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Commentary

Favourable outcomes for young lymphoma patients but age-old problems persist

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In this retrospective cohort study, Lamure and colleagues provide a timely summary of outcomes in 89 patients with lymphoma who were hospitalized with COVID-19 across three French regions [1]. The 30-day mortality of almost 30%, rising to 55% in those aged over 70 years, is sobering. It is a little reassuring that patients younger than age 70 have a 30-day survival of 88%, comparable to population risk of mortality from COVID-19 in hospitalised patients in France and Germany [2]. However, this comparison is not as robust as a case-control study with locally admitted patients matched for gender, age, weight and co-morbidity.

The urgent need to address the impact of the COVID-19 pandemic on cancer patients has led to the development of guidelines from Europe [3], the United States [4] and Australia [5], largely based on expert opinion and early Chinese data. The heterogeneity of patients with cancer, potential for further mutation of the SARS-CoV-2 virus and biological differences between patient groups in different countries are barriers to generalizing from early data. Indeed, the original publication [6] only included a single patient with lymphoma.

The study by Lamure and colleagues confirms some findings of earlier reports, such as the association between age and hypertension with higher mortality. Conversely, the lack of any association with gender, body mass index or smoking status is surprising, and we note all six patients with death specifically attributed to COVID-19 were male. It is possible that the significant immunosuppressive effects of lymphoma and associated therapies on immunity act as an equaliser, and that a larger data set may be necessary to reveal the less pronounced influence of these factors. In addition to clinical risk factors for mortality in COVID-19 patients, levels of D-dimer and fibrin degradation products have been shown to correlate with risk of death [7], with lower rates of mortality reported in patients who received heparin-based anticoagulation [8]. One limitation of this study is the lack of D-dimer reporting. This is notable in light of the relatively high rate of thrombocytopenia (39%), which may limit the use of heparins in these patients.

COVID-19 is phenotypically diverse, with a spectrum of disease from asymptomatic carriage to fulminant respiratory failure. Evidence is urgently needed to guide risk-based selection of therapy for patients with lymphoma and enhance prognostication to identify those patients with a history of lymphoma with COVID-19 who warrant close telehealth monitoring or hospital admission. This study identified a significantly higher mortality in the patients classified as having relapsed/refractory disease. The requirement for patients to have had at least 2 lines of prior therapy to be classified as having relapsed/refractory disease is unorthodox, however, and these more heavily pre-treated patients are already at increased risk of lymphoma- and treatment-related mortality.

Although bendamustine therapy within one year is associated with an increased mortality in this study, the authors suggest that this is due to a strong association between relapsed/refractory disease and bendamustine use. Nonetheless, we feel that the effect of bendamustine therapy may be clinically meaningful with its notable immunosuppressive effect well beyond two years [9]. Even when adjusted for other factors including relapsed/refractory status of the lymphoma, recent bendamustine use remains a risk factor for mortality with a hazard ratio of 3.20 (1.33–7.72). An Australian and New Zealand consensus guideline on the management of lymphoma in the COVID-19 era [5] advises caution on the use of bendamustine containing regimens and this study supports this recommendation.

No increase in mortality was noted in patients with a history of anti-CD20 immunotherapy or autologous stem cell transplantation in this study. A recent American Society for Clinical Oncology guideline [4] counsels against the use of maintenance anti-CD20 therapy in indolent lymphoma due to an equivocal benefit in overall survival and the potential to impair the B-cell immune response to SARS-CoV-2 infection. While a larger body of evidence is needed, the study by Lamure et al. does suggest that the effect of anti-CD20 therapies on the immune response against SARS-CoV-2 may be less than previously thought. Nonetheless, the authors raise a sobering point – that patients with a history of haematological malignancy or who have received therapy which impair the humoral immunity may be poor responders to a future SARS-CoV-2 vaccine.

In a disease characterised by rapid deterioration requiring intubation in some patients, this study may provide clinicians with some

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guidance in patient selection for monitoring in hospital vs home. In addition to known risk factors of older age and hypertension, the study suggests the influence of additional lymphoma-specific risk factors of relapsed/refractory disease and recent bendamustine use. The clinical care of these high-risk patients must include strict education around the merits of quarantine, vigilant hygiene, strict social distancing, and mask use.

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