REVIEW

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Efficacy and Safety of Ibrutinib for Chronic Graft-Versus-Host Disease: A Systematic Review

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Abstract

Introduction: Allogeneic hematopoietic cell transplantation (allo-HCT) serves as a potentially curative intervention for various hematologic disorders. However, its utility can be limited by the emergence of chronic graft-versus-host disease (cGVHD). The clinical manifestations of cGVHD result from a complex immune response characterized by the involvement of both B and T cells. Ibrutinib, a pharmacological agent, acts as an inhibitor of Bruton's tyrosine kinase (BTK) pathway, which becomes activated through the B-cell receptor and regulates B-cell survival. By exerting inhibitory effects on both BTK and inhibitor of interleukin-2 inducible T-cell kinase (ITK), ibrutinib exhibits promise as a therapeutic approach for managing cGVHD. Ibrutinib may be considered as a viable treatment option for active cGVHD in cases where patients exhibit an inadequate response to corticosteroid-based therapies. This systematic review seeks to assess the efficacy and safety of ibrutinib in the context of cGVHD patient management. **Method:** We incorporated search engines from PubMed, Embase, Cochrane Library, Scopus, Web of Science, and ClinicalTrials.gov. The study was performed following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 and Assessing The Methodological Quality of Systematic Review (AMSTAR). We used Risk of Bias- 2 (RoB-2) tool for assess the risk of bias in randomized controlled studies (RCTs) and Newcastle Ottawa Scale (NOS) for observational and open-label studies. **Results:** A total of 7 studies were included in this study consisted of four open-label studies, two retrospective cohort studies, and one RCT study. These studies compared Ibrutinitib with standard therapies. Two studies investigated the pediatric population, and five studies investigated the adult population. Overall, these studies reported the overall response rate (ORR) of ibrutinib for cGVHD were 54%-78%. The results showed that in pediatric patients, the ORR were 54-78%. The results also showed that in adult patients, the ORR were 67%-76%. The most common adverse effects observed across the seven studies included pyrexia, diarrhea, abdominal pain, cough, nausea, stomatitis, vomiting, headache, bleeding and bruising, infection, muscle aches, fatigue, oral bleeding, elevated transaminases, lower gastrointestinal bleeding, persistent dizziness, sepsis, pneumonia, reduced platelet count, exhaustion, sleeplessness, peripheral edema, and fatigue. **Conclusion:** The majority of studies have indicated that ibrutinib exhibits a high ORR and provides long-lasting responses, while also having manageable side effects.

Keywords: Ibrutinib- chronic graft-versus-host disease- treatment- systematic review

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Introduction

Allogeneic hematopoietic cell transplantation (allo-HCT) can be a curative treatment for several types of blood-related conditions, but it may be limited by chronic graft-versus-host disease (cGVHD). cGVHD is a common and serious complication of allo-HCT that can lead to long term patient suffering and decreased quality of life (Burger et al., 2019). Around 70% of patients who receive allo-HCT develop cGVHD, and about 30%-40% of them require systemic treatment for this condition. The usual first-line treatment for cGVHD is corticosteroids, but their prolonged use can cause side effects and worsen patient health. There is a need for alternative, non-steroidal or steroid-sparing treatment options to improve cGVHD outcomes (Burger et al., 2019; Ogawa et al., 2023). Corticosteroids, commonly utilized as the initial standard treatment, are typically administered for a median duration of 2 to 3 years, contributing to significant morbidity. Attempts to reduce

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corticosteroid dosages have led to their combination with other immunosuppressive agents like cyclosporine, tacrolimus, and sirolimus, in both first-line and second-line treatment strategies (Burger et al., 2019). However, despite these combinations, there is a lack of clinical evidence supporting enhanced efficacy when these agents are used in conjunction with corticosteroids. Patients who experience persistent cGVHD following first-line therapy and necessitate a change in their treatment plan face a 2.5-fold elevated risk of nonrelapse mortality (Ogawa et al., 2023). Regrettably, there is currently no established standard of care or approved second-line treatment for such cases. The absence of an effective therapeutic option for cGVHD patients who do not respond to initial therapy remains a critical unmet medical need in this context (King-Kallimanis et al., 2020).

The clinical symptoms of cGVHD are caused by a complex immune response involving both B and T cells. Ibrutinib is a medication that inhibits the Bruton's tyrosine kinase (BTK) pathway, which is activated by the B-cell receptor and controls B-cell survival. It also inhibits the interleukin-2 inducible T-cell kinase (ITK), which plays a role in the activation of T-cell subsets that contribute to immune reactivity against healthy tissues (King-Kallimanis et al., 2020; Ogawa et al., 2023). By blocking both BTK and ITK, ibrutinib has shown promise as a treatment for cGVHD. Iburitib may be employed as a therapeutic option for the management of active cGVHD when patients exhibit an insufficient response to treatments containing corticosteroids. Previous studies have demonstrated that ibrutinib is effective and well-tolerated in patients with relapsed chronic lymphocytic leukemia after undergoing allo-HCT. Ibrutinib has been approved in the United States for adult patients with cGVHD who have not responded to at least one systemic therapy (King-Kallimanis et al., 2020).

To the best of our knowledge, there are still no systematic reviews available to assess the efficacy and safety of ibrutinib in cGVHD. The aim of this systematic review is to determine the efficacy and safety of ibrutinib for cGVHD patients.

Materials and Methods

This systematic review study has been registered in Research Registry with unique identifying number (reviewregistry1709). The study was performed following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 and AMSTAR (Assessing The Methodological Quality of Systematic Review) (Page et al., 2021; Shea et al., 2017).

Search Strategy

We incorporated search engines from PubMed, Embase, Cochrane Library, Scopus, Web of Science, and ClinicalTrials.gov. MeSH Terms used were ((Chronic Graft-Versus-Host Disease OR cGVHD OR Graft-Versus-Host Disease OR GVHD) AND (Ibrutinib OR PCI-32765)) AND (Placebo OR standard therapy OR control) AND (Efficacy OR effectiveness OR safety OR adverse effects OR toxicity OR mortality).

Patient, Intervention, Comparison and Outcome (PICO) of the Study

The PICO for this study are:

- Population: patients with cGVHD
- Intervention: ibrutinib therapy
- Comparison: Placebo or standard therapy
- Outcome: Efficacy and safety of ibrutinib

According to the 2014 National Institutes of Health (NIH) criteria, a diagnosis of cGVHD necessitates either (a) the presence of at least one diagnostic clinical manifestation, or (b) the confirmation of a single distinctive clinical manifestation through biopsy or testing, whether it occurs in the same affected organ or a different one. Manifestations that are considered "diagnostic" and individually sufficient to establish the diagnosis of cGVHD can be observed in various anatomical sites, including the skin, oral cavity, gastrointestinal tract, lungs, fascia, and genitalia. Examples of such "diagnostic" manifestations include lichen planus or lichen sclerosis, poikiloderma, sclerosis, or esophageal webs (Jagasia et al., 2015).

In our systematic review, a critical aspect of our evaluation centered on assessing the outcomes pertaining to adverse effects associated with the administration of ibrutinib for the management of cGVHD. We systematically examined and analyzed data to determine the incidence, severity, and types of adverse effects reported in clinical trials and studies involving cGVHD patients treated with ibrutinib. This comprehensive assessment of adverse effects provides valuable insights into the safety profile of ibrutinib as a therapeutic intervention for cGVHD, enabling a more thorough understanding of the potential risks and benefits associated with its use.

Eligibility Criteria

The process of searching for relevant studies involved exporting all results into Mendeley reference manager. Duplicate studies were removed, and the titles and abstracts of the remaining research were examined. We included only randomized controlled trial study, open-label study and observational studies that met the following criteria: (1) Published in English language and in peer-reviewed journal; (2) Studies that include patients with cGVHD who received ibrutinib; and (3) Reported adverse effects of ibrutinib in cGVHD. Authors were contacted for additional information when necessary. Studies that did not report on the efficacy and safety of ibrutinib for cGVHD were excluded, as were review articles, letters to the editor, and case report studies.

Study Selection

The results of the systematic search were entered into a reference management software and duplicates were removed. Two reviewers, K.T. and D.R, independently evaluated the articles based on their titles, abstracts, and full texts to determine if they met the eligibility criteria. After an initial screening of titles and abstracts, we meticulously conducted a full-text assessment of the selected articles to ensure that they met our predefined inclusion criteria. Any discrepancies between the two reviewers were resolved through discussion and agreement. If necessary, a third author (D.S) was involved

in resolving disagreements.

Quality Assessment

We used the Cochrane Risk of Bias tool (RoB-2) for assess the risk of bias in randomized controlled studies (RCTs) and Newcastle Ottawa Scale (NOS) for observational and open-label studies (Lo et al., 2014; Minozzi et al., 2020; Cortegiani et al., 2021). The RoB-2 is a widely used tool for assessing the risk of bias in RCTs included in systematic review. It assesses the following domains:1) Bias arising from the randomization process, 2) Bias due to deviations from intended interventions, 3) Bias due to missing outcome data, 4) Bias in measurement of the outcome, 5) Bias in selection of the reported result.

The NOS assesses the following domains: a) Selection of study groups, b) Comparability of groups, c) Ascertainment of exposure, d) Outcome assessment, and e) Follow-up. The study scores were determined by evaluating the quality of the study's selection process (up to 4 points), the comparability of study groups (up to 2 points), and the outcomes of the study participants (up to 3 points). A study's overall quality was categorized as poor (score of 0-3), fair (score of 4-6), or good (score of 7-9) based on these evaluations.

Data Extraction

The following information was collected from the included studies: number of participants, age, gender, primary diagnosis, details of the transplantation including graft source and type of transplant, cGVHD type, involved organ and grade, Ibrutinib dose, setting of Ibrutinib administration (treatment naïve or subsequent line), overall response rate (ORR), duration of response (DOR), event-free survival (EFS), failure free survival (FFS), outcome parameters during the follow-up period, as well as study characteristics such as first author, year of publication, design of the study and length of follow-up period. We collected all the data following the guidelines of the PRISMA 2020. In cases where the studies did not provide sufficient information, we contacted the authors to confirm the data or obtain additional information.

Results

Study selection

Figure 1 depicted the selection procedure for studies. With the aid of an electronic search technique, we located 904 studies that might be pertinent. A total of 200 research studies were excluded due to duplicates, and 704 articles were screened based on their titles and abstracts. The following factors led to the exclusion of 82 of these studies: non-ibrutinib for cGVHD (n = 23), repeated studies (n = 12), studies that were irrelevant topic (n = 20), review articles (n = 5), and case reports (n = 22). A total of seven studies were included in this study consisted of four open-label studies, two retrospective cohort studies, and one RCT study. Two studies investigated the pediatric population, and five studies investigated the adult population (Table 1).

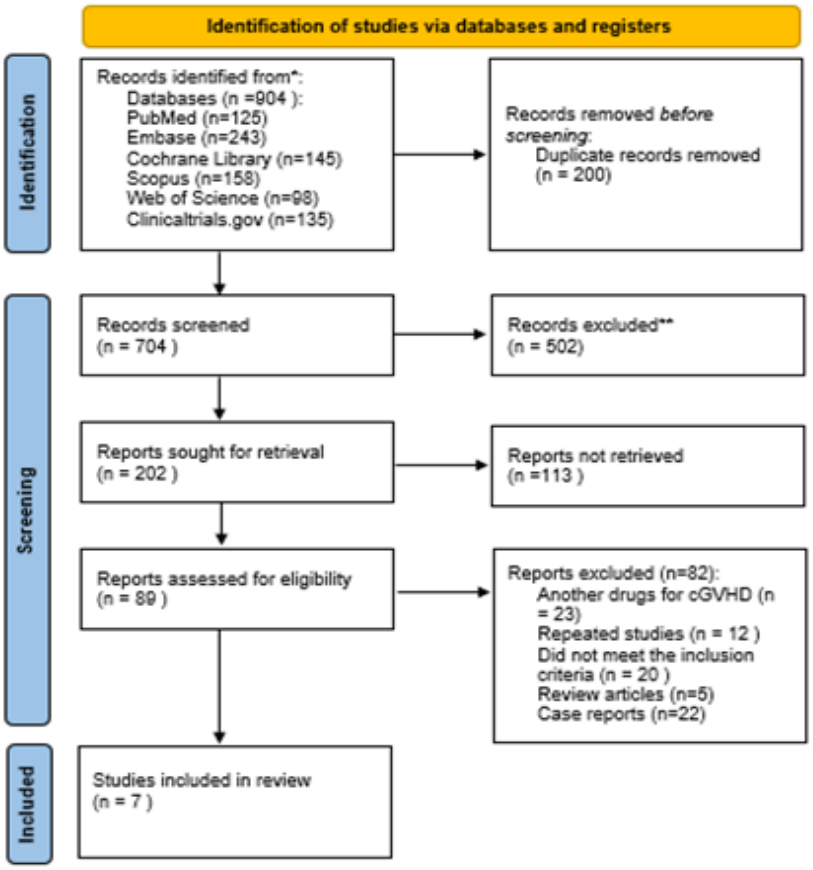

Figure 1. PRISMA Guideline of the Included Studies

Table 1. Characteristics of the Included Studies

Study(first author, publish year)	Sample size	Median age (range), years	Type of Study	Primary Diagnosis	Type of transplant	Graft source	Most common organs involved	Initial Ibrutinib dose, mg/day
Carpenter et al.(Carpenter et al., 2022) (2022)	59 children patients (42 male/17 female)	13.0 years	Multicenter Open-label study (not single arm)	Moderate-severe cGVHD	Allogenic transplant	N/A	Skin (80%), mouth (63%), and eyes (58%)	240 mg/m^2
Chin et al.(Chin et al., 2021) (2021)	122 adult patients (86 male/26 female)	56.5 years	Cohort retrospective study	Moderate-severe cGVHD	Allogenic transplant	PMB (n = 50; 94%)	Skin (n = 34; 64%) and mouth (n = 28; 53%)	N/A
Cross et al.(Teusink-Cross et al., 2020)(2020)	22 children patients	13.5 years	Cohort retrospective study	Mild, moderate, and severe cGVHD	Allogenic transplant	PBSC, bone marrow,cord	Skin (n = 16), eyes (n = 10), and lungs (n = 10)	250 mg/m^2
Doki et al.(Doki et al., 2021(2021)	19 adult patients (12 male/7female)	40 years	Multicenter, Open-label, single-arm study	Moderate-severe cGVHD	Allogenic transplant	N/A	Skin (73,7%),mouth (73,7%), eyes (47,4%)	420 mg
Miklos et al.(Miklos et al., 2017) (2017)	42 adult patients (22 male/20 female)	56 years	Open-label study (not single-arm study)	Moderate-severe cGVHD	Allogeneic transplant	PBSC, BM, CB	Skin and mouth	420 mg
Miklos et al.(Miklos et al., 2023) (2023)	193 adult patients (126 male/67 female)	51 years	RCT study	Moderate-severe cGVHD	Allogeneic transplant	PBSC, BM, CB	Skin, mouth, eyes	420 mg
Waller et al.(Waller et al., 2019) (2019)	42 adult patients	N/A	Multicenter, Open-label (not-single arm study)	Moderate-severe cGVHD	Allogeneic transplant	N/A	N/A	N/A

Treatment response for cGVHD in pediatric patients

A total of two studies reported the treatment response for cGVHD pediatric patients (Carpenter et al., 2022; Teusink-Cross et al., 2020). Study by Carpenter et al. (2020) found that the ORR was 78% overall (n = 46 of 59) with a median study follow-up duration of 20 months (range: 1.6 to 31.7 months), including 83% (n = 10 of 12 for the treatment-naïve (TN) subgroup) and 77% (n = 36 of 47 for the R/R subgroup cGVHD pediatric patients). Three patients (25%) in the TN subgroup experienced a complete response (CR), while seven (58%) experienced a partial response (PR). In the subgroup of patients with R/R disease, 34 individuals (72%) achieved a partial response, while 2 patients (4%) also reached a partial response. The estimated 18-month DOR was 58% (95% CI, 40% to 73%), including 60% (95% CI, 25% to 83%) in the TN subgroup and 58% (95% CI, 35% to 75%) in the relapsed/refractory (R/R) subgroup, among all patients who had a PR or CR at any point during the study. The median of DOR was not reached overall.

Teusink-Cross et al. (2020) found that at 6 months, all of the 22 patients had an ORR of 54%. In two individuals, ibrutinib was stopped three months after starting because of progressive disease (PD). Clinical improvement was observed in all patients who responded—all but two—by 6–8 weeks. At 3 months, the remaining two patients' conditions were stable, and over the ensuing three months, they began to improve. A total of 4 of the 14 patients who were evaluable for responses had cGVHD with sclerotic skin, and while three of these patients improved with ibrutinib, one patient's sclerosis worsened (Teusink-Cross et al., 2020).

Treatment response for cGVHD in adult patients

The treatment response for adult patients with cGVHD was reported in a total of 5 studies (Chin et al., 2021; Doki et al., 2021; Miklos et al., 2017, 2023; Waller et al., 2019). Study by Chin et al. found that two years after the initiation of ibrutinib treatment, the cumulative incidence of treatment change, relapse, and non-relapse mortality (NRM) were 83% (95% CI, 67% to 92%), 2% (95% CI, 0.1% to 9.5%), and 5.8% (95% CI, 1.5% to 15%), respectively (Chin et al., 2021). At 6 months after starting ibrutinib, 21 patients (or 40%) were still free of events. The 2-year FFS was 9% (95% CI, 2.6% to 20%), and the median FFS was 4.5 months (95% CI, 2.8 to 7.1 months). A total of 6 patients (12%) had a CR or PR, 34 (64%) had stable illness, and 13 (25%) had progressive disease at the time of an FFS event or the most recent follow-up. At the conclusion of the follow-up period, 11 patients (21%) continued to receive ibrutinib treatment. Doki et al. (2021) found that in the population of patients who received treatment as a whole, the best overall response rate (BORR) was 73.7% (14/19 patients; 95% CI, 48.8%; 90.9%); of the 14 responses, 2 patients had CR, and 12 patients had partial responses (PR); 2 of these patients had progressive disease after their initial responses as compared to their baseline (Doki et al., 2021). The average response time (CR or PR) was 2.79 months (interquartile range: 1.0 to 8.1). Stable illness was the best result in 5 non-responders. The responders' median DOR (interval:

Table 1. Continued

Study (first author, publish year)	Setting	ORR (%)	DOR	EFS	FFS	Median follow-up time (months)	Outcome	Adverse effect
Carpenter et al. (Carpenter et al., 2022) (2022)	First line: 12/59 (20%) Subsequent line: 47/59 (80%)	78	The predicted DOR over the next 18 months was 58% (95% CI, 40% to 73%)	N/A	Overall, the 18-month FFS estimate came in at 58% (95% CI, 44% to 69%).	20 months (range, 1.6 to 31.7 months)	The estimated survival rates at 12 months and 18 months were 95% with a confidence interval (CI) of 85% to 98% and 91% with a CI of 80% to 96%, respectively.	Pyrexia (31%), diarrhea (25%), abdominal pain(19%), cough (19%), nausea (17%), stomatitis (17%), vomiting (17%),and headache (15%)
Chin et al. (Chin et al., 2021) (2021)	First line: 20/53 (38%) Subsequent line: 33/53 (62%)	76	N/A	N/A	87% (median: was 4.5 months (95% CI, 2.8 to 7.1 months), and 2-year FFS was 9% (95% CI, 2.6% to 20%).	26 months (range, 1.3 to 39.5 months.	The median failure free survival (FFS) was 4.5 months (95% CI, 2.8 to 7.1 months), and 2-year FFS was 9% (95% CI, 2.6% to 20%).	Bleeding and bruising (hematoma, epistaxis),infection (lung, skin,enterocolitis), and muscle aches.
Cross et al. (Teusink-Cross et al., 2020) (2020)	First line: 3/22 (14%) Subsequent line: 19/22 (86%)	54	N/A	N/A	N/A	N/A	Fourteen of 22 patients were evaluated for responses at 6 months and 12 of those 14 (85.7%) had achieved a PR at that time	Recurrent fevers, muscle spasms, fatigue, oral bleeding, elevated transaminases, lower gastrointestinal bleeding, persistent dizziness, and sepsis.
Doki et al. (Doki et al., 2021 (2021)	First line: N/A Subsequent line: 19/19 (100%)	73.70	The DOR Kaplan-Meier estimate was 84.6% (95% CI, 51.2%; 95.9%) and 74.0% (95% CI, 38.2%; 91.0%) , respectively, at the 6-month and 9-month landmarks.	N/A	At the 6-month and 12-month landmarks, the Kaplan-Meier point estimates for FFS were 78.9% (95% CI, 53.2%; 91.5%) and 67.0% (95% CI, 40.4%; 83.8%), respectively.	11.9 (range 1.9 to 16.7+) months,	The best overall response rate (BORR) was 73.7% (14/19 patients; 95% CI, 48.8%; 90.9%) in the all-treated population.	Pneumonia and a reduced platelet count (4/19 [21.1%] patients each) were the most frequent TEAEs associated with ibrutinib10.0% of patients).
Miklos et al. (Miklos et al., 2017) (2017)	First line: N/A Subsequent line: 42/42 (100%)	67	N/A	N/A	N/A	13.9 months (range, 0.5-24.9 months)	The overall response rate (ORR) in the entire treated group was 67%, with a CR rate of 21% and a PR rate of 45%.	Most adverse events (AEs) were grade 1 or 2, with exhaustion, diarrhea, muscle spasms, nausea, and bruises being the most frequent. Pneumonia, tiredness, and diarrhea were the most often reported grade >=3 AEs.
Miklos et al. (Miklos et al., 2023) (2023)	First line: 45/95 (47%) Subsequent line: 50/95 (53%)	69	16 months was the median FFS (95% CI, 8 to 29).	15 months was the median EFS (95% CI, 6 to 27).	19 months was the median DOR (95% CI, 7 to not evaluable).	Median follow-up was 33 months (range, 0.03-47.20 months).	For ibrutinib-prednisone, the median EFS was 15 months (95% CI, 6 to 27) and for placebo-prednisone, it was 8 months (95% CI, 6 to 13) (hazard ratio [HR], 0.76; 95% CI, 0.54 to 1.07; P =.11).	The most frequent any-grade TEAEs in each arm were cough (21% and 30%), sleeplessness (28% and 19%), and peripheral edema (27% and 15%).
Waller et al. (Waller et al., 2019) (2019)	First line: N/A Subsequent line: 42/42 (100%)	69	N/A	N/A	N/A	Median follow-up was 26 months (range, .53–36.7 months)	The best overall cGVHD response rate was 69% (29 of 42) in the population treated as a whole, with 13 patients (31%) achieving a complete response and 16 (38%) achieving a partial response.	The most frequent grade 3 TEAEs, which affected 10% of patients, were pneumonia (14%), exhaustion (12%), and diarrhea (10%). The most frequent all-grade TEAEs (affecting 20% of patients) were fatigue (57%), diarrhea (40%), muscle spasms (33%), nausea (29%), and bruises (24%).

1.0 to 11.0+ months) was not attained. The Kaplan-Meier estimate for the DOR was 84.6% (95% CI, 51.2%; 95.9%) at the 6-month and 74.0% (95% CI, 38.2%; 91.0%) at the 9-month.

Miklos et al. (2017) found that according to National Institutes of Health (NIH) cGVHD Consensus Panel response criteria, the ORR in the entire treated group was 67%, with a CR rate of 21% and a PR rate of 45% (Miklos et al., 2017). Before a response assessment, five participants stopped their medication and quit the trial. If these 5 patients were not included, the ORR for the population with evaluable responses was 76%. In contrast, for the four responders who were enrolled following the protocol amendment and whose first response assessment took place at week five, the median duration to initial response was 30 days for the 24 responders whose first efficacy evaluation was completed at week thirteen. Another study by Miklos et al. also found that ibrutinib-prednisone had a median DOR of 19 months (95% CI, 7 to not evaluable) among patients having a CR or PR at any point throughout the study, compared to 10 months (95% CI, 6.5 to 17) for placebo-prednisone (p = 0.10). 45% (95% CI, 33 to 56) and 32% (95% CI, 22 to 42) were the 24-month DOR estimates, respectively (Miklos et al., 2017). The best overall cGVHD response rate was 69% (29 of 42) in the population that had been treated, according to a study by Waller et al. This included 13 patients (31%) who had a CR and 16 (38%) who had a PR. A total of 20 (69%), 18 (62%), and 16 (55%) of the 29 respondents showed sustained responses lasting 20, 32, and 44 weeks, respectively (Waller et al., 2019).

Organs affected in cGVHD

The majority of studies provided evidence indicating the involvement of various organ systems in cGVHD. These organ systems included the skin, mouth, lungs, gastrointestinal tract, eyes, joints, liver, and muscles. The data from these studies collectively supported the notion that cGVHD can manifest in multiple bodily systems, underscoring the complexity and systemic nature of this condition (Chin et al., 2021; Doki et al., 2021; Miklos et al., 2017, 2023; Waller et al., 2019).

Adverse effects of ibrutinib

The most commonly reported adverse effects associated with the use of ibrutinib for cGVHD were headache, pyrexia, diarrhea, abdominal pain, cough, nausea, stomatitis, and vomiting. Petechiae, epistaxis, contusions, and gingival bleeding, which occurred in 5% of all patients, were the most frequent types of bleeding (Chin et al., 2021; Miklos et al., 2017, 2023; Waller et al., 2019). A TN patient with a history of capillary leak syndrome experienced one hemothorax incident that was classified as a grade 1 significant treatment-emergent adverse event and required a chest tube. In 2 patients with R/R cGVHD there was grade 3 hypertension. It is interesting to note that one study discovered a range of cardiac problems, from a single incidence of cardiomyopathy that necessitated stopping treatment to multiple instances of atrial fibrillation that were treated medically (Chin et al., 2021).

Table 2. Risk of Bias of NOS for Observational and Open-label Studies

	Selection				Comparability	Outcome			
Author	Representative of the exposed study	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interes was not present at start of study	Comparability of study on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up cohorts	Total score
Carpenter et al. (2022)	1	1	1	1	0	1	1	1	7
Chin et al. (2021)	1	1	1	1	1	1	1	1	8
Cross et al. (2019)	1	1	1	1	1	1	1	1	8
Doki et al. (2021)	1	1	1	0	1	1	1	1	7
Miklos et al. (2017)	1	1	1	1	1	1	1	1	8
Waller et al. (2019)	1	1	1	1	0	1	1	1	7

Table 3. Risk of Bias RoB-2 Tool for the RCT Study

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Miklos et al. (2023)	+	+	+	+	+	?	+

Doki et al., (2021) found that ibrutinib was used to treat patients with cGVHD, and side effects included pneumonia and a decreased platelet count (4/19 (21.1%) patients each), cellulitis and stomatitis (3/19 (15.8%) patients each, and bronchiolitis, upper respiratory tract infection, purpura, and hypertension (2/19 (10.5%) patients each).

Overall Survival (OS)

Three studies reported the overall survival in cGVHD patients treated with ibrutinib (Carpenter et al., 2022; Miklos et al., 2017; Waller et al., 2019). Study by Carpenter et al., (2022) found that the median OS was not obtained, but the estimations for the 12-month and 18-month OS were 95% (95% CI, 85%-98%) and 91% (95% CI, 80%-96%), respectively (Carpenter et al., 2022). The TN subgroup's OS estimations (92% at 18 months; 95% CI, 54%-99%) and the R/R subgroup's (91% at 18 months; 95% CI, 78%-97%) were comparable. Miklos et al., (2017) found that the median OS was not attained in either arm, and the projected 24-month OS rates were comparable between treatments (HR, 1.06; 95% CI, 0.59-1.90) (Miklos et al., 2017). In the end, 22 patients (22%) in the placebo-prednisone group and 23 patients (24%) in the ibrutinib-prednisone group had died unexpectedly. Waller et al., (2019) found that the Kaplan-Meier point estimate for failure-free survival in all treated patients at 18 months was 51% in an exploratory analysis. Based on post hoc overall survival analysis, the predicted survival rate at 24 months was 71% (95% CI, 52%-83%) for patients who were followed for up to 37 months (median 26 months) (Waller et al., 2019).

Risk of bias

After three authors assessed the risk of bias, it was concluded that all of the studies had low risk of bias (Table 2 and Table 3). Chin et al., (2021), Cross et al., (2019), and Miklos et al., (2017) exhibit fewer potential sources of bias with high total scores of 8, suggesting overall robust methodology. Carpenter et al., (2022), Doki et al., (2021) and Waller et al., (2019) show more areas of potential concern with total scores of 7. These assessments provide valuable insights into the strengths and weaknesses of each study, helping researchers interpret their findings more accurately and make informed decisions in systematic reviews or meta-analyses. The RoB-2 tools for assessing research by Miklos et al., (2023) also showed low risk of bias.

Discussion

Ibrutinib is a BTK small molecule inhibitor that has showed promise in treating cGVHD, a condition that can happen after hematopoietic stem cell transplantation (Hui et al., 2020). The effectiveness and safety of ibrutinib in treating cGVHD have been examined in several clinical trials, and the findings are promising. Ibrutinib demonstrated an ORR of 67% in a phase 1/2 study of 42 patients with steroid-refractory cGVHD, with 21% of patients reaching a CR and 46% achieving a PR (Burger et al., 2015; Hui et al., 2020). While the median progression-free survival (PFS) was 6.6 months, the median duration of response was 11.5 months. Ibrutinib was assessed in a second phase 1/2 study involving 42 patients with steroid-dependent or refractory cGVHD. With a CR rate of 31% and a PR rate of 36%, the ORR was 67%. The median PFS was 9.2 months, while the median response duration was 12.5 (Burger and Buggy, 2013; Doki et al., 2021; Teusink-Cross et al., 2020).

These findings imply that ibrutinib may be a useful treatment choice for cGVHD patients who have not responded to or are dependent on steroid therapy. In addition, 42 patients who received ibrutinib treatment showed durable responses with a median follow-up of 36 months in a long-term follow-up trial. In these clinical trials, the safety profile of ibrutinib in cGVHD was also assessed. Diarrhoea, exhaustion, nausea, and decreased appetite were the most frequent side reactions (Burger et al., 2015; Carpenter et al., 2022; Teusink-Cross et al., 2020). Hematologic toxicities were also noted, with grade 3 or 4 neutropenia and grade 3 or 4 thrombocytopenia occurring in 24% and 14% of patients, respectively. Just 5% of patients experienced grade 3 or 4 infections, indicating a low frequency of serious illnesses (Burger et al., 2015; Teusink-Cross et al., 2020).

The current standard of care for cGVHD is corticosteroids, such as prednisone, which are used as a first-line treatment (Jain et al., 2015; Wilkinson et al., 2021). However, some patients may not respond adequately to steroids or may experience significant side effects, which can limit their long-term use. In a research conducted by Akpek in 2001, individuals suffering from severe and treatment-resistant cGVHD received high-dose pulse steroids, specifically methylprednisone at a rate of 10 mg/kg/day for four consecutive days, followed by a gradual reduction in dosage. The findings indicated that 48% of the patients achieved a significant improvement, while 27% displayed a partial response (Akpek et al., 2001). In these cases, second-line treatments such as ibrutinib may be considered. Ibrutinib is a safe and effective therapy choice for individuals with cGVHD who have tried other treatments or are dependent on steroids, according to the current data. To validate these results and determine the ideal dosage and course of therapy, additional research is required (Carpenter et al., 2022; Miklos et al., 2023; Waller et al., 2019). Additionally, more

studies are needed to investigate the long-term outcomes of patients treated with ibrutinib for cGVHD. Further details on the longevity of responses, the possibility of illness return, and the effect on quality of life will be available with longer follow-up periods. The efficacy of ibrutinib should be examined in particular patient groups, such as those with severe cGVHD or those who have had numerous lines of therapy. These trials may aid in determining which patients would benefit most from ibrutinib therapy (Saidu et al., 2020).

The study exhibits a strong point in its comprehensive data collection process. By systematically reviewing a broad range of primary research studies, it aims to provide a holistic overview of the available evidence on ibrutinib's efficacy and safety. This approach allows for a more robust analysis. Systematic reviews are inherently structured to offer an impartial and objective assessment of the extant body of literature. This impartiality helps in minimizing potential biases and ensuring that the findings are as reliable as possible. One significant limitation is the inherent heterogeneity of the included primary studies. The diversity in study designs, patient populations, and cGVHD severity may introduce variability in the results. The systematic review should acknowledge and attempt to address this limitation through appropriate statistical techniques.

In conclusion, Ibrutinib is a promising treatment option for patients with cGVHD who have not responded to or are dependent on steroid therapy. Clinical trials have demonstrated that ibrutinib has a high overall response rate and durable responses, with manageable side effects.

Nevertheless, it is imperative to emphasize the necessity for further research to substantiate these findings and establish the optimal dosage and treatment duration. This also entails investigating the long-term outcomes and efficacy within specific patient subsets. Ibrutinib, as a therapeutic option for cGVHD, holds significant promise, particularly for patients who have exhausted other available therapies. To comprehensively evaluate its comparative effectiveness against conventional treatments like corticosteroids or calcineurin inhibitors, the implementation of RCTs is crucial. Furthermore, there is a pressing need to explore the determination of the most suitable dosing regimen and treatment duration for ibrutinib. This will necessitate the execution of dose-ranging investigations and an assessment of whether adopting a gradual titration approach to treatment can mitigate adverse effects while preserving therapeutic efficacy.

Author Contribution Statement

Damai Santosa and Daniel Rizky: Conceptualization, Methodology, Software. Kevin Tandarto.: Data curation, Writing- Original draft preparation. Budi Setiawan and Eko Adhi Pangarsa: Visualization, Investigation. Catharina Suharti: Supervision.: Desta Nur Ewika Ardini, Ika Kartiyani and Vina Yunarvika: Writing- Reviewing and Editing.

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Data Availability

This work incorporates data previously published by other authors, with all data included in the findings section.

Ethical approval

This research did not involve human subjects; therefore, it was exempt from ethical clearance.

Conflict of Interest

The authors declare no conflict of interest in this study.

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