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REVIEW

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Bendamustine and pneumocystis pneumonia: A systematic review

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Abstract

Background: Bendamustine, a bifunctional mechlorethamine alkylating agent, is used in the treatment of patients with hematologic malignancies. Myelosuppression and cytotoxic effect arises quite often after bendamustine treatment. To date, there have been no recommendations for routine chemoprophylaxis for *Pneumocystis carinii* pneumonia (PCP) in patients under treatment with this agent. The present systematic review aimed to evaluate the existing data on bendamustine effects on pneumocystis pneumonia.

Method: English papers were systematically reviewed using Web of Science, Embase, Google Scholar, PubMed, and Cochrane library. There was no time constraint for the paper search. The used keywords included "Pneumonia, Pneumocystis"or "Pneumocystis Pneumonia"or "Pneumocystis jirovecii" and "Bendamustine hydrochloride or Bendamustine. "Through our search, 113 papers were found, 26 of which were chosen following a review of the titles and abstracts; ultimately, 10 were included in the research.

Result: A total of 10 studies (out of 113 studies) were retrieved. The papers were classified into seven case reports, two clinical trials, and one retrospective analysis study. The case reports included 14 patients diagnosed with PCP after bendamustine administration between 2003 and 2019. The patients' mean age was with a range of 66.8. Non-Hodgkin's lymphoma (including diffuse large B-cell lymphoma and mantle cell lymphoma) ($n = 9$, 60%), chronic lymphocytic leukemia ($n = 4$, 26.6%), and breast cancer ($n = 2$, 13.4%) were the most prevalent types of malignancy. Bendamustine, along with rituximab, were the most commonly prescribed chemotherapy regimens during the treatments. Finally, the mortality rate among the patients whose results were reported ($n = 9$) was 44.44% ($n = 4$).

Conclusion: The present review described PCP infection in patients with malignancies after the treatment with bendamustine, a chemotherapeutic agent associated with lymphopenia. Further research is required to determine the PCP risk

in patients with bendamustine treatment and identify individuals who may benefit from prophylaxis.

KEYWORDS

bendamustine, bendamustine hydrochloride, pneumocystis, pneumocystis pneumonia, *Pneumocystis jirovecii*, pneumonia, systematic review

1 | INTRODUCTION

Pneumocystis carinii pneumonia (PCP) is a well-known and potentially life-threatening infection, which typically occurs in immunocompromised hosts including HIV-infected patients, hematopoietic cell transplant recipients, and solid organ transplant recipients, as well as patients with hematologic malignancies such as acute lymphoblastic leukemia, those who are under long-term treatments with corticosteroids or number of other immunosuppressive medications.[1–3]

PCP clinical presentation is different in non-HIV and HIV patients. In non-HIV patients, the presentation is often acute in onset leading to fever, dry cough, and also respiratory failure. However, as the clinical understanding and laboratory diagnosis of PCP have improved, it is now common to diagnose PCP at mild-to-moderate severity. Some patients, especially older patients, still present with more severe infections accompanying respiratory compromise. The diagnosis is likely to be delayed in this population and the mortality rate has been reported to range between 30% and 60%.[4,5] In contrast, the clinical presentation of PCP in patients with HIV infection, are most commonly gradual in onset with a mortality rate of 10%–20%. It is usually characterized by nonproductive cough, and dyspnea, progressing over days to weeks. Some patients may present without any symptoms.[6,7] The severity of PCP can be classified as mild, moderate, and severe. The partial pressure of arterial oxygen (PaO_2) ≤ 70 mmHg or the alveolar-arterial oxygen difference ≥35 indicates moderate to severe cases.[8]

A definitive diagnosis of PCP requires the identification of microorganisms in bronchoalveolar lavage (BAL) fluid or induced sputum.[4] Since the burden of microorganisms in patients without HIV infection is significantly lower than that in patients with HIV, these diagnostic methods must be used carefully. BAL had a high sensitivity for the diagnosis of PCP (80%–95%).[4,9,10] The first-line treatment for PCP is trimethoprim/sulfamethoxazole (TMP/SMX), and intravenous pentamidine or primaquine in combination with clindamycin are the best alternative treatments in moderate to severe cases. The combination of high-dose TMP/SMX with caspofungin may also be considered.[11–13]

Even though the use of various immunosuppressive drugs including corticosteroids, purine analogs, such as fludarabine, tumor necrosis factor inhibitors, such as infliximab, and monoclonal antibodies, such as alemtuzumab are considered well-known risk factors for PCP,[14,15] there are also reports on this infection with other immunosuppressive drugs, including bendamustine.[16–18]

Bendamustine is a mechlorethamine derivative, a cytotoxic alkylating agent of mustard-nitrogen derivatives, containing butyric acid, mechlorethamine group, and a benzimidazole ring, which mimics the structure of a purine analog. Bendamustine is currently used alone or in combination therapy for the treatment of malignancies including multiple myeloma, non-Hodgkin's lymphoma (NHL), mantle cell lymphoma (MCL), and chronic lymphocytic leukemia (CLL).[19] It has also been studied in advanced small cell lung cancer.[20,21]

One of the major toxicities of bendamustine is myelosuppression, especially in patients who have received prior chemotherapy. Concerning other side effects, we could mention nausea, dry mouth, vomiting, allergic reactions, thrombophlebitis, taste changes, and abdominal pain.[19] Also, a decrease in CD4/CD8 ratio has been shown in bendamustine-receiving patients. It is not yet clear to what extent altered lymphocytes, especially CD4+ lymphocytes, and subsequent suppression of the T cell-mediated immunity lead to more opportunistic infections such as viral and PCP in these cases.[19,22] Although prolonged CD4 levels <200 cells/μl were considered a significant risk factor for PCP in some guidelines,[23] there are currently no studies showing the exact benefits of PCP prophylaxis in cancer patients with CD4 count <200 cells/μl and routine chemoprophylaxis is not recommended in these group of patients.[24]

The incidence of PCP with the use of bendamustine has been reported in studies. It should be noted that the mortality rate following PCP infection in cancer patients can be high; hence this review focuses on the existing data which evaluate bendamustine effects on pneumocystis pneumonia incidence.

2 | METHODS

This study conforms to the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" statement.[25]

2.1 | Search strategy

Databases of PubMed, Google Scholar, Embase, Cochrane, and Web of Science were searched to retrieve the relevant articles in the English language. The used keywords were as follows: "Pneumonia, Pneumocystis"or "Pneumocystis Jirovecii" and "Bendamustine hydrochloride or Bendamustine."

2.2 | Screening process and study selection

There were no restrictions on the publication date of the articles; however, only English studies were selected. The search was done by one of the authors. All the potentially English-relevant articles retrieved from each database were screened. Two researchers assessed the titles and abstracts and selected the papers that met the selection criteria for full-text assessment. Discrepancies were discussed with a third reviewer. Irrelevant articles were excluded. In the second round of screening, eligible studies were found according to the inclusion/exclusion criteria and full-text evaluation. Subsequently, the content was analyzed and data were extracted.

2.3 | Review criteria

There were no restrictions on the article's publication date. We examined all the case series, case reports, and cohort studies on the incidence of PCP in bendamustine-treatment patients. The papers with relevant information were included in the final analysis. The inclusion and exclusion criteria were used to examine the titles, abstracts, and full texts of the documented studies. The inclusion criteria were: 1) clinical trials, case reports, cohort studies, case series, and case letters on bendamustine with or without other chemotherapeutic regimens and PCP in refractory cases or as the first-line therapy. We selected the case reports, case series, and case letters with no date restriction, which included PCP diagnostic methods, clinical manifestations, and outcome, as well as the clinical trials or cohort studies reporting infectious adverse events, including PCP; 2) availability of the articles and their full-texts; 3) articles in the English language. Studies that did not address PCP and bendamustine were excluded from the analysis. Articles that lacked at least one of the following features were also excluded: 1) studies with nonrelevant information; 2) studies with any language other than English; 3) review articles; 4) duplicate studies; and 5) articles available only in abstract form. Following the analysis of all the investigations based on the inclusion and exclusion criteria, the relevant publications were chosen.

2.4 | Data extraction

The following information was gleaned from the study: the first author, sample size, study design, years, mean of age, drugs, dose, duration of treatment, and patient outcome. To abstract the papers, one of the authors evaluated different parts of the articles to ensure the relevance of the subject to the research objectives. The results of data classification were reviewed by one of the authors. Regarding article inclusion, in case of any disagreement between the two reviewers, another member of our research team was asked to address any inconsistencies.

3 | RESULTS

Figure 1 represents the process of selecting papers. In the first round of the review, 113 articles were initially retrieved from databases, and after deleting duplicates, 76 articles were reviewed on the basis of titles and abstracts, out of which 50 were excluded and 26 entered the next step. Afterward, the articles were reviewed on the basis of the full-text and exclusion/inclusion criteria, and finally, 10 articles were included in the study.

In terms of the type of studies, 10 articles were described and classified into seven case reports, two clinical trials, and one retrospective analysis study. The majority of the studies were case reports and included 14 patients diagnosed with PCP after bendamustine administration between 2003 and 2019. The case reports were conducted in the USA, Germany, Ireland, France, and Korea. Patients mean age were with a range of 66.8.[16–18,26–29] Tables 1 and 2 provide further details about the studies.

The most frequent types of malignancies were as follows: NHL (including diffuse large B-cell lymphoma and MCL) ($n = 9$, 60%), CLL ($n = 4$, 26.6%), and breast cancer ($n = 2$, 13.4%). Bendamustine, along with rituximab, were the most commonly prescribed chemotherapy regimens during the treatments. The mortality rate among the patients was 44.4%.

The prevalence, risk factors, and types of infection complications in adult cases with NHL treated with bendamustine and a CD20 targeted monoclonal antibody (rituximab or ofatumumab) were assessed in the retrospective investigations. Following completion of the therapy, the patients were monitored for a year. Out of 416 patients, only five cases (6%) of PCP were reported.[30]

In Phase 1/2 multicenter and open-label nonrandomized trials, the addition of lenalidomide to rituximab-bendamustine was evaluated as a first-line treatment for elderly cases with MCL. The patients older than 65 years with untreated MCL Stages 2–4 were eligible for inclusion. Among the studied 51 patients (median age of 71 years), infection was the most common nonhematologic complication and occurred in 21 patients (42%), among whom, two cases of PCP were reported.[31]

Two North American multicenter investigations intended to study bendamustine's safety and efficacy in refractory rituximab cases with indolent B cell NHL. The opportunistic infections, including PCP, were relatively uncommon, and PCP was detected in only two (1.1%) out of 176 patients.[32] The most common type of lymphoma was follicular lymphoma.

4 | DISCUSSION

Bendamustine is an alkylating compound with antimetabolite effects, which consists of a mechlorethamine group and a unique purine-like benzimidazole ring.[33] This myelosuppressive and cytotoxic drug can reduce the CD4+ lymphocyte count, thereby decreasing the CD4/CD8 ratio, which causes immunosuppression in a dose-dependent manner. This compound has been shown to affect B lymphocytes and natural killer cells as well.[19,32,34] Lymphocyte

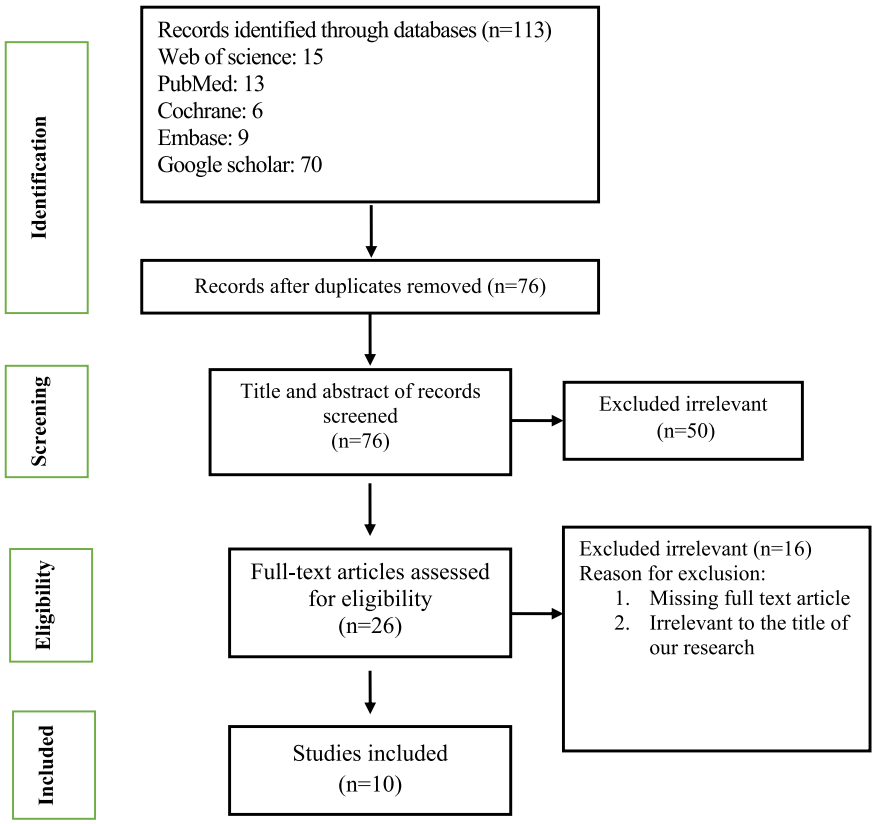

FIGURE 1 Flowchart of study selection for inclusion in the systematic review.

TABLE 1 Detailed characteristics of seven case reports including treatment regimens, underlying disease, and outcomes

Year	Publication	Underlying disease	Age (year)/gender	Chemotherapy regimen	No. of cycle	Outcome
2003	Klippstein et al.[16]	Advanced invasive ductal breast carcinoma	48/F	Bendamustine 150 mg/m^2	5	Expired
2011	Carter et al.[29]	Lymphoma	74/M	Bendamustine (90 mg/m^2) + rituximab (375 mg/m^2)	5	Complete remission
2012	Reinbolt et al.[28]	Breast cancer	47/F	Bendamustine 100 mg/m^2 + erlotinib 100 mg orally	6	Expired
2014	Abkur et al.[27]	CLL (2) NHL (2)	4 Cases 3 (2)	Bendamustine (100 mg/m^2) + rituximab (375 mg/m^2)	1 (1) 2 (1) 3 (2)	Complete remission
2015	Groarke et al.[26]	CLL (2) NHL (3)	5 Cases 68–74/F(2)–M(3)	Not reported	1 (1) 2 (2) 3 (1) 10 months postcycle 6 (1)	Not reported
2016	Ha et al.[17]	DLBCL	74/M	Rituximab 375 mg/m^2 + bendamustine 90 mg/m^2	1	Expired
2019	Dumont et al.[18]	T-cell lymphomas	Not reported	Bendamustine 120/mg^2 + brentuximab vedotin 1.8 mg/kg	Not reported	Not reported

Abbreviations: CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; F, female; M, male; NHL, non-Hodgkin lymphoma.

toxicity with bendamustine puts patients at a greater risk of infectious complications including PCP. The risk of these complications has not been fully elucidated, and various studies have reported infection rates between 6.2% and 55%.[35] PCP is one of the severe opportunistic infections among immunocompromised patients including HIV and non-HIV patients. However, there have been no extensive analyses of PCP and chemotherapy containing bendamustine. On the other hand, since the diagnosis of PCP could be

TABLE 2 Detailed characteristics of one retrospective and two RCT studies

Study, year	Design	Sample size	Mean of age	Hematologic malignancies	Chemotherapeutic regimen	PCP incidence	Infectious complication
Sarlo et al.,[30] 2019	Retrospective	416	67.5	FL (35.6%) SLL/CLL (28.1%) MCL (14.7%) MZL (12.5%) WM (4.8%) DLBCL (4.3%)	Bendamustine + rituximab (97.1%) Bendamustine + ofatumumab (2.9%)	6%	20%
Albertsson et al.,[31] 2016	RCT	51	71	Mantle cell lymphoma	Lenalidomide + rituximab + bendamustine	9.5% 1 Case during induction 1 Case after cycle 13	42%
Cheson et al.,[32] 2010	RCT	176	61	Follicular (68%) CLL/SLL (20%) Marginal zone (11%) Lymphoplasmacytic/ waldenestrom macroglobulinemia (1%)	Bendamustine	1.1%	61%

Abbreviations: CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; PCP, *Pneumocystis carinii* pneumonia; RCT, randomized controlled trial; SLL, small lymphocytic lymphoma; WM, Waldenstrom macroglobulinemia.

challenging in cancer patients, its accurate rate of incidence is likely to be underestimated. Unfortunately, those with concurrent malignancy and PCP become more rapidly decompensated than HIV-infected patients.[27]

A great deal of evidence has suggested that PCP may be caused by a decrease in CD4+ lymphocytes with bendamustine. For example, Klipsstein et al.[16] propose that bendamustine can induce a reduction in CD4+ lymphocyte counts, causing severe cellular immunosuppression. Measuring CD4+ lymphocyte counts may help determine the risk of PCP in patients treated with bendamustine. One study described pneumonia as a significant complication of bendamustine, but the incidence of PCP was not specified.[36] In the study by Layman et al.,[37] the combination of bendamustine and erlotinib in triple-negative breast cancer patients was associated with an unacceptable rate of significantly prolonged lymphopenia leading to life-threatening opportunistic infections.

It is well described that TMP/SMX is the first-line prophylaxis agent which significantly reduces the incidence of PCP by over 90%. Due to side effects, including nausea, skin rash, and myelosuppression, prevention should be considered for high-risk patients.[27,38] As it appears in the review of reports, this infection seems to have a high mortality rate in cancer patients, making the timely diagnosis of this infection very important. Nevertheless, unlike the HIV population, there is no consensus on the appropriate initiation of PCP chemoprophylaxis in patients receiving bendamustine.

According to a meta-analysis of randomized controlled trials of PCP prevention in immunocompromised cases without HIV, PCP prophylaxis is indicated when the risk of PCP in adults is greater than 3.5%.[23,39] In a review study on practical recommendations regarding managing bendamustine therapy in NHL patients optimally, no prevention was recommended. However, in another study, 2-month monitoring of CD4+ T helper cells level and initiation of PCP prophylaxis with TMP/SMX is recommended for cases with a CD4 count of <200 cells/μl.[40] There are currently a few randomized controlled trials addressing chemoprophylaxis, particularly with bendamustine treatment.

The limitations of the present study were as follows: there were a limited number of articles including complete data about PCP prevalence in patients under treatment with bendamustine; a number of published reports did not meet the inclusion criteria of this study. Moreover, some of the papers did not have enough data to be included in this study. Future investigations are required to evaluate the prevalence of PCP in these patients and also the need for chemoprophylaxis.

5 | CONCLUSION

This review study described PCP infection in patients with various malignancies after the treatment with bendamustine, a chemotherapeutic agent associated with profound lymphopenia. Due to the

fact that bendamustine is increasingly used in malignant patients, clinicians should be aware of its potentially infectious and severe effects. Considering the lethality of PCP, further clinical evaluation is recommended to investigate the need for monitoring lymphocyte count during the treatment with bendamustine and identification of patients who may benefit from prevention.

AUTHOR CONTRIBUTIONS

Atousa Hakamifard: Conceptualization, and writing–review and editing. **Mohammad Javad Nasiri**: Review and editing. **Masoud Mardani**: Review and editing. **Tahereh Gholipur-Shahraki**: Writing–review and editing.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this published article (and its Supporting Information).

TRANSPARENCY STATEMENT

None declared.

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