haematologica
Journal of the Ferrata Storti Foundation

More is not always better, sometimes it is just more

by Antonio Salar Silvestre

Received: February 7, 2024.
Accepted: March 20, 2024.

Citation: Antonio Salar Silvestre. More is not always better, sometimes it is just more. Haematologica. 2024 Mar 28. doi: 10.3324/haematol.2024.285019 [Epub ahead of print]

More is not always better, sometimes it is just more.

Antonio Salar Silvestre

Lymphoma Unit, Department of Hematology, Hospital Clínico Universitario Virgen de la Arrixaca, Murcia, Spain

Correspondence.

Antonio Salar Silvestre

Lymphoma Unit.

Department of Hematology.

Hospital Clínico Universitario Virgen de la Arrixaca.

Ctra. Madrid-Cartagena s/n. CP 30120. Murcia. Spain.

Tlfno(+34)968369532. Fax (+34)968369088.

Email: antonio.salar2@carm.es

Disclosures.

AS has received honoraria from Beigene, Incyte, Ipsen and Roche. These relationships do not raise a conflict of interest regarding the published work.

Authorship contributions.

AS designed and wrote the manuscript, and reviewed and approved the final version of the manuscript.

In this issue of Haematologica,[1] Stathis et al report on the results of an international phase 2 study of chlorambucil and subcutaneous (SC) rituximab as first line systemic treatment in extranodal marginal zone lymphomas of mucosa-associated lymphoid tissue (MALT) lymphomas. The authors conclude that although induction with chlorambucil and SC rituximab is safe, it does not improve responses, although the addition of maintenance with SC rituximab can prolong long-term disease control.

MALT lymphomas are considered indolent lymphomas, but recently published studies settle that MALT lymphoma carries a modest but statistically significant compromise to life expectancy.[2] MALT lymphoma-specific mortality is typically very low in patients with cutaneous (now recognized as primary cutaneous marginal zone lymphoproliferative disorder in the International Consensus Classification)[3] or localized gastric involvement. However, non-gastric MALT lymphomas and those with stage II to IV are associated with a higher risk of lymphoma-related mortality. Therefore, the treatment of MALT lymphoma deserves further investigation through well-designed clinical trials.

Despite improved response rates achieved with first-line rituximab-containing regimens in MALT lymphoma, relapses still persist once the treatment is completed. For improving outcome, one strategy could be deepening the intensity of the response with the potential elimination of residual disease through more active immunochemotherapies and the other to control potential residual lymphoma cells by extending treatment over time with the use of maintenance therapy once a response has been achieved with prior induction therapy.

The IELSG38 is the first prospective clinical trial which specifically assessed the use of SC rituximab in MALT lymphomas. The SPARKTHERA and SABRINA trials have demonstrated that a fixed dose of 1,400 mg of SC rituximab has noninferior pharmacokinetics and efficacy in follicular lymphoma than BSA-adjusted intravenous (IV) rituximab. Additionally, a more efficient delivery of rituximab shows greater satisfaction and time saving for patients.[4,5] Unfortunately, the IELSG38 trial has showed that chlorambucil plus SC rituximab did not improve the complete remission (CR) rate at end of induction (57%), which was the primary end-point, in comparison with previously observed results in the IELSG19 trial (63.4% with chlorambucil, 78.8% with chlorambucil plus IV rituximab).[6] Reasons that might have contributed to this fact are

the slightly greater risk in the IELSG38 patients, despite identical inclusion criteria as in the IELSG19, as well as the utilization of updated response definitions in the IELSG38. Regarding this last point, in the MALT lymphoma cohort of the GALLIUM trial,[7] the CR rate with rituximab-chemotherapy was very different when evaluated by CT (17.7%) compared to when PET was used (59.4%). In any case, as the authors mentioned, selection of this primary outcome was a serious weakness.

Similarly to IELSG19, the CR rates at 6 months in the IELSG38 with chlorambucil plus SC rituximab were remarkably different between patients with gastric (84%) versus non-gastric MALT lymphomas (46%). Although overall CR rates progressively improved with SC rituximab maintenance (70% at end of SC rituximab maintenance), this improvement was more relevant in patients with non-gastric MALT. Furthermore, it must be taken into account that there is great disparity in access to SC rituximab across countries and centers. If we consider that switching from IV to SC rituximab was associated with non-inferiority results regarding response or survival, it is reasonable to infer that switching from SC to IV maintenance will result in similar outcomes and might be an option for those centers where there is no access to SC rituximab.

More is not always better. Is the opposite true? In the phase 2 MALT2008-01 trial,[8] CR rates achieved with bendamustine and IV rituximab (BR) were above 95% at end of therapy, and the high efficacy of this regimen in MALT lymphomas has been confirmed by an international retrospective study including 237 patients, with a CR above 80%.[9] Comparisons between these 2 studies and others, including the IELSG38, should be made with caution. But, in any case, 6 cycles of BR, that is, 6 months of treatment, provides CR rates above 80%, and without observing differences between gastric and non-gastric MALT. And to top it off, in those rapid responders, only 4 cycles of BR might be enough, and, therefore, this limits the time in treatment to only 4 months.

The complete IELSG38 treatment program, that is, induction plus 2 years of maintenance, provides a 5-year event free survival and progression free survival (PFS) of 84% and 87%, respectively, both superior to those achieved in the IELSG19. It may be worth noting that, more is better in the IELSG38, at least in terms of quality of response and PFS. Patients achieving CR had more prolonged remissions and, considering the different 5-year PFS, SC rituximab maintenance may be particularly useful for patients in PR, regardless of the initial site of disease.

Finally, the authors addressed the essential question of safety. In the GALLIUM study, rituximab/obinutuzumab with chemotherapy (CVP, CHOP or bendamustine) followed by rituximab/obinutuzumab maintenance for 2 years was associated with a higher toxicity rate than expected. In the IELSG19 trial, patients treated with the combination arm showed higher hematologic toxicities than those treated with chlorambucil or rituximab alone. As expected, hematologic toxicity was frequent in the IELSG38 trial, but not unexpected safety signals were observed during induction or maintenance. Overall, the treatment was well-tolerated.

In the near future, other ongoing molecules under investigation such as BTK inhibitors, both covalent and non-covalent, with activity in relapsed MALT lymphoma must go ahead to the first line. In fact, the ongoing IELSG47/MALIBU phase 2 trial is exploring efficacy and safety of rituximab plus ibrutinib in untreated MZL. Nonetheless, results in MALT lymphomas are yet to be presented and are eagerly awaited. Additional therapies with bispecific anti-CD20xCD3 antibodies and CAR-T therapy for relapsed disease represent new strategies to reach the ultimate goal of increasing the rate of cure for patients with intermediate or high-risk MALT lymphomas.

In my view, chemotherapy plus rituximab remains the standard in first-line for symptomatic MALT lymphomas requiring systemic treatment. Bendamustine as a chemotherapy backbone achieves fast and deep responses which provide prolonged PFS although no impact on OS has yet been demonstrated. Bendamustine-containing regimens should be used with caution not only because T-cell depletion increases the risk of infection, especially in elderly patients or in those with comorbidities, but also because it could have some impact on the few MALT lymphoma patients who may require subsequent therapies mediated by T-cells such as CAR T-cells or bispecifics monoclonal antibodies. Furthermore, for elderly or less fit patients, chlorambucil plus rituximab might be a sensible option, with SC rituximab maintenance in those non achieving CR with the induction. For frail or unfit patients, either monotherapy with rituximab or chlorambucil are adequate options, considering that OS is not statistically affected. Finally, I would like to acknowledge the IELSG for this major international effort due to the rarity of the disease. International networks and close collaborations are crucial to further improve treatment strategies for MALT lymphoma patients.

References

1. Stathis A, Pirosa MC, Orsucci L, et al. IELSG38: Phase 2 trial of frontline chlorambucil plus subcutaneous rituximab induction and maintenance in MALT lymphoma. Haematologica. xxx
2. Cerhan JR, Habermann TM. Epidemiology of Marginal Zone Lymphoma. Ann Lymphoma. 2021;5:1.
3. Campo E, Jaffe ES, Cook JR, et al. The International Consensus Classification of Mature Lymphoid Neoplasms: a report from the Clinical Advisory Committee. Blood. 2022;140(11):1229-1253.
4. Salar A, Avivi I, Bittner B, et al. Comparison of subcutaneous versus intravenous administration of rituximab as maintenance treatment for follicular lymphoma: results from a two-stage, phase IB study. J Clin Oncol. 2014;32(17):1782-1791.
5. Davies A, Merli F, Mihaljevic B, et al. Pharmacokinetics and safety of subcutaneous rituximab in follicular lymphoma (SABRINA): Stage 1 analysis of a randomised phase 3 study. Lancet Oncol. 2014;15(3):343-352.
6. Zucca E, Conconi A, Martinelli G, et al. Final results of the IELSG-19 randomized trial of mucosa-associated lymphoid tissue lymphoma: Improved event-free and progression-free survival with rituximab plus chlorambucil versus either chlorambucil or rituximab monotherapy. J Clin Oncol. 2017;35(17):1905-1912.
7. Herold M, Hoster E, Janssens A, et al. Immunochemotherapy and Maintenance With Obinutuzumab or Rituximab in Patients With Previously Untreated Marginal Zone Lymphoma in the Randomized GALLIUM Trial. Hemasphere. 2022;6(3):E699.
8. Salar A, Domingo-Domenech E, Panizo C, et al. Long-term results of a phase 2 study of rituximab and bendamustine for mucosa-associated lymphoid tissue lymphoma. Blood. 2017;130(15):1772-1774.
9. Alderuccio JP, Arcaini L, Watkins MP, et al. An international analysis evaluating frontline bendamustine with rituximab in extranodal marginal zone lymphoma. Blood Adv. 2022;6(7):2035-2044.

Table 1. First-line chemoimmunotherapies for MALT lymphomas

Author, year	Study phase	Regimen	Number of patients	Median age (range), years	Gastric origin (%)	Stage III-IV (%)	ORR (CR) EOI (%)	5-y PFS (%)	5-y OS (%)
Zucca, 2017	3	Chorambucil Rituximab Chlorambucil/Rituximab	131 138 132	60 (26-80) 62.5 (27-81) 59.5 26-79()	43.5 44.2 40.1	40.6 45.6 44.7	85.5 (63.4) 78.3 (55.8) 94.7 (78.8)	59 57 72	89 92 90
Salar, 2017	2	Bendamustine/Rituximab	60	62 (26-84)	33	34	100 (98)	92.8*	100*
Alderuccio, 2022	Retrospective	Bendamustine/Rituximab	237	63 (21-85)	17.3	75.5	93.2 (81)	80.5	89.6
Stathis, 2024	2	Chlorambucil/Rituximab** + Rituximab maintenance**	112	66 (32-86)	32	56	86 (57)	87	93

ORR: overall response rate; CR: complete remission; EOI: end-of-induction; PFS: progression free survival; OS: overall survival; *: at 7 years; **subcutaneous rituximab