Do We Need Maintenance with Anti-CD20 Antibody after First-Line Therapy for All Newly Diagnosed Follicular Lymphoma Patients?

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Introduction
Follicular lymphoma (FL) is one of the most common subtypes of lymphoma in Western countries, accounting for 10-20% of all newly diagnosed non-Hodgkin’s lymphomas. Clinical course of FL is typically indolent, with impressive responses to initial treatments. Nevertheless, frequent relapses with shorter remission duration occur that need additional therapeutic interventions and increase the risk of drug resistance.

Treatment options for treatment-naive or recurring follicular lymphoma patients are still controversial, ranging from watch and wait to hematopoietic stem-cell transplantation. When a treatment is indicated, chemotherapy is usually prescribed. In most recent years, the advent of anti CD20 monoclonal antibody Rituximab (R) has dramatically changed the approach to this disease, and immunotherapy is at present considered the standard of care for patients diagnosed with high tumor burden FL, leading at advances in Progression Free Survival (PFS) and Overall Survival(OS)1-3.

Discussion
In order to prolong remission duration, the use of maintenance strategies after the first treatment has been considered over a long time. The use of interferon was first evaluated, showing benefits in terms of duration of remission and survival3; however, the safety profile of the drug and the low manageability of treatment has led most physicians to abandon this treatment option.

The availability of rituximab as an effective and low toxic single agent has suggested to explore the possibility to use it not only to improve efficacy of chemotherapy in first line therapy, but also to delay progression after initial treatment reflecting the ideal maintenance strategy which involve clinical benefit, good tolerance and convenient administration.

The PRIMA trial clearly showed that rituximab maintenance in patients achieving a response to initial chemoimmunotherapy results in an improved outcome in terms of prolonged PFS and made a step forward in the management of patients with FL5. However, one important question that can be raised is whether this approach is really needed for all patients with FL or if some of them could benefit from a risk adapted maintenance strategy, intensifying treatment in those recognized at high risk of recurrence, and reducing it in patients at lower risk. For example, in patients with low tumor burden who received front line rituximab, the RESORT study clearly showed that retreatment with rituximab instead rituximab maintenance was associated with an excellent outcome (86% chemotherapy free at 3 years), lack of Quality of Life difference and fewer rituximab doses required.6

Recently, response to therapy assessed either with fluorodeoxyglucose-positron emission tomography (PET) or with highly sensitive molecular techniques targeting the t(14;18) chromosomal translocation (Minimal residual disease — MRD) have been suggested as important prognostic factors and are both identified as pivotal tools to achieve the goal of personalized treatment. The predictive value of PET and MRD is clearly recognized based on a large bulk of published evidence, and might be used to better tailoring post induction treatment in patients achieving satisfactory response with rituximab containing regimens.

Post-induction FDG-PET provides powerful prognostic information in FL. About 80-85% of patients achieve a complete metabolic response (CMR) following immunochemotherapy and have an excellent outcome irrespective of whether rituximab maintenance is given (~95% survival at 6 years). In contrast, the ~15-20% of patients who fail to achieve a CMR are expected to have a significantly worse outcome.7, 8

Several studies indicate that, regardless to the treatment administered, the absence in the bone marrow and peripheral blood of neoplastic cells bearing the bcl-2/IgH rearrangement during the follow-up was strongly associated with a reduced risk of recurrence, clearly suggesting the need for MRD detection in FL9-12

In the year 2012 the Fondazione Italiana Linfomi (FIL) launched the prospective randomized FOLL12 trial, with the aim of verifying
whether combining clinical response assessed on FDG-PET scan and molecular response measured through MRD detection could permit to single out patients at different risk of progression and to consequently modulate maintenance.

In April, 2018 the planned accrual has been reached, with the accrual of 807 cases. Patients randomized to standard Arm received two years of rituximab maintenance according to the PRIMA schedule. Those in the experimental Arm and at low risk defined by post induction PET and MDR negativity, did not receive any further maintenance; however, 4 weekly doses of rituximab were allowed in case of MDR positivity during follow-up, for a maximum of three re-treatments. On the contrary, patients at high risk (post induction PET positive), received intensified maintenance with $^{90}$Y Ibritumomab Tiuxetan followed by rituximab maintenance for 2 years.

Some very preliminary analyses of the study will be presented at conference site.

**Conclusion**

Despite rituximab maintenance has shown its beneficial effect in prolonging PFS, its ability in improving OS is still questionable. In this context we believe that the results of the FOLL12 study would provide a more rationale use of currently available diagnostic and therapeutic resources, thus offering the opportunity of better tailoring maintenance therapy in patients responding to first line chemoimmunotherapy.

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