Efficacy and Safety of Bortezomib Combined with the Chemotherapeutic Regimen in the Treatment of Mantle Cell Lymphoma and Follicular Lymphoma: A Meta-analysis

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Abstract. Objective: To systematically evaluate the efficacy and safety of bortezomib with chemotherapy in the treatment of mantle-cell lymphoma and follicular lymphoma. Methods: Randomized controlled clinical trials are conducted. Odd ratios and 95% confidence intervals were applied to pool the effect size. Results: This study identified 3 eligible studies, including 1179 patients with mantle-cell lymphoma or follicular lymphoma. Bortezomib-based chemotherapy treatment was presented to increase the proportion of complete response (OR=1.56, 95%CI=1.20-2.02) in a fixed-effect model, with no heterogeneity among the three studies ($I^2=0.0\%$, $P=0.883$). Odd ratios of overall response (OR=1.61, 95%CI=0.81-3.20) had no statistically significant difference; however, the heterogeneity was significant among the three studies ($I^2=64.5\%$, $P=0.060$). The risk of any adverse events (grade≥3) and peripheral neuropathy (all grades) were estimated by Odd ratios. There was an increasing risk of any adverse events (grade≥3) in the group with bortezomib (OR=3.15, 95%CI=2.26-4.40), with no heterogeneity ($I^2=0.0\%$, $P=0.594$). No significant difference was founded to estimate the risk of peripheral neuropathy (all grades) (OR=4.14, 95%CI=0.43-40.23), and we examined a considerable heterogeneity ($I^2=92.2\%$, $P=0.000$). Conclusion: The chemotherapy protocol with bortezomib is superior to the protocol without bortezomib according to CR. The regimen with bortezomib increases the incidence of any adverse effects (grade≥3) with no statistical difference of peripheral neuropathy (all grades).

Introduction

Mantle-cell lymphoma (MCL) and follicular lymphoma (FL) account for approximately 4-7% [1,2] and 22% [3] of non-Hodgkin’s lymphoma (NHL). Both MCL and FL are generally incurable, distinct and typically aggressive subtype of B-cell NHL. Additionally, both of them have unfavorable long-term outcomes and MCL just have a median failure-free survival of 12 to 16 months [4,5]. R-CHOP (rituximab with cyclophosphamide, vincristine, doxorubicin, prednisone) is employed as the standard chemotherapy regimen for MCL [5], while the median overall survival of FL has improved over the past few years [6]. However, the relapsing course is still a quintessential and crucial problem.
Bortezomib as a proteasome inhibitor is initially applied to a front-line therapeutic approach in multiple myeloma, and it has been employed to treat for B-cell NHL [7]. The antineoplastic effect of bortezomib encompasses different mechanisms, such as impairing cell-cycle progression, promoting cell apoptosis, blocking NF-kB [8-11], indicating it could contribute to treat MCL and FL. A multitude of results confirm that bortezomib plays an indispensable role in newly diagnosed MCL or in relapsed/refractory MCL, and predictable and under-controlled toxicities are still unsettled [12,13]. Addition of bortezomib to rituximab alone or plus other chemotherapy drugs showed anti-tumor effect and well tolerability in early-phase studies of MCL and FL [2,14-18]. Although different chemotherapy regimens are applied in MCL and FL with a great progress, relapsed cases and some adverse events should be taken into considered. Bortezomib presented well effect in the patients suffered from relapsed/refractory MCL and FL [19,20]. Bortezomib with R-CHOP are approved to be safe and results are enhanced justifying by randomized studies compared with R-CHOP alone [21].

Up to now, there is no published data investigating the efficacy and safety between the randomized groups with or without bortezomib in MCL and FL. It is feasible to compare the regimens for providing a novel therapeutic direction. So we conducted a meta-analysis to evaluate the efficacy and safety of bortezomib-based or non-bortezomib-based treatment in MCL and FL.

Methods

Search Strategy and Study Selection

Pubmed (2006 to May 2016), ISI Web of science (2006 to May 2016) and the Cochrane central register of controlled trials were searched. The following search terms utilized were “bortezomib”, “velcade”, “mantle cell lymphoma”, “follicular lymphoma”. There were no restrictions on language, journal type, or publication date. All papers were examined by the EndNote to exclude the duplication after identified by the initial search. In accordance with the criteria for inclusion or exclusion, eligible studies were selected finally. Forums or other libraries were courted to contribute the full text or complete papers since some trial reports were published only as abstracts.

Criteria for Inclusion

The eligible studies had to meet the following criteria: 1) the papers should be randomized-controlled trials; 2) all patients were diagnosed with MCL or FL; 3) the group with bortezomib and without were matched in age, sex, ECOG scores and serum LDH level; 4) the international curative effect evaluation standard proposing the assessment of efficacy and disease recurrence [22]; 5) the results were presented in complete response (CR), overall response (OR), any adverse events (AE) (grade≥3) and peripheral neuropathy (PN) (all grades); 6) publication as a full paper.

Criteria for Exclusion

Studies were excluded based on the following criteria: 1) non-randomized studies, duplicated studies, reviews, letters, unpublished data, and comments; 2) the original article could not give the chance to extract or calculate the data; 3) non-human subjects; 4) including non-lymphoma patients.
Data Extraction

All data of the eligible studies were extracted independently by two investigators (Wei and Wu). And any disagreement about the abstracted data was resolved by consensus. Additionally, the following clinical outcomes were extracted: first author, year of publication, country of origin, sample size, clinical stage, chemotherapy regimen (including dose and schedule of individual drugs with it), CR, OR, overall number of AE (grade≥3) and PN (all grades) reported. We just browsed other end points, such as duration of follow-up, duration of response (DOR), progression-free survival (PFS) and overall survival (OS) rates, but not directly compared in this meta-analysis.

Data Synthesis and Statistical Analysis

Among the three studies heterogeneity was evaluated by the Cochrane I-square to determine whether significant statistical heterogeneity existed in the pooled estimates. Statistical heterogeneity was gonging to define a significant meaning when the pooled data drew a $P$ value $<0.1$ [23]. Additionally, $I^2$ values of 25%, 50% and 75% were considered low, moderate and high degrees of heterogeneity, respectively; therefore we measured the degree of heterogeneity through the index of $I^2$ among the included publications. A random effects model was used to pool the data. However, if the $P$-value was more than 0.10 and $I^2$ test less than 30% assessing the heterogeneity, we would use the fixed effects model; otherwise, the random effects was employed. Actually, if high heterogeneity existed, we would prefer to adopt a random effects model and give sensitivity analysis or explanation, whereas the fixed effects model just assumed similar true genetic effects between the studies [24]. The proportions of CR, OR, AE (grade≥3) and PN (all grades) were measured by odd ratios (ORs) and 95% confidence intervals (CI).

Stata/SE 12.0 analysis software (Stata Corporation, College Station, TX, USA) was used to generate the Forest plots of pooled ORs for results with their associated 95% CI. All statistical texts were two-side.
Results

Description of Studies Included

- citations identified by search strategy (n=263, Pubmed=14, Cochrane=42, ISI Web of science=207)
  - irrelevant, duplicates or not original articles identified (n=135)
  - potential citations concerning the current topic (n=128)
    - title and abstract revealed not appropriate (n=111)
  - full-text articles assessed for eligibility (n=17)
    - excluded: non-randomized study (n=4)
    - without useful data (n=10)
    - duplicated data(n=1)
  - publications included (n=3):
    - VR-CAP vs R-CHOP are treated with newly diagnosed MCL (n=1)
    - Addition of bortezomib to CHOP in the relapsed MCL (n=1)
    - BR vs rituximab in the relapsed FL (n=1)

Figure 1. Flow diagram of assessment of studies identified in the meta-analysis.

Fig.1 illustrated flow diagram showing the steps we searched in the electronic database to yielded 263 citations. After applying the software Endnote and manual check for duplicates, 3 articles were included in this meta-analysis including 1179 participants with the sample size range from 46 to 457 participants. One of the three eligible randomized trials was compared VR-CAP (bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisone) with R-CHOP in the newly diagnosed MCL [25]; while another one was designed with B-CHOP (bortezomib with cyclophosphamide, vincristine, doxorubicin and prednisone) vs CHOP to treat with relapsed MCL [21]; additionally, bortezomib plus rituximab vs rituximab alone were applied into relapsed FL [26]. Table 1 and Table 2 listed the main characteristics of eligible and included studies, including first author, publication year, country, the scope of the participants’ age, sample size, clinical stage, the type of disease and the chemotherapy regimen. And Table 3 summarized the main results of the included studies.
Table 1. Main characteristic of the included studies.

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>country</th>
<th>Age</th>
<th>Patients</th>
<th>clinical stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Robak T</td>
<td>2015</td>
<td>Switzerland</td>
<td>26-88</td>
<td>457 228 229</td>
<td>II-IV(newly diagnosed)</td>
</tr>
<tr>
<td>Furtado M</td>
<td>2014</td>
<td>UK</td>
<td>48-83</td>
<td>46 23 23</td>
<td>- (relapsed)</td>
</tr>
<tr>
<td>Coiffer B</td>
<td>2011</td>
<td>France</td>
<td>21-89</td>
<td>676 336 340</td>
<td>- (relapsed)</td>
</tr>
</tbody>
</table>

Table 2. Specific chemotherapy regimen of the analyzed trials.

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Types</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Robak T</td>
<td>2015</td>
<td>MCL</td>
<td>R-CHOP</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(6-8)*21-d cycles: replace V of R-CHOP to B:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>R: 375 mg/m²;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>C: 750 mg/m²;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>D: 50 mg/m², all IV day 1;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P: 100 mg/m², PO day 1-5;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>V: 1.4 mg/m² (max 2 mg), IV day 1.</td>
</tr>
<tr>
<td>Furtado M</td>
<td>2014</td>
<td>MCL</td>
<td>VR-CAP</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(4-8)*21-d cycles: CHOP plus B 1.6 mg/m², IV day 1, 8 (max eight cycles).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>C: 750 mg/m²;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>D: 50 mg/m², all IV day 1;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P: 100 mg/m², PO day 1-5;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>V: 1.4 mg/m² (max 2 mg), IV day 1.</td>
</tr>
<tr>
<td>Coiffer B</td>
<td>2011</td>
<td>FL</td>
<td>R</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5*35-d cycles: R plus B 1.6 mg/m², IV (3-s to 5-s bolus) on days 1, 8, of cycle 1, and on day 1 of cycles 15, and 22 of all cycles.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>BR</td>
</tr>
</tbody>
</table>

Notes: R, rituximab; c, cyclophosphamide; D, doxorubicin; P, prednisone; V, vincristine; B, bortezomib.

Table 3. Index of the retrieved articles to be pooled.

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>With bortezomib</th>
<th>Without bortezomib</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>CR  OR  AE  PN</td>
<td>CR  OR  AE  PN</td>
</tr>
<tr>
<td>Robak T</td>
<td>2015</td>
<td>122 211 238 73</td>
<td>95 204 238 69</td>
</tr>
<tr>
<td>Furtado M</td>
<td>2014</td>
<td>8   19   16   6</td>
<td>5    11  12  3</td>
</tr>
<tr>
<td>Coiffer B</td>
<td>2011</td>
<td>79  199  152  54</td>
<td>59  160 70  2</td>
</tr>
</tbody>
</table>

Notes: CR, complete response; OR, overall response; AE, any adverse events (grade ≥ 3); PN, peripheral neuropathy not elsewhere classified, including peripheral sensory neuropathy, neuropathy peripheral, peripheral sensorimotor neuropathy, and peripheral motor neuropathy (all grades).

Quality Assessment of Studies Included

Three references were included in this study and two of the studies were just in the mentioned “random”, but there were no more details to be described. Besides, the two articles
were not reported blinding methods and allocation concealment. The last one presented specific randomization schedule; an interactive voice response system and permuted-blocks central randomization was used. And this one got 33 score by means of Follicular Lymphoma International Prognostic Index (FLIPI) (low: 0-1, intermediate: 2, high: ≥3).

**Clinical Outcomes**

**Outcomes of efficacy:** There were 209 patients acquired completed response in the group (587 patients) with bortezomib; however, the group without bortezomib was 159/592. The rate of CR was higher in the bortezomib-based treatment group (35.6% versus 26.9%). The pooled ORs illustrated a significant difference between the two arms (OR=1.56, 95%CI=1.20-2.02), which indicated that the individuals with bortezomib chemotherapy had a better outcomes than the patients who had not been underwent the regimen with bortezomib (Fig. 2). No heterogeneity was presented in the pooled CR ($I^2=0.0\%$, $P=0.883$). According to the index of overall response (OR) (OR=1.61, 95%CI=0.81-3.20) in a random-effect model, there was no statistical significance among the patients whether they were accepted bortezomib or not. We found the heterogeneity ($I^2=64.5\%$, $P=0.060$) was far higher than the outcomes that we expected before. No prior advantages were presented by the group with bortezomib in this data, which the rate of overall response (OR) was 73.1% versus 65.0% (Fig. 3).

<table>
<thead>
<tr>
<th>Study</th>
<th>OR (95% CI)</th>
<th>Events</th>
<th>Events, %</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Robak T (2015)</td>
<td>1.62 (1.12, 2.35)</td>
<td>122/228</td>
<td>95/229</td>
<td>47.80</td>
</tr>
<tr>
<td>Furtado M (2014)</td>
<td>1.92 (0.52, 7.12)</td>
<td>8/23</td>
<td>5/23</td>
<td>3.54</td>
</tr>
<tr>
<td>Coiffier B (2011)</td>
<td>1.46 (1.00, 2.14)</td>
<td>79/336</td>
<td>59/340</td>
<td>48.66</td>
</tr>
<tr>
<td>Overall (I-squared = 0.0%, $p = 0.883$)</td>
<td>1.56 (1.20, 2.02)</td>
<td>209/587</td>
<td>159/592</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Figure 2. Forest plot for risk ratios of complete response of the regimen with and without bortezomib. $P=0.883>0.10$, overall OR of complete response was evaluated using fixed effects model and no heterogeneity. Bortezomib-based chemotherapy treatment was presented to increase the proportion of CR (OR=1.56, 95% CI= 1.20-2.02).
Figure 3. Forest plot clinical outcomes of overall response of the protocol with and without bortezomib. 

Outcomes of Safety: The data of AE (grade≥3) and PN (all grades) from the yielded citations were summarized and evaluated. ORs of AE was 3.15 (95%CI=2.26-4.40) with no heterogeneity ($I^2$=0.0%, $P=0.594$), which suggested the chemotherapy without bortezomib favored the arm with bortezomib (Fig. 4). Actually, patients underwent bortezomib were more easily to present a variety of adverse events. Hematologists preferred to pay more attention to the adverse events--PN that would put severe pain to the acceptors and have a terrible influence on their quality of life. As was shown in Fig. 5, no significant difference was noted between these two arms (OR=4.14, 95%CI=0.43-40.23) with a dramatically big heterogeneity ($I^2=92.2\%$, $P=0.000$) in a random-effect model.
Figure 4. Risk ratios of any adverse events (grade≥3) the regimen with bortezomib compared the regimen without. Bortezomib. \( P=0.594>0.10 \), fixed effects model was used with no heterogeneity. There was an increasing risk of any adverse events (grade≥3) in the group with bortezomib (OR=3.15, 95%CI=2.26-4.40).

![Risk ratios of any adverse events (grade≥3) the regimen with bortezomib compared the regimen without.](image)

<table>
<thead>
<tr>
<th>Study</th>
<th>Events, %</th>
<th>OR (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Robak T (2015)</td>
<td></td>
<td>2.00 (0.36, 11.02)</td>
<td>238/242 4.96</td>
</tr>
<tr>
<td>Coiffer B (2011)</td>
<td></td>
<td>3.21 (2.28, 4.51)</td>
<td>70/339 95.04</td>
</tr>
<tr>
<td>Overall (I-squared = 0.0%, p = 0.594)</td>
<td></td>
<td>3.15 (2.26, 4.40)</td>
<td>308/581 100.00</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis

Figure 5. Risk ratios of peripheral neuropathy (all grades) in comparison of the protocol with and without Bortezomib. \( P=0.000<0.10 \), random effects model was used to calculate OR of PN with significant heterogeneity. There was no statistic difference.

![Risk ratios of peripheral neuropathy (all grades) in comparison of the protocol with and without Bortezomib.](image)
Discussion

MCL and FL, a heterogeneous group of lymphomas, are considered an aggressive lymphoma. The median survival is 3 to 4 years if the patients would not receive intensive chemotherapy followed or autologous stem-cell transplantation [27]. Furthermore, most of the patients experienced relapses after the first chemotherapy treatment and the resistance to chemotherapeutics is the character of relapse with a shorter remission duration [20]. First-line therapeutic approach still wouldn’t get a consensus typically for the elderly patients suffered from MCL and FL.

The first proteasome inhibitor-- bortezomib was approved by the United States Food and Drug Administration (FAD) for the treatment of multiple myeloma (MM) and relapsed/refractory MCL. Addition of bortezomib to R-CHOP chemotherapy was safely administered and gave a favorable outcomes in DLBCL [28]. CR and overall survival at 2 years could reach a high level after treated with bortezomib MM [29]. Bortezomib combined with R-CHOP appeared to be prolonged significance for newly diagnosed MCL with 2-year PFS and OSR (62%, 85%); and the rate of PN (grade≥3) was 5% [30]. Most of patients with previously untreated advanced-stage FL went through relapse after first chemotherapy treatment. Overall response rate (ORR) was 83% under the bortezomib plus R-VAP (rituximab, cyclophosphamide, vincristine, and prednisone) while only 5% of patients developed grade 3 neurotoxicity with largely reversible [31]. The regimen R/PAD+C (rituximab, bortezomib, doxorubicin, dexamethasone and chlorambucil) appeared a better CR rates and represented a promising therapeutic option as front-line therapy for elderly MCL patients [32]. The protocol of lenalidomide with rituximab compared with chemoimmunotherapy in a randomized fashion have successfully illustrated the efficacy in the new patient with low grade FL [33]. Those studies with strong evidence illustrated that bortezomib added to other chemotherapies tended to enhance the results. However, it was reported that the incidence of the AE was higher in the schedule of bortezomib compared to the schedule without bortezomib. Among those adverse effects, many hematologists took neurotoxicity seriously and they suggested that neurotoxicity was one of the characters to evaluate the safety. It was a dose-limiting adverse event that the incidence neurotoxicity increased with the cumulative dose of bortezomib as a single-agent for MM. Once dose reduction or regimen pause, the reversible adverse effect got the improved development or disappeared [31]. Weekly bortezomib versus bi-weekly bortezomib in MCL and FL, the former schedule had better activity and less toxicity though the latter one of ORR was superior (50% vs. 18%, P=0.02) and there was no difference in PFS [34]. For other adverse events like hematologic events (neutropenia, thrombocytopenia, anemia, leukopenia, lymphocytopenia, febrile neutropenia), gastrointestinal events (diarrhea, constipation, nausea), infections (pneumonia, sepsis), other (pyrexia, fatigue, cough, decreased appetite, asthenia, peripheral edema), had a higher incidence of bortezomib also got a great improvement after drug withdrawal.

In this meta-analysis, although OR had no difference between the schedule with bortezomib and without bortezomib, the outcome of CR (OR=1.56, 95%CI=1.20-2.02) favored to the former schedule. It had a large statistical significance of AEs indicating an increasing risk applying bortezomib. Bortezomib had a severe PN and many patients couldn’t tolerate this side effect and had to discontinue medication. However, there was no difference for the rate of PN between the bortezomib-based regimen and non-bortezomib-based regimen with a considerable heterogeneity. AEs were reversible and could develop improvement with protocol discontinuation.
The meta-analysis evaluated and summarized the efficacy of the randomized control trials with or without bortezomib. There were some limitations of this meta-analysis: the chemotherapy protocol except bortezomib was different containing drugs and cycles and the factors, such as age, clinical stage, new diagnosed or relapsed patients, and one sample was little smaller than the other two samples respectively, which added the degree of heterogeneity.

In summary, the study suggests that bortezomib-based regimen is a prior protocol for newly diagnosed or relapsed/refractory MCL and FL. This regimen contributes to CR, although the incidence of AEs increased. Therefore, it is indispensable to launch a series of multicenter studies, more well-designed, large-scale randomized trials by the blinding methods and allocation concealment to determine the value of adding bortezomib to standard chemotherapy regimen remains.

**Competing Interests**

The authors declare that they have no conflict of interest.

**References**


