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Original Article

Efficacy and safety of rituximab in marginal zone lymphoma: a meta-analysis of 13 studies

Fuli Fan[1*], Wei Wang[1*], Guanglun Li[1], Xiaoyan Ju[1], Xiaodan Liu[1], Xue Shi[1], Xianghui Bu[3], Xu Hou[2], Yangang Wang[2]

[1]Department of Hematology, [2]Department of Endocrinology, The Affiliated Hospital of Qingdao University, Qingdao, China; [3]Department of General Surgery, Cheng Xin Hospital, Heze, China. [*]Equal contributors.

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Abstract: Background: Rituximab had been reported effective on follicular lymphoma. Marginal zone lymphoma and follicular lymphoma both derived from B cell lymphoma. This meta-analysis aimed to evaluate the effectiveness and safety of rituximab treatment in marginal zone lymphoma patients. Methods: Two investigators searched for eligible studies in MEDLINE, Embase and Cochrane Library electronic databases up to November 2015, independently. The patients used rituximab monotherapy were included. We used overall response rate (ORR) and complete response (CR) to evaluate the efficacy of rituximab. Statistical heterogeneity was calculated by using the I^2 P statistic and Cochrane's Q test. We used random-effects models if $I^2 > 50\%$ or $P < 0.1$. Otherwise, we used fixed-effects models. Results: Thirteen studies which included 237 patients were eligible in the meta-analysis. The ORR was 81% (95% CI=72-88%, 13 studies including 237 patients) and CR rate was 50% (95% CI=39-61%, 13 studies including 237 patients). As for toxicities, the most frequent nonhematologic toxicity was mild infusion-related symptoms. Conclusions: In this meta-analysis, available evidence suggests that rituximab seems to be a safe and effective therapy for marginal zone lymphoma. Therefore, rituximab provides a good way to treat marginal zone lymphoma.

Keywords: Rituxima, marginal zone lymphoma, meta-analysis, safety

Introduction

Marginal zone lymphoma (MZL) is classified into three different subtypes by the World Health Organization (WHO), including extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma), nodal marginal zone B-cell lymphoma (NMZL) and the splenic marginal zone lymphoma with or without villous lymphocytes (SMZL). The MZL have been recently defined as a group of related diseases that probably arise from a common cell of origin, the marginal zone B cell [1]. MZL has been shown to be responsible for approximately 8% of all non-Hodgkin lymphomas (NHLs). SMZL and NMZL primary originate from spleen and peripheral lymph nodes, respectively. They are uncommon, which represent approximately less than 2% of the NHLs. MALT lymphoma usually arises from extranodal and organs, which are associated with mucosa or glandular epithelium. It has been shown to account for approximately 7-8% of all NHL [2].

The treatment of MZL is very complicated. Different kinds of MZLs have different solved ways. For gastric MALT lymphoma, we usually use antibiotics to eradicate H. Pylori [3]. For non-gastric MALT lymphoma, oral alkylation agents (either cyclophosphamide or chlorambucil) or purine nucleoside analogues (fludarabine, cladribine) are effective as single agents [4]. The therapeutic options of SMZL are splenectomy and chemotherapy. It is shown that alkylation agents (i.e., chlorambucil or cyclophosphamide) alone or in combination (i.e., CHOP) with fludarabine monotherapy is effective on SMZL [5]. There are no definite guidelines for the management of NMZL and no large prospective trials have been reported, so there is no uniform treatment plan.

B-lymphocytes is the target of rituximab, which is a monoclonal antibody directed against the CD20 antigen [6]. It has been reported effective for the treatment of $CD20^+$ B cell NHL [7]. The rituximab monotherapy or in combination

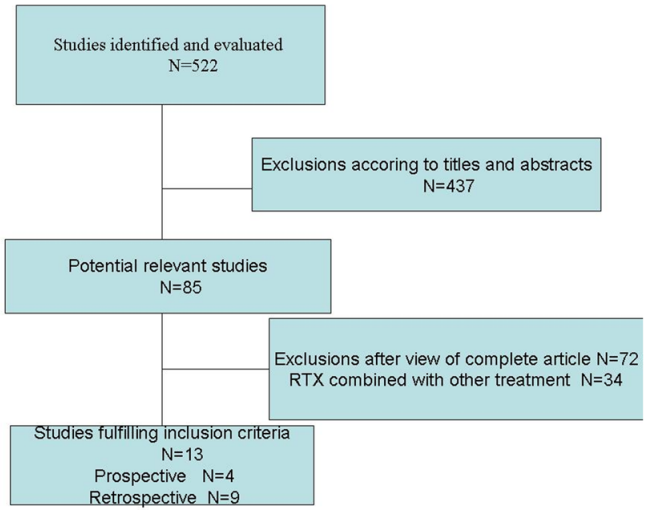

Figure 1. Flow diagram of the published articles evaluated for inclusion in this meta.

with chemotherapy has been successfully used in treating MZL [15]. Although many reports indicated that rituximab was an effective drug in MZL, retrospective studies and case reports assessing anti-CD20 antibodies were mostly small, which did not allow us to draw firm conclusions on efficacy and safety. Hence, we conducted a meta-analysis to evaluate the efficacy and safety of rituximab in MZL.

Methods

Data sources and searches

The meta-analysis was reported according to the MOOSE and PRISMA guidelines [8, 9]. An electronic search was performed in three different databases (MEDLINE; Embase; Cochrane Library electronic databases). We searched all published studies that specifically examined rituximab treatment efficacy on MZL. The keywords which were determined before data collection were Marginal Zone Lymphoma (Medical Subject Heading, MeSH) and Rituximab. The references lists of all related systematic reviews and studies were also manually searched. The initial search retrieved 522 citations. Eventually 13 studies enrolling 237 patients fulfilled the inclusion criteria.

Study selection

Study selection was independently done by two investigators. Inclusion criteria: 1) observational studies that included SMZL, NMZL and MALT lymphoma patients treated with rituximab monotherapy were selected; 2) articles published in English, up to November 2015; 3) sufficient information in the literature to calculate ORR and CR; 4) full text of the study should be available; 5) study were included if data could be extracted separately; 6) retrospective and prospective were included; 7) letters were also included. Exclusion criteria: 1) studies enrolling less than five patients were excluded; 2) repeated reports; 3) studies which used rituximab and other chemotherapy drug together were eliminated.

Data extraction and quality assessment

Discrepancies between the two reviewers were resolved through discussion and consensus. The extracted study characteristics included the first author's name, median age, year of publication, sex, design (prospective or retrospective) and population. MZL was classified as median age older than 60 or younger than 60, SMZL, NMZL and MALT. Baseline demographical data, dosage and schedule of rituximab, toxicities were extracted. The definite of treatment efficacy of each study were taken into considered, because no international consensual definition of treatment response existed. We extracted the number of patients with overall response rate and complete response. We used overall response rate (ORR) and complete response (CR) to evaluate the efficacy of rituximab. There were no unified evaluation criteria for the quality assessment of studies, so we use classic quality assessment scales.

Data synthesis and analysis

All analyses were performed using R Software. The main analyses were to calculate the mean rates of ORR and CR with their 95% confidence interval (95% CI). We calculated the weighted mean proportion to estimated rituximab efficacy and toxicity. The heterogeneity was taken into consideration. We used I^2 statistic and Cochrane's Q test to represent heterogeneity. *P*-value < 0.1 or I^2 statistic > 50% indicated substantial heterogeneity, and the random-effects model was used. The fixed effects model method was used when heterogeneity was not obvious [10, 11]. To explain heterogeneity, we used logarithmic mixed-effects meta-

Table 1. The characteristics of the 13 studies

Study	Popopulation	Median age	Sex	Previous treatment	RTX dose
Bennett, 2005	SMZL	75	5F6M	chlorambucil&prednisone, splenectomy, prednisone fludarabine cyclophosphamide	375 mg/m^2 once a week for 4 weeks
Tsimberidou, 2006	SMZL	65	NA	NA	375mg/m^2 once a week for 4 or 8 weeks
Kalpadakis, 2007	SMZL	57	2F14M	NA	375 mg/m^2 once a week for 6 weeks
Kalpadakis, 2013	SMZL	64	32F26M	splenectomy	375 mg/m^2 once a week for 6 weeks
Else, 2012	SMZL	NA	NA	NA	375 mg/m^2 once a week for 4 weeks
Okamura, 2015	MALT	61	4F4M	NA	375 mg/m^2 once a week for 4 or 8 weeks
Ferreri, 2005	MALT	51.5	7F1M	NA	375 mg/m^2 once a week for 4 weeks
Raderer, 2003	MALT	NA	4F5M	NA	375 mg/m^2 once a week for 4 weeks
Mino, 2014	MALT	70	4F5M	NO	375 mg/m^2 per day intravenously every 4 weeks
Martinelli, 2005	MALT	53	NA	Antibiotic eradication, Surgery, Chemotherapy	375 mg/m^2 once a week for 4 weeks
Conconi, 2003	MALT	57	23F11M	systemic chemotherapy,	375 mg/m^2 once a week for 4 weeks
Annibali, 2015	MALT	57	4F2M	NO	375 mg/mq every 3 weeks intravenously for 6 cycles
Lossos, 2007	3 NMZL 1SMZL 12MALT	55	8F8M	Antibiotics, radiation therapy	375 mg/m^2 per day intravenously every 4 weeks

NA: not available; NO: no previous treatment; MALT: mucosa-associated lymphoid tissue lymphoma; SMZL: splenic marginal zone lymphoma; NMZL: nodal marginal zone lymphoma; F: Female; M: Male, RTX: Rituximab.

Table 2. The definitions of treatment efficacy and toxicities

Study	CR definition	PR definition	Toxicities
Bennett, 2005	Absence of a palpable spleen, disappearance of villous lymphocytes from the peripheral blood and complete blood count.	At least a 50% decrease in spleen size and improvement in blood counts	NA
Tsimberidou, 2006	The complete disappearance of all detectable clinical and radiographic evidence of disease for at least 1 month	A reduction ≥ 50% in the sum of the products of the greatest dimensions of bidimensionally measurable disease	NA
Kalpadakis, 2007	Complete resolution of symptoms, normalization of peripheral blood counts, absence of detectable disease by clinical staging including bone marrow biopsy.	≥ 50% decrease in the spleen size and the percentage of bone marrow infiltration along with improvement of blood counts over baseline	8 infusion-related side effects 1 mild-to-moderate neutropenia.
Kalpadakis, 2013	The resolution of symptoms and organomegaly, normalization of blood counts and no evidence of bone marrow infiltration on immunohistochemistry.	The resolution of symptoms and ≥ 50% decrease in spleen size and a decrease in the level of lymphoid infiltration in the bone marrow along with improvement in blood counts over baseline.	1 Grade III thrombocytopenia ,2 severe adverse events, 3 Grade II neutropenia, 1 Reactivation ofherpes zoster.
Else, 2012	Resolution of organomegaly, normalization of the blood counts and no (or minimal) evidence of bone marrow infiltration	50% or greater improvement in the disease manifestations with 50% reduction of the spleen size.	1 patient had Toxicities
Okamura, 2015	NA	NA	1 infusion-related reaction
Ferreri, 2005	NA	NA	0
Raderer, 2003	NA	NA	2 experiencing transient reactions
Mino, 2014	NA	NA	NA
Martinelli, 2005	The complete absence of neoplastic lymphoid cells or presence of lymphocytes and plasma cells scattered or in small aggregates	The persistence of atypical lymphoid cells in larger sheets, with or without lymphoepithelial lesions, respectively	1 experienced severe infusion-related symptoms, 1 developed pneumonia
Conconi, 2003	Complete histologic regression was obtained when the posttreatment biopsies showed an empty lamina propria with small basal clusters of lymphocytes and scattered plasma cells and no sign of remaining lymphoma	Posttreatment biopsy samples revealing either focal atypical lymphoid cells or focal lymphoepithelial lesions and an empty lamina propria as signs of lymphoma regression	experienced 29 events include 1 infection, 1 bronchospasm, and 1 glottis edema 1 case did an infection
Annibali, 2015	NA	NA	1 presented herpetic keratitis
Lossos, 2007	NA	NA	0

NA: not available; CR: complete response; PR: partial response.

Table 3. The quality of the 13 studies

Study	Prospective	Retrospective	Individual data	Type of article
Bennett, 2005		+	+	Letter
Tsimberidou, 2006		+		
Kalpadakis, 2007		+	+	Letter
Kalpadakis, 2013		+		
Else, 2012		+		
Okamura, 2015		+	+	
Ferreri, 2005	+		+	Letter
Raderer, 2003		+	+	
Mino, 2014		+	+	Letter
Martinelli, 2005	+		+	
Conconi, 2003	+		+	
Annibali, 2015		+	+	
Lossos, 2007	+		+	Letter

regressions to investigate the effects of covariates on response rate. The funnel plot was used to determine the risk of publication bias. We further used Egger's test to evaluate publication bias [12]. A *P*-value < 0.05 was defined as statistically significant for all outcomes.

Results

Study selection

We used electronic searching or manual search-ing, and identified 522 studies, of which 437 were excluded after scanning the titles and abstracts because of they were obviously not relevant to the meta-analysis. 72 studies were further excluded for the following reasons: 34 studies for the used of rituximab combined with other treatments, 36 studies for less than five patients, and 2 studies for other language. Finally, 13 studies with a total of 237 patients were included in our meta-analysis. Details about retrieval circumstances were given in **Figure 1**.

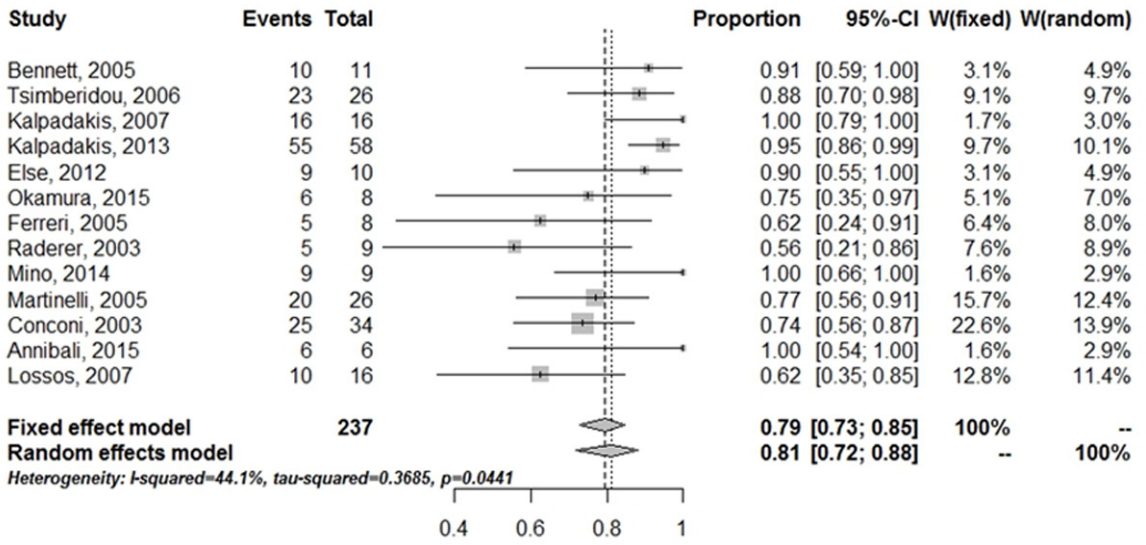

Figure 2. Global ORR forrest plot.

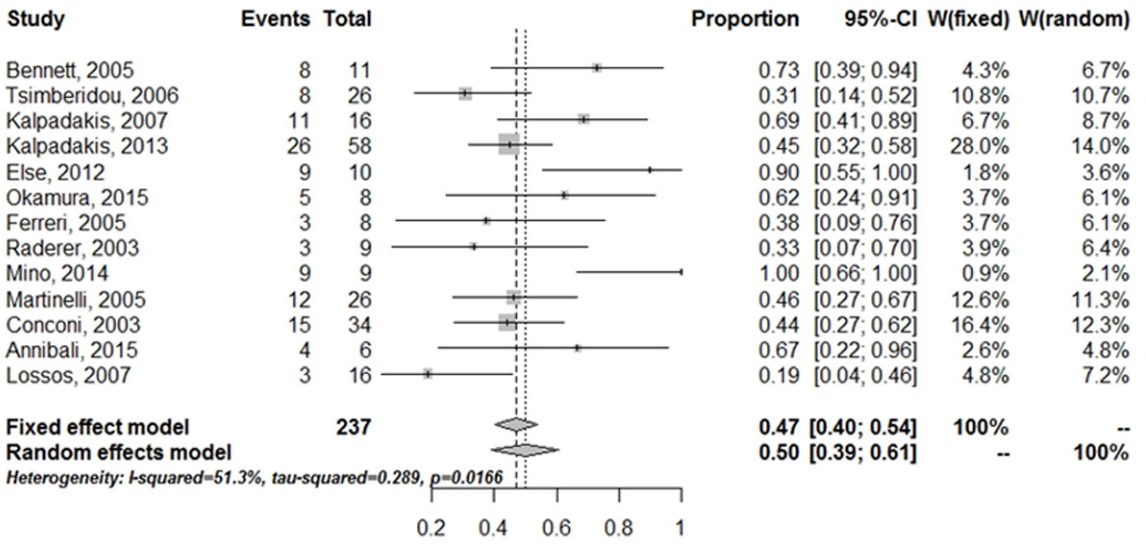

Figure 3. Global CR forrest plot.

Table 4. The ORR and CR rates depending on MZL types

	n, N	Model	ORR	n, N	Model	CR
MALT	8, 112	Fixed	73%	8, 112	Fixed	45%
SMZL	6, 122	Fixed	92%	6, 122	Random	58%

MALT: mucosa-associated lymphoid tissue lymphoma; SMZL: splenic marginal zone lymphoma n: number of studies; N: number of patients; ORR: overall response rate, CR: complete response.

Characteristics of the included studies

Those studies included 9 retrospective studies [13, 16-18, 21-25] and 4 prospective studies [14, 15, 19, 20]. Randomized controlled trials have not been reported. Three of the thirteen studies were letters. The quality assessment result is shown on **Table 3**. Six studies focused on SMZL and eight studies focused on MALT lymphoma, and only one study included NMZL. Because the sex ratio of two studies was not clear [15, 17], so the other 11 studies with a total number of 175 patients containing 93 females (53.2%) and 82 males (46.8%) were included. Most studies received a dose of 375 mg/m^2/week for 4 consecutive weeks, two studies used a dose of 375 mg/m^2/

Table 5. The ORR and CR rates depending on median age

Median age	n, N	Model	ORR	n, N	Model	CR
> 60	5, 112	Fixed	90%	5, 112	Random	54%
< 60	6, 106	Fixed	73%	6, 106	Fixed	46%

n: number of studies; N: number of patients; ORR: overall response rate, CR: complete response.

week for 6 consecutive weeks, and one study received 6 cycles of rituximab 375 mg/mq every 3 weeks intravenously (**Table 1**). The definition of CR was different, but it contained both in clinical response and hematologic response aspects. Four studies of PR were defined by at least a 50% decrease in spleen size and improvement in blood counts (**Table 2**).

Overall response

ORR was reported in all included studies in the meta-analysis. Because of the significant heterogeneity (I^2 = 44.1%, P = 0.0441), we used a random effects model. The ORR of 13 studies which included a total of 237 patients was 81% (95% CI=72-88%) (**Figure 2**). For CR, there was also significant heterogeneity (I^2 = 51.3%, P = 0.0166), and the CR was 50% (95% CI=39-61%) (**Figure 3**).

Subgroups analyses

Because of the significant heterogeneity, we made subgroups analyses. We divided those studies into three groups according to the types of the disease: MALT lymphoma, NMZL, and SMZL. The ORR of MALT lymphoma which included 8 studies and 112 patients [13-16, 18-21] was 73% (95% CI=63-80%) and the CR was 45% (95% CI=36-55%). Six studies with 122 patients were included in SMZL [17, 19, 22-25], whose ORR was 92% (95% CI=85-96%) and the CR was 58% (95% CI=39-75%). One study reported 3 patients was included in NMZL [19], and the ORR of which was 33% (95% CI=1-91%) (**Table 4**). For the median age older than 60 years old (5 studies included 112 patients) [16, 17, 21, 22, 25], the ORR was 90% (95% CI=83-95%), the CR was 54% (95% CI=35-73%). For the median age younger than 60 years old (6 studies included 106 patients) [13-15, 19, 20, 23], the ORR was 73% (95% CI=63-81%), the CR was 46% (95% CI=36-56%) (**Table 5**).

Safety of rituximab

There were 53 adverse events in 191 patients reported by 10 studies. The overall adverse event rate was 28% (95% CI=22-35%). The most frequent toxicity was mild infusion-related reaction (74%), and 14 more sever events (26%) had been reported: 4 neutropenia, 1 sever hypotension, 1 grade III thrombocytopenia, 2 severe adverse events, 1 reactivation of herpes zoster, 2 pneumonia, 1 bronchospasm, 1 glottis edema, and 1 herpetic keratitis. The event of lethal by used rituximab had not been reported.

Publication bias

We used both funnel plot and Egger's test to detect publication bias. For ORR, funnel plot didn't have a tendency of publication bias (Egger's regression test, P = 0.09574) (**Figure 4**). Funnel plot of CR was also not in favor of publication bias (Egger's regression test, P = 0.09375) (**Figure 5**).

Discussion

This is the first meta-analysis assessing the efficacy and safety of rituximab in MZL. The ORR rate in MZL treated with rituximab was up to 80%, and 50% of patients achieved complete remission. Our study divided the patients into different subgroups according to the disease classification and median age: NMZL, SMZL, MALT, and median age above 60 and under 60 years old. The ORR of MALT lymphoma was 73% and CR was almost 50%. A study which used mitoxantrone, chlorambucil and prednisone together has reported that the CR was 53% [30]. The CR of the rituximab monotherapy in our meta-analysis was closed to the study which combination of chemotherapy. It has been shown that rituximab monotherapy is effective on MZL. The ORR and CR of SMZL (92%, 58%) are higher than MALT lymphoma. These results suggest that the efficacy of rituximab is very well. Corresponded to another study which compared splenectomy and rituximab therapy, it has been suggested that splenectomy should no longer be considered as initial therapy for SMZL because of its' adverse reactions. Therefore rituximab has gained an important place in the treatment of SMZL [29]. For NMZL, because of the lack of published studies and the inclusion criteria, we only found 1 study included 3 patients in our meta-analysis. However, the ORR was only 33%. The efficacy was very well to rituximab treatment no

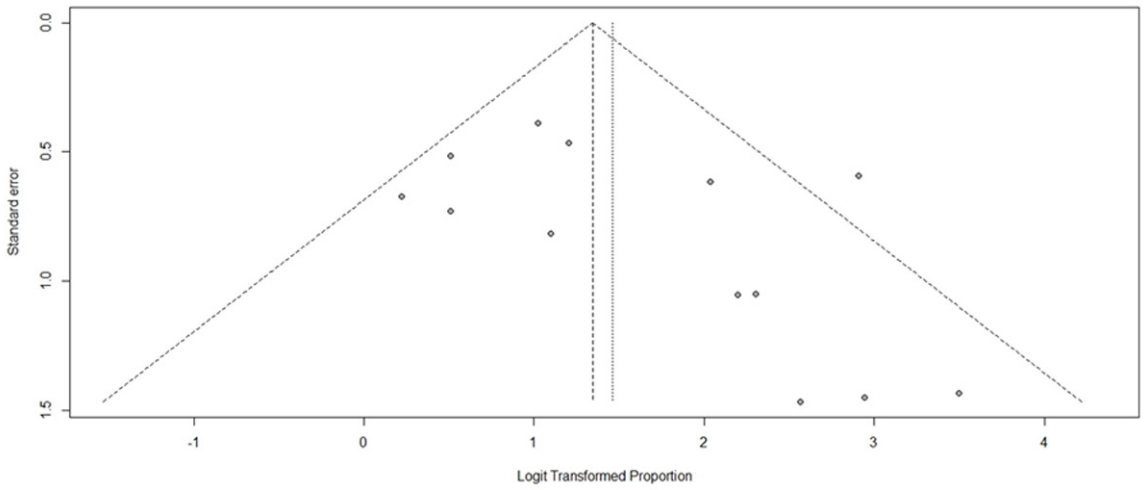

Figure 4. Global ORR funnel plot.

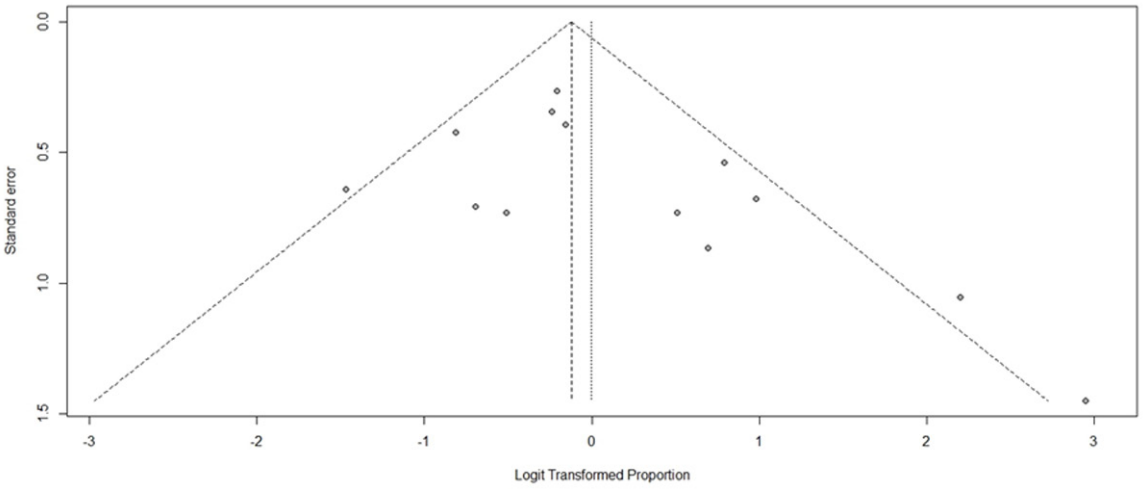

Figure 5. Global CR funnel plot.

matter in studies of patients median age above 60 (90%, 54%) or under 60 years old (73%, 46%). Interestingly, the patients in median age older than 60 years were mostly SMZL, and the majority of MALT lymphoma was included in median age younger than 60 years old. It may because different type of lymphoma had different susceptible time. All in all, these results suggest that rituximab is a useful, valuable treatment for patients with MZL.

MZL belongs to NHLs and derives from marginal zone B cell, so B-cells have been demonstrated to play a key role in the pathogenesis of MZL. We have an attractive therapy in current available therapies against the B-cell compartment. Rituximab, an anti-CD20 monoclonal antibody, causes a profound and prolonged depletion of most peripheral B-cells. There are three putative mechanisms to explain the mechanism of rituximab that leads to the depletion of peripheral B-cells, which include complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity (ADCC) and the promotion of apoptosis [6, 26]. A few of meta-analysis have been published to show the efficacy and safety of rituximab therapy in diffuse large B-cell lymphoma [27, 28]. However, there is a paucity of evidence that we can evaluate the use of rituximab in MZL treatment.

Rituximab therapy in MZL is well tolerated in the patients of most studies. The main adverse effects of rituximab are mostly mild to moder-

ate infusion-related side effects, such as fever, headache, nausea and chills. Most of these events occur during the first infusion and are easily controlled with the administration of appropriate support and infusion of rituximab at a lower rate. The severe events such as neutropenia, thrombocytopenia and infections accounted for only 7% of patients. Most of this event could be controlled by symptomatic supportive treatment. In addition, there was no evidence to suggest that the dose of rituximab is related to adverse effect. From our review, we can conclude that rituximab was safe in the treatment of MZL.

However, limitations of our meta-analysis study should be considered. Firstly, the number of patients in our studies was different, small studies had less patients, while large studies had more patients. It maybe leads to possibilities of publication bias and sampling errors, in other words, the efficacy of rituximab in smaller studies are likely to be good than in larger studies. Similarly, heterogeneity could lead to asymmetry. Secondly, no randomized controlled trial was included. The reason maybe is the morbidity is low or the placebo is difficult to design. Thirdly, lack of studies about children and studies about NMZL, the number of patients was too small in these studies, usually was case reporter, so according to the exclusion criteria we had excluded from our meta-analysis. Moreover, to explain the heterogeneous efficacy of rituximab in MZL. These factors should be taken into consideration: disease duration, the sex of the patient, demographic characteristics encompassing age and the prior treatment. Some patients accepted prior treatment, such as the splenectomy in SMZL, or chemotherapy in MZL. In our meta-analysis, several problems are due to intrinsic properties of studies: the population heterogeneity, the stage of the disease and the small number of selected patients.

In conclusion, the observational studies have shown that rituximab is effective in MZL, and the tolerance in most patients is very well. Compared with splenectomy, rituximab therapy has less damage to the body of the human in terms of SMZL. So in SMZL, rituximab maybe suggested as a first-line treatment prior than splenectomy. Although more studies are still needed to confirm the efficacy and safety, rituximab should be first considered in elder patients who cannot tolerate adverse response of the large dose chemotherapy.

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Disclosure of conflict of interest

None.

Address correspondence to: Xu Hou and Yangang Wang, Department of Endocrinology, The Affiliated Hospital of Qingdao University, 16 Jiangsu Rd, Qingdao 266003, China. Tel: +86 532 82911383; Fax: (86)0532-82911740; E-mail: jacob72hou@yahoo.com (XH); wangyg1966@126.com (YGW)

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