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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 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 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 (Table 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 zero conversion 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 (figure 1 B) 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-CoV2 survival (figure 2B). The results were the same in both analyses. Patients previously exposed to bendamustine had a far higher rate of COVID related infection, hospitalization, ICU 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 this 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 Galliuim 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, 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 six to 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.

MCL 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 BTKinhibitors. (11) We should not lump these MCL patients in with FL patients when make decisions about maintenance rituximab.

New therapeutics such as CAR-T and bispecific antibodies will increasingly be used for indolent lymphomas. Yet, we much 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 need to pay attention to the benefit *and* the risk of infection.

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 when ever feasible. We can also counsel regarding 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.

References:

1. Serna A, Navarro V and Iacoboni G, et al. Rituximab maintenance after bendamustine-based treatment for follicular lymphoma and mantle cell lymphoma may exert a negative influence on SARS-CoV-2 infection outcomes. Haematologica. xxx
2. . Rummel MJ, Niederle N, Maschmeyer G, et al. Bendamustine plus Rituximab versus CHOP plus Rituximab as First-Line Treatment for Patients with Indolent and Mantle-Cell Lymphomas: An Open-Label, Multicentre, Randomised, Phase 3 Non-Inferiority Trial. Lancet. 2013;381(9873):1203-1210.
3. Flinn IW, van der Jagt R, Kahl BS, et al. Randomized Trial of Bendamustine-Rituximab or RCHOP/ R-CVP in First-Line Treatment of Indolent NHL or MCL: The BRIGHT Study. Blood. 2014;123(19):2944-2952
4. Hiddemann W, Barbui AM, Canales MA, et al. Immunochemotherapy With Obinutuzumab or Rituximab for Previously Untreated Follicular Lymphoma in the GALLIUM Study: Influence of Chemotherapy on Efficacy and Safety. J Clin Oncol. 2018;36(23):2395-2404.
5. Olszewski AJ, Butera JN, Reagan JL, Castillo JJ. Outcomes of bendamustine- or cyclophosphamide-based first-line chemotherapy in older patients with indolent B-cell lymphoma. Am J Hematol. 2020;95(4):354-361.
6. Bachy E, Seymour JF, Feugier P, et al. Sustained Progression-Free Survival Benefit of Rituximab Maintenance in Patients With Follicular Lymphoma: Long-Term Results of the PRIMA Study. J Clin Oncol. 2019;37(31):2815-2824.
7 Rummel MJ, Knauf W, Goerner M, et al. Two years rituximab maintenance vs. observation after first-line treatment with bendamustine plus rituximab (B-R) in patients with mantle cell lymphoma: First results of a prospective, randomized, multicenter phase II study (a subgroup study of the StiL NHL7-2008 MAINTAIN trial). J Clin Oncol. 2016;34(15 suppl):7503.
8. Martin P, Cohen JB, Wang M, et al. Treatment Outcomes and Roles of Transplantation and Maintenance Rituximab in Patients With Previously Untreated Mantle Cell Lymphoma: Results From Large Real-World Cohorts. J Clin Oncol. 2023 Jan 20;41(3):541-554.
8. Wang Y, Larson MC, Kumar A, et al. Benefit of rituximab maintenance after first-line bendamustine-rituximab in mantle cell lymphoma. J Clin Oncol. 2024;42(16 suppl):7006.
10. Sarkozy C, Thieblemont C, Oberic L, et al. Long-Term Follow-Up of Rituximab Maintenance in Young Patients With Mantle-Cell Lymphoma Included in the LYMA Trial: A LYSA Study. J Clin Oncol. 2024;42(7):769-773.
11. Dreyling M, Doorduijn J, Giné E, et al. Ibrutinib combined with immunochemotherapy with or without autologous stem-cell transplantation versus immunochemotherapy and autologous stem-cell transplantation in previously untreated patients with mantle cell lymphoma (TRIANGLE): a three-arm, randomised, open-label, phase 3 superiority trial of the European Mantle Cell Lymphoma Network. Lancet. 2024;403(10441):2293-2306.