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Excellent Efficacy and Survival Using Ibrutinib-Based Chemotherapy Regimen for Untreated or Relapsed/Refractory Non-Hodgkin's Lymphoma

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Abstract

Although ibrutinib has shown significant therapeutic advantages in the front-line treatment of chronic lymphocytic leukaemia compared to current chemotherapy drugs, the fundamental question of whether ibrutinib improves anticancer efficacy and tolerability in patients with untreated or relapsed/refractory NHL, especially for specific histological subtypes, remains unanswered. We conducted a systematic literature search for clinical trials investigating the efficacy and safety of ibrutinib in NHL. The search yielded 22 non-comparative clinical studies that meet inclusion criteria, with a total of 1062 patients. Our study demonstrated a significant survival benefit for ibrutinib with a pooled ORR of 51% (95% CI: 41–60%). Furthermore, the results of subgroup analyses based on different histo logic subtypes of patients were as follows: the pooled ORR for MCL, FL, DLBCL and MZL were 71%, 43%, 35% and 33%, respectively. The mean PFS was 16.5 months (95% CI: 13.14-18.15) and the mean OS was 22.14 months (95% CI: 18.60-24.19). Most frequently occurred grade 3 to 5 toxicities included lymphopenia (45%), neutropenia (23%) and anaemia (13%). No new adverse events were observed. In summary, ibrutinib is an effective cyto toxic drug with reasonable toxicity for the chemotherapeutic treatment of untreated or relapsed/refractory NHL, especially the MCL subtype.

Keywords: Ibrutinib; Non-Hodgkin's lymphoma; Efficacy; Survival; Toxicity

Introduction

Non-Hodgkin's lymphoma (NHL) is the most common hematologic malignancy [1]. 544,352 new cases of NHL were reported globally in 2020, ranking 13th among all new cases of malignant tumors, and 259,793 deaths from NHL were reported globally in 2020, ranking 12th among all deaths from malignant tumors [2]. NHL is classified as of T/NK-cell origin and of B-cell origin. B--cell lymphoma is the main source, which includes highly aggressive (eg, highly aggressive B-cell lymphoma), aggressive (eg, diffuse large B-cell lymphoma), and painless disease (follicular B-cell lymphoma, marginal zone lymphoma). By far the most common NHL subtypes in developed countries are diffuse large B-cell lymphoma (approximately 30%) and follicular lymphoma (approximately 20%). The frequency of all other NHL subtypes is less than 10% [3,4].

Currently, most patients with aggressive NHL will be induced with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) or a similar regimen, which has been the standard of care in diffuse large B-cell lymphoma for 20 years, and cure will be achieved in approximately two-thirds of patients with R-CHOP induction [5,6]. For patients with inert B-cell lymphoma, bendamustine and rituximab/ Obinutuzumab offer excellent upfront response and durability [7,8]. However, many patients fail to be cured with standard therapy and have severe disease and high relapse rates. In addition, these regimens are associated with a range of acute and long-term toxicities, including, but not limited to, febrile neutropenia, which is a significant cause of treatment failure in patients with NHL. Thus, there is a need for new therapies, particularly drugs that target the pathogenesis of the disease with greater efficacy and fewer and less severe adverse events.

B-cell receptor (BCR) signalling regulates the differentiation and function of normal B cells. The activation of BCR may be extrinsic or intrinsic via acquired mutations or auto antigens in the signalling pathway [9]. Histologic subtypes of NHL may depend on chronic BCR pathway activation. Bruton's tyrosine kinase (BTK) is an attractive target for treating B-cell diseases because inactivating mutations lead to B-cell aplasia in humans. Ibrutinib (PCI-32765) is a bio available, selective and irreversible small-molecule inhibitor of BTK. Furthermore, ibrutinib has significant clinical benefit in the treatment of several B-cell malignancies and has been approved by the US Food and Drug Administration (FDA) for the treatment of chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL) and relapsed MCL [10,11]. In addition, a phase I study showed that orally administered ibrutinib was well tolerated and improved response rates in patients with B-cell NHL who relapsed or were refractory to standard therapy. Most AEs were mild (grade 1 or 2) and thus easily managed or reversible.

Although several trials have been conducted with the aim of investigating the efficacy and safety of ibrutinib, it is difficult to draw clear conclusions in terms of the value of ibrutinib to treat NHL and its subtypes due to the following: (1) small sample size of each single trial; (2) different disease subtypes, which varied among studies; and (3) various study designs. Therefore, this first meta-analysis was conducted with the aims of (1) investigating the efficacy of ibrutinib for patients with untreated or relapsed/refractory NHL or other various histologic subtypes and (2) assessing the safety of ibrutinib in patients with untreated or relapsed/refractory NHL.

Methods

Literature Search

The systematic literature search was conducted in the PubMed, EMBASE, Clinical Trials.gov, Cochrane Library, Web of Science, Google Scholar and Med Line databases for pertinent studies published until to April 2023. Moreover, reference lists of retrieved studies were also searched to identify potentially relevant articles. Key words included "ibrutinib" OR "Bruton's Tyrosine Kinase Inhibitor" OR "PCI-32765" AND "Cell Malignancies" OR "mantle cell lymphoma" OR "Follicular lymphoma" OR "diffuse large B-cell lymphoma" OR "Marginal zone lymphoma" OR "non-Hodgkin's lymphoma". Two authors independently made the selections, and any disagreement between the authors was resolved by discussion.

Inclusion and Exclusion Criteria

Studies were included in the meta-analysis if they met the following criteria: (1) results were expressed as an ORR with a clear definition; (2) patients were diagnosed with NHL; (3) more than 10 eligible patients; (4) articles were published in English; (5) full paper or conference abstract was available. Exclusion criteria included the following: (1) outcome data were incomplete; (2) patients were diagnosed with another malignancy; (3) research design was not clear; (4) studies were published as reviews, meta-analyses or comments.

Quality Assessment of the Studies

We assessed the quality of included studies using the Methodological Index for Non-Randomized Studies (MINORS) form [12]. Each study was scored according to 8 items: (1) a clearly stated aim; (2) inclusion of consecutive patients; (3) prospective data collection; (4) endpoints appropriate to the study aim; (5) unbiased assessment of the study endpoint; (6) a follow-up period appropriate to the aims of the study; (7) loss to follow up less than 5%; and (8) prospective calculation of the study size. Each item was scored as 0, 1, or 2, and the ideal global score for non-comparative studies was 16.

Data Extraction

Two investigators independently extracted relevant characteristics and outcomes from eligible studies. The following information was collected from each study: first author's last name, publication year, histologic subtype, design of study, number and age of patients, percentage of male patients, ECOG performance status primary end point, intervention, outcome data and adverse events.

Statistical Analysis

The meta-analysis was performed using the pooled estimate proportion of ORR and adverse events. Subgroup analysis was also performed on the histologic subtype and median age of patients. Heterogeneity between studies was assessed by Q statistic [13] and I2. A random-effects model (DerSimonian-Laird test) was adapted if significant heterogeneity was detected ($P < 0.05$ or $I2 > 50\%$); otherwise, a fixed-effects model (Mantel-Haenszel test) was used [14]. Funnel plots as well as Begg's and Egger's test were used to detect publication bias [15]. An Egger's regression intercept with $aP < 0.05$ was considered significant for publication bias. Time-to event end points including overall survival (OS) and progression-free survival (PFS) were estimated using the Kaplan-Meier method. All of the analyses were performed with R software version 3.5.2 (R Foundation for Statistical Computing, Lan zhou, China, meta package, Meta Surv package and digitize package).

Results

Study Identification and Selection

A total of 104 potentially relevant articles were obtained from several electronic databases after removing duplicates (Figure 1). Forty-seven studies were excluded by searching titles and abstracts. Of the remaining records, 35 articles were excluded because they were the incorrect type (reviews, meta-analyses, or case reports), they reported on other tumours, they had incomplete data, or the primary end point was not ORR. Finally, a total of 22 non-comparative studies were considered eligible for this meta-analysis according to the selection criteria, [36,37].

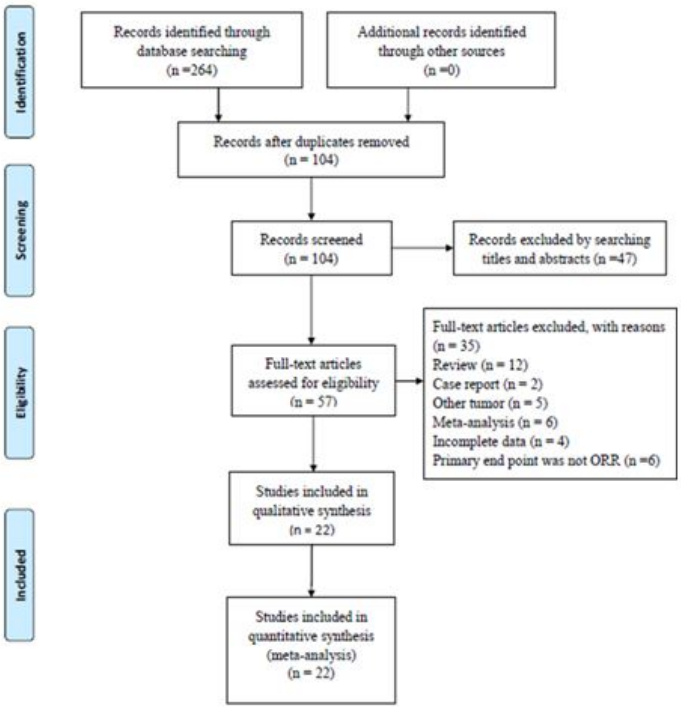

Figure1: Flowchart of the study selection process for the meta-analysis.

Characteristics of the Included Studies

The detailed characteristics of all of the eligible studies are described in Table 1, including author, publication year, histo logic subtype, study design, number and age of patients, percentage of male patients, ECOG performance status, number of cases, details of interventions performed, and outcome data.

Table 1: Characteristics of the included studies.

Study	Year	Histologic Subtype	Design	Number	Age	Male (%)	ECOG Performance Status	Primary End Point	Intervention
Bartlett NL et al.[16]	2018	R/R FL	phase 2	40	64 (46-82)	70	≤2	ORR	ibrutinib
Ariela Noy et al.[17]	2017	R/R MZL	phase 2	63	66 (30-92)	41	≤2	ORR	ibrutinib
Ujjani CS et al.[18]	2018	U FL	Phase 1	22	53.5 (36-81)	68	≤1	ORR	ibrutinib+rituximab+lenalidomide
Wilson WH et al.[19]	2015	R/R DLBCL	phase 2	80	28-92	71	≤2	ORR	ibrutinib
Kami Maddocks et al.[20]	2015	U/R/R NHL	phase 1	48	62 (23-84)	77	≤2	ORR	ibrutinib+rituximab+bendamustine
Anas Younes et al.[21]	2014	U NHL	phase 1b	32	60·5 (22–81)	52	≤2	ORR	ibrutinib+R-CHOP regimen
Advani RH et al.[22]	2012	R/R NHL	phase I	36	NR	NR	NR	ORR	ibrutinib
Fowler NH et al.[23]	2012	R/R FL	Phase I	16	60 (41–71)	50	NR	ORR	ibrutinib
Bartlett NL et al.[24]	2014	R/R FL	phase 2	40	64 (46-82)	70	NR	ORR	ibrutinib
Winter AM et al.[25]	2017	R/R DLBCL	retrospective cohort study	54	62 (38-88)	61	NR	ORR	ibrutinib
Robert Chen et al.[26]	2017	R/R MZL	phase 2	60	66 (30-92)	NR	NR	ORR	ibrutinib
Wilson WH et al.[27]	2012	R/R DLBCL	phase 2	70	63 (28–92)	71	NR	ORR	ibrutinib
Christian BA et al.[28]	2015	R/R NHL	phase I	25	67 (45-85)	64	≤2	ORR	ibrutinib+lenalidomide
Blum KA et al.[29]	2012	R/R NHL	phase I	11	72 (45–84)	82	NR	ORR	ibrutinib+rituximab+bendamustine
Wang ML et al.[30]	2013	R/R MCL	phase 2	111	68 (40-84)	77	0-5	ORR	ibrutinib
Naveed Ali et al.[31]	2017	R/R NHL	retrospective cohort study	11	73 (49-96)	NR	NR	ORR	ibrutinib
Wang LH et al.[32]	2014	R/R MCL	phase 2	45	NR	NR	NR	ORR	ibrutinib+rituximab
Ariela Noy et al.[33]	2016	R/R MZL	phase 2	63	66 (30-92)	NR	≤2	ORR	ibrutinib
Anas Younes et al.[34]	2017	R/R NHL	phase 1/2a study	85	65 (20-89)	61.7	NR	ORR	ibrutinib+nivolumab
Wang M et al.[35]	2014	R/R MCL	phase 2	120	67.5 (35-85)	NR	≤2	ORR	ibrutinib

Andre Goy et al.[36]	2017	R/R MCL	Phase Ib-II	14	67.5 (47-81)	78.6	NR	ORR	ibrutinib+lenalidomide
Maruyama D et al.[37]	2016	R/R MCL	phase 2	16	72.0 (55–83)	75	≤1	ORR	ibrutinib

Abbreviations: FL, Follicular lymphoma; MCL, Mantle Cell Lymphoma; BLBCL, Diffuse Large B-cell Lymphoma; MZL, Marginal Zone Lymphoma; NHL, non-Hodgkin lymphoma; R/R, relapsed or refractory; U, untreated; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; NR, not reported.

As shown, all of the studies were published between 2012 and 2022. A total of 1062 patients with untreated or relapsed/refractory NHL were included in the 22 non-comparative studies, which contained 11 phase II studies, 7 phase I studies, 2 retrospective studies, 1 phase Ib-II study and 1 phase I/IIa study. The size of the study populations ranged from 11 to 120 subjects. The majority (50 – 82%) of patients were male, and the ECOG performance status was as ≤ 2 for most cases. In the 22 included studies, patients were treated with ibrutinib-based chemotherapy. ORR outcomes were available for all 22 trials, and the value ranged from 9.09% to 95.45% (Table 2).

Table 2: Outcomes data of the included studies.

Study	Histologic Subtype	Outcomes Data				
		CR(n)	**PR(n)**	**ORR(n)**	**Total(n)**	**ORR(%)**
Bartlett NL et al.[16]	FL	5	10	15	40	37.50%
Ariela Noy et al.[17]	MZL	2	27	29	60	48.33%
Ujjani CS et al.[18]	FL	8	13	21	22	95.45%
Wilson WH et al.[19]	DLBCL	8	12	20	80	25.00%
Kami Maddocks et al.[20]	NHL	24	9	33	46	71.74%
	MCL	13	3	16	17	94.12%
	DLBCL	5	1	6	16	37.50%
	FL	5	4	9	10	90.00%
	MZL	0	1	1	1	100.00%
Anas Younes et al.[21]	NHL	23	7	30	32	93.75%
Advani RH et al.[22]	NHL	6	10	16	36	44.44%
	MCL	3	4	7	9	77.78%
	DLBCL	0	2	2	7	28.57%
	FL	3	3	6	16	37.50%
	MZL	0	1	1	4	25.00%
Fowler NH et al.[23]	FL	3	3	6	16	37.50%
Bartlett NL et al.[24]	FL	1	11	12	40	30.00%
Winter AM et al.[25]	DLBCL	5	10	15	54	27.78%
Robert Chen et al.[26]	MZL	2	27	29	60	48.33%
Wilson WH et al.[27]	DLBCL	3	10	13	60	21.67%
Christian BA et al.[28]	NHL	NR	NR	7	18	38.89%
Blum KA et al.[29]	NHL	2	1	3	8	37.50%

Wang ML et al.[30]	MCL	23	52	75	111	67.57%
Naveed Ali et al.[31]	NHL	1	0	1	11	9.09%
	MCL	1	0	1	4	25.00%
	DLBCL	0	0	0	3	0.00%
	FL	0	0	0	2	0.00%
	MZL	0	0	0	2	0.00%
Wang M et al.[32]	MCL	17	22	39	45	86.67%
Ariela Noy et al.[33]	MZL	6	26	32	63	50.79%
Anas Younes et al.[34]	NHL	9	19	28	85	32.94%
	DLBCL	6	10	16	45	35.56%
	FL	3	9	12	40	30.00%
Wang M et al.[35]	MCL	25	50	75	120	62.50%
Andre Goy et al.[36]	MCL	NR	NR	6	10	60.00%
Maruyama D et al.[37]	MCL	NR	NR	14	16	87.50%

Abbreviations: FL, Follicular lymphoma; MCL, Mantle Cell Lymphoma ; BLBCL, Diffuse Large B-cell Lymphoma; MZL, Marginal Zone Lymphoma; NHL, non-Hodgkin lymphoma; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; CR, Complete response; PR, Partial response; ORR, Overall response rate; NR, not reported.

Quality Assessment

The methodological quality of the included non-comparative studies was assessed using the MINORS form. The MINORS quality scores of the non-comparative studies are presented in Table 3. The mean score was 14.6 (range 13–16), which indicated that there was considerable variability in the evidence base.

Table 3: The study designs and MINORS appraisal scores for the non-comparative studies.

MINORS Methodological Criteria										
Study	**Study Design**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**Total**
Bartlett NL et al.[16]	non-comparative	2	2	2	2	2	2	2	1	15
Ariela Noy et al.[17]	non-comparative	2	2	2	2	1	2	2	2	15
Ujjani CS et al.[18]	non-comparative	2	2	2	2	1	2	1	2	14
Wilson WH et al.[19]	non-comparative	2	2	2	2	2	2	2	2	16
Kami Maddocks et al.[20]	non-comparative	2	2	2	2	0	2	2	2	14
Anas Younes et al.[21]	non-comparative	2	2	2	2	2	1	2	1	14
Advani RH et al.[22]	non-comparative	2	2	2	2	2	0	2	2	14
Fowler NH et al.[23]	non-comparative	2	2	2	2	2	2	2	2	16
Bartlett NL et al.[24]	non-comparative	2	2	2	2	2	1	2	1	14
Winter AM et al.[25]	non-comparative	2	2	2	2	2	1	2	2	15
Robert Chen et al.[26]	non-comparative	2	2	2	2	2	1	2	2	15

Wilson WH et al.[27]	non-comparative	2	2	1	2	2	1	2	2	14
Christian BA et al.[28]	non-comparative	2	2	2	2	2	1	0	2	13
Blum KA et al.[29]	non-comparative	2	2	2	2	2	2	0	1	13
Wang ML et al.[30]	non-comparative	2	2	2	2	2	2	2	2	16
Naveed Ali et al.[31]	non-comparative	2	2	2	2	2	2	2	2	16
Wang LH et al.[32]	non-comparative	2	2	2	2	2	0	2	1	13
Ariela Noy et al.[33]	non-comparative	2	2	2	2	2	2	2	2	16
Anas Younes et al.[34]	non-comparative	2	2	0	2	2	2	2	2	14
Wang M et al.[35]	non-comparative	2	2	2	2	2	2	2	2	16
Andre Goy et al.[36]	non-comparative	2	2	2	2	2	2	2	1	15
Maruyama D et al.[37]	non-comparative	2	2	2	2	2	1	2	1	14

Abbreviations: The MINORS criteria include the following items:(1) a clearly stated aim; (2) inclusion of consecutive patients; (3) prospective data collection; (4) endpoints appropriate to the aim of the study; (5) unbiased assessment of the study endpoint; (6) a follow-up period appropriate to the aims of the study; (7) Loss to follow up less than 5%; (8) Prospective calculation of the study size

The items are scored as follows: 0 (not reported); 1 (reported but inadequate); or 2 (reported and adequate). The ideal global score would be 16 for the non-comparative studies.

Meta-Analysis Results

The ORR data were extracted from all of the included studies (1062 patients). A random-effect model was adapted to perform the meta-analysis because significant heterogeneity was observed between trials (I2 = 86%, P < 0.01). The pooled proportion of ORR was 51% (95% CI: 41–60%, Figure 2).

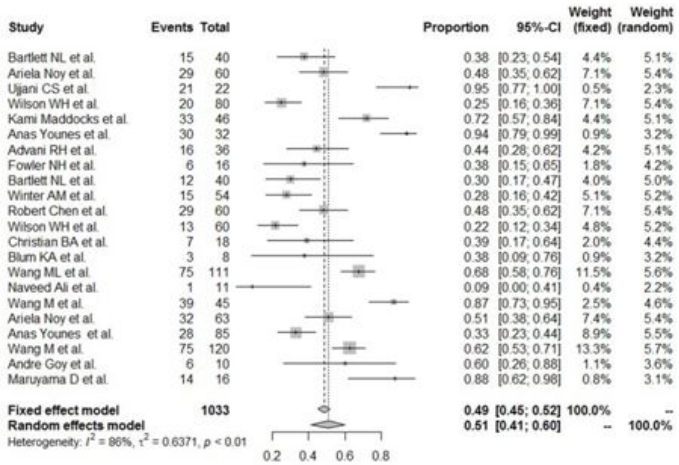

Figure 2: Forest plot of all included studies' pooled estimate of overall response rate.

Subgroup Analysis

When all of the outcome data were pooled together, significant heterogeneity emerged. Thus, we performed subgroup analysis to decrease heterogeneity and obtain more reliable results. We first stratified the studies by the median age of patients. In the subgroup analysis, the pooled proportion of ORR for patients with a median age > 65 was 54% (95% CI: 45–63%), which was slightly higher than the younger subgroup (pooled ORR = 49%; 95% CI: 33–65%) (Figure3).

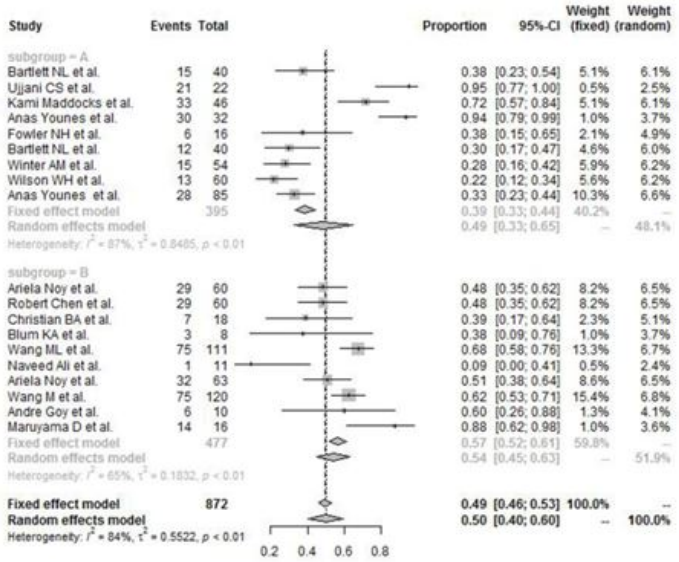

Figure 3: Forest plot of pooled estimate of overall response rate in subgroups which were stratified by the median age of patients. (sub group =A, median age of patients ≤ 65 years old; subgroup =B, median age of patients > 65 years old.).

However, high heterogeneity was still observed among these studies. Thus, other subgroup analysis was performed to explore other factors that affecting the heterogeneity. Of all the included studies, 4 evaluated ORR-based DLBCL patients, 4 investigated the FL patients, 6 examined MCL patients, and 3 involved MZL patients. Therefore, we stratified the studies based on NHL histo logic subtypes. The pooled proportion of ORR for the DLBCL, FL, MCL, and MZL subgroups was 35% (95% CI: 24–46%; I2 = 0%), 43% (95% CI: 20–70%; I2 = 63%), 71% (95% CI: 53–84%; I2 = 53%) and 33% (95% CI: 9–71%; I2 = 0%), respectively. No evidence of high heterogeneity among the individual studies was observed (Figure 4).

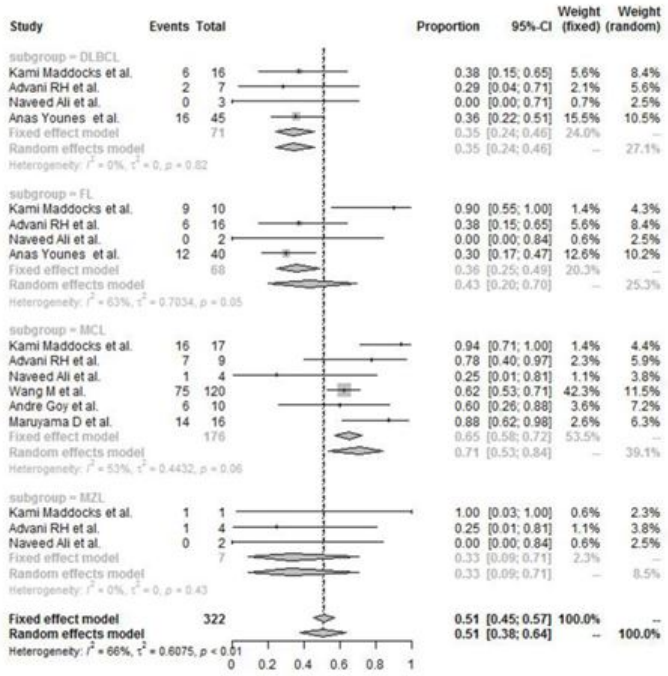

Figure 4: Forest plot of pooled estimate of overall response rate in subgroups which were stratified by the histo logic sub type.

In the included studies, 2 investigated the previously untreated NHL patients and 19 investigatedrelapsed/refractory NHL patients. Hence, we stratified the studies by the characteristic of patients. The pooled proportion of ORR for previously untreated NHL patients and relapsed/refractory NHL patientswas74% (95% CI: 7–99%; I2 = 92%) and 49% (95% CI: 39–59%; I2 = 85%), respectively

(Figure 5).

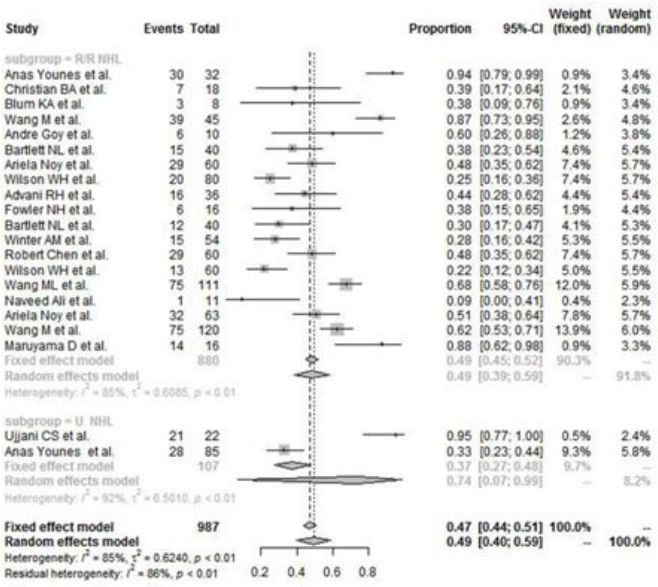

Figure 5: Forest plot of pooled estimate of overall response rate in subgroups which were stratifiedby the characteristic of patients. (subgroup =R/R NHL, relapsed/refractory NHL patients; subgroup =U NHL, previously untreated NHL patients).

In order to precisely investigate the efficacy of ibrutinib,further analysishad been conducted. We perform the meta-analysis for patients who received ibrutinib monotherapy and stratified those patients by the NHL histologic subtypes. The pooled proportion of ORR was 43% (95% CI: 33–53%, Figure 6).

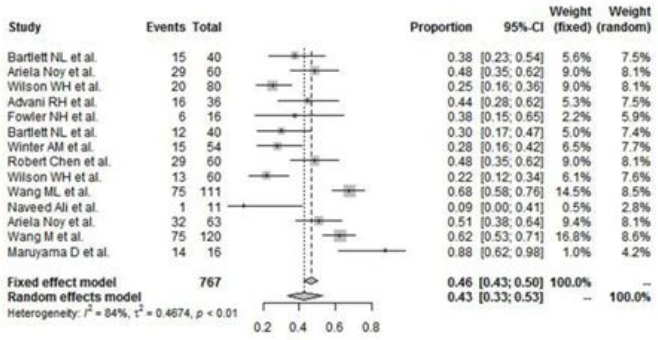

Figure 6: Forest plot of pooled estimate of overall response rate for patients who received ibrutinibm on therapy.

The pooled proportion of ORR for different histologic subtype of NHL patients who received ibrutinib monotherapy as follows: DLBCL was 25% (95% CI: 19–31%; I2 = 0%), FLwas 35% (95% CI: 26–44%; I^2 = 0%), MCLwas66% (95% CI: 60–71%; I^2 = 39%) and MZL subgroups was48% (95% CI: 41–56%; I^2 = 0%). No evidence of high heterogeneity among the individual studies was observed (Figure 7).

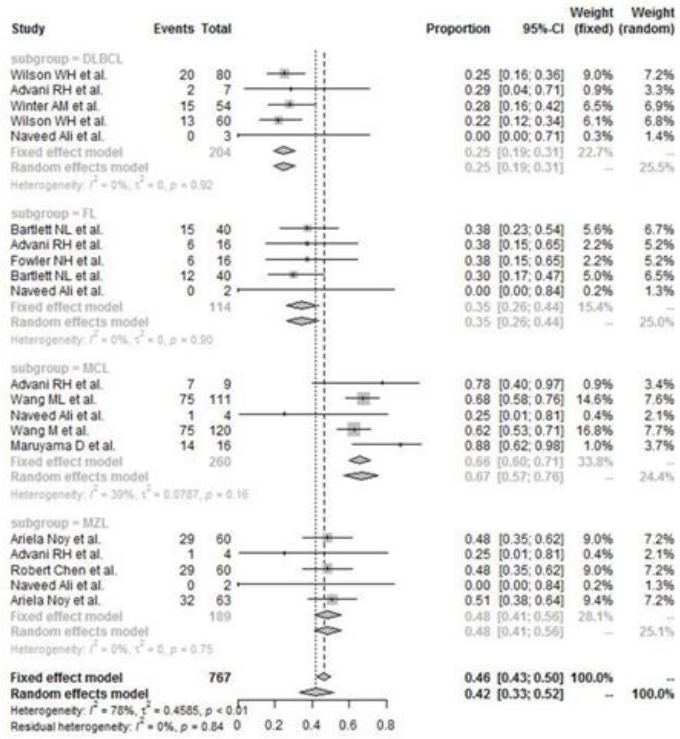

Figure 7: Forest plot of pooled estimate of overall response rate in subgroups which were stratifiedby the histologic subtype of NHL patients who received ibrutinib monotherapy.

Survival Analysis

Four studies contributed to the pooled analysis of PFS and OS using R software. The median PFS was 15.04 months (95% CI: 9.21-17.96) and the median OS was also not reached. The mean PFS was 16.5 months (95% CI: 13.14-18.15) and the mean OS was 22.14 months (95% CI: 18.60-24.19) (Figure 8).

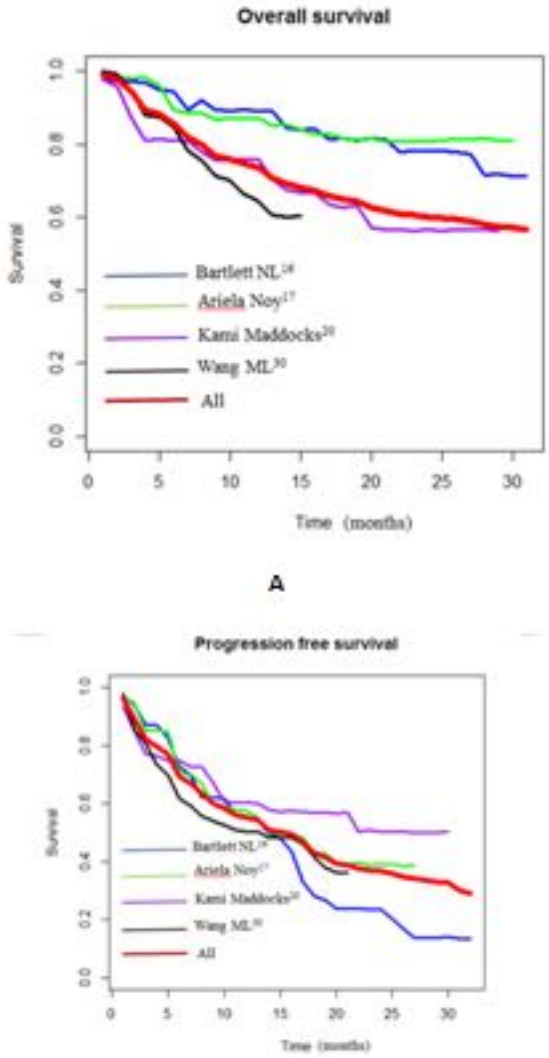

Figure 8: Pooled survival from 4 included studies (A) Overall survival (B) Progression free survival.

In order to further understand the efficacy of Ibrutinib, survival analysis had been conducted for 211 relapsed/refractory NHL patients who received ibrutinib mono therapy. The median PFS was 13.56 months (95% CI: 7.81-16.61) and the median OS was also not reached. The mean PFS was 15.37 months (95% CI: 11.91-16.90) and the mean OS was 23.18 months (95% CI: 18.62-24.82) (Figure 9).

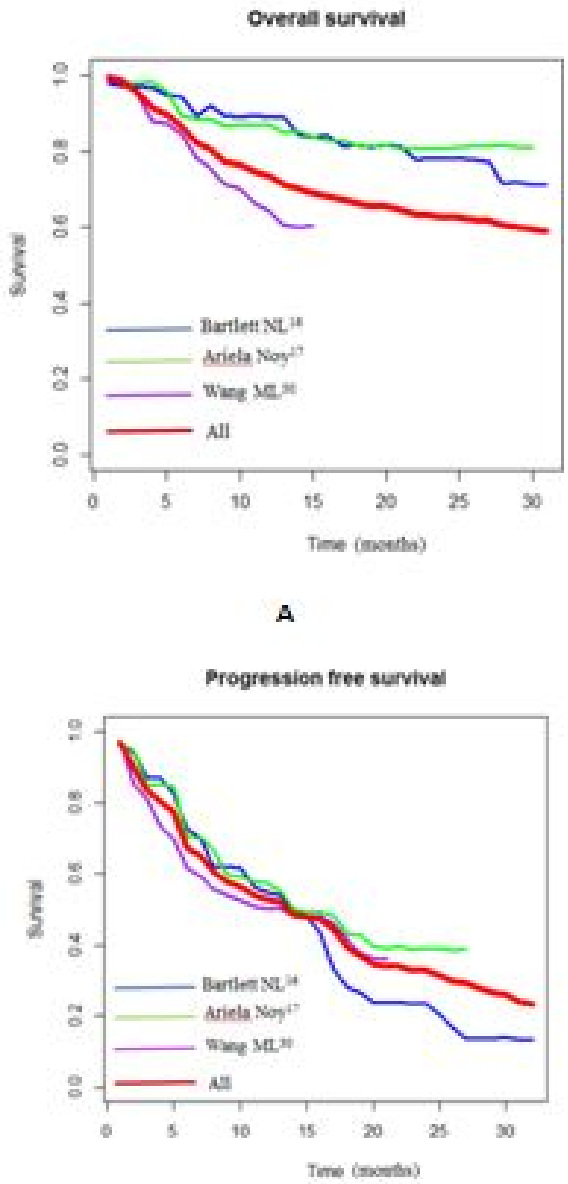

Figure 9: Pooled survival from 3 included studies which consisted of relapsed/refractorypatients who received ibrutinib monotherapy. (A) Overall survival (B) Progression free survival.

Toxicity

A random-effects model was adapted for this toxicity meta-analysis because statistical heterogeneity was observed among individual trials (I^2 = 82%, P < 0.01). The incidence of adverse events (≥ grade 3) was low for patients treated with ibrutinib (pooled ORR = 8%, 95% CI: 6–10%). Furthermore, subgroup analysis was performed according to 12 different adverse events (anaemia, atrial fibrillation, lymphopenia and neutropenia, thrombocytopenia, febrile neutropenia, bleeding, vomiting, diarrhoea, fatigue, rash, hypertension and nausea). Fixed-effects models were applied to pool estimates for the adverse events of anaemia, atrial fibrillation, bleeding, diarrhoea, fatigue, hypertension, nausea, thrombocytopenia and vomiting, whereas random-effects models were used for other adverse events. The results for the subgroup analysis are listed in Figure 10.

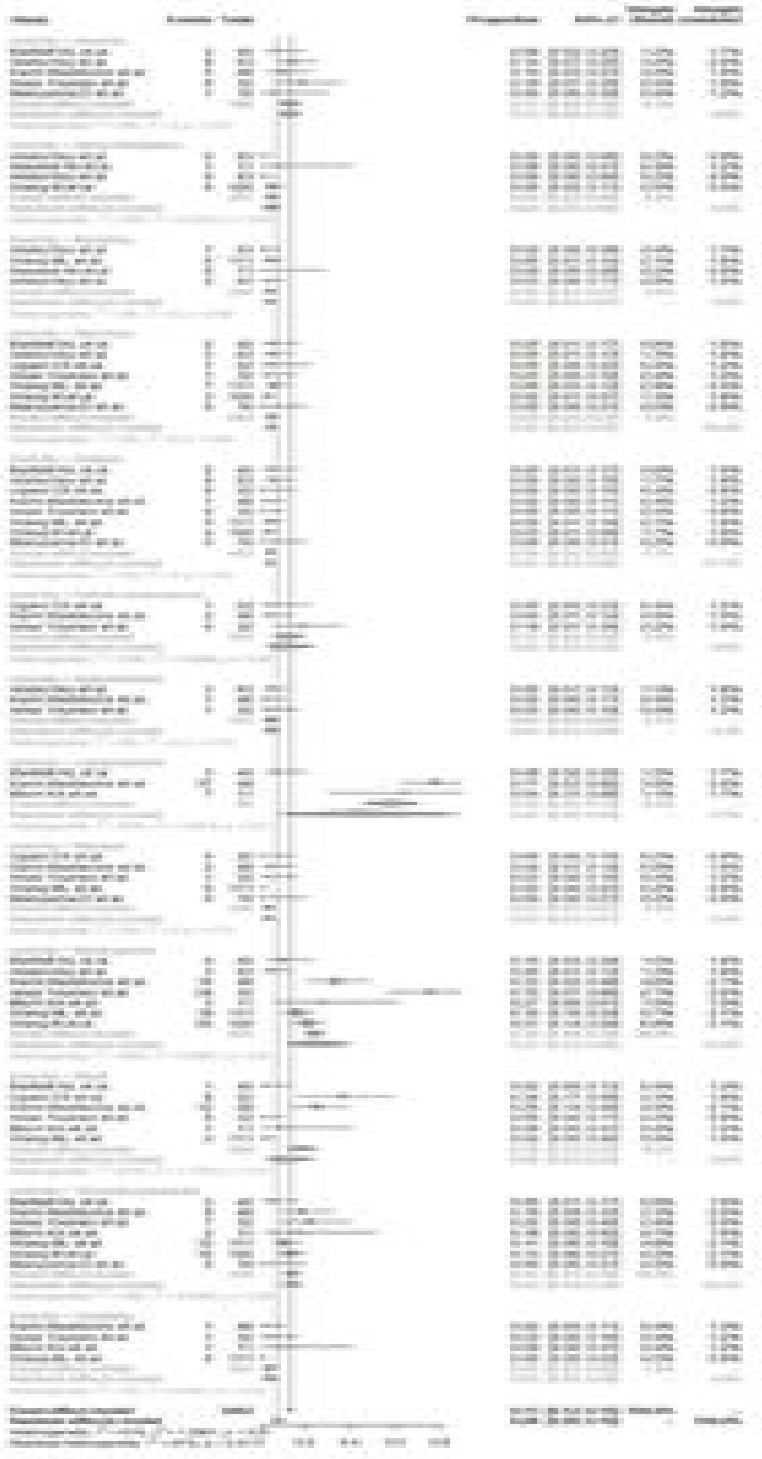

Figure 10: Forest plots of treatment effect for side effects.

The pooled frequencies of ≥ grade 3 hematologic toxicities were as follows: anaemia (13%; 95% CI: 9–18%), lymphopenia (45%; 95% CI: 8–88%), neutropenia (23%; 95% CI: 12–40%), thrombocytopenia (14%; 95% CI: 11–18%) and febrile neutropenia (9%; 95% CI: 3–24%), bleeding (4%; 95% CI: 2–7%).The pooled estimates for ≥ grade 3 non-hematologic adverse events were as follows: atrial fibrillation (4%; 95% CI: 1-9%), vomiting (3%; 95% CI: 1–8%), diarrhoea (5%; 95% CI: 3–7%), fatigue (4%; 95% CI: 3–6%), rash (8%; 95% CI: 3–24%), hypertension (4%; 95% CI: 2–9%) and nausea (3%; 95% CI: 1–7%).

Analysis of Publication Bias

The funnel plots were symmetrical for the ORRs (Figure 11), indicating that there was no obvious evidence of publication bias. In addition, no indication of publication bias was observed for Egger's test (P = 0.62) or Begg's test (P = 0.62).

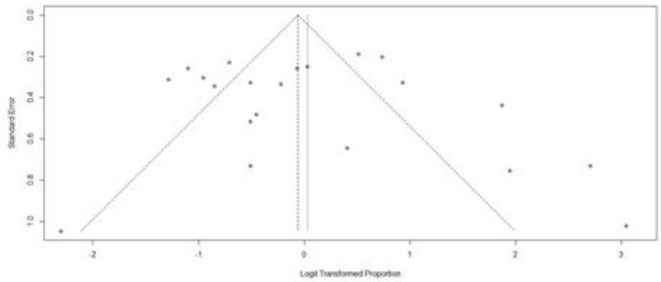

Figure 11: The funnel plots for assessing publication bias.

Discussion

The common approach for treating NHL has ranged from single-agent chemotherapy to a more aggressive approach using chemo immune therapy. However, many patients are not cured by standard therapy and experience serial relapses. Thus, improved outcomes from novel regimens are needed. Ibrutinib, an orally administered irreversible inhibitor of BTK, was designed as a breakthrough agent and has revolutionized the treatment of B-cell malignancies. Although several published studies have shown that ibrutinib significantly improved the outcomes of relapsed and refractory CLL, whether it also exhibits good efficacy and safe outcomes for relapsed/refractory NHL is unclear. Therefore, there is an urgent need for evidence to help clinicians make decisions and develop optimal treatments. In this systematic review and meta-analysis, we demonstrate that ibrutinib is an effective cytotoxic drug with reasonable toxicities for untreated or relapsed/refractory NHL patients, especially those with the MCL histo logic subtype.

To the best of our knowledge, this study is the first review to systematically investigate the efficacy and safety of ibrutinib for patients with NHL. In this study, we identified 22 non-comparative studies that examined FMT ibrutinib for untreated or relapsed/refractory NHL patients. The ORR was 519 of 1033 (50%) patients. Notably, Begg's test and Egger's test indicated that there was no publication bias for ORR. A subgroup meta-analysis according to the median age of patients showed a pooled estimate for achieving ORR of 54% in the elderly subgroup, which was slightly higher than that in the younger subgroup. However, a high probability of heterogeneity existed in the results, which might limit the applicability of the conclusions. Therefore, we conducted other subgroup meta-analysis based on the NHL histologic subtype. The pooled proportions of ORR for MCL, FL, DLBCL and MZL were 71%, 43%, 35% and 33%, respectively. The results of the subgroup analysis indicated that ibrutinib is more active to treat MCL than FL, DLBCL and MZL. Another subgroup analysis result showed that ibrutinib plays a more important role for relapsed/refractory NHL patients than previously untreated NHL patients. In addition, when ORR was pooled estimate for patients who received ibrutinib monotherapy, results indicated that ibrutinib existed excellent efficacy especially those with the MCL histologic subtype. Furthermore, a trial conducted by Fowler NH et al. showed that patients who received ibrutinib at 5 mg/kg had a higher PFS than those who received ibrutinib at 2.5 mg/kg, indicating that PFS was associated with ibrutinib dose [29]. Importantly, the Kaplan–Meier survival curves demonstrated a significant benefit in both PFS and OS with ibrutinib-base therapy for untreated or relapsed/refractory NHL patients. Furthermore, survival analysis for relapsed/refractory NHL patients who received ibrutinib mono therapy demonstrated longer mean overall survival. Therefore, our results demonstrated that ibrutinib is an imperative therapy for untreated or relapsed/refractory NHL patients, in terms of response, PFS and OS.

In terms of treatment-related toxicities, the most common ≥grade 3 hematologic adverse events were anaemia (13%), lymphopenia (45%), neutropenia (23%), thrombocytopenia (14%) and febrile neutropenia (9%). It is necessary to note here that the pooled estimates in our study were similar to those from a large clinical study by Kami Maddocks et al [24]. With regard to non-haematological toxicity, adverse events such as diarrhoea, fatigue and rash occurred more frequently. The results from our study showed that no new adverse events were observed, which agrees with a meta-analysis studying MCL conducted by Simon Rule et al [38]. In addition, it should be noted that patients who received ibrutinib therapy suffered a lower rate of hematologic adverse events in this study compared to patients who received other regimens in Flinn's trial [36] Bleeding and atrial fibrillation have emerged as two fatal adverse effects of ibrutinib therapy. The incidence rates of bleeding and atrial fibrillation were reported in only 4 studies in our meta-analysis, which were all grade 1-3 events, except for 2 incidences of grade 5 cerebral haemorrhage. Thus, it is conceivable that ibrutinib might reduce toxicity and increase tolerability.

Although this is a large comprehensive systematic review including high-quality trials, several limitations are worth noting. First, heterogeneity existed among the trials enrolled in our analysis when assessing ORR and adverse events. Although we performed subgroup analyses that were stratified by the median age and histo logic subtype of patients, the heterogeneity was not completely resolved. This might be due to several reasons, including different study locations and different numbers of patients. Second, although adverse events were reported for some of the included trials, the lack of sufficient data in this study was due to the absence of reported AEs in most studies. Third, most of the patients included in this study were male, which might have caused a sex bias. Fourth, responses for patients with Walden strom cannot be pooled due to insufficient data. Fifth, the lack of control groups in all of the included non-comparative studies might have undermined the authenticity of this assessment. Additional clinical trials are required to supplement further evaluations. In general, despite these limitations, this was the first meta-analysis to investigate the efficacy and safety of ibrutinib-based chemotherapy for patients with untreated or relapsed/refractory NHL.

Conclusions

In conclusion, our results indicate that ibrutinib is an effective regimen for untreated or relapsed/refractory NHL management, especially for MCL patients. In addition to its demonstrated antitumor activity, it is an extremely well-tolerated drug. Furthermore, more controlled clinical trials are needed to determine whether ibrutinib monotherapy is more effective than other chemotherapy drugs and whether ibrutinib monotherapy is better than ibrutinib-based combination therapy.

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