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Blasting high-burden T-large granular lymphocytic leukemia with bendamustine

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In the current issue of *Haematologica*, Massarotti et al. report significant results from a retrospective series of patients with T-cell large granular lymphocytic leukemia (T-LGLL) associated cytopenias treated with the bifunctional alkylator/purine analogue bendamustine.[1]

T-LGLL is a chronic cytokine-driven clonal proliferation of terminal effector T-lymphocytes that can induce severe anemia and/or neutropenia with resultant infections, transfusion dependence, and impaired quality of life.[2] Limited therapies exist for the treatment of T-LGLL, particularly in relapsed/refractory disease outside of immune-suppressive agents.[3-5] Novel agents such as ruxolitinib have shown promise, but are not universally available across the European Union and worldwide, making the availability of additional treatments an area of clear unmet need.[6]

In this study, Massarotti et al evaluated 12 patients with T-LGLL, including both untreated (n=4) and relapsed patients (n=8). Notably, patients were required to have what the authors termed 'high burden' T-LGLL with a median circulating T-LGLL lymphocyte count of >3 $x10^9$/L or >/= 30% marrow involvement. Patients were treated with IV bendamustine at doses ranging from 60-90 mg/m2 on day 1-2 of a 28-day cycle, for 4-6 cycles. Dose and duration of response were based upon age and clinical factors, but the details were not included in this report. Clinical response was assessed with standard criteria, measured by improvement in cytopenias (PR) and resolution of the T-LGLL clone by flow cytometry (CR).[5] All patients responded (67% CR, 33% PR), including patients with anemia, neutropenia, and those with STAT3 mutations. Response to treatment was overall durable. With a median follow-up of 37.5 months, the median PFS, response duration (DOR), and OS were not reached, though

estimated to be 56%, 61%, and 91% respectively. Patients with CR had significantly longer remission duration vs those who attained a PR (median DOR not reached vs 8 months). Side effects were largely expected with bendamustine therapy, including neutropenia, anemia, and gastrointestinal symptoms.

This report makes several novel observations that will inform therapy for patients with T-LGLL. Purine analogues, such as pentostatin and fludarabine have previously been reported in small case series to be effective in patients with T-LGLL.[3,7-9] Response rates vary, and are difficult to interpret given the lack of clear response criteria, age of the data, and limited numbers of patients, but are generally reported in the 50-75% range.[3] Conversely, in this report, the authors present a well-described cohort of 12 patients with high-burden T-LGLL using defined response criteria with a 100% ORR, including 67% CR. Response rates in T-LGLL typically hover around 50%, making these data compelling. Further, the authors present mechanistic data showing bendamustine induces dose-dependent cytotoxicity in *ex vivo* T-LGLL patient samples potentially through a substantial reduction in phospho-STAT3; a key transcription factor critical to the pathogenesis of T-LGLL. The observation that bendamustine acts by inhibiting STAT3 activity, a key mechanistic pathway in T-LGLL, combined with a well-described cohort of 12 patients who all responded, provides a strong rationale for the use of bendamustine in T-LGLL. This, combined with the fact that similar translational data have not been reported with other chemotherapy agents, makes the level of evidence presented here, while retrospective, stronger.

Given the chronic nature of T-LGLL, it is important to put the results of this report into the context of currently available therapies, with a careful evaluation of potential side

effects of bendamustine in this disease. Bendamustine can induce anemia and neutropenia, which can, in turn, lead to infectious complications in patients. As patients with T-LGLL requiring therapy by definition have existing cytopenias, the use of bendamustine should be approached with caution and always within the clinical context of each individual patient to avoid significant toxicity. While the authors reported no AE-associated deaths in this cohort, they did observe grade 3-4 AEs in 42% of patients, including grade 3-4 neutropenia (3 patients) and grade 3-4 anemia in 1 patient. These results should be evaluated against existing therapies for T-LGLL, particularly in the frontline setting. In a recent phase III trial in untreated T-LGLL, 12 months of oral cyclophosphamide was superior to oral methotrexate in reducing cytopenias, with an ORR of 80% in T-LGLL, with durable results and acceptable side effect profile.[10] While the full results of this report are not yet published, cyclophosphamide is likely to become the preferred frontline therapy for T-LGLL. Methotrexate, and other immune-suppressive agents remain the backbone of T-LGLL therapy, with ORR in the 40-50% range, with a favorable side effect profile, though these agents take months to achieve a clinical benefit, and require indefinite therapy.[3-5] When comparing the results in Massarotti et al with existing data, it should also be noted that this was a retrospective study of patients treated with bendamustine, and not a prospective designed clinical trial in a very specific population of T-LGLL patients with high T-LGLL burden. Prospective data are needed to validate these results and inform the best dosing and duration for bendamustine therapy in T-LGLL.

Nevertheless, these data suggest that bendamustine should be considered in patients with high-burden, aggressive T-LGLL for whom an immediate response is needed, or in

patients with high-burden relapsed/refractory T-LGLL. Due to its cost profile, bendamustine is also likely to be particularly important in health systems around the world in which patients have limited or no access to clinical trials, or expensive novel agents such as JAK inhibitors that require indefinite therapy. The data presented in the Massarotti paper provides for a new therapeutic approach in high burden T-LGLL, with compelling translational data suggesting this agent targets the underlying STAT3-driven pathogenic pathway in T-LGLL. While further prospective evaluation in a well-designed clinical trial is needed to determine the best dosing and duration of therapy, these results present bendamustine as a promising new treatment in a rare disease with few therapeutic options.

REFERENCES

1. Massarotti L, Rampazzo E, Calabretto G, et al. Bendamustine monotherapy induces high response rates and STAT3 inhibition in high burden T-cell large granular lymphocytic leukemia. Haematologica. xxx
2. Marchand T, Lamy T, Loughran TP, Jr. A modern view of LGL leukemia. Blood. 2024;144(18):1910-1923.
3. Braunstein Z, Mishra A, Staub A, Freud AG, Porcu P, Brammer JE. Clinical outcomes in T-cell large granular lymphocytic leukaemia: prognostic factors and treatment response. Br J Haematol. 2021;192(3):484-493.
4. Bareau B, Rey J, Hamidou M, et al. Analysis of a French cohort of patients with large granular lymphocyte leukemia: a report on 229 cases. Haematologica. 2010;95(9):1534-1541.
5. Loughran TP, Jr., Zickl L, Olson TL, et al. Immunosuppressive therapy of LGL leukemia: prospective multicenter phase II study by the Eastern Cooperative Oncology Group (E5998). Leukemia. 2015;29(4):886-894.
6. Marchand T, Pastoret C, Damaj G, et al. Efficacy of ruxolitinib in the treatment of relapsed/refractory large granular lymphocytic leukaemia. Br J Haematol. 2024;205(3):915-923.
7. Mercieca J, Matutes E, Dearden C, MacLennan K, Catovsky D. The role of pentostatin in the treatment of T-cell malignancies: analysis of response rate in 145 patients according to disease subtype. J Clin Oncol. 1994;12(12):2588-2593.
8. Fortune AF, Kelly K, Sargent J, et al. Large granular lymphocyte leukemia: natural history and response to treatment. Leuk Lymphoma. 2010;51(5):839-845.
9. Sternberg A, Eagleton H, Pillai N, et al. Neutropenia and anaemia associated with T-cell large granular lymphocyte leukaemia responds to fludarabine with minimal toxicity. Br J Haematol. 2003;120(4):699-701.
10. Lamy T, Pastoret C, Damaj G, et al. Prospective, multicentric, phase II randomized controlled trial comparing the Efficacy and Toxicity of Methotrexate to Cyclophosphamide in Large Granular lymphocyte leukemia: a French national study. Blood. 2024;144(Supplement 1):979.