Comment on "Rituximab maintenance for patients with aggressive B-cell lymphoma in first remission: results of the randomized NHL13 trial"

We read with interest the recent report of the NHL13 randomized trial, which evaluated a 2-year rituximab maintenance program *versus* no further treatment in patients with diffuse large B-cell lymphoma (DLBCL; n=662) or follicular lymphoma grade 3b (n=21), who had achieved a complete remission (CR) or CR unconfirmed (CRu) with 4-8 cycles of CHOP or similar chemotherapy and 8 rituximab applications.[1] Overall, NHL13 was a "negative" trial: the 3-year event-free survival (EFS) was 80.4% in the rituximab maintenance arm *versus* 76.5% in the observation arm (*P*=0.14), while 3-year overall survival (OS) remained unchanged (92.0% *vs.* 90.4%). However, subgroup analysis revealed very interesting findings. Although rituximab maintenance did not work in females at all and toxicity was higher, males enjoyed a statistically and numerically significant benefit with a 3-year EFS of 84.1% *versus* 74.4% for rituximab maintenance *versus* observation (*P*=0.03), and a 3-year progression-free survival (PFS) of 89.0% *versus* 77.6% (*P*=0.006), but again with no impact on OS. Indeed, rituximab maintenance might have overcome the reduced exposure of elderly males to rituximab due to its faster clearance,[2] similarly to what was observed in the SEXIE-R trial, where higher rituximab doses in induction obscured the adverse significance of male sex.[3] A closer look at Figure 3[1] also reveals that a potential benefit from rituximab maintenance was more prominent in good risk patients according to most International Prognostic Index (IPI) factors (stage I/II, performance status 0-1, low LDH, <2 extranodal sites). As a result, low IPI risk males had the best outcomes. A notable exception to this "rule" was the observation that the 74 patients with bone marrow (BM) involvement (approx. 10% of the total number of patients), a feature associated with adverse prognosis, gained the most significant benefit from rituximab maintenance compared to any other patient subgroup (hazard ratio 0.31, 95%CI: 0.13-0.71, *P*=0.006 *vs.* a hazard ratio of 0.90, 95%CI: 0.64-1.26, *P*=0.53 for patients without BM involvement).

Bone marrow involvement is observed in 13%-20% of patients with DLBCL.[4-8] Bone marrow can be infiltrated by large cells in slightly more than 50% of these cases.[4,7,8] This "concordant" BM involvement is independently associated with poor PFS and OS[4,7,8] and a higher rate of primary refractory disease.[7] In the remaining DLBCL patients with involved BM, the infiltration is due to the presence of small cells, resulting in "discordant" histology between the primary (nodal or extranodal) site and BM. Such cases of BM involvement are not independently associated with prognosis[4,7,8] and may reflect the presence of an underlying low-grade lymphoma component, which is usually, but not always, of follicle-center cell origin.[9] Such small cell BM populations are often, although not invariably,[9] clonally related to the original neoplastic DLBCL cell, and may potentially lead to a subsequent relapse that pursues a course resembling more to that of an indolent follicular lymphoma rather than DLBCL. In the NHL13 study, the frequency of BM involvement was 10.8%,[1] i.e. somewhat lower than expected for an unselected DLBCL series. This can be explained by the inclusion criteria, since only patients with CR/CRu were eligible. However, it would be reasonable to speculate that the study population could be enriched with cases of "discordant" bone marrow involvement, because those with "concordant" histology probably had a lower chance of achieving CR/CRu. Thus, it seems likely that patients with BM involvement might have gained the maximal benefit from rituximab maintenance due to the over-representation of cases with "discordant" histology, which might follow a more indolent, follicular lymphoma-like course. Indeed, rituximab maintenance prolonged enormously the duration of response in indolent follicular lymphomas in the PRIMA trial.[10] This hypothesis may also explain why males did not enjoy a survival benefit, despite a more than 10% increase in EFS/PFS. This hypothesis may also explain why males did not enjoy a survival benefit, despite a more than 10% increase in EFS/PFS. This would be unlikely in DLBCL, where only approximately 1 in 3 of relapsing patients ultimately survive, but might be compatible with the prolonged life expectancy of patients who experience relapses with a more indolent histology. Indeed, a minority of DLBCL patients present with indolent histology at the time of disease relapse.[4] Finally, it is important to note that EFS curves diverged after 1.5 years but reached the maximal difference after four years, due to the development of late events (which might have been represented by relapse) between four and seven years, which are rather infrequent in DLBCL.

In conclusion, the more than 10% EFS/PFS benefit of rituximab maintenance in males with DLBCL appears to be important and worthy of further testing, despite the absence of an OS benefit. However, the results of NHL13 could be more accurately estimated if data on "concordant" and "discordant" bone marrow involvement, as well as data on cell of origin (germinal center or non-germinal center), could be analyzed. Finally, histological data at the time of relapse would be helpful, as this is even more important for patients with "late" relapses.

Theodoros P. Vassilakopoulos,[1] John Apostolidis[2] and Maria K. Angelopoulou[1]

[1]Department of Haematology, Laikon General Hospital, National and Kapodistrian University of Athens; and [2]Department of Haematology, Evangelismos General Hospital, Athens, Greece

Correspondence: tvassilak@med.uoa.gr

doi:10.3324/haematol.2015.133223

Key words: rituximab maintenance, aggressive B-cell lymphoma, first remission, randomized trial.

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. 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.
2. Muller C, Murawski N, Wiesen MH, et al. The role of sex and weight on rituximab clearance and serum elimination half-life in elderly patients with DLBCL. Blood. 2012;119(14):3276-3284.
3. Pfreundschuh M, Held G, Zeynalova S, et al. Increased rituximab (R) doses and effect on risk of elderly male patients with aggressive CD20+ B-cell lymphomas: Results from the SEXIE-R-CHOP-14 trial of the DSHNHL. J Clin Oncol. 2014; 32 (15_Suppl): abstr. 8501.
4. Sehn LH, Scott DW, Chhanabhai M, et al. Impact of concordant and discordant bone marrow involvement on outcome in diffuse large B-cell lymphoma treated with R-CHOP. J Clin Oncol. 2011;29(11):1452-1457.
5. Gutierrez-Garcia G, Colomo L, Villamor N, et al. Clinico-biological characterization and outcome of primary nodal and extranodal diffuse large B-cell lymphoma in the rituximab era. Leuk Lymphoma. 2010;51(7):1225-1232.
6. Sieniawski M, Bhartia S, Wilkinson J, Proctor SJ. Incidence and outcome of patients with diffuse large B cell lymphoma with marrow involvement and preliminary experience of an adult acute lymphoblastic leukemia protocol (NEALL VI) in cyclophosphamide, doxorubicin, vincristine, and prednisolone – rituximab refractory

patients. Leuk Lymphoma. 2009;50(10):1726-1730.
7. Chigrinova E, Mian M, Scandurra M, et al. Diffuse large B-cell lymphoma with concordant bone marrow involvement has peculiar genomic profile and poor clinical outcome. Hematol Oncol. 2011; 29(1):38-41.
8. Shim H, Oh JI, Park SH, et al. Prognostic impact of concordant and discordant cytomorphology of bone marrow involvement in patients with diffuse, large, B-cell lymphoma treated with R-CHOP. J Clin Pathol. 2013;66(5):420-425.
9. Kremer M, Spitzer M, Mandl-Weber S, et al. Discordant bone marrow involvement in diffuse large B-cell lymphoma: Comparative molecular analysis reveals a heterogeneous group of disorders. Lab Invest. 2003;83(1):107-114.
10. 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.

© Ferrata Storti Foundation