Identifying potential factors of variable response to mogamulizumab in adult T-cell leukemia/lymphoma between Japanese and other populations

We read with great interest the paper by Phillips *et al*. on the use of mogamulizumab *versus* investigator choice in relapsed/refractory adult T-cell leukemia/lymphoma (ATLL).[1] ATLL is a rare malignancy, and outside of some areas endemic for human T-lymphotrophic virus 1, such as Japan, conducting a randomized study on this disease is challenging. The collaboration of the group of investigators based outside of Japan who performed this randomized trial should therefore be commended. In their trial, the rates of response of relapsed/refractory ATLL to mogamulizumab were not significantly better than those to investigator-chosen chemotherapy, with an overall response rate of 11%. In contrast, the overall response rate to mogamulizumab for relapsed ATLL in the phase II single-arm trial that led to approval of the use of this drug in Japan was 50%.[2] The authors attribute this difference to three factors: different time windows for response confirmation between the studies (8 weeks *versus* 4 weeks), more aggressive nature of the ATLL in the present study (which included patients with refractory disease), and an ethnically more diverse population leading to possible differences in disease biology. The median progression-free survival of 5.2 months in the Japanese study argues against the response confirmation window being a factor, but we agree with the latter two points. Other biological factors which could have contributed are the rate of CCR4 mutations, different dosing schedules, and prior therapy with histone deacetylase inhibitors.

We have shown that differences in disease biology are possible between Japanese and North American variants, and hence genomic profiling to understand differences could be valuable.[3] In a recent study, CCR4 gain-of-function mutations were observed in 32.8% of 116 patients from Japan and were found to be prognostic of treatment response with a 5-year overall survival difference of 80% in the group with CCR4 gain-of-function mutations *versus* 24.7% in the group without these mutations.[4] In a group of 53 predominantly North American patients with ATLL, 14 (26%) had a CCR4 gain-of-function mutation.[5] While genomic analyses have not yet been reported for this trial, this finding underlies the importance of performing such studies in phase II trials.

The phase I trial of mogamulizumab established that the half-life of the antibody is approximately 18 days when it is given at a dose of 1 mg/kg for four weekly administrations, with the trough level required for efficacy hypothesized to be 10 μg/mL based on *in vitro* data.[6] Importantly, it took the fourth weekly dose to achieve that trough, indicating that the drug may not have had time to be effective for some the patients with clinically aggressive refractory ATLL enrolled on this trial. The Japanese phase II trial included 8 weekly doses, in contrast to the present trial in which mogamulizumab was given weekly for 5 weeks and then every other week. Zinzani *et al*. also reported that this could be one of the factors influencing efficacy in their phase II study of mogamulizumab in relapsed, refractory peripheral T-cell lymphoma in Europe in which a similar dosing schedule was used.[7] Two fewer doses of mogamulizumab in this trial, combined with the possibility of different rates of antibody metabolism due to the ethnic diversity, may therefore have played a role in the low overall response rate.

Finally, histone deacetylase inhibitors, such as vorinostat and romidepsin, decreased CCR4 expression in preclinical trials, and could have affected the efficacy of mogamulizumab.[8] Since more than half of the patients were enrolled in North America, and approximately 72% had received other prior treatments (i.e. not combination chemotherapy, interferon, azidothymidine, pralatrexate, or an autologous transplant), it would be interesting to know the proportion of patients who received histone deacetylase inhibitors and to see whether there were differences between those who received them immediately prior to mogamulizumab and those who did not. Even though this study failed to show a difference, translational studies may help to understand the biological differences observed in the study or sub-populations of patients with ATLL who could benefit from the administration of this drug.

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doi:10.3324/haematol.2019.217232

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

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