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Efficacy and safety evaluation of fludarabine-based chemotherapy regimen for patients with non-Hodgkin lymphoma

A meta-analysis

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Abstract

This meta-analysis was performed to evaluate the efficacy and safety of fludarabine (F)-based regimen for the treatment of non-Hodgkin lymphoma (NHL) compared with other regimens with no F contained.

PubMed, Embase, Cochrane Library, Wanfang, VIP, and CNKI databases were searched to identify eligible literatures. R software version 3.12 was used for statistical analysis. Odds ratio (OR) with 95% confidence interval (CI) were utilized to express the complete response, overall response and adverse events outcomes. Egger test was carried out to examine the publication bias and sensitivity analysis was performed to evaluate the stability of our results.

Twelve eligible literatures consisting of 1587 patients were included in this study. Greater complete response (OR = 1.66, 95% CI: 0.98–2.80) and overall response (OR = 1.38, 95% CI: 0.85–2.24) were found for patients who received F-based regimen than those received other regimens, although the results were not statistically significant. In addition, F-based regimen was associated with significantly lower risk of adverse events compared with other regimens (OR = 0.46, 95% CI: 0.28–0.74). Results of subgroup analysis showed that significantly lower incidence was presented only for constipation among the 7 specific adverse events (OR = 0.03, 95% CI: 0.01–0.14).

F-based chemotherapy regimen was an effective and well-tolerated treatment for patients with NHL.

Abbreviations: BR = bendamustine, rituximab, CdA = cladribine, CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone, CHVP = cyclophosphamide, doxorubicin, vindesine, prednisone, CI = confidence interval, CVP = cyclophosphamide, vincristine, prednisone, EPOCH = etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, F = fludarabine, FI = fludarabine, ifosfamide, FM = fludarabine, mitoxantrone, FMD = fludarabine, mitoxantrone, dexamethasone, FR = fludarabine, rituximab, NHL = non-Hodgkin lymphoma, OR = odds ratio, PFS = progression-free survival, RCTVP = rituximab, cyclophosphamide, pirarubicin, vindesine, prednisone, RFT = rituximab, fludarabine, pirarubicin.

Keywords: adverse events, complete response, fludarabine, meta-analysis, non-Hodgkin lymphoma, overall response

1. Introduction

The non-Hodgkin lymphoma (NHL) is a group of heterogeneous neoplasms which develops usually in lymphoid tissues but can occur in almost any tissue.[1] Approximately, 85% to 90% NHL derives from B lymphocytes and the remainder arises from T lymphocytes or NK lymphocytes.[2] Under the most recent World Health Organization classification revised in 2016,[3] over 60 specific subtypes of NHL are recognized in which diffuse large B cell lymphoma, follicular lymphoma, and mucosa-associated lymphoid tissue lymphoma occur most frequently. NHL makes up about 4.6% of all cancer diagnoses and is the fifth or sixth common cancer in women or men.[1] Overall, NHL is a curable tumor that needs effective treatments.

Chemotherapy is one of the effective treatments for NHL in addition to radiation therapy, immunotherapy, and radioimmunotherapy.[4–6] Various chemotherapy regimens such as CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) and CVP (cyclophosphamide, vincristine, prednisone) have high efficiency but are associated with poor progression-free survival (PFS).[7–9] The disease relapses inevitably, and multiple cycles of same regimen are commonly performed to achieve further remission.[10] In contrast, fludarabine (F), a purine analog has been reported to have a helpful influence on median PFS[10] and also presents a relatively satisfactory clinical efficacy on relapsed and indolent NHL.[11,12] Furthermore, F-based regimen is strongly recommended by National Comprehensive Cancer Network as a second-line treatment.

However, controversies exist regarding the efficacy and safety of F-based chemotherapy regimen for patients with NHL. Klasa et al[10] have reported the superiority of this regimen on median PFS. In addition, it is suggested as a safe regimen with negligible

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complications by several clinical trials.[13,14] However, no significant improvement on PFS is detected in the study of Zinzani et al,[15] and it is accused to be unbearable for the reason of severe toxicity.[16] Therefore, a meta-analysis is urgently needed to achieve a comprehensive conclusion, which is rarely studied by other investigators.

Meta-analysis is an analytical technique that combines the results of multiple studies, and it increases the sample size and thus the power to study effects of interest.[17] In this study, a pairwise meta-analysis was performed to evaluate the efficacy and safety of F-based chemotherapy regimen for the treatment of NHL compared with other chemotherapy regimens which did not contain F.

2. Methods

2.1. Data acquisition and search strategy

A systematic literature search was conducted on PubMed, Embase, Cochrane Library, Wanfang, VIP, and CNKI databases. Additionally, reference lists of relevant literatures were also searched manually to identify eligible literatures. Key words included: fludarabine, non-Hodgkin lymphoma, and non-Hodgkin's lymphoma. Relevant studies were obtained until January 2017, and there was no language restriction.

2.2. Selection criteria

Inclusion criteria were: full-published articles in Chinese or English; patients with NHL; patients in intervention group received single F chemotherapy or F-based chemotherapy regimen, such as FM (fludarabine, mitoxantrone), RFT (rituximab, fludarabine, pirarubicin), FMD (fludarabine, mitoxantrone, dexamethasone), FI (fludarabine, ifosfamide), and FR (fludarabine, rituximab); patients in control group received other chemotherapy regimens with no F contained, such as CHOP, CVP, CHVP (cyclophosphamide, doxorubicin, vindesine, prednisone), BR (bendamustine, rituximab), RCTVP (rituximab, cyclophosphamide, pirarubicin, vindesine, prednisone), CdA (cladribine), and EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin); parameters regarding the efficacy and safety could be extracted. Reviews, reports, comments, and letters were excluded for the final analysis.

2.3. Data extraction

Data were extracted by 2 investigators from the eligible literatures independently, such as name of first author, year of publication, location of study, year of study, the specific subtypes of NHL, number of patients, and demographic characteristics (sex ratio, age, etc.). Disagreements were settled by group discussion with a third investigator.

2.4. Statistical analysis

The meta-analysis was performed by using R software version 3.12 (R Foundation for Statistical Computing, Beijing, China, meta package). Odds ratio (OR) with 95% confidence interval (CI) were utilized to evaluate the effect of chemotherapy for all dichotomous outcomes. The potential heterogeneity was assessed by Q statistic[18] and I^2. A random-effects model was used to pool the effect size if significant heterogeneity was detected ($P < .05$ or $I^2 > 50\%$), otherwise, a fixed-effects model was adopted.[19] Egger test and funnel plot were carried out to examine the publication bias,[20] and trim and fill method was applied to recount the effect size if publication bias was detected.[21] Furthermore, the sensitivity analysis was conducted by removing one literature at a time to evaluate the stability of our results.[20]

3. Results

3.1. Eligible literatures

Figure 1 shows the flow diagram of literature selection. A total of 1069 literatures (348 in PubMed, 453 in Embase, 102 in Cochrane Library, 49 in Wanfang, 55 in VIP, and 62 in CNKI database) were obtained by using the search strategy. After removing 498 duplicates and 463 irrelevant articles, a full-text review was applied to the remaining 108 articles. Ninety-six articles (15 letters, 16 case series or reports, 33 reviews, 11 articles with irrelevant data, 14 articles without clear clarification of the kind of chemotherapy in control group and 7 reduplicative studies) were further excluded. Finally, 12 eligible studies were included in this meta-analysis.[10,15,22–31]

The characteristics of all eligible literatures are listed in Table 1. A total of 1587 patients (804 patients in intervention group and 783 patients in control group) were included in this study. Studies were conducted between 1993 and 2014, and published between 1999 and 2015. Most of the patients suffered from indolent, advanced, or relapsed NHL. Locations of studies included Italy, France, Germany, Canada, and China. Age of patients differed obviously among different literatures, but no significant difference was found between 2 groups in every single literature. Sex distribution between the intervention and control groups was similarly balanced in every eligible literature. Follicular NHL took up a large proportion among all specific subtypes of NHL for patients enrolled in our study. In addition, most of the patients were diagnosed as III or IV stage according to the Ann Arbor staging system.

3.2. Complete response

Evidence of heterogeneity was shown ($I^2 = 76.6\%$, $P < .0001$) across the 11 studies[10,15,22–27,29–31] that reported complete response data, thus a random-effects model was applied to calculate the pooled effect size. Pooled estimates indicated that patients in intervention group obtained greater complete response than those in control group (OR = 1.66, 95% CI: 0.98–2.80), but the results did not reach statistical significance (Fig. 2A). Among

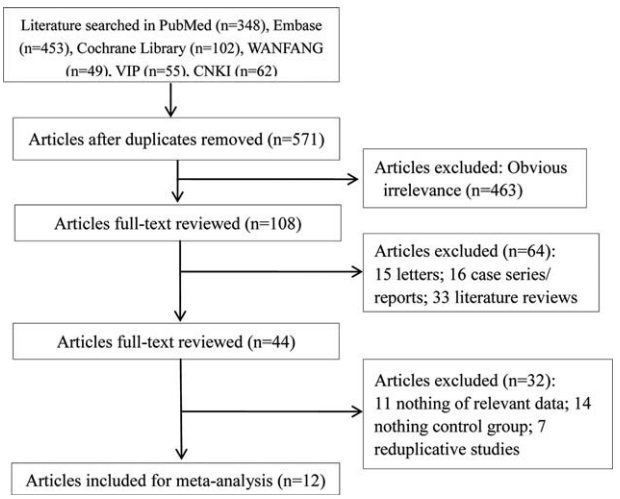

Figure 1. Flow chart of study selection.

Table 1

Characteristics of eligible studies.

Author	Publication year	Location	Style	Study year	Group	N	Median age, years (range)	Gender (M/F)	Follicular NHL	Ann Arbor stage (II/III/IV)
Foussard C	2005	France	Advanced low-grade	1995.11–1999.12	FM	72	66 (55–75)	35/37	44	3/9/60
					CHVP	72	65.5 (55–75)	38/34	42	3/7/62
Hagenbeek A	2006	NA	Low-grade malignant	1993–1997	F	194	57 (24–76)	104/90	56	0/47/146
					CVP	187	55 (28–79)	98/88	56	0/42/144
Hou Y	2012	China	Indolent	2002.1–2010.12	RFT	127	62 (21–78)	69/58	106	44/83 (III, IV)
					RCTVP	121	60 (22–80)	63/58	101	46/75 (III, IV)
Klasa RJ	2002	Canada	Recurrent low-grade	1993.10–1996.12	F	47	58 (32–81)	27/20	12	1/15/29
					CVP	44	54 (36–77)	19/25	18	4/14/26
Rummel M	2016	Germany	Relapsed indolent	2003.10–2010.8	FR	105	66.4 (59.3–73.7)	NA	53	0/25/62
					BR	114	68.5 (59.0–74.0)	NA	58	0/25/80
Tondini C	2000	Italy	Low-grade	1993.1–1997.7	F	25	NA	NA	NA	NA
					CdA	29	NA	NA	NA	NA
Zinzani PL	2004	Italy	Follicular lymphoma	1999.10–2002.4	FM	72	52 (26–70)	37/35	72	12/16/44
					CHVP	68	54 (31–70)	38/30	68	8/14/46
Sweetenham J	1999	UK	Indolent B-cell	1977–1997	F	50	Median age: 62.5	NA	NA	2/48 (III, IV)
					CHOP	48	Median age: 59	NA	NA	2/46 (III, IV)
Yan-hong H	2015	China	NA	2011.3–2014.4	FMD	43	24–68	49/37	NA	NA
					CHVP	43			NA	NA
Xue-dong Y	2013	China	Relapsed indolent	2010.1–2012.9	FMD	16	41.6 ± 8.9	19/13	NA	NA
					EPOCH	16			NA	NA
Chang-yun Y	2009	China	Relapsed	2007.1–2008.12	FMD	17	40.6 (28–61)	10/7	NA	NA
					EPOCH	14	42.3 (30–63)	9/5	NA	NA
Chun-sen W	2007	China	Relapsed indolent	2003.5–2005.11	FI	16	53.3 (32.0–70.0)	19/11	18	NA
					CVP	16				NA

BR = bendamustine, rituximab, CdA = cladribine, CHOP = cyclophosphamide, doxorubicin, vincristine, prednison, CHVP = cyclophosphamide, doxorubicin, vindesine, prednisone, CVP = cyclophosphamide, vincristine, prednisone, EPOCH = etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, F = fludarabine, FI = fludarabine, ifosfamide, FM = fludarabine, mitoxantrone, FMD = fludarabine, mitoxantrone, dexamethasone, FR = fludarabine, rituximab, M/F = male/female, NA = not available, NHL = non-Hodgkin lymphoma, RCTVP = rituximab, cyclophophamide, pirarubicin, vindesine, prednisone, RFT = rituximab, fludarabine, pirarubicin.

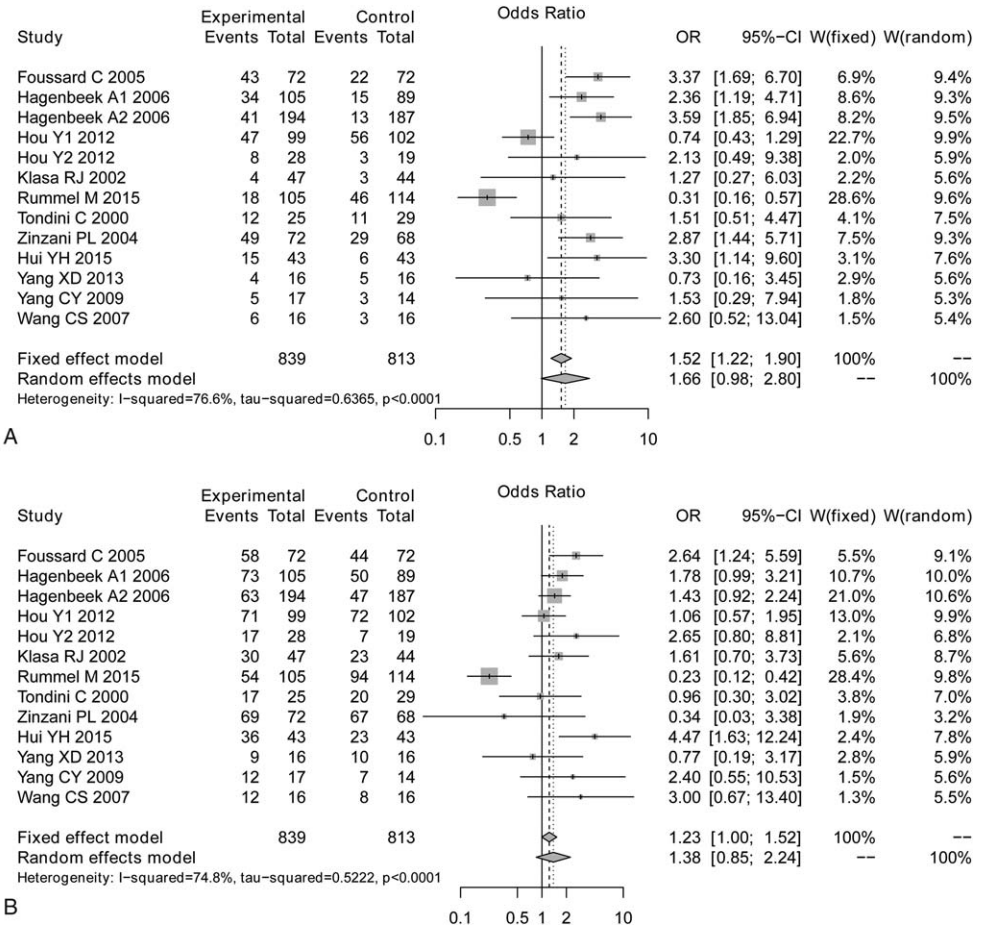

Figure 2. Forest plots of treatment effect for (A) complete response and (B) overall response.

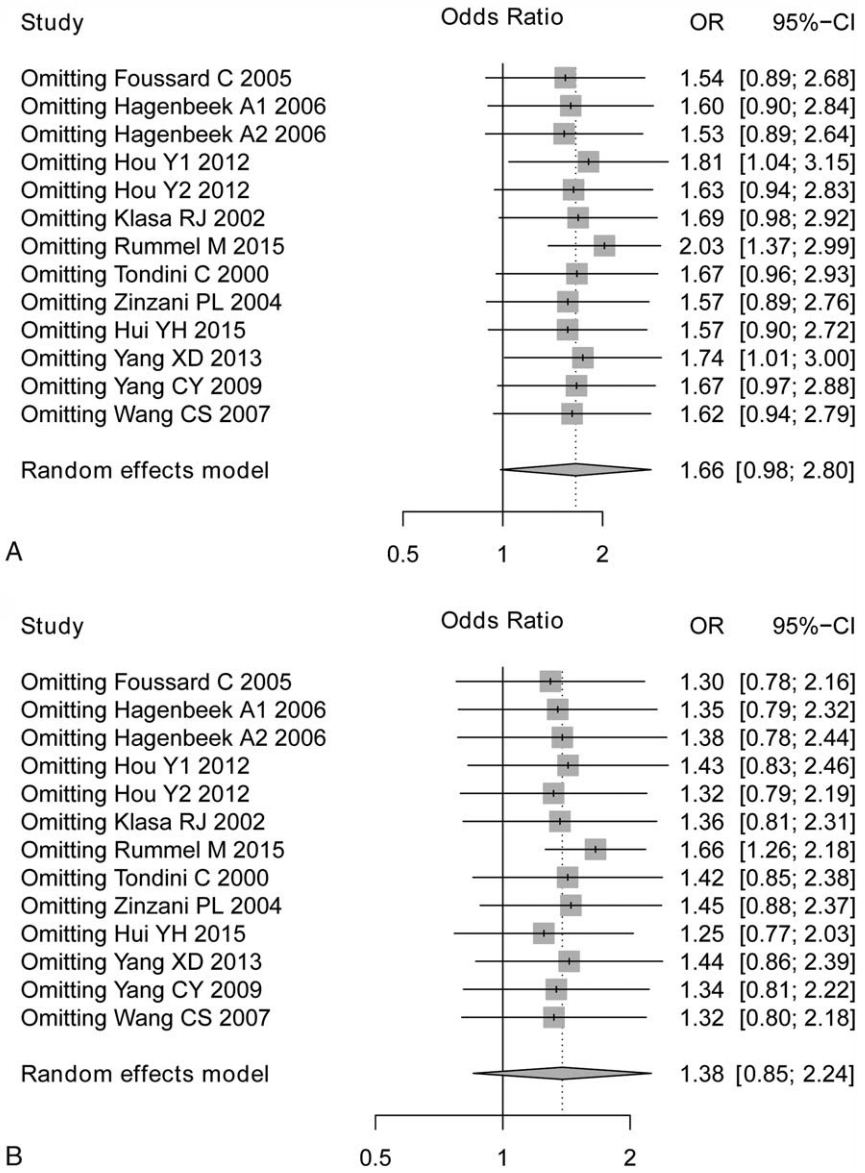

Figure 3. Sensitivity analysis of treatment effect for (A) complete response and (B) overall response.

these 11 studies, only the study of Rummel et al[27] exhibited significantly worse response for patients in intervention group than those in control group (OR = 0.31, 95% CI: 0.16–0.57; Fig. 2A). To be noted, significant difference was shown after omitting this study for the parameter of complete response (OR = 2.03, 95% CI: 1.37–2.99; Fig. 3A). No publication bias was detected across the studies ($t = 0.38$, $P = .71$). As shown in the funnel plot, no publication bias was existed (Fig. 4A).

3.3. Overall response

According to the WHO criteria, overall response rate was defined as the sum of complete response rate and partial response rate. A random-effects model was used to pool the estimates since heterogeneity was detected ($I^2 = 74.8\%$, $P < .0001$). Pooled estimates suggested that patients in intervention group obtained higher overall response rate than those in control group (OR = 1.38, 95% CI: 0.85–2.24), but the results had no statistically significant (Fig. 2B). Similar to the complete response, significantly decreased overall response rate was found in intervention group in the study of Rummel et al[27] (OR = 0.23, 95% CI: 0.12–0.42; Fig. 2B), which was unique among the 11 relevant studies.[10,15,22–27,29–31] Significant difference was also exhibited with the omission of this study for the parameter of overall response (OR = 1.66, 95% CI: 1.26–2.18; Fig. 3B). No publication bias was detected across the studies ($t = 0.60$, $P = .56$). As shown in the funnel plot, no publication bias was existed (Fig. 4B).

3.4. Adverse events

A random-effects model was used since there was heterogeneity for studies related with adverse events ($I^2 = 80.7\%$, $P < .0001$). Incidence of adverse events was significantly lower for patients in

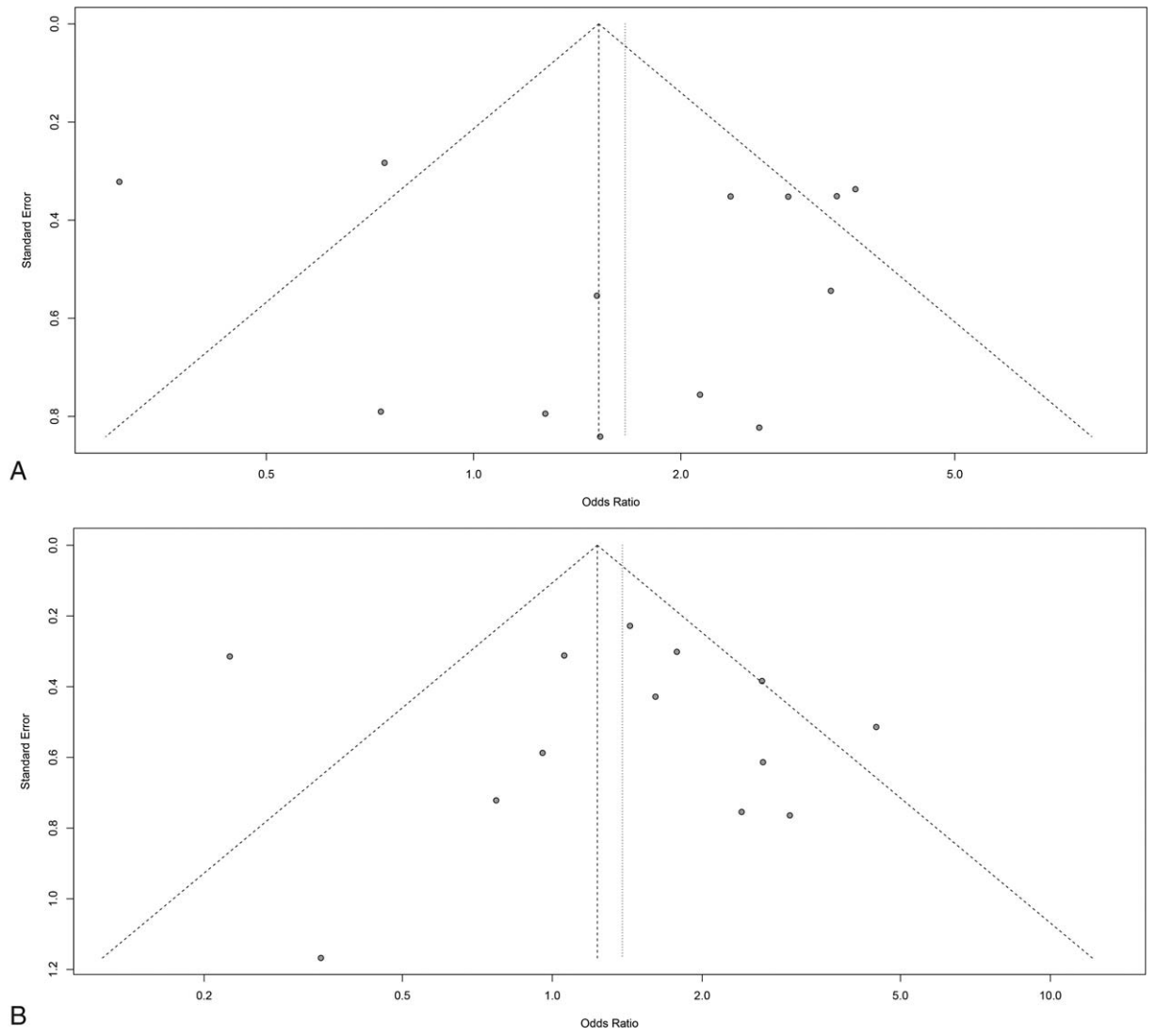

Figure 4. Funnel plot for (A) complete response and (B) overall response.

intervention group than those in control group (OR = 0.46, 95% CI: 0.28–0.74; Fig. 5).

Furthermore, subgroup analysis was performed regarding 7 different adverse events (diarrhea, nausea and vomiting, alopecia, infection, peripheral neurotoxicity, constipation, and fever). Random-effects models were applied to pool estimates for adverse events of alopecia, nausea and vomiting and peripheral neurotoxicity while fixed-effects models were used for other adverse effects. Results of subgroup analysis are listed in Table 2. Significantly decreased incidence was found only in constipation subgroup (OR = 0.03, 95% CI: 0.01–0.14) among the 7 specific adverse events.

Subgroup analysis regarding ages (≥60 group and <60 group) was performed, and the result is shown in Table 3. It showed that there was no statistically significant difference in ≥60 group for complete response and overall response, but statistically significant difference was existed in <60 group for complete response ($P < .001$) and overall response ($P = .0057$).

4. Discussion

In the present study, we performed a pairwise meta-analysis to evaluate the efficacy (in terms of complete response and overall response) and safety (in terms of adverse effects) of F-based chemotherapy regimen for the treatment of NHL based on 12 eligible trials. Greater complete response and overall response were found for F-based regimen, but the results were not statistically significant. However, the results reached a statistical significance with the omission of the study of Rummel et al. In addition, patients treated with F-based regimen had significantly decreased incidence of adverse events, but only the outcome of constipation was significant among the 7 specific adverse events according to the subgroup analysis.

F is a member of purine analog family. It yields a metabolite of 2F-ara-ATP under the function of DNA cytosine kinase which interferes the duplication of DNA subsequently by suppressing the activity of DNA polymerase, DNA ligase, and ribonucleotide reductase.[32] Other agents contained in the regimens had different mechanisms of action, such as cyclophosphamide working as alkylating agent and doxorubicin working as intercalating agent.[33] Our results showed that F-based regimen performed better on complete response and overall response compared with other regimens, which was in line with a number of clinical trials. Single administration of F was reported to present better complete response and overall response in

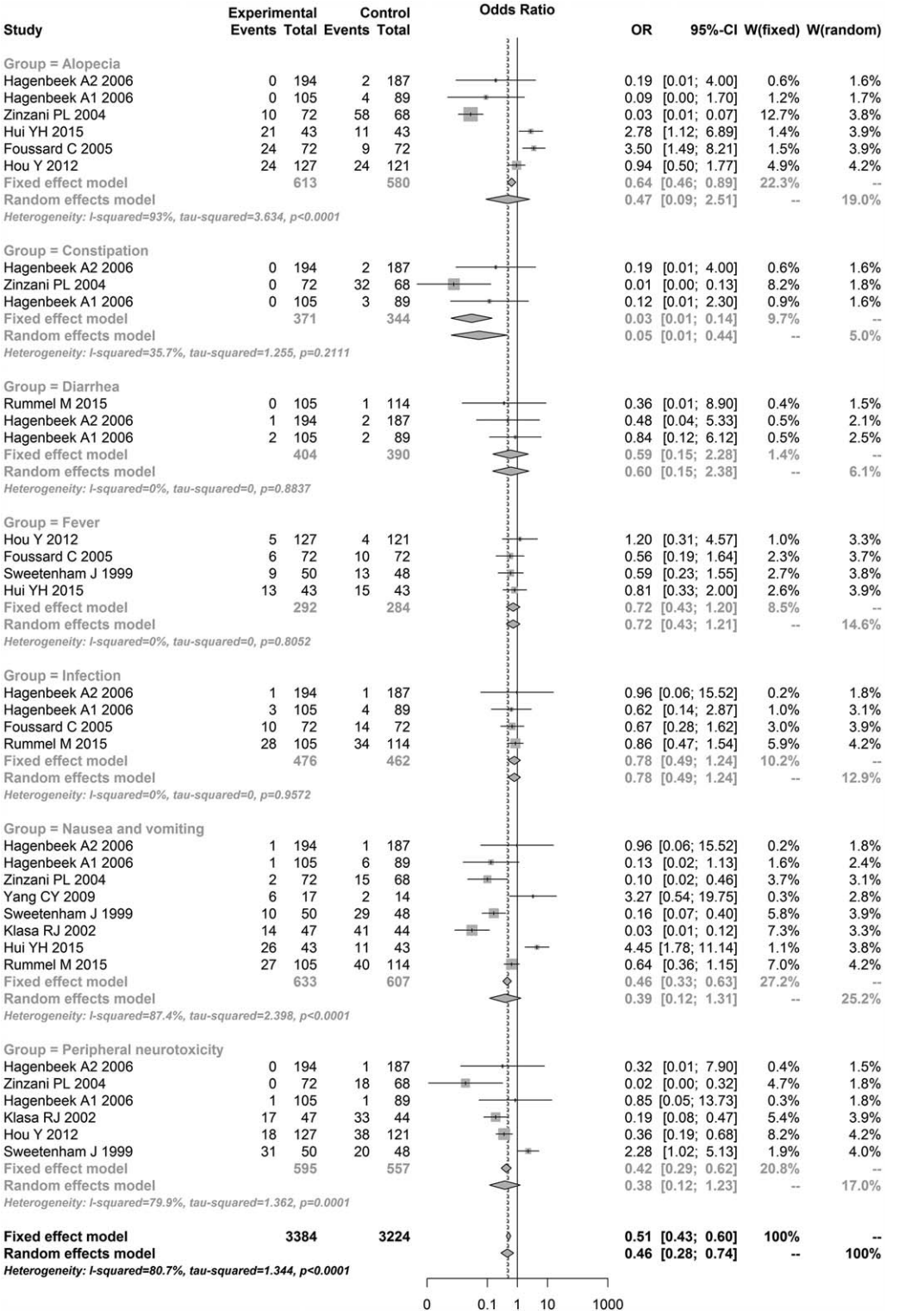

Figure 5. Forest plots of treatment effect for adverse events.

untreated NHL patients,[25] and it showed greater PFS in recurrent NHL patients compared with CVP chemotherapy regimen.[10] Similar improvement was also shown for combined administration of F-based regimen.[22,24,26,34]

Among the 7 specific adverse events, only constipation showed a significantly lower incidence of patients treated with F-based chemotherapy regimen in our study. Constipation was a common adverse event for patients treated with various chemotherapy regimens.[25,35,36] Two relevant clinical trials provided a support for our analysis, which reached an exact consensus of lower risk of constipation for single and combined F chemotherapy.[15,25]

Subgroup analysis for ages showed that there was no statistically significant difference in ≥60 group, but statistically

Table 2

Subgroup analysis of adverse events.

Adverse events	*k*	OR	95% CI	I^2 (%)	*P*	Model
Alopecia	6	0.47	0.09–2.51	93.0	<.0001	Random
Constipation	3	0.03	0.01–0.14	35.7	.21	Fixed
Diarrhea	3	0.59	0.15–2.28	0	.88	Fixed
Fever	4	0.72	0.43–1.20	0	.81	Fixed
Infection	4	0.78	0.49–1.24	0	.96	Fixed
Nausea and vomiting	8	0.39	0.12–1.31	87.4	<.0001	Random
Peripheral neurotoxicity	6	0.38	0.12–1.23	79.9	.0001	Random

CI = confidence interval, OR = odds ratio.

Table 3

Subgroup analysis of ages.

		Sample size		Test of association				Test of heterogeneity[*,†]		
Variable	Group	Fludarabine	Control	OR (95% CI)	*Z*	*P*	Model	*Q*	*P*	I^2 (%)
Complete response	≥60	304	307	1.0700 [0.3520–3.2523]	0.12	.9051	R	27.16	<.0001	89
	<60	467	434	2.5272 [1.7850–3.5781]	5.23	<.001	F	4.80	.5694	0
Overall response	≥60	304	307	1.0864 [0.3307–3.5684]	0.14	.8914	R	30.49	<.0001	90.2
	<60	467	434	1.5277 [1.1312–2.0630]	2.76	.0057	F	4.02	.6735	0

CI = confidence interval, F = fixed-effect model, R = random-effects model.

[*] Random-effects model was used when the *P* for heterogeneity test <.05, otherwise the fixed-effect model was used.

[†] $P < .05$ is considered statistically significant for *Q* statistics; OR = odds ratio.

significant difference was existed in <60 group for complete response and overall response, which suggested that F-based chemotherapy regimen was a more effective treatment for NHL patients <60 years old. However, because age used for the present statistical analysis is an average, more studies about ages are needed in future researches to get more accurate conclusions.

Besides, F may exert its functions on patients with NHL through both distorting the phosphate backbone and also the base pairing mechanism, which is different from alkylating reagent such as cyclophosphamide.[37] But further studies are needed for the detailed and accurate molecular mechanisms.

To the best of our knowledge, this was the first meta-analysis conducted to evaluate the efficacy and safety of F-based chemotherapy regimen. However, the results should be interpreted under some limitations. Firstly, heterogeneity existed across the trials enrolled in our analysis for assessing complete response, overall response, and adverse events. It might due to several reasons, such as huge age gap of patients, different number of patients, and different study location. The heterogeneity was not settled by subgroup analysis or meta-regression analysis since inadequate data were provided by relevant trials. Secondly, several complications which were referred to frequently for F-based chemotherapy regimen such as myelosuppression and hematological toxic events were not evaluated in our analysis, because less than 2 trials reported the raw data regarding these complications. Thirdly, Rummel et al declared a superiority of bendamustine over F on effectiveness for NHL. Hence, cautious explanation of our conclusion was necessary with respect to the study of Rummel et al. Fourthly, NHL could be derived from B lymphocytes, T lymphocytes, or NK lymphocytes, but there was not information about the origin of NHL in some of the included studies. Thus, we do not know if there is a difference in terms of efficacy and tolerance of F-based regimen between different cell types. Further studies about this question are needed.

In conclusion, F-based chemotherapy regimen was an effective and well-tolerated treatment for patients with NHL, especially for patients <60 years old. Thus, other things being equal, F-based chemotherapy regimen may be the preferred choice for the treatment of NHL in clinical practice. However, large scale of randomized controlled trials is needed to confirm the conclusion.

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