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COMMENTARY

COVID-19 infection in primary central nervous system lymphoma treatment: Who is most at risk?

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Commentary on: Ferreri et al. Impact of SARS-CoV2 infection on the outcome of primary CNS lymphoma treatment: a study of the International PCNSL Collaborative Group. Br J Haematol. 2022 (Online ahead of print). Manuscript ID 1098.

In their paper, Ferreri et al.[1] from the International PCNSL Collaborative Group report on the clinical outcomes of patients with primary central nervous system lymphoma (PCNSL) and SARS-CoV-2 infection.[2] This retrospective observational study comprises an impressive cohort of 91 patients given the rarity of this lymphoma subtype. In this study, 70% were infected with SARS-CoV-2 close to or during first-line treatment, 23% in follow up and 7% during salvage therapy. Among them, 16 participants were vaccinated, with the majority (88%) also infected during first-line treatment.

There are several striking findings in this study. Hospitalisation rates for COVID-19 pneumonia were highest in those infected whilst undergoing systemic anti-cancer treatment (Figure 1). All 23 deaths resulting from COVID-19 or related infections also occurred in this group. The unvaccinated recipients treated with high-dose cytarabine, or a higher cumulative dose of steroid (>100 mg dexamethasone equivalent) or prolonged steroid use (more than two weeks) were associated with an increased risk of COVID-19 pneumonia. The other significant observation in this study is that 21/26 patients who had

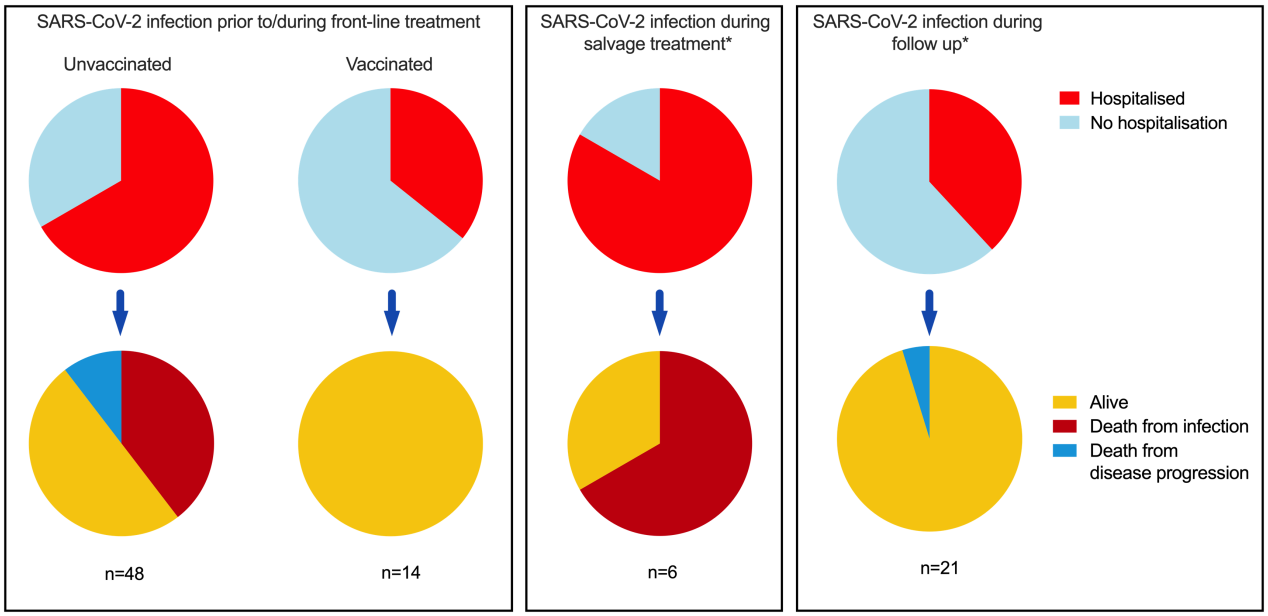

FIGURE 1 Clinical outcomes of COVID-19 in patients with primary central nervous system lymphoma. * One participant was vaccinated within each group.

viral persistence died of infection or lymphoma progression. Three of five individuals who recommenced treatment despite viral persistence, also succumbed to infection.

The number of vaccinated patients was low, and assessment of vaccine efficacy is complicated by the simultaneous administration of therapeutic COVID-19 medicines. However, the protective effect of vaccination is strongly suggested by the following observations: 36% of 14 vaccinated patients developed pneumonia compared to 68% of 47 unvaccinated patients following COVID-19 infection prior to/during first-line treatment; all 16 vaccinated patients cleared the virus and resumed chemotherapy with a median delay of 8 days compared to 25 days in unvaccinated individuals; no vaccinated individuals died of COVID-19.

Several studies have demonstrated impaired antibody responses to SARS-CoV-2 vaccination in lymphoma but lack direct correlation with clinical outcomes.[3,4] The Group assessed seroconversion in 30 participants after SARS-CoV-2 infection and noted 61% seroconversion in 18 vaccinated patients and 50% in 12 unvaccinated patients. The low level of seroconversion in the unvaccinated patients might be due to the early time point at which antibodies were measured after infection, that is, median 10 days (range 1–244 days). Assuming IgG antibodies were measured, seroconversion might take 2 weeks or longer to develop after primary infection.[5] The relatively low rate of seroconversion in vaccinated patients is consistent with previous reports in lymphoma.[4] However, it is noteworthy that despite the lack of detectable antibodies, this group had better outcomes compared to the unvaccinated group. The other interesting observation is that prior rituximab administration, which profoundly depletes B cells and abrogates the antibody response, did not correlate with inferior clinical outcomes. This lends support to current views which suggest that T-cell responses are important in reducing the severity of SARS-CoV-2 infection.[6]

The negative impact conferred by prolonged or high cumulative steroid dosing on COVID-19 recovery has also been observed in other diseases where prolonged corticosteroid therapy is administered.[7] Corticosteroids can directly suppress the initiation of T-cell responses upon SARS-CoV-2 infection to reduce T-cell costimulation and expansion.[8] Likewise, high-dose cytarabine has also been shown to be directly cytotoxic to T cells *in vitro*.[9]

Despite the relatively favourable outcomes observed in the vaccinated group, there is no room for complacency in managing SARS-CoV-2 infection in this population. Among 14 vaccinated individuals, 36% developed pneumonia and required hospitalisation, which would have delayed systemic anti-cancer treatment and increased the risk of disease progression. The study compellingly shows that viral clearance is the strongest positive prognostic indicator on multivariable analysis. Thus, these patients, and others with lymphoma who are undergoing highly immunosuppressive treatments, should be prioritised for rapid deployment of therapeutic COVID-19 medicines such as combined administration of anti-viral and monoclonal antibodies against SARS-CoV-2 if they are infected during treatment, to increase the speed of virus eradication, and enable subsequent resumption of systemic anti-cancer treatment.

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