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

Michael Dickinson^{1,2}, Robert Weinkove^{3,4}

¹ Clinical Haematology, Peter MacCallum Cancer Centre and Royal Melbourne Hospital

² University of Melbourne, Parkville, Australia

³ Malaghan Institute, Wellington, New Zealand

⁴ Wellington Blood & Cancer Centre, Wellington, New Zealand

Corresponding Author: Michael Dickinson, Michael.Dickinson@petermac.org

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/ μ L 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.

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: [10.1111/imj.14453](https://doi.org/10.1111/imj.14453)

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.

1. Trotman J, Cheah CY, Marlton P, Opat S. Front-line management of non-Hodgkin lymphoma in Australia. Part 1: follicular lymphoma. *Intern Med J.* 2019;49(4):422-33.
2. Radford J, Davies A, Cartron G, Morschhauser F, Salles G, Marcus R, et al. Obinutuzumab (GA101) plus CHOP or FC in relapsed/refractory follicular lymphoma: results of the GAUDI study (BO21000). *Blood.* 2013;122(7):1137-43.
3. Marcus R, Davies A, Ando K, Klapper W, Opat S, Owen C, et al. Obinutuzumab for the First-Line Treatment of Follicular Lymphoma. *N Engl J Med.* 2017;377(14):1331-44.
4. Hiddemann W, Barbui AM, Canales MA, Cannell PK, Collins GP, Durig J, 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):2395-404.
5. Schuster SJ, Svoboda J, Chong EA, Nasta SD, Mato AR, Anak O, et al. Chimeric Antigen Receptor T Cells in Refractory B-Cell Lymphomas. *N Engl J Med.* 2017;377(26):2545-54.
6. Allen ES, Stroncek DF, Ren J, Eder AF, West KA, Fry TJ, et al. Autologous lymphapheresis for the production of chimeric antigen receptor T cells. *Transfusion.* 2017;57(5):1133-41.

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

Michael Dickinson^{1,2}, Robert Weinkove^{3,4}

¹ Clinical Haematology, Peter MacCallum Cancer Centre and Royal Melbourne Hospital

² University of Melbourne, Parkville, Australia

³ Malaghan Institute, Wellington, New Zealand

⁴ Wellington Blood & Cancer Centre, Wellington, New Zealand

Corresponding Author: Michael Dickinson, Michael.Dickinson@petermac.org

Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:

Dickinson, M;Weinkove, R

Title:

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

Date:

2019-10-01

Citation:

Dickinson, M. & Weinkove, R. (2019). Maintaining a fit T-cell compartment: lymphoma treatment sequencing in the era of chimeric antigen receptor T-cell therapies. INTERNAL MEDICINE JOURNAL, 49 (10), pp.1338-1338. <https://doi.org/10.1111/imj.14453>.

Persistent Link:

<http://hdl.handle.net/11343/286464>