Received: 14 June 2022 | Accepted: 5 July 2022

DOI: 10.1111/bjh.18363

BJHaem
BRITISH JOURNAL OF HAEMATOLOGY

COMMENTARY

A new paradigm for the management of ATL

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Commentary on: Shichijo T. *et al*., Beneficial impact of first-line mogamulizumab-containing chemotherapy in adult T-cell leukaemia/lymphoma, pending references. Br J Haematol, 2022;198:983-987.

The position of the anti-C-C chemokine receptor type 4 (CCR4) monoclonal antibody, mogamulizumab, in the management of adult T-cell leukaemia is uncertain. The report by Shichijo *et al*. places mogamulizumab in first-line for the majority, namely those for whom transplantation is not an option. Further refinement will follow but this represents a significant advance in a disease where progress tends to be slow.

Human T-cell lymphotropic virus type 1 (HTLV-1) infects millions worldwide with little or no effort to prevent infection, exceptions being rare, despite it being the cause of adult T-cell leukaemia/lymphoma (ATL).[1] Advances seen elsewhere in oncohaematology have not impacted ATL, with survival of aggressive disease (median survival time for acute leukaemia 8.3 months and for lymphoma 10.6 months) unimproved from the 1980s.[2] HTLV-1-infected lymphocytes can be identified by a combination of surface markers with $CD4^+CD26^-CCR4^+$ accounting for the majority of HTLV-1 proviral loads with loss of CD7 an additional marker for ATL cells. The development of a humanised defucosylated anti-CCR4 IgG monoclonal antibody[3] has been greeted with considerable enthusiasm, providing an alternative to chemotherapy for a condition which is chemotherapy-resistant. An early phase 2 study in Japan reported a 50% overall response rate in patients with relapsed ATL and a median overall survival of 13.7 months[4] following which mogamulizumab was licensed in Japan for this population. This was followed in 2014 with approval for mogamulizumab to be given with first-line therapy once its addition to the first four cycles of first-line chemotherapy (the mLSG15 regimen of VCAP-AMP-VECP) was shown to increase the complete response rate from 33% to 52%.[5] Outside of Japan mogamulizumab is not licensed for the treatment of ATL. In a multinational randomised controlled study of patients with relapsed or refractory aggressive ATL mogamulizumab was compared to second-line or salvage chemotherapy with a confirmed overall response rate of 11% compared to no response to further chemotherapy.[6] Given that 60% of patients in this study progressed during the first month no difference in progression-free survival was observed. However, clinically significant responses with mogamulizumab were seen in individuals, especially with chronic ATL.[7] A major concern with the use of mogamulizumab is the risk of severe steroid-refractory acute graft-versus-host disease (GVHD) following allo-stem cell transplantation (SCT) with high rates of acute (88.9%) and severe (grade 3–4) GVHD (33.3%) reported,[8] leading to the clinical recommendation of a minimum washout of 60 days between mogamulizumab administration and allogeneic transplant.

The report by Shichijo *et al*. of the outcomes of patients in Japan, considered by their physicians to be ineligible for allo-SCT, treated with first-line chemotherapy alone or with the addition of mogamulizumab significantly augments the clinical field. Although retrospective, with all the inherent difficulties, the observation period includes years 2010–2014 before mogamulizumab was approved in Japan, the majority of subjects were older than 65 years and had intermediate- or high-risk prognosis whilst a quarter had an Eastern Cooperative Oncology Group (ECOG) score of 2–4. The key finding, clinically and statistically significant, is the improved overall survival (OS) with mogamulizumab with a hazard ratio of 0.42. That four-year OS increased from 20.6% to 46.3% and median survival time from 7.8 to 36.1 months is particularly noteworthy when compared to the 2015 study above in which progression-free survival was not significantly improved by the addition of mogamulizumab (8.5 months) to first-line VACP-AMP-VECP (6.3 months). Here mogamulizumab was most commonly added to a cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP)-like regimen which is most commonly used when

prescribing chemotherapy for ATL in the UK. Furthermore, the benefit of adding mogamulizumab to chemotherapy was seen regardless of age or prognosis. Intriguingly, mogamulizumab was not always administered during the first cycle but numbers are likely too few to tease out whether delay reduced or increased the benefit or whether delivery at some time point is more important than timing of delivery, as was reported with zidovudine/interferon given with or after chemotherapy.[9] Given the mechanisms of action which likely include increased CD8 cytotoxic T lymphocyte (CTL) activity secondary to the depletion of regulatory T-cells in addition to the intended antibody-dependent cellular cytotoxicity (ADCC), infusion prior to chemotherapy should also be explored.

Allo-SCT is seen as the only treatment option with a reasonable chance of cure but the reality is that for most patients, even in Japan, this is not an option and finding a suitable donor is particularly difficult for many non-Japanese cohorts, compounded by patient fitness, opportunistic infections and the challenge of maintaining a durable response. The window of opportunity for allogeneic transplant is narrow as relapse is common even after achieving a complete response. These new data, despite the retrospective nature, provide a compelling argument to add mogamulizumab to the treatment of transplant-ineligible patients with ATL now. At four years OS is 46.3% with the Kaplan–Meier plots suggesting that survival beyond two years may indicate a good subsequent prognosis, a pattern also seen with zidovudine/interferon.[9] It was recently reported that non-transplanted patients with activating CCR4 mutations benefited from mogamulizumab, compared with those without mutations.[10] From a comparable period in Japan the four-year OS is 16% for acute leukaemia and 19% for lymphoma[11] whilst Ito *et al.* report a 45% two-year OS following allo-HCT in a prospective study.[12] More recent prospective data on the use of haploidentical transplant suggest significantly improved survival (73% two-year OS), albeit in small numbers.[13] Whilst these findings need further validation, they also make it difficult to be prescriptive about the benefits of mogamulizumab for all patients. Depletion of T-regulatory cells may be part of the benefit of mogamulizumab but this is a cause for concern for allo-HCT, with high rates of acute (88.9%) and severe (grade 3–4) GVHD (33.3%) reported.[8] Learning how to safely use mogamulizumab-related regulatory T-cell depletion may lead to the best of both worlds. We thus eagerly await the outcomes of the ongoing prospective trials in Japan evaluating this approach in the front-line setting: UMIN000019357 (MogaCHOP14) and UMIN000022819 (CHOP21 × 3 followed by eight mogamulizumab infusions), to determine what may become the new standard of -line care.

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How to cite this article: Taylor GP, Cook LB. A new paradigm for the management of ATL. Br J Haematol. 2022;198:941–942. https://doi.org/10.1111/bjh.18363