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Maintaining a fit T-cell compartment: lymphoma treatment sequencing in the era of CAR T-cell therapies

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We welcome the recent publication by Trotman *et al.* presenting approaches to front-line treatment of follicular lymphoma (FL) in Australia(1). Trotman *et al.* highlight the potential application of bendamustine-combinations for FL frontline and in relapsed disease (2). In the absence of an overall survival benefit (OS) favouring a particular chemotherapy backbone, both bendamustine and CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) are recommended by the authors, in combination with an anti-CD20 antibody (1). There are benefits of bendamustine in terms of lower early toxicity and longer progression-free survival, at the potential cost of increased late infection and second malignancy rates (1, 3, 4). We highlight an additional factor of emerging importance in treatment selection for non-Hodgkin lymphoma: the potential impact on subsequent chimeric antigen receptor (CAR) T-cell therapy.

Chimeric antigen receptor (CAR) T-cell therapies directed against CD19 are licensed for relapsed and refractory aggressive B-cell lymphoma treatment internationally, including in Australia. Early-phase trials indicate CD19 CAR T-cells are similarly able to induce durable remissions in other B-cell lymphomas, including FL (5). If the apparent plateau of relapses seen in aggressive B-cell lymphomas holds true in larger FL trials, CAR T-cells have the potential to compete with allogeneic stem cell transplantation to deliver long term remission.

Trotman et al. note the prolonged T-cell lymphopenia associated with bendamustine use (1, 4) Production of CAR T-cells requires an adequate T-cell harvest, circulating T-lymphocyte levels < 350/µL being strongly associated with CAR T-cell production failure.(6) Treatments that cause prolonged T-cell lymphopenia therefore have the potential to preclude subsequent CAR T-cell therapy.

Units across Australia are already delivering CAR T-cell therapies. This includes a trial in high-risk, relapsed follicular lymphoma (NCT03568461). Until results of this and similar trials are available, the role of CAR T-cells for FL remains uncertain. However, we believe that, as OS is similar between the front-line treatment options, avoiding T-cell depleting chemotherapy regimens should be a consideration when discussing treatment options with younger patients who are potential future CAR T-cell therapy candidates.

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In summary, because chemotherapy is not curative for advanced FL, it is critical to maintain a long-term perspective of treatment options. Maintaining a 'fit' T-cell compartment may be an increasingly important consideration in the era of CAR T-cells.

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