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Original Article

Lenalidomide alone or in combination with chemotherapy treatment for subtypes of diffuse large B cell lymphoma: a systematic review and meta-analysis

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Abstract: Lenalidomide has been shown to produce durable responses in patients with relapsed or refractory diffuse large B cell lymphoma (DLBCL). In order to gain better understanding of the efficacy of lenalidomide and compared the difference in clinical outcome between two subtypes of DLBCL. Seven eligible trials involving 375 adult patients were included in this meta-analysis. The patients in non-germinal center B-cell (non-GCB) subtype had higher overall response (OR) rate compared with GCB patients (P=0.21). In subgroup analysis, as first-line and second-line treatment for DLBCL patient, GCB DLBCL did not show significantly better outcome compared with non-GCB subtype patients (P=0.96; P=0.27). More importantly, after lenalidomide treatment, the patients with non-GCB DLBCL did not show significantly worse progression-free survival (PFS) and overall survival (OS) compared with GCB subtype. Lenalidomide as treatments for DLBCL patients, non-GCB DLBCL patients did not show significantly worse prognosis compared with GCB DLBCL.

Keywords: Diffuse large B cell lymphoma, subtypes, lenalidomide, meta-analysis

Introduction

Diffuse large B-cell lymphoma (DLBCL), the most common type of non-Hodgkin's lymphoma (NHL), has an aggressive natural history [1]. The addition of the anti-CD20 monoclonal antibody rituximab to a regimen of cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) has achieved significant improvement in overall survival in DLBCL patients. Approximately 40% of the patients with DLBCL relapse after initial immunochemotherapy [2-5]. However, efforts to improve R-CHOP by increasing dose intensity are not successful, so the regimen is still six cycles of R-CHOP every 21 days (R-CHOP21) worldwide. The best way to improve R-CHOP21 could be the addition of novel agents rather than the adjustment of dose intensity. The development of a more effective initial therapy is essential for improving long-term outcomes in DLBCL patients.

According to the molecular profiling by gene expression profiling (GEP), DLBCL is divided into two major subtypes: germinal center B-cell (GCB) subtype and activated B-cell-like (ABC) subtype. These two subtypes derive from different cells of origin and have distinct clinical features [6, 7]. The ABC subtype is also referred to non-germinal center B-cell (non-GCB) subtype according to immunohistochemistry (IHC)-based classifications [8]. Many researchers have demonstrated that the addition of rituximab to standard chemotherapy drugs significantly improves the prognosis of DLBCL patients with both GCB and non-GCB subtypes [9]. Non-GCB subtype of DLBCL has a significantly worse clinical outcome compared with GCB subtype, even after rituximab treatment. Therefore, novel treatment regimens are needed, particularly for non-GCB DLBCL patients.

Lenalidomide is an oral immunomodulatory agent that exerts anticancer effects through

multiple mechanisms [10]. Recently, synthetic lethality of lenalidomide in ABC DLBCL patients has been reported, providing mechanistic insights into the efficacy of lenalidomide in the ABC DLBCL patients. Lenalidomide selectively kills ABC DLBCL cells by targeting IRF-4 directly and causing an increase in IFN-β production [11]. Indeed, a number of studies have reported positive findings regarding the use of lenalidomide in the treatment of DLBCL patients in recent years [12-15].

To gain better, more complete understanding of the efficacy and safety of lenalidomide, we conducted a systematic review and meta-analysis of relevant literatures and compared the efficacy of lenalidomide alone and in combination with chemotherapy treatment in DLBCL patients. We also compared the difference in clinical outcome between two subtypes of DLBCL patients when treated with lenalidomide.

Materials and methods

Search strategy

Literature searches were conducted through PUBMED, EMBASE, and COCHRANE databases. Search terms included lenalidomide or revlimid, diffuse large B-cell lymphoma and lymphoma. We also searched the ClinicalTrials.gov registry (http://clinicaltrials.gov/) and the conference proceeding of the American Society of Hematology (ASH), the American Society of Clinical Oncology (ASCO), and the European Society of Medical Oncology (ESMO) for relevant clinical trials. The search was limited to human studies without language limitation. In addition, we also screened the reference citations in all retrieved articles so as not to miss any eligible studies. The last search was performed on September 30, 2014.

Selection criteria

In this analysis, randomized and controlled trials, or retrospective or prospective cohort studies with a control (concurrent or historical) group were included. The articles also included direct comparison of the efficacy of lenalidomide between GCB and ABC/non-GCB subtypes. Studies were excluded from our analyses if the outcomes of interest were not clearly reported or if duplicate reporting of patient cohorts was found.

Data collection

The data from all eligible studies that meet the inclusion and exclusion criteria were extracted by two independent researchers. The disagreement between two researchers was resolved by the third researcher. The researchers who screened the studies independently performed data extraction and quality assessment of all included articles.

In each study, both overall survival (OS) and progression-free survival (PFS) were considered as endpoints for survival analysis. We assessed the efficacy of treatment for each study using hazard ratio (HR) and the 95% confidence interval (95% CI) value. The value of HR and its standard error were extracted directly from the publications if they were available; otherwise, HR was estimated by a method depending on the data in the publication. For those studies that did not report the HR but provided sufficient data on survival, the log HRs and variances were estimated based on the method by Parmar *et al*. [16]. If the only available data were presented in the form of graphical survival curves, the freely available Engauge Digitizer software version 4.1 (SourceForge) was used to extract survival rate at specific time points, assuming that the rate of patient censoring was constant throughout follow-up period. HR was then calculated using data points in each group.

Statistical analysis

Statistical heterogeneity among studies was assessed with the Cochran's Q test and the I^2 statistics. I^2 values of 25%, 50% and 75% were assigned as low, moderate, and high estimates, respectively. Heterogeneity was considered significant for $P<0.10$. In the presence of statistically significant heterogeneity, a random-effect model was applied. The efficacy of treatment in each study was expressed as a HR of the lenalidomide treatment arm over the non-lenalidomide treatment arm. For binary data, the risk ratio (RR) was used as an indicator of treatment efficacy, the Mantel-Haenszel and DerSimonian-Laird methods were used to pool RR for fixed effect and random effect model, respectively. The endpoints are overall response (OR), OS and PFS. Response was defined according to the International Working Group Criteria. Statistical analysis was conducted by

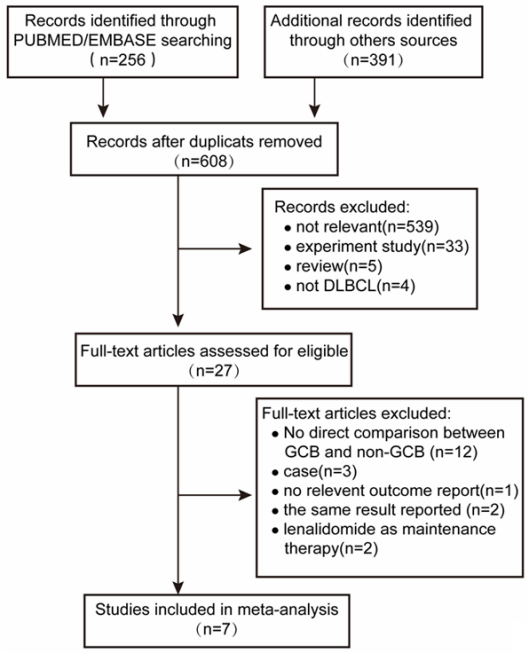

Figure 1. The systematic search procedure for literatures.

Review Manager 5.1 (Cochrane Collaboration, http://www.cc-ims.net/RevMan/relnotes.htm). All reported *P* values are two-sided and $P<0.05$ was considered as statistically significant in all included studies.

Results

Characteristics of studies

The selection procedure of eligible studies was shown as a flow chart (**Figure 1**). According to the literature search strategies, a total of 647 studies (256 studies from PubMed and EMBASE, and 391 studies from other sources) were screened but 640 studies were excluded according to the inclusion and exclusion criteria. Seven studies were included in the systematic research and meta-analysis, which included 375 adult patients and met all inclusion and exclusion criteria (**Table 1**) [12-15, 17-19]. The trial results were published between 2010 and 2014 and with sample size ranging from 15 to 87 patients. The study by Hernandez *et al*. was reported in the abstract from the 2010 ASCO Annual Meeting [18], while another study only provide the report for clinical trials but was not published [19]. In seven studies, four trials investigated whether the addition of lenalidomide therapy improved outcomes for DLBCL patients who previously received at least one anti-lymphoma therapy [12, 13, 17, 18]. Three trials investigated the initial therapeutic effect of lenalidomide in newly diagnosed DLBCL patients [14, 15, 19].

Overall response

Six studies reported the OR in the two subtypes of DLBCL [12, 13, 15, 17-19]. Nowakowski *et al.* [14] only reported the effect of lenalidomide treatment on survival in diagnosed DLBCL patients, so this trial was not included in our analysis. In **Figure 2**, forest plots were used to summarize the results of the meta-analyses and compare the OR between GCB and non-GCB DLBCL patients. The data from 182 patients were analyzed for OR. Among all patients, 29 of 86 patients in the GCB group responded to lenalidomide treatment, while 50 of 96 patients in the non-GCB group responded to lenalidomide treatment. Thus, the patients in the non-GCB subtype showed a higher OR rate compared with the GCB subtype (RR=0.61, 95% CI: 0.28-1.32, $P=0.21$). In subgroup analysis, as a first-line treatment for newly diagnosed DLBCL patients, the GCB DLBCL patients did not have a significantly better outcome compared with non-GCB subtype DLBCL patients (RR=0.99, 95% CI: 0.77-1.28, $P=0.96$). As a second-line treatment, four trials of lenalidomide treatment compared the OR between GCB subtype and non-GCB subtype patients, similar results were observed (RR=0.34, 95% CI: 0.05-2.34, $P=0.27$). However, the number of included patients was too small to yield statistical significance. The difference between these two subgroups was not significant ($P=0.28$).

Progression-free survival

Four trials compared the PFS in patients treated by lenalidomide between GCB and non-GCB subtypes [12, 14, 15, 18]. We included the data from three of four trials in our analysis and excluded the data from one trial in which HR was not calculated directly from the available data. A fixed-effect statistical model revealed that the increased PFS after lenalidomide treatment was not significantly different between non-GCB subtype and GCB DLBCL patients (HR=0.56, 95% CI: 0.28-1.15, $P=0.12$) (**Figure 3**). In subgroup analysis, as first-line and second-line treatments for DLBCL patients, patients with non-GCB DLBCL did not show signifi-

Table 1. Summary of trials included in the meta-analysis

Study [reference]	Year	Age (median, range)	Number of patients			Determining cell of origin	Study arms	Previous therapy
			Total	GCB	Non-GCB			
Celgene [19]	2014	NA	51	23	28	IHC (Hans)	LE	No
			51	25	26		Single agent therapy (gemcitabine, oxaliplatin, rituximab or etoposide)	No
Hernandez [18]	2010	NA	18	9	9	IHC (Hans)	LE	Yes
Hernandez [12]	2011	66 (43-80)	40	23	17	IHC (Hans)	LE	Yes
Vitolo [15]	2014	69 (64-71)	32	16	16	IHC (Hans)	LE+RCHOP	No
Wang [13]	2013	65 (24-84)	26	10	16	IHC (Visco-Young)	LE+R	Yes
Nowakowsk [14]	2014	65 (22-87)	55	33	22	IHC (Hans)	LE+RCHOP	No
		61 (41-86)	87	59	28		RCHOP	No
Feldman [17]	2014	61.5 (41-75)	15	5	10	IHC (Hans)	RICER	Yes

Abbreviations: IHC: immunohistochemistry; LE: lenalidomide; R: rituximab; GCB: germinal center B-cell; Non-GCB: non-germinal center B-cell; RCHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; RICER: lenalidomide, rituximab, ifosfamide, carboplatin, etoposide; NA: not available.

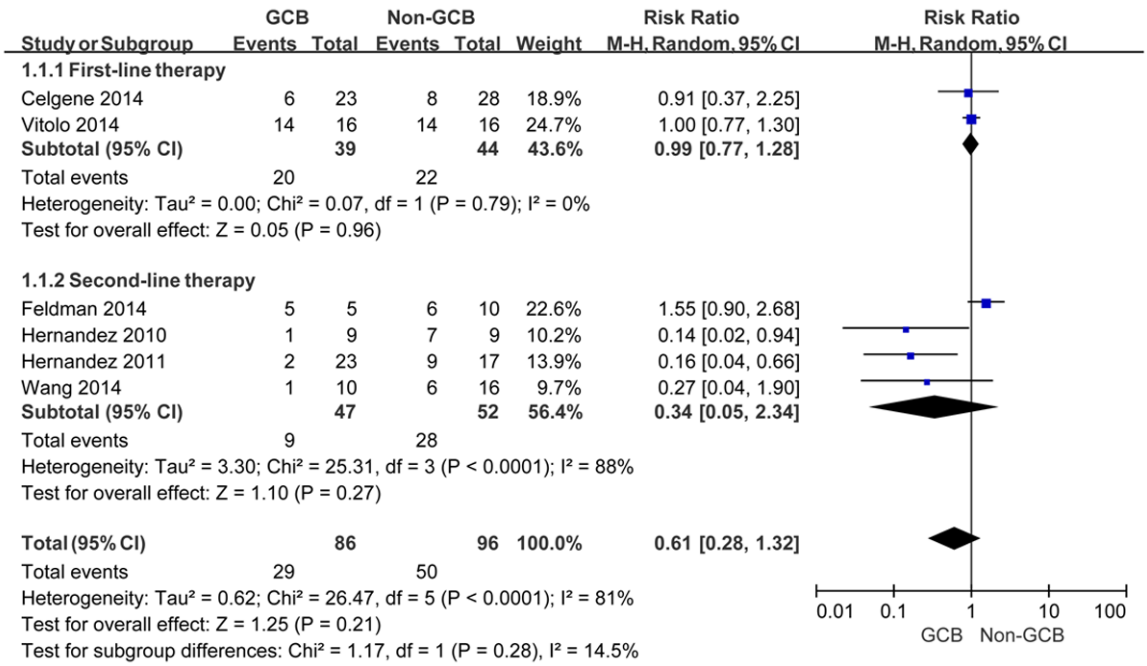

Figure 2. Meta-analysis of individual trials and overall response rates between two subtypes of DLBCL patients receiving lenalidomide therapy (first-line therapy and second-line therapy). Squares on the risk ratio plot are proportional to the weight of every study, which is determined by the Mantel-Haenszel (M-H) method. Risk ratios are presented with 95% confidence intervals (CIs).

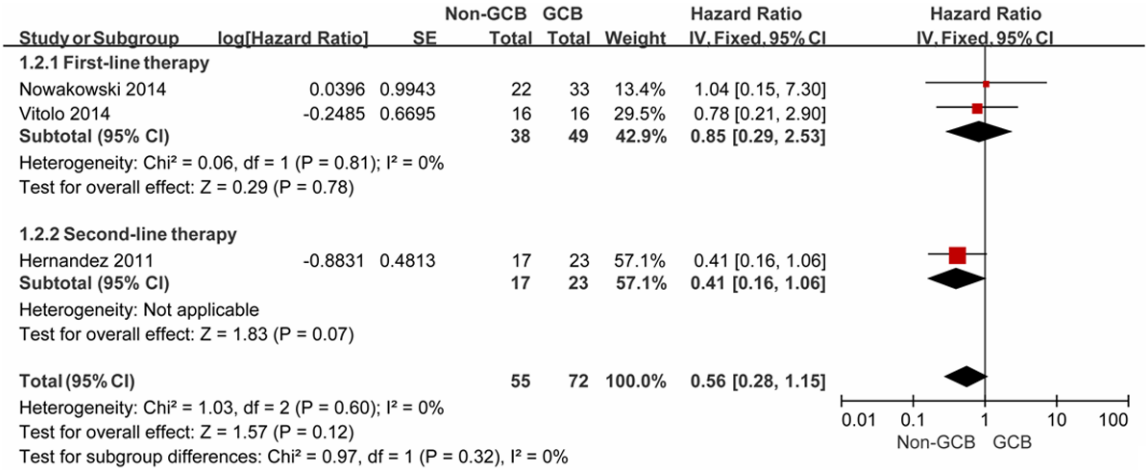

Figure 3. Meta-analysis of individual trials and overall hazard ratios for progression-free survival between two subtypes of DLBCL patients receiving lenalidomide therapy (first-line therapy and second-line therapy). Squares on the hazard ratio plot are proportional to the weight of every study, which is determined by the inverse variance (IV) method. Hazard ratios are presented with 95% confidence intervals (CIs).

cantly worse PFS compared with GCB DLBCL patients (HR=0.85, 95% CI: 0.29-2.53, *P*=0.78; HR=0.41, 95% CI: 0.16-1.06, *P*=0.07). There was no evidence of significant heterogeneity among the trials (I^2=0%). There was only one trial compared the PFS after combined treatments of lenalidomide and chemotherapy between GCB and non-GCB subtype DLBCL patients. The PFS of non-GCB DLBCL patients treated with R-CHOP appeared inferior to those of patients treated with R2CHOP (28% *vs*. 60% at 2 years), while the PFS of GCB DLBCL

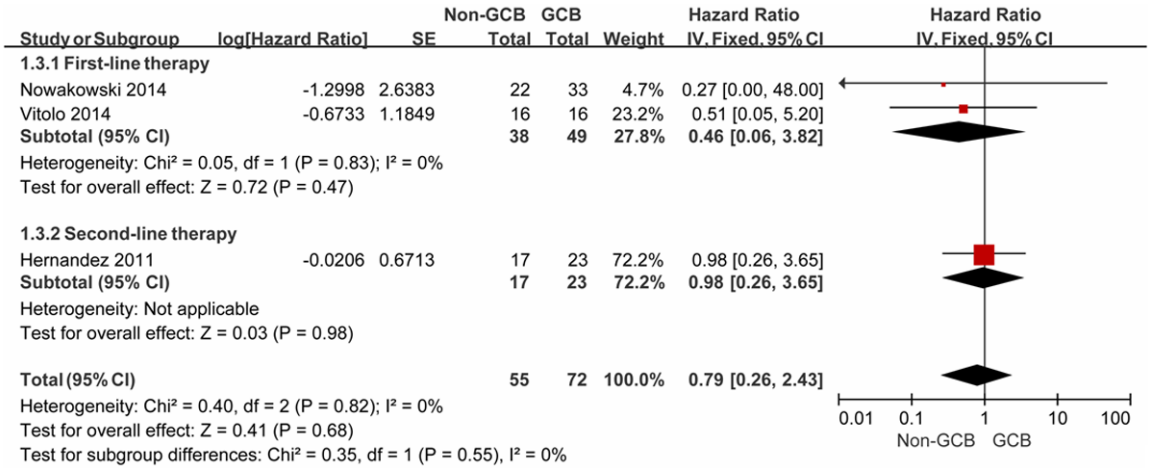

Figure 4. Meta-analysis of individual trials and overall hazard ratios for overall survival between two subtypes of DLBCL patients receiving lenalidomide therapy (first-line therapy and second-line therapy). Squares on the hazard ratio plot are proportional to the weight of every study, which is determined by the inverse variance (IV) method. Hazard ratios are presented with 95% confidence intervals (CIs).

patients treated with R-CHOP appeared similar to those of patients treated with R2CHOP (64% *vs*. 59% at 2 years) [14].

Overall survival

We included data from three of four trials in our analysis and excluded the data from one trial that HR was not calculated indirectly from the available data [12, 14, 15]. OS data were available for 127 patients receiving lenalidomide treatment. Although there was a trend for increased OS in non-GCB DLBCL patients, our meta-analysis revealed that there was no statistically significant difference in OS between two subtypes (HR=0.79, 95% CI: 0.26-2.43, *P*=0.68) (**Figure 4**). In subgroup analysis, as first-line and second-line treatments for DLBCL patients, non-GCB DLBCL patients did not show significantly worse OS compared with GCB DLBCL patients (HR=0.46, 95% CI: 0.06-3.82, *P*=0.47; HR=0.98, 95% CI: 0.26-3.65, *P*=0.98). There was also no evidence of significant heterogeneity among the trials (I^2=0%). Moreover, there was only one trial compared the OS after combined treatments of lenalidomide and chemotherapy between GCB and non-GCB subtype DLBCL patients. The OS in non-GCB DLBCL patients treated with R-CHOP appeared inferior to those of patients treated with R2CHOP regime (46% *vs*. 83% at 2 years). The PFS of GCB DLBCL patients treated with R-CHOP appeared similar to those of patients treated with R2CHOP regime (78% v 75% at 2 years) [14].

Discussion

The addition of the rituximab to a regimen of CHOP (R-CHOP) has achieved substantial advances. Patients with ABC DLBCL have a significantly worse outcome when treated with R-CHOP or R-CHOP-like chemotherapy [9]. However, to date, no therapy has been proven to improve the outcome of ABC DLBCL patients. Consequently, R-CHOP is considered as a standard therapy for newly diagnosed DLBCL patients, regardless of molecular subtype.

Lenalidomide is an oral immunomodulatory agent that exerts anticancer effects through multiple mechanisms, including the inhibition of angiogenesis, recruitment of natural killer cells, upregulation of CD80 and CD40, impairment of inflammatory cytokines and effects on the tumor microenvironment [10]. *In vitro* studies elucidated the mechanism of synthetic lethality of lenalidomide, which occurred preferentially in the ABC subtype DLBCL. In ABC DLBCL cell lines, lenalidomide seems to work via downregulation of IRF-4 and requires the expression of the E3 ubiquitin ligase complex co-receptor protein cereblon [11]. In last several years, a number of studies have examined the efficacy and safety of lenalidomide for the treatment of DLBCL patients. Single-agent lenalidomide or in combination with rituximab

has been shown to produce durable responses in patients with relapsed or refractory DLBCL. Witzig *et al*. reported the efficacy of lenalidomide in 217 NHL patients including 108 DLBCL patients. Twenty-eight percent of the DLBCL patients achieved a response (13% CR), and the median PFS rate was 2.3 months. The median response time was 4.5 months [20]. Recently, Hernandez-Ilizaliturri *et al*. retrospectively analyzed the response to lenalidomide in 40 relapsed/refractory DLBCL patients with GCB and non-GCB subgroups using Hans' algorithm. The ORR rate was significantly higher in patients with non-GCB DLBCL than in GCB DLBCL patients (52.9 *vs*. 8.7%, *P*=0.006) [12]. This led to the development of R2CHOP (RCHOP + lenalidomide), which has now been shown to be safe in two phase I trials that included patients with both GCB and non-GCB subtypes [21, 22]. Hence, we performed a meta-analysis in an attempt to gain further insights into the efficacy of this treatment.

In accordance with previous retrospective analyses, our study confirmed that lenalidomide alone or in combination with chemotherapy treatment improved the survival of DLBCL patients. More importantly, non-GCB DLBCL patients do not show significantly worse outcome compared with GCB DLBCL patients. The addition of lenalidomide to R-CHOP appears to mitigate the negative impact of non-GCB phenotype on the outcome. A randomized phase 2 study of RCHOP *vs*. R2CHOP led by the Eastern Cooperative Oncology Group (E1412) and is currently ongoing to classify DLBCL subtypes by gene expression profiling (Clinical trial information: NCT00670358).

In summary, we have confirmed that lenalidomide therapy significantly improved the survival of DLBCL patients with GCB or non-GCB subtypes, but the different pathogenesis of two DLBCL subtypes led to different survival outcomes when treated with lenalidomide. Our study has also shown that the survival of non-GCB DLBCL patients was not inferior to that of GCB DLBCL patients after lenalidomide treatment. However, because the number of the enrolled patients was small, prospective studies with a larger number of patients treated with lenalidomide plus standard chemotherapy are needed to confirm these findings.

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Disclosure of conflict of interest

None.

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