Effectiveness of Bendamustine-Rituximab Compared to R-CHOP/R-CVP as a First-Line Treatment of Indolent Non-Hodgkin's Lymphoma or Mantle-Cell Lymphoma

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ABSTRACT

Background: *R-CHOP/R-CVP is the only recommended first-line treatment for Non-Hodgkin's Lymphoma (NHL). Limited treatment alternatives often lead to relapse and refractory NHL, which increases disease progressivity and worsens prognosis. Bendamustine-rituximab is being studied for its potential as a superior first-line therapy for indolent NHL and mantle-cell NHL (MCL); however, it is not in the national guidelines. Evidence-based research is needed to demonstrate the effectivity of bendamustine-rituximab compared to R-CHOP/R-CVP for a complete response of indolent NHL and MCL.* ***Methods:*** *A literature search was conducted using PubMed, Scopus, EBSCOHost, and Cochrane. Studies consistent with clinical question and eligibility criteria were included and critically appraised using the Oxford Centre for Evidence-Based Medicine (CEBM) tool.* ***Results:*** *Two randomized controlled trials (RCTs) were included in this study, both concluding that bendamustine-rituximab is superior to R-CHOP/R-CVP with a complete response, with RR values of 0.90 (95% CI 0.80 – 1.01) and 0.86 (95% CI 0.76 – 0.98).* ***Conclusion:*** *Bendamustine-rituximab is more effective than R-CHOP/R-CVP as a first-line treatment of indolent NHL or MCL.*

Keywords**:** *bendamustine-rituximab, R-CHOP/R-CVP, complete response, indolent non-Hodgkin's lymphoma, mantle-cell, NHL, MCL.*

INTRODUCTION

Non-Hodgkin's Lymphoma (NHL) is the most prevalent hematological cancer, comprising 2.8% of cancer incidence worldwide with 509,590 new cases and mortality rates almost half of the number of new cases (248,724 deaths).[1] In 2018, in Indonesia, NHL was ranked seventh on the list of the most prevalent of all types of cancer, affecting 14,164 citizens, and causing 7,565 mortalities. NHL has been well-known for its increased incidence in the last few decades, which cannot be clearly explained by theorems of etiology, risk factor, and pathogenesis.[3] Even though NHL survival rates top some cancer types, its mortality rate is almost half of its new cases.[1-3] NHL is classified into indolent (slowly-progressing) and aggressive (rapidly-progressing). Indolent NHL subtypes include follicular lymphoma, small lymphocytic lymphoma, chronic lymphocytic lymphoma, marginal zone lymphoma, and lymphoplasmacytic lymphoma. NHL can be

classified, using the Ann Arbor classification system, into four stages based on lymph node involvement. The stages of involvement are: one lymph node is stage I, two or more lymph node regions in one hemidiaphragm is stage II, at least one lymph node in two hemidiaphragms is stage III, and one or more extra lymphatic organs is stage IV.[4]

Referring to the national guidelines *Panduan Nasional Penatalaksanaan Kanker Limfoma Non-Hodgkin's (PNPK LNH)* published by Indonesia's Ministry of Health in 2015; the first-line chemotherapy used to treat stage I and stage II NHL is cyclophosphamide, hydroxydaunorubicin, oncovin/vincristine, prednisone/prednisolone combined with rituximab (R-CHOP) and stages II, III, and IV are treated by cyclophosphamide, vincristine, and prednisone/prednisolone combined with rituximab (R-CVP). If rituximab is contraindicated for stages II, III, or IV indolent NHL patients; then CHOP, COP, and procarbazine (COPP), or fludarabine (FND) can be considered as first-line chemotherapy regimens.[4] A limited number of chemotherapy regimens in Indonesia is a challenge for generating successful outcomes, especially in stages III and IV indolent NHL.[5] Even with a complete response to initial treatment there is still a high chance of relapse and treatment failure (non-complete response or a false complete response) when NHL becomes refractory and progresses faster into more advanced stages.[5] R-CHOP and R-CVP can no longer be used in patients with NHL resistant or refractory cancers.[5] This challenge could be overcome by alternative first-line chemotherapy agents that generate a greater complete response rate, in order to prevent refractory and relapse in patients who fail first-line chemotherapy.[5]

Bendamustine is an alternative chemotherapy regimen widely used in Europe as the first-line treatment of NHL. Based on the European Society for Medical Oncology (ESMO) guidelines, the bendamustine-rituximab combination is the first-line chemotherapy regimen for high-stage follicular lymphoma (Ann Arbor III-IV)[6] and follow-up chemotherapy for relapsed MCL.[7] However, the bendamustine-rituximab treatment efficacy compared to standard R-CHOP and R-CVP regimen is still being extensively researched. Bendamustine is considered to be superior to R-CHOP and R-CVP in its chemotherapy side effects (alopecia, neuropathy, infection, hematological toxicity, stomatitis, etc.), even though it increases the incidences of vomiting, drug hypersensitivity, and secondary malignancy.[8-10] Currently, bendamustine is currently self-produced in Indonesia and is covered by the national health insurance (*BPJS*) as stated in the National Drug Formularium 2018. This development supports bendamustine to be an accessible and applicable chemotherapy choice in Indonesia.[11,12] Therefore, an evidence-based review needs to be conducted to systematically assess bendamustine-rituximab efficacy compared to the current standards for first-line chemotherapy of indolent NHL and MCL.

CASE ILLUSTRATION

A male patient, 43 years old, was admitted to the hospital with a primary complaint of abdominal fullness for three months before admission. Physical examination showed hepatomegaly into the pelvic cavity and general lymph node swelling. Peripheral blood count results showed 12,600/µl leukocytes that consisted of 34% atypical lymphocytes.

Lymph node biopsy confirmed NHL, subtyped as small-cell follicular NHL. Flow cytometry showed 19.1% CD-1, 38.1% CD-10, 84.6% CD-19, and 80.5% CD-20. Test results were negative for Hepatitis B (HB) antigens and antibodies, hepatitis C virus (HCV), and human T- cell leukemia virus type 1 (HTLV-1). Early immunoglobulin (Ig) G antigen tests for Epstein Barr anti-virus and virus capsid IgM showed negative results, viral capsid antigen (VCA) IgG, and Epstein-Barr nuclear antigen (EBNA) showed positive results. Serum immunoglobulin demonstrated 674 mg/dL IgG, 85 mg/dL IgA, and 9 mg/dL IgM. The soluble interleukin (IL)-2 receptor value was 12.800u/mL. Lymphoma chromosomal analysis showed (A) 46XY, t(14:18) (q32;q21) in 1/10 metaphase, and (B) 46 (q32) in 9/10 metaphase. There were no changes in the Bcl-2 and chimeric IgH genes. Mutation tests for p53 genes and EB virus DNA were not conducted.

Table 1. Clinical Question.

Patient/Problem (P)	Intervention (I)	Comparison (C)	Outcome (O)
Patients with indolent NHL or MCL	Bendamustine-rituximab chemotherapy regimen	R-CHOP/R-CVP chemotherapy regimen	Complete Response
Type of Clinical Question	Therapeutic		
Study Design	A meta-analysis, systematic review, randomized controlled trial (RCT)		

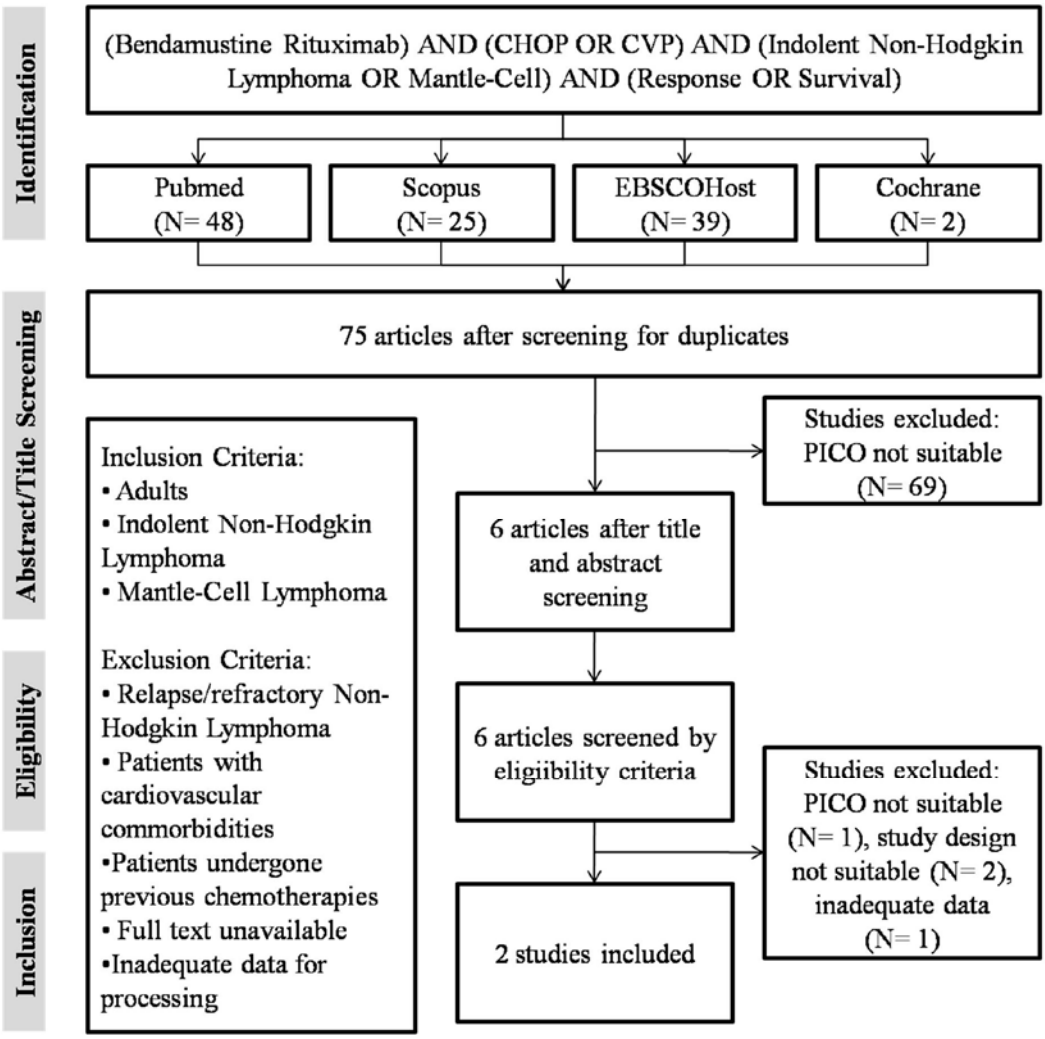

Figure 1. Article Selection Process.

After being told about his diagnosis, the patient stated that his cousin also had a severe case of NHL that progressed quickly. His cousin used an imported drug named bendamustine, which was effective in treating his cancer. The patient had heard that bendamustine was produced in Indonesia and asked if bendamustine was an option for him too.

(Case illustration was modified from a case report in reference.[13])

Clinical Question

"Is bendamustine-rituximab, compared to R-CHOP/R-CVP, more effective in increasing the complete response of indolent NHL or MCL?"

METHODS

A literature search for relevant studies was conducted on March 27-28, 2020, in four electronic databases: PubMed, Scopus, EBSCOHost, and Cochrane. The keywords and Boolean operators typed into the database search engine were "(Bendamustine Rituximab) AND (CHOP OR CVP) AND (Indolent Non-Hodgkin Lymphoma OR Mantle-Cell) AND (Response OR Survival)".

The keyword search in the four databases generated 114 results or 75 studies after duplicates were filtered out. After screening for title and abstract, the author deemed six studies relevant to the clinical question. Based on the eligibility criteria (**Figure 1**), two RCTs by Flinn, et al. and Rummel J, et al. were included. Included studies were critically appraised by the Oxford Center of Evidence-Based Medicine (CEBM) tool.

RESULTS

Two studies selected from the literature search by Flinn IW, et al. and Rummel J, et al. both had a 1b level of evidence, with study characteristics shown in **Table 1**.

A study by Flinn IW, et al. was a randomized clinical trial comparing the effectivity of bendamustine-rituximab to R-CHOP or R-CVP as the first-line therapy of NHL or MCL. Individuals who were eligible based on the study criteria (n=447) were assigned to receive either R-CHOP or R-CVP based on their clinical conditions. They were then stratified randomly to bendamustine-rituximab (n=224) or R-CHOP/R-CVP (n=223) intervention groups. Chemotherapy was given in six cycles, 28 days per cycle for bendamustine-rituximab, and 21 days per cycle for R-CHOP and R-CVP. The regimens used were as follows: Rituximab IV 375mg/m^2, bendamustine IV 90mg/m^2, cyclophosphamide IV 750 mg/m^2 (or 1000mg/m^{2}in R-CVP), vincristine 1.4 mg/m^2 (maximum dose of 2g), oral prednisone 100 mg/day, doxorubicin IV 50mg/m^{2}in the R-CHOP regimen. The primary outcome of this study was a complete response to therapy, meanwhile, the secondary outcome of this study was the overall response and the safety comparison between two regimens. This study is the initial review of the five-year follow-up study, researching the *progression-free survival* and quality-of-life between the two groups.[9]

A study by Rummel J, et al. was a multicenter randomized-controlled trial assessing the effectivity of bendamustine-rituximab compared to R-CHOP as the first-line therapy for indolent NHL and MCL. There were 549 patients randomized based on histological subtypes to either the bendamustine-rituximab intervention group (n=274) or the R-CHOP control group

Table 2. Characteristics of Selected Articles.

Author (Year)	Title	Study Design	samples	Results	Level of Evidence
Flinn IW, et al. (2014)[9]	Randomized Trial of Bendamustine-rituximab or R-CHOP/R-CVP in First-Line Treatment of Indolent NHL or MCL: The BRIGHT Study	RCT	447	CR BR, CR R-CHOP/R-CVP: 31% (95% CI 25.3, 28.2), 25% (95% CI 19.5, 31.7) *p-value for NI test* = 0.0225 (0.88 margin) OR BR, OR R-CHOP/R-CVP: 97%, 91% (p= 0.0102)	1b
Rummel J, et al. (2013)[10]	Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial	RCT	514	CR BR, CR R-CHOP/R-CVP: 40%, 30% (p = 0.021) Median PFS BR, R-CHOP/R-CVP: 69.5 months (26.1-not yet reached), 31.2 months (15.2–65.7) HR: 0.58 (95% CI 0.44–0.74; p<0,0001)	1b

*CR: Complete response, OR: Overall response, PFS: Progression-free survival, HR: Hazard ratio, BR: Bendamustine-rituximab

(n=275). Chemotherapy was prescribed in a maximum of six cycles, 28 days per cycle for bendamustine-rituximab, and 21 days for R-CHOP. The chemotherapy regimens used were as follows: Rituximab IV 375mg/m^2, bendamustine IV 90mg/m^2, cyclophosphamide IV 750mg/m^2, vincristine 1.4mg/m^2 (maximum dose of 2g), oral prednisone 100mg/day, doxorubicin IV 50mg/m^2. Baseline characteristics between the intervention and control groups are presented in **Table 2**. The primary outcome of this study was progression-free survival, meanwhile, its secondary outcomes were complete response, overall response, and comparison of safety.[10]

Both studies showed the complete response of bendamustine-rituximab was superior to R-CHOP/R-CVP, with a significant p-value.[9,10]

Critical Appraisal

Validity

Table 3. Validity Appraisal of Flinn IW, et al.[9]

Parameter		Flinn IW, et al.		Rummel J, et al.
Was the allocation to the intervention group randomized?	Yes	Patients who were already eligible to receive R-CHOP/R-CVP therapy were randomized into intervention and control groups. The method of randomization was not mentioned.	Yes	Randomization was conducted by the center of the study by a 1:1 method to allocate patients to either the bendamustine-rituximab or R-CHOP groups.
Were the initial characteristics of the participants in both groups similar?	Yes	Participants of both groups were similar in baseline characteristics of age, gender, histologic classification, ECOG performance status, Ann Arbor stage, FLIPI risk group, IPI risk group, and clinical manifestations.	Yes	Participants in both groups were similar in age, Ann Arbor stage, histological classification, clinical manifestations, bone marrow, and extra-nodal involvements, LDH levels, median B-2 microglobulin, IPI prognostic group, and FLIPI prognostic group.
Was the follow-up of patients complete?	Yes	The follow-up duration was adequate to judge the complete response, even though the authors did not distinguish between true complete response or relapse. The number of analyzed and excluded patients and reasons for exclusion was presented in the article.	Yes	*A follow-up* of 45 months was adequate to evaluate the complete response of therapies. All patients completed follow-up, though not all were analyzed (reasons elaborated in the study)
Were all patients accounted for in the analysis, according to the randomization groups?	No	Not all patients were accounted for in the analysis, eight out of 221 patients in the bendamustine-rituximab group were excluded, nine out of 215 patients in the R-CHOP/R-CVP group were excluded. However, the patients were analyzed according to their randomization groups.	No	Not all patients were accounted for in the analysis, 13 out of 274 patients in the bendamustine-rituximab group were excluded, 22 out of 225 patients in the R-CHOP/R-CVP group were excluded. The analysis of patients was according to their respective groups.
Were the interventions blinded?	Yes	Evaluation of response was evaluated using the patient's radiology and pathology results, and was conducted by clinicians and workers blinded to the diagnosis.	No	Clinicians, response evaluators, and participants knew the diagnosis and intervention given.
Besides the intervention given, did both groups receive the same treatment?	No	Supportive therapies (antipyretics, antiemetics, or antibiotics) were prescribed based on clinicians' clinical judgment, patients' condition, and health facility protocols.	Yes	All patients received prophylactic antiemetics and did not receive prophylactic antibiotics. G-CSF was given according to the American Society of Clinical Oncology guidelines.

Importance

Table 4. Importance Analysis of Flinn IW, et al.[9]andRummel J, et al.[10]

Parameter	Flinn IW, et al.	Rummel J, et al.
RR	RR = 0.90 (95% CI = 0.80 – 1.01)	RR = 0.86 (95% CI = 0.76 – 0.98)
CER	CER = 75.9%	CER =70.0%
EER	EER = 68.5%	EER = 60.2%
RRR	RRR =9.7%	RRR = 14.0%
ARR	ARR = 7.4% (95% CI =1.05– 15.85)	ARR = 9.8% (95% CI =1.60 – 17.99)
NNT	NNT = 13.51 (95% CI = 6.31 – 95.24)	NNT = 10.2 (95% CI = 5.56 – 62.5)

Applicability

Table 5. Applicability Appraisal of Flinn IW, et al. and Rummel J, et al.

Parameter	Flinn IW, et al.	Rummel J, et al.
Suitability of patient characteristics to study participants	Yes Data on NHL epidemiology in Indonesia was still limited. The average participant age was 60 years old which was in line with the age distribution of NHL patients in Southeast Asia. As appropriate to the characteristics of participants, patients in need of alternative first-line NHL therapy were patients with a high cancer stage, poor prognosis, and poor disease progression.[14]	Yes Study participants were primarily 60-70 years old. This is in line with the characteristics of patients with NHL in Southeast Asia. Patients in need of alternative therapies had higher stage cancers and poor prognostic risk.[14]
The capability of implementing intervention based on available resources	Yes Bendamustine is self-produced in Indonesia and is in the 2018 list of National Drugs Formularium. Bendamustine is available as 25mg and 100mg of injection powder and 100mg, accessible in third level healthcare facilities.[12]	Yes Bendamustine is self-produced in Indonesia and is in the list of National Drugs Formularium 2018. Bendamustine is available as 25mg and 100mg of injection powder and 100mg, accessible in third level healthcare facilities.[12]
Risk and benefit evaluation of intervention	Yes Bendamustine had a superior complete response compared to standard regimens(31.4% to 24.1%) and was proven to decrease incidences of alopecia and neuropathy. Bendamustine was given twice every 28-days cycle, was more cost-effective than CHOP – cyclophosphamide was given every three weeks and vincristine every five days.[12] However, bendamustine increased the incidence of vomiting and increased drug hypersensitivity reactions.	Yes Bendamustine had a superior complete response compared to standard regimens(39.8% to 30%) and was proven to decrease incidences of alopecia, hematological toxicity, neuropathy, infection, and stomatitis. Bendamustine was given twice every 28-days cycle, was more cost-effective than CHOP – cyclophosphamide was given every three weeks and vincristine every five days.[12] However, bendamustine increased the incidence of vomiting and increased drug hypersensitivity reactions.

DISCUSSION

Analysis of Literature Search Results

Alternative therapies to the standard R-CHOP/R-CVP regimen are needed for first-line therapy of indolent NHL and MCL to help solve poor therapy response, minimize relapse, limit complications, and avoid secondary diseases. Bendamustine-rituximab is a combination chemotherapy frequently researched for its potential as a more effective and prognosis-increasing first-line therapy of NHL and MCL.

Both studies reviewed after an evidence-based literature search demonstrated that the combination of bendamustine-rituximab

had a statistically significant (p 0.0225[9], p 0.021[10]) greater complete response compared to R-CHOP/R-CVP (31% to 25%[9], 40% to 30%[10]). Its relative risks were 0.90 (95% CI = 0.80 – 1.01) in Flinn IW, et al. and 0.86 (95% CI = 0.76 – 0.98) in Rummel J, et al. Both results indicated bendamustine-rituximab as a first-line therapy had greater success in eliminating cancer cells compared to the standard regimen of R-CHOP/R-CVP. Even so, the confidence interval of relative risk in Flinn IW spanned through 1.0, while the confidence interval of absolute risk reduction (ARR) and number needed to treat (NNT) in both studies were wide in range.

Besides greater complete response, according to Rummel J, et al., bendamustine-rituximab also had longer progression-free survival compared to R-CHOP (69.5 months to 31.2 months).[10] The results of the Flinn et al. five-year follow-up study also showed better five-year progression-free survival in the bendamustine-rituximab group compared to the R-CHOP group (65.5% to 55.8%).[8] Both results were consistent with a retrospective study by Mondello P, et al. which reported that long-term progression-free survival of 3A follicular lymphoma treated with bendamustine-rituximab was 15 years, while those treated with R-CHOP/R-CVP only had long term progression-free survival of 11.7 years (p 0.03).[15] This suggested that besides being more effective in eradicating cancer cells on initial therapies, bendamustine-rituximab was also better in preventing relapse and cancer progression in the long run.

As for its safety, bendamustine-rituximab decreased incidences of alopecia, hematological toxicity, neuropathy, infection, and stomatitis.[9,10] However, it is also important to consider the fact that bendamustine increased incidences of secondary malignancy,[11] vomiting,[9,] and hypersensitivity reactions[10].

Bendamustine-rituximab is also feasible in implementation, as it is already available in third level healthcare with R-CHOP and R-CVP. Bendamustine-rituximab is also considered more cost-effective, as it has only two types of drugs consumed more infrequently compared to R-CHOP/R-CVP.[12]

Strengths and Limitations of the Study

The strength of this evidence-based case report is being able to analyze the short and long-term effectivity of the regimens and compare their safety profiles. Studies included in this report had met the review's very specific eligibility criteria, resulting in values almost representative of the genuine effect of an intervention on the outcome.

However, this evidence-based case report is limited since it could not confirm the direct effects of bendamustine-rituximab on the indolent NHL subset nor other subsets. This study was also unable to identify the controls as R-CHOP and R-CVP separately. This is caused by the limited amount of studies available.

CONCLUSION

A combination of bendamustine-rituximab is more effective than R-CHOP/R-CVP in generating a complete response against indolent NHL or MCL.

Bendamustine-rituximab should be considered as an alternative to R-CHOP/R-CVP as a first-line therapy for indolent NHL and MCL. More researches comparing bendamustine-rituximab to R-CHOP and R-CVP as different control subgroups, and in each lymphoma subsets, are needed to provide a more accurate representation of their efficacy and safety.

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