More is not always better, sometimes it is just more

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In this issue of *Haematologica*, Stathis *et al.*[1] report on the results of an international phase II 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, even if the addition of maintenance with SC rituximab can prolong long-term disease control.

MALT lymphomas are considered indolent lymphomas, but recently published studies have confirmed that they have a modest but statistically significant negative impact on 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-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 the 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 to deepen the intensity of the response with the potential elimination of residual disease through more active immunochemotherapies; another could be 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 non-inferior pharmacokinetics and efficacy in follicular lymphoma to BSA-adjusted intravenous (IV) rituximab. Additionally, a more efficient delivery of rituximab results in greater patient satisfaction and is also time-saving for them.[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) (Table 1).[6] Reasons that might have contributed to this 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 computed tomography (17.7%) compared to when positron emission tomography was used (59.4%). In any case, as the authors mentioned, selection of this primary outcome was a serious weakness. Similarly to the IELSG19, the CR rates at six months in the IELSG38 with chlorambucil plus SC rituximab differed remarkably between patients with gastric (84%) *versus* non-gastric (46%) MALT lymphomas. 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 different countries and centers. If we consider that switching from IV to SC rituximab was associated with non-inferior 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. But is the opposite true? In the phase II MALT2008-01 trial,[8] CR rates achieved with bendamustine and IV rituximab (BR) were >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 >80% (Table 1).[9] Comparisons between these 2 studies and others, including the IELSG38, should be made with caution. But, in any case,

Table 1. First-line chemoimmunotherapies for mucosa-associated lymphoid tissue lymphomas.

Author, year	Study phase	Regimen	N of patients	Median age in years (range)	Gastric origin, %	Stage III-IV, %	ORR (CR) EOI, %	5-yr PFS,%	5-yr OS, %
Zucca *et al.*, 2017[6]	III	Chorambucil	131	60 (26-80)	43.5	40.6	85.5 (63.4)	59	89
		Rituximab	138	62.5 (27-81)	44.2	45.6	78.3 (55.8)	57	92
		Chlorambucil/ rituximab	132	59.5 (26-79)	40.1	44.7	94.7 (78.8)	72	90
Salar *et al.*, 2017[8]	II	Bendamustine/ rituximab	60	62 (26-84)	33	34	100 (98)	92.8*	100*
Alderuccio *et al.*, 2022[9]	Retrospective	Bendamustine/ rituximab	237	63 (21-85)	17.3	75.5	93.2 (81)	80.5	89.6
Stathis *et al.*, 2024[1]	II	Chlorambucil/ rituximab** plus rituximab maintenance**	112	66 (32-86)	32	56	86 (57)	87	93

N: number; ORR: overall response rate; CR: complete remission; EOI: end-of-induction; yr: year; PFS: progression-free survival; OS: overall survival. *At 7 years. **Subcutaneous rituximab.

6 cycles of BR (i.e., 6 months of treatment) provide CR rates >80%, without observing any differences between gastric and non-gastric MALT. And to top it off, in those rapid responders, only 4 cycles of BR might be enough, thus limiting duration of treatment to only four months. The complete IELSG38 treatment program (i.e., induction plus 2 years of maintenance) provides a 5-year event-free survival and progression-free survival (PFS) of 84% and 87%, respectively, which are 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 the 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 partial response (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 two 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 both covalent and non-covalent Bruton's tyrosine kinase inhibitors, with activity in relapsed MALT lymphoma must be brought forward to the first line. In fact, the ongoing IELSG47/MALIBU phase II trial is exploring efficacy and safety of rituximab plus ibrutinib in untreated marginal zone lymphoma. Nonetheless, the eagerly awaited results in MALT lymphomas are yet to be presented. Additional therapies with bispecific anti-CD20x-CD3 antibodies and chimeric antigen receptor (CAR) T-cell 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 first-line approach 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 bispecific monoclonal antibodies. Furthermore, for elderly or less fit patients, chlorambucil plus rituximab might be a sensible option, with SC rituximab maintenance in those not 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.

Disclosures

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