Intensified Therapy Followed by Autologous Stem-Cell Transplantation (ASCT) versus Conventional Therapy as First-Line Treatment of Follicular Lymphoma

Lida Wang1, Liping Liu1, Huanwen Ma2 and Zhixin Sheng*2

1E.N.T department
2Department of Hematology, Affiliated Weifang People’s Hospital of Weifang Medical University

Abstract
To define the treatment effect of intensified therapy followed by autologous stem-cell transplantation (ASCT) compared with conventional therapy as first-line treatment of patients with follicular lymphoma (FL) in terms of overall survival (OS) and event-free survival (EFS). Medline, Embase, the Cochrane controlled trials register and the Science Citation Index were searched. Four trials were identified, covering a total of 941 subjects. The random-effects summary Hazard Ratio (HR) comparing the treatment effect on OS between intensified and conventional therapy was 0.95 [0.70, 1.30] (P=0.75), indicating that no additional survival benefit was derived from the intensified therapy followed by ASCT. A significant benefit of intensified therapy followed by ASCT as first-line treatment was detected in terms of EFS: the random-effects summary HR (intensified versus conventional therapy) was 0.59 [0.44, 0.79] (P<0.001). In conclusion, despite its superior EFS, intensified therapy followed by ASCT does not improve OS compared with conventional therapy.

Keywords: Follicular lymphoma; Autologous stem cell transplantation; First-line therapy.

Introduction
Follicular lymphoma (FL) is B-cell malignancy characterized by a slowly progressive clinical course [1-3]. Although, FL still remains incurable, our approach to the treatment of FL has evolved apparently in the past two decades. Especially, new agents, particularly rituximab, have improved survival outcome in patients with FL [4,5]. During this rapidly evolving era, the role of intensified regimens with autologous stem-cell transplantation (ASCT) still remains poorly defined. The superiority of intensified therapy as a salvage treatment for relapsing patients on survival have been demonstrated compared with conventional chemotherapy [6,7]. Whereas, only few trials evaluating the role of intensified therapy as a first-line treatment for patients with FL were published, and the results remain variable [8-12]. And no reference first-line treatment is clearly defined. So we did this meta-analysis to primarily evaluate the treatment effect of intensified therapy followed by ASCT as first-line treatment of patients with FL in terms of overall survival (OS) and event-free survival (EFS).

Methods

Literature search strategy
Medline, Embase, the Cochrane controlled trials register and the Science Citation Index were searched for randomized control trials (RCTs) using the medical subject headings “follicular lymphoma”, “autologous stem-cell transplantation”, and “chemotherapy”. Reference lists from studies selected for this review, and from other published systematic reviews and practice guidelines were also hand-searched.

Selection of studies
Studies were eligible for inclusion in the meta-analysis if they met all the following criteria: (1) They were published up to June 2011 and written in English. (2) They dealt only with patients with FL in the first-line setting. (3) They provided data on EFS, OS and (or) secondary tumor rate. (4) Intervention: intensified therapy followed by ASCT. (5) control: conventional therapy. Multiple reports of a single study were considered as one publication, and only the most recent and complete data was examined. All potentially relevant articles were reviewed by two independent investigators (L.D.W and Z.X.S.).

Outcome measures
The primary outcome of our analysis was OS. And, we considered the treatment effect on EFS and secondary tumor (myelodysplastic syndromes(MDS), acute myeloblastic leukemias (ALL), and other secondary tumors) rate as secondary outcomes. EFS was measured from the date of enrollment, randomization or treatment start until disease progression, relapse, or death. OS was measured from the date of enrollment, randomization or treatment start until death from any cause.

Quality assessment
Two reviewers (L.D.W and Z.X.S.) independently assessed the quality of selected studies using the following criteria: (1) generation of allocation concealment, (2) description of drop-outs, (3) masking of randomization, intervention, outcome assessment, (4) intention-to-treat (ITT) analyses. Each criterion was rated as yes, no or unclear.

Statistical analysis
All survival data (EFS, OS) were pooled and reported as Hazard

*Corresponding author: Zhixin Sheng, Department of Hematology, Weifang People’s Hospital, Weifang 261041 (PR China), Tel: +86 159 4975 2090; Fax: +86 536 8192116; E-mail: shengzhixin6569@126.com
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Ratio (HR) with genetic inverse variance method. The secondary tumor rate were pooled as Risk Rito (RR). For each included RCT, for the purpose of analysis, we calculated the logrank of HR, and its standard error to perform this meta-analysis. A value less than 1.0 means that the treatment effect is more favorable in patients with intensified therapy followed by ASCT compared with conventional therapy, whereas a value greater than 1.0 means the opposite. When not available from the trial reports, they were estimated with the methods proposed by Parmar et al. [13] and described elsewhere [14]. A random-effects model was used for all the analyses, which incorporates the variability of results among trials and provided a more conservative estimate of an effect size by producing greater confidence intervals (CIs) [15].

We tested for heterogeneity of between-study with the Cochrane χ² test (considered significant at the 0.10 level) and quantified its extent with the P statistic. If significant heterogeneity existed, it would be appropriate to pool the data using random-effects model, but not fixed-effect model.

There are substantial differences in study characteristics (the presence or absence of rituximab and interferon, different conditioning regimens including specifically TBI or not) between the pre-rituximab and rituximab trials. We evaluated the possible influence of these combined characteristics on estimated survival effects as dichotomous variable (pre-rituximab vs rituximab trials) via separate meta-regression analyses. We used the presence or absence of those combined study characteristics in the meta-regression.

Begg’s funnel plots [16] and Egger’s test [17] were used to detect possible publication bias (considered significant at the 0.15 level). All meta-analyses were completed using Review Manager (version 5.1, The Cochrane Collaboration, Oxford, England) and Stata ver. 11.0 software (College Station, TX, USA). Statistical significance was defined as a P value of less than 0.05 for all tests except those for heterogeneity and publication bias.

**Results**

A comprehensive search of Medline, Embase, the Cochrane controlled trials register and the Science Citation Index yielded 359 articles, of which 4 studies met the predetermined inclusion criteria. The four trials enrolled a total of 941 patients. Their characteristics are described in Table 1. None was double-blinded. All studies reported intention-to-treat (ITT) analyses and description of drop-outs except for only one [10]. We did not find any graphical or statistical evidence of publication bias for all outcomes.

As shown in Figure 1, the random-effects summary relative HR comparing the treatment effect on OS between intensive treatment and conventional therapy was 0.95 [0.70, 1.30] (P=0.75), indicating that no additional survival benefit was derived from the intensified therapy followed by ASCT. The between-study heterogeneity was little (P=0.83, I²=0%).

As shown in Figure 2, a significant benefit of intensified treatment followed by ASCT as first-line treatment was detected in terms of EFS, the random-effects summary relative HR (intensified versus conventional therapy) was 0.59 [0.44, 0.79] (P<0.001).

In the regression model, the combined study characteristics was

| Author, year | N   | Therapy Regimen          | Follow-up Period |
|--------------|-----|--------------------------|------------------|
| Lenz 2004[10]| 240 | E: CHOP×(4-6)cyc, Dex + BEAM, TBI, CY | 4.2 years        |
|              |     | C: CHOP×(4-6)cyc, CHOP×2cyc + IFNo |                  |
| Sebbon 2006[11]| 401| E: CHOP×4cyc, CY, VP16, TBI | 7.7 years        |
|              |     | C: CHTP×12cyc + IFNo      |                  |
| Ladetto 2008[9]| 134| E: (APOxDHAP)×2cyc, R×2cyc, CY±R×2cyc | 4.3 years        |
|              |     | C: CHOP×6cyc + Rx(4-6)cyc |                  |
| Gyan 2009[12]| 166| E: VCAP×3cyc, DHAP×3cyc or IMVP16, TBI, CY | 9 years          |
|              |     | C: CHVP×12cyc + IFNo-2b   |                  |

Abbreviations: CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; cyc: cycles, Dex: dexamethasone; BEAM: BCNU, melphalan, etoposide, cytarabine; TBI: total body irradiation; CY: cyclophosphamide; CHTP: cyclophosphamide,doxorubicin, teniposide, prednisone; APO: doxorubicin, vincristine, prednisone; DHAP: dexamethasone, high dose of cytarabine, and cisplatin. R: rituximab; VCAP: vindesine, cyclophosphamide, doxorubicin, prednisone; IMVP16: ifosfamide, methotrexate, and VP-16; CHVP: cyclophosphamide, doxorubicin, vepeside, prednisone.

Table 1: Characteristics of included studies.
Discussion

Whatever treatment, FL is still a fatal illness after a prolonged course [18]. One of the best treatments showing high efficacy in patients with FL was high-dose therapy (HDS) followed by ASCT. However, the place of intensified therapy in the therapeutic strategy of FL remains not yet clearly determined. The benefit of ASCT have been documented compared with conventional chemotherapy in relapsing patients with follicular lymphoma [19]. However, only few phase 3 studies of autologous transplantation as the first-line treatment of FL have been reported [8-12], and the results remain somehow discrepant.

Our analysis makes an important contribution to the FL field. The first and primary finding of our analysis was that our meta-analysis helps to clarify the impact of intensified regimens followed by ASCT as first-line treatment of FL on survival compared with conventional therapy, and clearly indicates that no survival benefit was shown in the intensified arms. The degree of heterogeneity with respect to OS between included studies was little. This treatment effect on OS was consistently seen across all included studies. Prior to this analysis, the benefit of EFS obtained with intensified versus conventional treatment was a matter of debate, our pooled data also demonstrated that intensified therapy did attain a statistical EFS benefit. However, it should be still noted that approximately 30% of patients in the conventional arm still attained a prolonged disease-free period, and patients with relapsed or refractory disease following conventional therapy can be rescued with ASCT with a 3-year EFS of 70% [9]. Especially for only few patients, the use of intensified therapy was not feasible because of eligibility issues and the feasibility rate seems similar to that observed at diagnosis [9]. More data from previous trials have provided mature evidence to show that a good long-term outcome for patients receiving ASCT as second-line treatment, suggesting that intensified regimens retain high efficacy at least when used as first salvage treatment [20]. The extremely high early relapse rate following conventional chemotherapy is well balanced by the good survival outcome of patients undergoing intensified therapy as salvage treatment, resulting into a similar prolonged survival rate in the 2 arms [9]. These data strengthen the proposal that ASCT is not superior to conventional chemotherapy in the first-line treatment of patients with FL.

Additionally, to address the question of whether the distinct combined characteristics (the presence or absence of rituximab and interferon, different conditioning regimens including specifically TBI or not) between pre-rituximab and rituximab trials would influence the estimated effects of survival (OS and PFS), we conducted a separate meta-regression analysis. In the regression analysis, we did not find that the combined study characteristics significantly related to OS and PFS. Some caveats should be noted in this meta-regression analysis: First, there are only four trials included in this analysis, maybe it is not enough powerful to detect a significant relation. Second, the influence of specific study characteristic was not evaluated respectively, because of lacking individual data.
Although, the high rate of secondary malignancies, including MDS/AML and other secondary tumors in the ASCT arm was not detected in the pooled-analysis, the significant extramortality from secondary tumors in the ASCT arm of GOELAMS trial still needs particular consideration [8]. The factors of the use of TBI-containing regimen and (or) systematic cell purging might contribute to the increased incidence of MDS/AML, solid tumors [21,22]. This potential increased risk of secondary tumors might counteract the survival benefit of autologous transplantation [8]. Additionally, currently effective approaches are available to treat even late-phase FL, while sMDS/AML remains a rapidly fatal disease. This issue, together with the observation that no survival benefit in the intensified arm, indicates that first-line intensified therapy would probably be an overtreatment for patients with FL, and suggests that ASCT seems to be considered as a reference treatment for relapsing patients, but not in the first-line setting.

This finding should not be overemphasized and several limitations need cautious consideration: Firstly, we had no access to primary data and only used abstracted data, while an individual patient data based meta-analysis would have provided a more robust estimate of the efficacy of intensified therapy followed by ASCT in the first-line setting. Secondly, as is often the case with meta-analysis, the effect of heterogeneity usually needs to be taken into account.

In conclusion, despite its superior EFS, intensified therapy followed by ASCT does not improve OS compared with conventional therapy. So, ASCT should not be recommended as first-line treatment of FL.

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