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Full Length Research Paper

Effects of bortezomib on the prognosis of the newly-diagnosed multiple myeloma patients with renal impairment

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To analyze the effects of bortezomib on the prognosis of the newly-diagnosed multiple myeloma patients with renal impairment, newly-diagnosed multiple myeloma patients with renal impairment (serum creatinine [Scr] ≥178 μmol/L) were studied in Beijing Chaoyang Hospital. According to the regimen with or without bortezomib, the patients were divided into two groups: bortezomib group (n=25) and non-bortezomib group (n=38). The outcomes of the combination therapies were evaluated. There were 63 patients who could be evaluated. The remission rate (complete remission (CR), very good partial remission (VGPR) and partial remission (PR)) of bortezomib group was higher than that of non-bortezomib group (70.8% versus 47.2%, P<0.01) especially the CR rate and VGPR rate (16.7% versus 5.6% and 25.0% versus 11.1%). There was no significant difference on the time to reversing renal function (1.4 months versus 1.5 months, P>0.05). But the ration of renal function reversal in patients with bortezomib-combined regimen was statistically higher than that of classical chemotherapy without bortezomib (79.2% versus 50%, P<0.05). The 2-year overall survival rate of bortezomib group was 69.0%, but the non-bortezomib group was 34.0%. Patients in the bortezomib group were superior to the patients in the non-bortezomib group by Kaplan-Meier analysis (P=0.041). The main toxicities in the bortezomib group included thrombocytopenia, peripheral neuropathy (PN), infection, Herpes Zoster, etc., and there was a low incidence of grade 3 and 4 adverse events. The bortezomib-based combination chemotherapy can improve the prognosis of the newly-diagnosed multiple myeloma patients with renal impairment and may become the front-line therapy for these patients.

Key words: Multiple myeloma, bortezomib, renal impairment, prognosis.

INTRODUCTION

Renal impairment is a common feature of multiple myeloma (MM) that may provide a clue to diagnosis and cause a major management problem. Depending on the definition that renal impairment is defined by a serum creatinine ≥ 178 μmol/L, this complication occurs in 20 to 40% of newly diagnosed MM patients, with up to 13% having end-stage organ dysfunction requiring dialysis support. The major causes of renal impairment are the precipitation of monoclonal light chains in distal and collecting renal tubules and hypercalcemia. Dehydration, hyperuricemia and administration of analgesics and antibiotics with nephrotoxic potential also contribute to its development. The median survival of patients with MM has been about 3 years. After the introduction of novel agents, such as bortezomib, the prognosis of myeloma patients is steadily improving. The median survival of patients with MM and renal impairment has been less than 2 years, but this figure is likely to improve with the incorporation of the novel agents including bortezomib. Bortezomib (PS-341, Velcade®; Millennium Pharmaceuticals,

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Cambridge, MA, USA) is a potent, selective and reversible proteasome inhibitor that has been shown to induce cell death in several tumors including MM. The drug has potent anti-myeloma activity in the treatment of both relapsed/refractory and newly diagnosed MM. Adverse events in patients undergoing dialysis are largely similar to those observed in controls and in those with mild-to-severe impairment, with the exception of renal and metabolic adverse events, which were found to be more common in patients undergoing dialysis. We found out that bortezomib can not only enhance the efficacy of chemotherapy, but also reverse the renal failure of the patients (Yang et al., 2010). The prognosis of the MM patients may be improved reasonably with the widespread use of bortezomib, clinically. We retrospectively summarized the efficacy of bortezomib combined chemotherapy for the newly-diagnosed multiple myeloma patients with renal impairment in order to analyze the effects of bortezomib on the prognosis of the patients.

CLINICAL DATA

Patients

Sixty-three newly-diagnosed multiple myeloma patients with renal impairment were studied in Beijing Chaoyang Hospital. All the patients must be newly-diagnosed and untreated (Kyle et al., 2009). Renal impairment was defined as a serum creatinine (Scr) ≥178 μmol/L at the time of diagnosis (Dimopoulos et al., 2010). According to the regimen with or without bortezomib, the patients were divided into two groups, bortezomib group (n=25) and non-bortezomib group (n=38). The outcomes of combination therapies were retrospectively evaluated. This study has been approved by the Ethics Committee of Chaoyang Hospital, Capital Medical University.

Therapeutic regimens

In the bortezomib group, patients were treated with PD±T regimen (bortezomib 1.0 to 1.3 mg/m^2/day: days 1, 4, 8 and d11; dexamethasone 20 to 40 mg/day: days 1 to 4; with or without thalidomide 100 mg daily; 3 weeks is one cycle) or with PAD±T regimen (bortezomib 1.0 to 1.3 mg/m^2/day: days 1, 4, 8 and 11; doxorubicin 20 mg/day: days 1 to 4; dexamethasone: 20 to 40 mg/day: days 1 to 4; with or without thalidomide 100 mg daily; 3 weeks is one cycle).

In the non-bortezomib group, the patients were treated with VAD regimen (vindesine 1 mg/day: days 1 to 4; doxorubicin 20 mg/day: days 1 to 4; dexamethasone 20 to 40 mg/day: days 1 to 4, days 9 to 12 and days 17 to 20; 4 weeks is one cycle), TAD regimen (thalidomide 100 mg daily; doxorubicin 20 mg/day: days 1 to 4; dexamethasone 20 to 40 mg/day: days 1 to 4, days 9 to 12 and days 17 to 20; 4 weeks is one cycle) or TD±CTX regimen (thalidomide 100 mg daily; dexamethasone 20 to 40 mg/day, days 1 to 4 and days 9 to 12; with or without cyclophosphamide 300 mg/m^2/day: days 1 to 5; 4 weeks is one cycle).

Besides antimyeloma treatment, all patients received intensive supportive care including intravenous hydration, alkalinization of urine, correction of hypercalcemia and discontinuation of all potential nephrotoxic agents. Renal dialysis was offered to all patients (n=18) with an appropriate indication that 8 patients were in the bortezomib group and the others in the non-bortezomib group.

Follow up and evaluation of efficacy

The endpoint of follow up was patients' death, lose to follow up or October 31, 2010. The efficacy of was evaluated as previously reported (Durie et al., 2006). The main indexes included the overall remission (OR), complete remission (CR), very good partial remission (VGPR) and partial remission (PR), in which OR equals to the summary of CR, VGPR and PR. The renal function was assessed according to the method reported by Kellum et al. (2008). The reversal of renal function was defined as the serum creatinine level was decreased and maintained at<133 μmol/L after treatment. The improved renal function was defined as that which the serum creatinine level was decreased by 50% or patients treated with hemodialysis did not receive hemodialysis after treatment. Ineffectiveness was defined as the decrease in the serum creatinine level was less than 50% or the hemodialysis continued after treatment.

Statistical analysis

Statistical analysis was performed with Statistical Processor System Support (SPSS) 13.0 statistical software. The efficacy was evaluated by Chi square test. Survival analysis was performed with Kaplan-Meier survival curve. A value of $P<0.05$ was considered statistically significant. The adverse effects were defined according to a comprehensive grading system for the adverse effects of cancer treatment developed by the national cancer institute USA (Trotti et al., 2003).

RESULTS

General characteristics

Among 63 patients, there were 35 males and 28 females with a median age of 63 years (range: 38 to 82 years). Immunoglobulin G (IgG) MM was found in 27 patients, immunoglobulin A (IgA) in 12 patients, immunoglobulin (IgD) in 9 patients, λ-light chain MM in 6 patients and κ-light chain MM in 9 patients. The stages were determined by the International Staging System for MM: stage II in 2 patients and stage III in 61 patients. The median serum creatinine level was 256 (179 to 1036 μmol/L). Among these patients, 3 patients withdrawed from the study (after 2 courses of treatment) and more than 2 courses of treatment were regularly performed in the other patients (n=24 in the bortezomib group and n=36 the non-bortezomib group). There were no statically difference in the type of M-protein, sex ratio, median age and stage of International Staging System between two groups ($P>0.05$).

Efficacy analysis

In the appraisable patients, the OR rate was 70.8% (17/24) in the bortezomib group and 47.2% (17/36) in the non-bortezomib group ($P<0.01$). Furthermore, the proportion of patients with CR or VGPR in the bortezomib group was higher than in the non-bortezomib group ($P<0.05$) (Table 1).

Table 1. Efficacy of different regimens in newly diagnosed MM patients with renal impairment.

Group	Patient number	CR rate	VGPR rate	PR rate	Overall effective rate
Bortezomib	24	4/24% (16.7)	6/24% (25.0)	7/24% (29.2)	17/24% (70.8)
Non-bortezomib	36	5.6% (2/36)*	11.1% (4/36)*	11/36% (30.6)	17/36% (47.2)**

*Compared with the bortezomib group, P < 0.05. **Compared with the bortezomib group, P < 0.01.

Table 2. Impact of different group on renal function of newly diagnosed MM patients.

Group	Number	Reversal of renal function	Improvement in renal function	Overall effective rate	Median time to renal function reversal (%)
Bortezomib group	24	8/24% (33.3)	11/24% (45.8)	19/24% (79.2)	0.7 - 3% (1.4)
Hemodialysis patients	8	0	6/8% (75.0)	6/8% (75.0)	-
Non-bortezomib group	36	5/36% (13.9)	13/36% (36.1)	18/36% (50.0)*	1 - 3% (1.5)§
Hemodialysis patients	10	0	4/10% (40.0)	4/10% (40.0)	-

*Compared with the bortezomib group, P < 0.05; §Compared with the bortezomib group, P > 0.05.

Reversal of renal function

As shown in Table 2, no significant difference in the time to renal function reversal was observed between the two groups (1.4 and 1.5 months, P>0.05). However, the percentage of patients with improvement in renal function (improved renal function and renal function reversal) in the bortezomib group was markedly higher than in the non-bortezomib group (79.2% versus. 50.0%, P<0.05).

Prognosis and outcome

The median follow up period was 13 months (range: 3 to 24 months) in the bortezomib group (n=24) and the 2-year overall survival rate of bortezomib group was 69.0%. However, the median follow up period was 12 months (range: 1 to 80 months) in the non-bortezomib group (n=36) and the 2-year overall survival rate of bortezomib group was 34.0%. The patients in the bortezomib group were superior to the patients in the non-bortezomib group by Kaplan-Meier analysis (P=0.041) (Figure 1). All the patients that died early in the study had significantly increased serum creatinine levels at initial diagnosis, in whom 6 patients were initially diagnosed as “primary renal failure” resulting in long-lasting misdiagnosis and mistreatment (3 to 13 months).

Toxicities

The main toxicities in the bortezomib group included thrombocytopenia, peripheral neuropathy (PN), infection, Herpes Zoster, etc. In the non-bortezomib group, the toxicities were infection, myelosuppression, etc. The incidence of grade 3 and 4 adverse events was low (Table 3). The thrombocytopenia in the bortezomib group was reversible. Once the treatment is discontinued, the amount of platelet reached the normal level or the pre-treatment level.

DISCUSSION

The remission rate (CR, VGPR and PR) of bortezomib group was higher than that of non-bortezomib group (70.8% versus 47.2%, P<0.01), especially, the CR rate and VGPR rate (16.7% versus 5.6% and 25.0% versus 11.1%). There was no significant difference on the time to reversing renal function (1.4 months versus 1.5 months, P>0.05). But the ratio of renal function reversal in the patients with bortezomib-combined regimen was statistically higher than that of classical chemotherapy without bortezomib (79.2% versus 50%, P<0.05). The 2-year overall survival rate of bortezomib group was 69.0%, but the non-bortezomib group was 34.0%. Patients in the bortezomib group were superior to patients in the non-bortezomib group by Kaplan-Meier analysis (P=0.041). The main toxicities in the bortezomib group included thrombocytopenia, peripheral neuropathy (PN), infection, Herpes Zoster, etc., and there was a low incidence of grade 3 and 4 adverse events. The bortezomib-based combination chemotherapy can improve the prognosis of the newly-diagnosed multiple myeloma patients with renal impairment and may become the front-line therapy for these patients.

Renal impairment is one of the severe complications of MM. The most common cause is irreversible cast nephropathy secondary to excess serum free light chains, while, in many instances, renal impairment associated with MM may be linked to additional reversible complications including volume depletion, hypercalcemia,

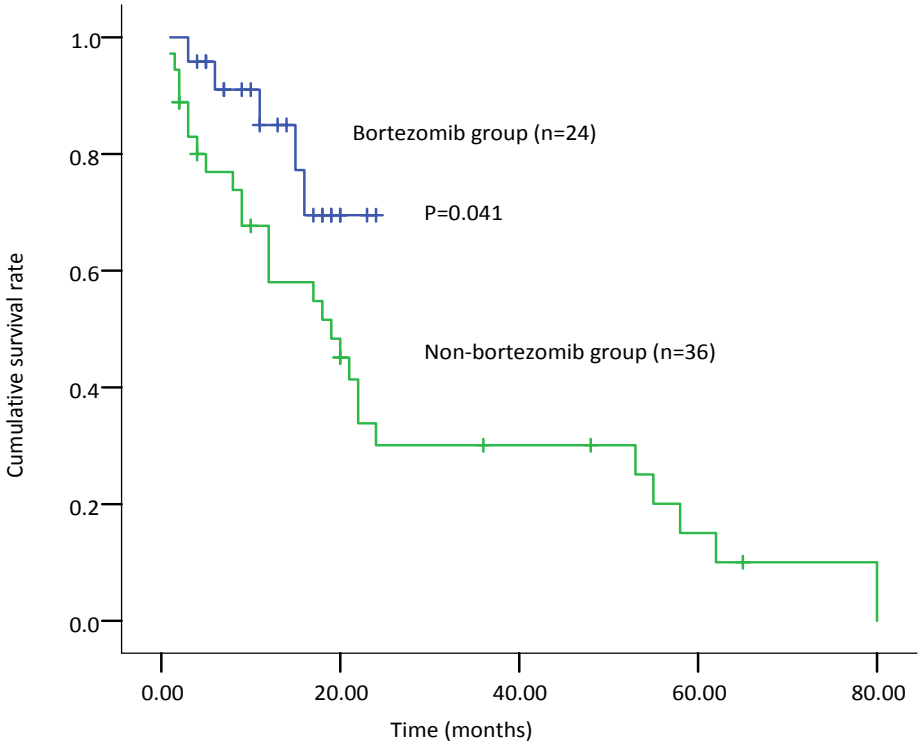

Figure 1. Survival analysis of patients in each group. The median follow up period was 13 months (range: 3 to 24 months) in the bortezomib group (n=24) and the 2-year overall survival rate of bortezomib group was 69.0%. The median follow up period was 12 months (range: 1 to 80 months) in the non-bortezomib group (n=36) and the 2-year overall survival rate of bortezomib group was 34.0%. The patients in the bortezomib group were superior to the patients in the non-bortezomib group by Kaplan-Meier analysis (P=0.041).

Table 3. Incidence of toxicities in each group.

Toxicities	Bortezomib group (n=24)	Non-bortezomib group (n=36)
Myelosuppression		
Grade 1 - 4	12.5%(3/24)	16.7%(6/36)
Grade 3 - 4	0%(0/18)	5.6%(2/36)
Thrombocytopenia	25.0%(6/24)	8.3%(3/36)
Infection	20.8%(5/24)	33.3%(12/36)
Herpes Zoster	16.7%(4/24)	5.6%(2/36)
Peripheral neuropathy		
Grade 1 - 4	37.5%(9/24)	11.1%(4/36)
Grade 3 - 4	8.3%(2/24)	0%(0/36)

exposure to contrast material, non-steroidal anti-inflammatory drugs, angiotensin converting enzyme inhibitors and tumor lysis syndrome. The mortality in MM patients with acute renal failure is as high as 30% within the initial 2 months, but that in MM patients with normal renal function was only 7% (Augustson et al., 2005). Haynes et al. (2010) summarized the clinic characters of the MM patients with severe renal failure (Scr ≥500 μmol/L) (n=107) in a single center. The incidence was about 5% and the median survival was only 10.2 months. In addition, in patients with long lasting misdiagnosis (primary renal failure) and mistreatment, the probability of renal function reversal was extremely low. Therefore, early, active and effective treatment is crucial for favorable outcomes.

Bortezomib is a proteasome inhibitor and has powerful

anti-myeloma activity. It can improve renal function through decreasing the level of monoclonal light chain and suppressing nuclear factor-κb in the tubular cells leading to improved inflammatory response (Kaposztas et al., 2009). The metabolism of bortezomib is independent of the kidney and not affected by renal function. Therefore, the dose of bortezomib is not required to be adjusted in patients with renal impairment. More recently, serum cystatin-C, a marker of renal impairment and tumor burden was reduced after bortezomib therapy, thus reflecting drug-induced anti-myeloma activity and possibly a direct effect on renal function. This provided the theoretical basis of the therapy with bortezomib for the MM patients with renal impairment (Chen, 2008).

Bortezomib-based combination treatment with dexamethasone, or with the addition of doxorubicin or with melphalan-prednisone, has been shown to be highly effective and to rapidly induce tumor response. In a phase II study, Ludwig et al. (2010) treated the MM patients with light chain-induced acute renal failure (n=68) with bortezomib-doxorubicin-dexamethasone (BDD) therapy. By intent-to-treat analysis, a myeloma response was obtained in 72% of 18 previously and 50 not previously treated patients (CR/near CR [nCR], 38%; VGPR, 15%; PR, 13%; minor response [MR], 6%). Renal response was achieved in 62% of patients (renal CR, 31%; renal PR, 7%; renal MR, 24%). Median progression-free survival was 12.1 months. One- and 2-year survival rates were 72 and 58%, respectively. The most common grade 3 or 4 toxicities were infection (19.1%), thrombocytopenia (14.7%), neutropenia (14.7%), fatigue/weakness (10.3%) and polyneuropathy (8.8%). In our study, we found out that the combined regimens with bortezomib were superior to the conventional chemotherapy without bortezomib, the incidence of severe toxicities was low, and the patients had good tolerance and maybe a longer survival.

Other investigators also applied bortezomib based chemotherapy in 20 patients with newly diagnosed or recurrent or refractory MM (Roussou et al., 2008). About 40% of the patients achieved renal function reversal and the median time to renal function reversal was 17 days. In addition, decrease in the serum creatinine level was greater than 50% in 10 patients with a median time of 35 days. These results were consistent with our study. Furthermore, the toxicities in MM patients with renal impairment after bortezomib treatment were similar to those with normal renal function.

To summarize, our study along with those of the literature provides evidence for the efficacy and safety of bortezomib-based regimens in the subset of MM patients with renal impairment. Early diagnosis and early, active and effective treatment are critical for the newly diagnosed MM patients with renal impairment. Our study indicated that the bortezomib-based combination chemotherapy can improve the prognosis of the newly-diagnosed multiple myeloma patients with renal impairment and may become the front-line therapy for these patients. However, due to the small sample size and the retrospective analysis of the study, further controlled studies are required.

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