EDITORIAL

Help or hindrance? Rituximab maintenance and COVID

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In this retrospective study across six Spanish centers, Serna *et al.*[1] explore the impact of rituximab maintenance during the SARS-CoV-2 (COVID) pandemic. Immunocompromised people had, and still have, a higher risk of complications with COVID infection. Not surprisingly, hematologic malignancy patients treated with B-cell depleting therapies suffered disproportionately due to the lack of antibody response, particularly at the height of the pandemic before vaccines were available. It is expected that the depth of immunosuppression and the duration of suppression contribute to increased risk.

To explore this further, Serna *et al*. analyzed 215 patients, 178 (83%) with follicular lymphoma (FL) and 37 (17%) with mantle cell lymphoma (MCL) who began maintenance rituximab after induction chemoimmunotherapy with rituximab-bendamustine or RCHOP/RCVP. The maintenance had to be received from March 2000 to March 2022, during the height of the COVID pandemic, although they could have started maintenance prior to March 2020. Of note, few patients received bendamustine-based induction (see Table 1[1]). In the FL group, only 14 (7%) were treated with BR induction, while 164 (76%) received cyclophosphamide-containing regimens. The MCL cohort included only 6 (3%) patients treated with bendamustine and 31 (14%) patients with cyclophosphamide regimens. Those receiving RCVP due to cardiac co-morbidities totaled 6 FL and 2 MCL.

The study had a number of interesting findings relating to COVID in the setting of B-cell depleting antibodies, including the expected low seroconversion rate to COVID vaccine (22%), 44% maintenance interruption, and 22% maintenance discontinuation. The most notable finding, however, was the impact of the induction chemotherapy itself on the outcomes during the maintenance phase. The authors analyzed this directly (see Figure 1B[1]) and by an inverse probability of treatment weighting (IPTW) ATE analysis performed according to the type of first-line treatment (bendamustine- or cyclophosphamide-containing regimens) to adjust for potential imbalances in other prognostic variables between both groups in SARS-CoV-2 survival (see Figure 2B[1]). The results were the same in both analyses. Patients previously exposed to bendamustine had a far higher rate of COVID-related infection, hospitalization, Intensive Care Unit admission and death. Given the prolonged T-cell suppression of bendamustine and the need for T-cell response during the later phases of viral clearing, this is not an entirely unexpected result. However, we should note a comparison with those not receiving maintenance was not performed.

How should this study be put into context? The authors mention several other indolent front-line studies all performed far before COVID. The two randomized trials, Stil[2] and Bright,[3] showed non-inferiority for R-bendamustine compared to R-CHOP/R-CVP and, in fact, had improved and clinically meaningful progression-free survival (PFS), albeit without overall survival benefit, fewer infections, and better tolerability with respect to factors such as alopecia and neuropathy. In contrast, the Gallium trial[4] did suggest more infections for bendamustine compared to CHOP irrespective of rituximab or obinutuzumab. Real-world analysis[5] also suggested more infections with benadmustine-based induction. Thus, overall, it is likely the overall benefit still favors R-bendamustine, though the Spanish centers clearly prefer RCHOP for their patients.

Moreover, as Serna *et al*. note,[1] they did not compare their results to those receiving induction chemoimmunotherapy without maintenance rituximab. After first-line induction, the benefit of rituximab maintenance for FL has no impact on OS, and the PFS benefit must be weighed carefully in a disease we are treating for control and palliation.[6] The Serna study adds indirect evidence that rituximab maintenance may be harmful during a pandemic and with continued circulation of the COVID virus, as it adds ongoing immunosuppression during a time when B-cell recovery is expected 6-12 months after the last dose of induction rituximab. With an expanding list of potent treatment options beyond first line, maintenance rituximab is of decreasing value.

Mantle cell lymphoma is a different disease, and the calculus is different for those with the virulent form of MCL. Specifically, while maintenance rituximab did not improve

PFS and OS in a subset study of the prospective Stil trial,[7] some 'real-world' retrospective analyses found maintenance rituximab added substantial value.[8,9] Moreover, maintenance rituximab is currently standard after first-line therapy followed by consolidative autologous stem cell transplant[10] or as part of an induction incorporating Bruton tyrosine kinase inhibitors.[11] We should not group these MCL patients together with FL patients when making decisions about maintenance rituximab.

New therapeutics such as chimeric antigen receptor T-cell therapy and bispecific antibodies will increasingly be used for indolent lymphomas. Yet we must be mindful of the prolonged immunosuppression of both B and T cells, especially if we incorporate these agents into earlier lines of therapy in the future where they might be used for an increasingly larger proportion of patients. Serna *et al*. demonstrate we also need to pay attention to the risk of infection and not only to the benefits of such a therapeutic approach.

Finally, what take home message should we have for our patients? While the COVID vaccination seroconversion rates were low (22%), many of these patients would have already received their induction chemoimmunotherapy prior to the availability of vaccines in early 2021. Although not detailed in the paper, the conversion rate must be presumed higher if vaccination precedes chemoimmunotherapy induction. In light of ongoing vaccine hesitancy in general and COVID complacency, it is imperative we, the providers, advocate for vaccination against COVID and other viruses prior to the start of therapy whenever feasible. We can also advise prompt treatment of COVID infection with antivirals and prophylaxis with monoclonal antibody when available and appropriate. We have an opportunity and a mandate to save lives.

Disclosures

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