Efficacy of rituximab maintenance therapy for aggressive B-cell lymphoma depends on use of rituximab in induction therapy: a meta-analysis of randomized controlled trials

Contrary to the established role of rituximab maintenance therapy for advanced follicular lymphoma with a high tumor burden,[1] it remains controversial as to whether rituximab confers advantageous effects for aggressive lymphoma when used as maintenance therapy. Recently, a cardinal study from an Austrian group reported the results of the randomized NHL13 trial, which demonstrated no significant prolongation in event-free survival (EFS) by adding rituximab maintenance for patients with aggressive lymphoma who achieved CR/CRu with R-CHOP-like regimens.[2] The interpretation of this study and previous trials featuring rituximab maintenance for aggressive lymphoma, suffers from the problem of inconsistent results, which are probably attributable to the different study designs among trials. Therefore, we conducted a meta-analysis to inquire into those features connected to the benefits associated with rituximab maintenance.

We extracted studies by searching Medline (years dating from 1960 to May 2015), The Cochrane Library, and ongoing and unpublished trials.[3,4] The terms "rituximab", "maintenance", and "lymphoma" were cross-searched. Out of the 739 candidate papers and clinical study registries, we extracted prospective randomized controlled trials where case cohorts were administered with single-agent rituximab as maintenance therapy for responding patients (PR or better) to induction treatments, with or without consolidative autologous stem-cell transplantation (ASCT), and were compared with control cohorts who were followed with observation alone. Studies focusing mainly on mantle cell lymphoma were excluded as the basic treatment scheme for mantle cell lymphoma differs to that for aggressive lymphoma. As a result, we extracted 4 relevant reports.[2-5-7] The details of these studies are shown in Table 1. Three studies targeted untreated patients and the other targeted patients with relapsed/refractory status. Induction regimens included rituximab in two studies, and not in one. The remaining study had randomized patients into two arms of those receiving rituximab-containing and non-rituximab containing regimens before maintenance therapy, thus patients in this study were divided into rituximab-naïve or not in the subgroup analysis.[6] The pooled estimates of the effect were calculated using the random effects model using the DerSimonian-Laird method with inverse-variance weighting. Hazard ratio (HR) was selected to measure responses, and adverse effects were evaluated by using risk difference (RD). Three of the studies examined event-free survival (EFS) and one examined failure-free survival (FFS), and we used these parameters to estimate treatment effects, considering the similarity of endpoints. When HR was not available for a given study, data measurement was estimated using methods described by Tierney et al.[8] We assessed the heterogeneity of the trial results using a chi-squared test of heterogeneity and the I^2 measure of inconsistency. We analyzed the data for the 1546 patients with aggressive lymphoma from the 4 studies, which comprised 773 subjects in maintenance and 773 patients in observation arms. Overall, rituximab maintenance had significant impact on EFS (HR): 0.74, 95% confidential interval (CI): 0.62 – 0.89, P=0.0015). Heterogeneity among the trials was not statistically significant (P=0.58). To investigate the factors associated with the significant impact of rituximab maintenance, we performed subset analyses according to various parameters inherent to the study design of each report. The nonuse of rituximab as part of induction treatment prior to randomization was significantly associated with better EFS in the rituximab maintenance arm (HR: 0.52, 95% CI: 0.37 – 0.77, P<0.001). In contrast, rituximab maintenance had no impact on outcomes when patients had already received rituximab in induction therapy (HR: 0.84, 95%CI: 0.67 – 1.04, P=0.11). Furthermore, rituximab maintenance had positive effects when used for first-line therapy (HR: 0.70, 95% CI: 0.57 - 0.87, P=0.0012), but not in later lines of treatment (HR: 0.87, 95% CI: 0.61 – 1.23, P=0.42). When ASCT was not included in the treatments prior to randomization, rituximab maintenance significantly improved EFS (HR: 0.71, 95% CI: 0.56 – 0.91, P=0.006), whereas this effect was not significant when ASCT was included (HR: 0.79, 95% CI: 0.59 – 1.05, P=0.10). In order to examine the relative impact of these features, we conducted meta-analyses using mixed effects models treating these parameters (the conduct of ASCT prior to rituximab maintenance, the use of rituximab in induction treatment and first-line therapy for lymphoma) as categorical moderators. Rituximab administration prior to randomization remained the sole

Table 1. Summary of abstracted studies.

Study name	Age	Histology	Setting	Status at randomization	Prior Therapy	Maintenance	End-point	No. total	Ref. (case/control)
NHL13	>18	DLBCL / FL3B	Untreated	CR/CRu	R 8 courses & CHOP-like 4 to 8 courses	375mg/m^2 q 2 months for 6 doses or 12 doses (amendment)	EFS	683 (338/345)	2
CORAL	18-65	Aggressive lymphoma	Relapsed/ Refractory	CR/CRu/PR (before ASCT)	R-ICE or R-DHAP & ASCT	375mg/m^2 q 8 weeks for 6 doses	EFS	242 (122/120)	5
LNH 98-3	18-60	DLBCL/other high grade lymphoma	Untreated	CR/CRu/PR	ACVBP or AC/ACE 4 courses & ASCT	375mg/m^2 q per week for 4 doses	EFS	269 (139/130)	7
ECOG 4494	60 or over	DLBCL	Untreated	CR/PR	CHOP 6 courses with or without R 4 to 5 courses	375mg/m^2 q 6 months for 4 doses	FFS	352 (174/178)	6

DLBCL: diffuse large B-cell lymphoma; CR: complete response; CRu: CR undetermined; R: rituximab; EFS: event-free survival; FFS: failure-free survival.

significant factor (rituximab during induction; (HR: 1.83, 95% CI: 1.08 – 3.09, P=0.025), ASCT before rituximab maintenance; (HR: 1.46, 95% CI: 0.75 – 2.83, P=0.26), rituximab as first-line therapy; (HR: 1.38, 95% CI: 0.62 – 3.07, P=0.42). This result suggests that rituximab maintenance does not have a positive effect on EFS when induction therapy contains rituximab. This result is important because rituximab is widely used as induction therapy for CD20-positive B-cell lymphoma in current practice. We also examined the side effects of rituximab maintenance therapy. Rituximab maintenance was associated with a higher incidence of neutropenia (RD: 0.06, 95% CI: 0.01 – 0.12, P=0.026) and a non-significant increase of infection (RD: 0.14, 95% CI: -0.08 – 0.36, P=0.21) in patients, compared with those in observation alone.

Considering that, in the rituximab era, the role of consolidative autologous stem-cell transplantation proved to be ambiguous even for high-risk aggressive lymphoma,[9] we should make an attempt to explore other modalities. Alternatively, identifying the beneficial features for patients from these consolidative treatments would be a realistic approach. Indeed, the NHL 13 study revealed an apparent difference of the effect of rituximab maintenance between male and female patients; only the males experienced a significant benefit, even following induction containing rituximab.[2] This effect was likewise observed in the SMARTE-R-CHOP-14 study where rituximab administration was moved to a later phase, after induction.[10] These results are attributed to higher rituximab clearance in males who are undertreated without rituximab maintenance.[11] The risk of relapse at onset (age-adjusted International Prognostic Index) or disease status after induction (CR or PR) would also affect the applicability of rituximab maintenance and should be clarified.

In conclusion, rituximab maintenance was not associated with better EFS in subjects generally. Rituximab has a positive effect on EFS only when it was not used in induction therapy, which is a rare situation nowadays, negating the practical usefulness of adding rituximab maintenance for aggressive lymphoma.

Yasuhito Nannya,[1,2] Naoe Goto,[2] Masahito Shimizu,[2] Mitsuru Seishima,[1,3] and Hisashi Tsurumi[2]

[1]Department of Transfusion Medicine, Gifu University School of Medicine, Gifu; [2]Department of Hematology, Gifu University Graduate School of Medicine, Gifu; [3]Department of Informative Clinical Medicine, Gifu University Graduate School of Medicine, Gifu, Japan

Correspondence: htsuru@gifu-u.ac.jp
doi:10.3324/haematol.2015.136622

Key words: rituximab maintenance, meta-analysis, aggressive lymphoma.

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

References

1. Salles G, Seymour JF, Offner F, et al. Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): a phase 3, randomised controlled trial. Lancet. 2011;377(9759):42-51.
2. Jaeger U, Trneny M, Melzer H, et al. Rituximab maintenance for patients with aggressive B-cell lymphoma in first remission: results of the randomized NHL13 trial. Haematologica. 2015;100(7):955-963.
3. http://www.controlled-trials.com/
4. http://www.clinicaltrials.gov/ct
5. Gisselbrecht C, Schmitz N, Mounier N, et al. Rituximab maintenance therapy after autologous stem-cell transplantation in patients with relapsed CD20(+) diffuse large B-cell lymphoma: final analysis of the collaborative trial in relapsed aggressive lymphoma. J Clin Oncol. 2012;30(36):4462-4469.
6. Habermann TM, Weller EA, Morrison VA, et al. Rituximab-CHOP versus CHOP alone or with maintenance rituximab in older patients with diffuse large B-cell lymphoma. J Clin Oncol. 2006;24(19):3121-3127.
7. Haioun C, Mounier N, Emile JF, et al. Rituximab versus observation after high-dose consolidative first-line chemotherapy with autologous stem-cell transplantation in patients with poor-risk diffuse large B-cell lymphoma. Ann Oncol. 2009;20(12):1985-1992.
8. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials. 2007;8:16.
9. Stiff PJ, Unger JM, Cook JR, et al. Autologous transplantation as consolidation for aggressive non-Hodgkin's lymphoma. N Engl J Med. 2013;369(18):1681-1690.
10. Pfreundschuh M, Poeschel V, Zeynalova S, et al. Optimization of rituximab for the treatment of diffuse large B-cell lymphoma (II): extended rituximab exposure time in the SMARTE-R-CHOP-14 trial of the german high-grade non-Hodgkin lymphoma study group. J Clin Oncol. 2014;32(36):4127-4133.
11. Pfreundschuh M, Muller C, Zeynalova S, et al. Suboptimal dosing of rituximab in male and female patients with DLBCL. Blood. 2014; 123(5):640-646.