely remission (CR), very good partial remission (VGPR), partial remission (PR), Stable disease and progression of disease (PD). Make efficacy evaluation to patient before and after the transplant and during the long term follow-up visits. Observe the patients of incidence and severity of peripheral neuritis, deep vein thrombosis, abdominal pain and diarrhea and the intestinal obstruction, and assess the adverse drug reactions on incidence of viral infection.

Follow-up visits

The follow-up visits ended at May 31 of 2015, all patients will receive the follow-up visits of more than one year. The overall survival (OS) period was defined from the diagnosis date to patient death or the end of follow-up visit, the progression-free survival (PFS) period was defined from the diagnosis date to palindromia or patient death or the end of follow-up visit.

Statistical treatment

It will use SPSS 17.0 statistical software for analysis and the data will be represented with x±s, uses pairing *t* test and χ^2 test for comparison between two groups. The rates comparison will use Fisher exact probability method and the survival analysis will use Kaplan-Meier curve evaluation. Difference of $P<0.05$ was considered statistically significant.

Results

General clinical features

Among the 137 patients, 35 cases are male and 20 of female. Median age was 50 (33~65) years old, 30 of IgG, 16 of IgA, 4 of IgD, 4 of light chain and 1 of oligosecretory secretion. 51 in III phase and 4 in II phase in D-S staging, 16, 19 and 14 (of which 6 cases were unavailable for staging) are respectively for I, II and III phase of ISS staging. The basic feature for patients in induction therapy group respectively based on new medicine and conventional chemotherapy can be seen in detail in **Table 1**, no visible demographic and baseline difference found between patients form two groups. 123 patients in total were detected with chromosome karyotype, 102 cases with molecular cytogenetics were all from induction group of new medicine, see **Table 2** about details of cytogenetic abnormalities.

Patient response to treatment

① Before transplant: After induction therapy, overall response rate of the conventional chemotherapy group is 70.6%, no patient of com-

Table 3. Univariate analysis on Effect on PFS by D-S staging, ISS staging, extramedullary invasion, pretransplant efficacy and cytogenetic abnormalities

	PFS				PFS		
	+	-	*P* value		+	-	*P* value
	Median/n	Median/n			Median/n	Median/n	
P53	28.09/102	56.41	0.004	Complex	50.00/123	50.76	0.652
1Q21	39.06/75	72.12	0.013	Hypodiploid	50.00/123	65.24	0.879
RB-1	39.06/102	56.41	0.008	Hyerdiploid	50.78/123	54.21	0.951
CCND1	54.2/95	56.41	0.581	Others	50.76/123	91.69	0.397
FGFR3	42.68	56.21	0.053	Extramedullary encroachement	28.09/120	56.21	0.058
	PFS				PFS		
		Median/n	*P* value			Median/n	*P* value
D-S	II	39.43/118	0.296	New drug induction	CR	NR/120	0.000
	III	59.76/118			PR	48.13/120	
ISS	I	72.12/110	0.010	Conventional chemotherapy	PR	30.00/17	0.012
	II	65.24/110			<PR	11.00/17	
	III	39.06/110					

Table 4. Univariate analysis on Effect on OS by D-S staging, ISS staging, extramedullary invasion, pretransplant efficacy and Cytogenetic abnormalities

	OS				OS		
	Median/n	Median/n	*P* value		Median/n	Median/n	*P* value
P53	32.65/102	NR	0.026	Complex	NR/123	NR	0.611
1Q21	67.68/75	NR	0.048	Hypodiploid	66.30/123	119.00	0.595
RB-1	69.5/102	NR	0.088	Hyerdiploid	74.15/123	NR	0.384
CCND1	NR/95	NR	0.283	Others	76.02/123	NR	0.380
FGFR3	NR	NR	0.481	Extramedullary encroachement	32.65/120	78.68	0.047
	PFS				PFS		
		Median/n	*P* value			Median/n	*P* value
D-S	II	66.30/118	1.000	New drug induction	CR	NR/120	0.123
	III	78.69/118			PR	67.86/120	
ISS	I	NR/110	0.229	Conventional chemotherapy	PR	40.00/17	0.141
	II	NR/110			<PR	30.00/17	
	III	69.52/110					

pletely remission, 4 cases (23.5%) of near to completely remission (nCR), 4 cases (23.5%) of VGPR, 4 cases (23.5%) of PR, 5 cases (29.4%) of SD. No SD patient in induction therapy based on new medicine and all (100%) are ORR, of which 41 cases (34.2%) of CR, 45 (37.5%) cases of nCR, 13 cases (10.8%) of VGPR and 21 cases (17.5%) of PR. The remission rate in induction therapy based on new medicine is much higher ($P<0.05$) and cases of deep remission are more than that of conventional therapy group ($P=0.000$) (**Table 3**). ② After transplant: 1 patient of 134 MM patients to be treated with ASCT occurred palindrome and the rest were all successfully transplanted, after transplant, the early overall response rate is 99.3% (133/134), of which PR 11.2% (15/134), VGPR 38.1% (51/134), CR 51.5% (69/134). An early treatment analysis to the 133 MM patients to be successfully transplanted showed that in induction therapy based on new medicine, there were 11 cases (9.3%) of PR, 7 cases (5.9%) of VGPR, 33 cases (27.9%) of Ncr, 67 cases (56.8%) of CR, while in conventional chemotherapy group, they were respectively PR 4 cases (26.7%), VGPR 2 cases (13.3%), nCR 8 cases (53.3%), CR 1 cases (6.7%) and we can found that the deep remission rate in new med-

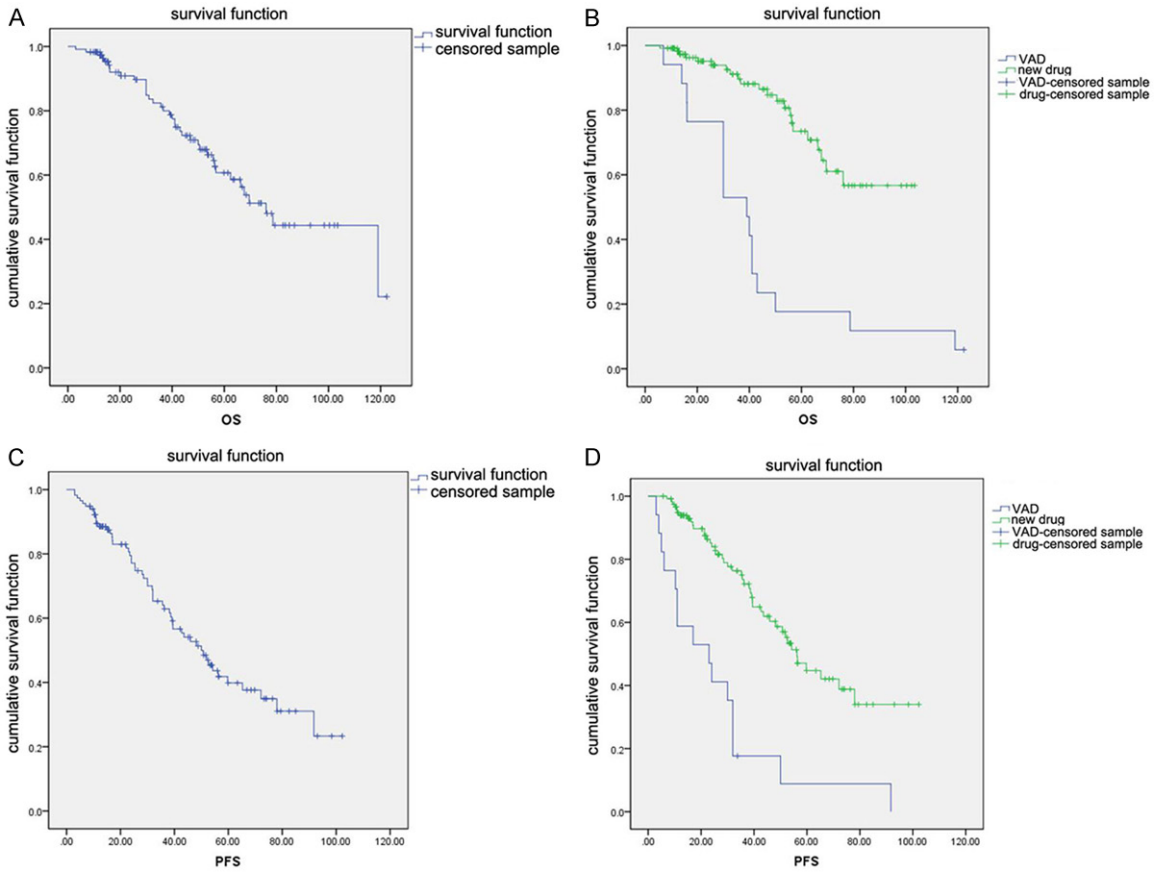

Figure 1. Analysis of long-term survival of OS in conventional chemotherapy group and new medicine based group.

icine based therapy is higher than that of conventional chemotherapy group (**Table 4**).

Hematopoietic stem cell engraftment

3 patients dead during the engraftment and the rest 134 patients succeed, the time for neutrophil engraftment (≥0.5 × 10^9/L) and infusion without platelet were respectively 11 (10~14) days and 13 (10~44) days.

Analysis of long-term survival

The follow-up visits ended at May 31 of 2015, among all the patients with a period of 35.98 (5.65~122.38) months, 22 with palindrome and 13 dead. Median PFS 50.0 months and 23.0 months for conventional chemotherapy group and PFS of three years is 17% while the in new medicine based group, the median PFS 56.2 months, 76% of PFS of three years and 43% for five years. Median OS of 76.025 months. Median PFS 39.0 months and 14% for five years of OS in conventional chemotherapy group while in new medicine based group, the median OS is 78.68 months and 73% for five years (**Figure 1**).

The known adverse factor to prognosis included: D-S staging, ISS staging, 17p loss of cytogenetic abnormalities, 1q21 amplification, RB-1, IgH/CCND1, IgH/FGFR3, IgH/MAF, complex karyotype, hypodiploid, hyperdiploid and other abnormalities, extramedullary invasion, pre-transplant remission depth. Through an univariate analysis on Effect on PFS by relevant factors, we found that only 17p loss, 1q21 amplification, RB-1, ISS staging in cytogenetic abnormalities have adverse effect while IgH rearrange, complex karyotype hypodiploid, hyperdiploid and other abnormalities had no visible effect to PFS through our overall treatment. Our study showed that no matter by conventional induction chemotherapy or new medicine based induction chemotherapy, the deeper of remission by patients before transplant, the

time for patient's survival without disease will be longer.

However, during the analysis to overall survival of patients, we found that only patients with 17p loss, 1q21 amplification and extramedullary invasion have poor prognosis and shorter surviving time, patients with other factors have relatively better prognosis.

Treatment-related toxicity

The death rate for transplant is 2.19% (3/137), there was 1 patient in new medicine induction group dead of SD, the transplant-related mortality in that group is 0.8%. While in conventional group, there were 2 patients dead during transplant with a transplant-related mortality of 11.7%, one dead from HF and another from severe infection secondary to multiple organ failure. Main adverse reactions of overall treatment included: peripheral neuropathy (41.8%), and 71.4% for peripheral neuropathy in patients treated with combination of bortezomib and thalidomide, higher than 33.3% of those not combined with thalidomide, and the latter had no PN of Grade III~IV. Infection of adverse Grade III~IV occurred 6 cases (3 each occurring during induction therapy and ASCT), there was no death of infection. 89.1% are oral ulcers or erosions and 83.6% are diarrhea, 9.1% are severe liver damage, 10.9% are zoster virus infection, they can recover by hematopoietic reconstitution and symptomatic treatment. No deep vein thrombosis (DVT) and lung injury occurred to any patient.

Discussion

In the past 20 years, the overall treatment for MM patients suitable for transplant had made great progress. Patients with treatment indications will be recommended with induction treatment combined with three kinds of medicine and then carried out collection of hematopoietic stem cells. The transplant should be made earlier or after reoccurrence still remains to be discussed. For now, high-dose melphalan is still standard regimen for pre-transplant. Patients did not reach CR after transplant should be provided with consolidate treatment, and high-risk patients will be provided with a maintenance treatment with bortezomib or lenalidomide so as to obtain long-term disease control and overall survival improvement. Applying new medicine into different phases of the MM overall regimen can change the results and be suitable for long-term disease control [5].

The induction regimen for patients suitable for transplant is expected to reduce malignant plasma cells load and increase remission depth [6]. Thus each Myeloma Cooperative Group who has worldwide reputation has made different treatment strategies to extend disease remission time and improve MM patient results [7]. The induction treatment will significantly increase remission rate and depth if combined with IMiD or PI and then further improve PFS and OS [5]. For now, standard induction treatment is the regimen combined with three kinds of medicine containing IMiD or PI while regimen combined with four or more kinds medicine failed to improve remission depth for patients in high-risk group due to adverse reaction [8, 9]. The previous study indicated that obtaining efficacy of VGPR and more implied the long-term disease control was available [10]. The induction regimen containing bortezomib designed by our center combined medicine of two, three, four and more kinds, the overall response rate is 100% with efficacy of PR and greater, of which patients obtained CR consist of 43.6%, improved a lot compared with patients provided with common chemotherapy in same phase and increased the remission depth. Currently, the clinical trials of phase III of regimen based on new medicine has not been compared, and after comparing the effect on prognosis by different induction regimen, we found that difference between PFS and OS in different group had no statistically significance (Results not shown), possibilities are lack of samples, much more regimen received during induction treatment and disunity of induction courses,

The election for ASCT time is always controversial, whether it is reasonable for patients to receive early transplant or it is preferable to delay transplant. The phase III clinical trials carried out decade ago indicated that the survival difference for patients in early period or later has no statistically significance and currently there is no clinical trials to provide effective evidence based medicine. The study by our center and many international studies showed that it was expected to help early ASCT patients obtain maximum benefit after the new medi-

cine included into overall treatment [11]. Among the patients in our center, the median PFS time is 54.2 months, PFS rate of two years is 86%, both are better than the median PFS time (38 months) for Mel 200 group of patients reported by Boccadoro [12] and PFS rate of two years (72%) for Mel group reported by Gay.

Both of the two above clinical trials did not apply bortezomib into induction and maintenance treatment which was main cause to poor results for clinical trials in our center and longer follow-up visits will be needed to determine existence of OS difference. The secondary ASCT should be provided to patients with reoccurrence at least 12-24 months after first ASCT. Double or sequential ASCT will result better to patients than single ASCT [14]. Currently, we cannot determine whether the sequential ASCT is better than the secondary ASCT after single transplant reoccurrence.

Patients did not reach CR after transplant should be provided with consolidate treatment, and high-risk patients will be provided with a maintenance treatment with bortezomib or lenalidomide so as to obtain long-term disease control and overall survival improvement [5]. We provide consolidate treatment containing bortezomib to patients available after transplant in the clinical trials to mainly determine which group of patient can benefit from consolidate treatment after clearing risk staging. However, the studies are intentional other than random clinical trials which resulting a lack of samples and no statistically significance for the moment.

Although there are more than half of patients occurred transplant-related complications in different grade which are mainly of neutropenia, thrombocytopenia, fever, mouth ulcers or erosions, diarrhea and liver dysfunction, it can be controlled and recovered after relevant anti-infection treatment, intensive care, symptomatic platelet transfusion and liver treatment. Thus it can be seen that, the MM efficacy is adequate and safety is better if provided with induction treatment based on new medicine and combined with peripheral ASCT regimen. The DT regimen used by our center for maintenance and consolidate treatment containing bortezomib can further reduce the pro-transplant residual tumor load, extend remission time and control disease in long term.

In summary, the overall treatment of new medicine combined with ASCT and then provided consolidate and maintenance treatment for MM patients suitable for bone marrow transplantation after newly diagnosed is safe and effect and has better efficacy than conventional chemotherapy, it should be regarded as one of standard treatment strategies for MM patients suitable for bone marrow transplantation after newly diagnosed.

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Disclosure of conflict of interest

None.

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