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Hematopoietic stem-cell transplantation for T-cell Large Granular Lymphocyte Leukemia: a retrospective study of the European Society for Blood and Marrow Transplantation (EBMT).

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Large Granular Lymphocyte (LGL) leukemia is a rare lymphoproliferative disorder characterized by clonal expansion of either CD3⁺ cytotoxic T lymphocytes or CD3⁻ NK cells.¹ World Health Organization classification has recognized LGL leukemia as a specific entity among the subgroup of mature peripheral T-cell neoplasms. Clinical presentation is dominated by splenomegaly, neutropenia with recurrent infections and autoimmune manifestations.² Due to low incidence and thus the lack of prospective studies, no standard treatment has been established in LGL leukemia. Although usually considered as an indolent disease, most patients will require therapy based on immunosuppressive drugs such as methotrexate, cyclophosphamide or cyclosporin.^{3,4} Despite of a good clinical response rate, long-term remissions are rarely observed. Patients who are refractory to immunosuppressive therapy or with initial aggressive clinical course should be offered alternative strategies because combined chemotherapy regimens such as CHOP-like regimens gives disappointing results.³ Few cases of aggressive LGL-leukemia have been described with an overall survival (OS) not exceeding 2 years.⁵ In this serious situation, intensification of therapy by high-dose chemotherapy may be considered. Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is the only curative treatment for several immune and hematologic disorders but is associated with a high toxicity mainly due to graft-versus-host disease (GVHD). Graft-versus-lymphoma effects have been proven in various lymphoproliferative disorders.⁶ However, the feasibility and efficacy of allo-HSCT in LGL leukemia has not been evaluated so far and data are only limited to few sporadic case reports.^{7, 8} Autologous hematopoietic stem cell transplantation (auto-HSCT) is associated with prolonged progression-free survival (PFS) in several lymphohematopoietic malignancies and represents a valuable option in peripheral T cell lymphoma.⁹

82 However, the value of auto-HSCT in relapsed or refractory LGL leukemia has not
83 been evaluated to date. In this letter, we report the outcome of 15 patients treated by
84 auto-HSCT or allo-HSCT for T-cell LGL leukemia and reported to the EBMT registry.

85 This is a registry-based retrospective multicentre study including patients 18
86 years or above who underwent allo-HSCT or auto-HSCT for T-cell LGL leukemia
87 between 1 January 2004 and 30 November 2011 while cases were reported to the
88 European Society for Bone and Marrow Transplantation (EBMT). EBMT is a
89 voluntary organization comprising more than 600 transplant centres mainly from
90 Europe. Accreditation as a member centre requires submission of minimal essential
91 data (MED-A form) (www.ebmt.org) from all consecutive patients to a central registry.
92 Informed consent for transplantation and data collection was obtained locally
93 according to regulations applicable at the time of transplantation. Baseline patient,
94 disease and transplant data were collected from MED-A forms. In addition, a
95 questionnaire was sent out to collect additional data including autoimmune disease,
96 clinical presentation, prior to transplantation administered therapies and updated
97 follow-up information. Centers were then contacted to provide written flow-cytometry
98 diagnostic reports in order to confirm the diagnosis of LGL leukemia. Conditioning
99 regimen intensity were defined according to definition recently proposed.^{10,11} GVHD
100 was graded according to consensus criteria.^{12,13} The primary end points studied were
101 2-year OS and 2-year PFS. Secondary endpoints were incidence of disease relapse
102 or progression (RI) and non-relapse mortality (NRM). Probabilities of PFS and OS
103 were calculated using the Kaplan-Meier estimate.

104
105 A total of 33 patients fulfilling the inclusion criteria were identified in the EBMT
106 registry (allo-HSCT 20, auto-HSCT 13). In 15 patients, the requested additional data

could be retrieved and the diagnosis of LGL finally confirmed in all (allo-HSCT 10, auto-HSCT 5). Most of these 15 patients had advanced disease with multi-organ involvement (n=9) including bone marrow (n=9), spleen (n=7), liver (n=3), skin (n=1) and central nervous system (n=1). Median number of prior therapy regimens was 2 (1-8). Eleven patients (73%) were previously treated with poly-chemotherapy. Median time from diagnosis to transplantation was 15 months (range: 7-211). Patient and treatment characteristics as well as outcome after HSCT are shown in **Table 1**.

Ten patients received an allo-HSCT at a median age of 49 years (range 29-66). Three of them were in complete remission (CR) at transplantation. Six patients were in partial response (PR) and one patient presented with refractory disease. All but two donors were HLA-matched. G-CSF mobilized peripheral blood progenitor cells were used in all but one patient. Intensity of conditioning regimen was reduced in 6 patients (40%) while conditioning was TBI-based in 7 patients. GVHD prophylaxis consisted of cyclosporin alone (n=3) or in combination with either methotrexate (n=3) or mycophenolate mofetil (n=2). One patient received a GVHD prophylaxis by sirolimus and mycophenolate mofetil and one patient had a syngeneic donor not requiring a GVHD prophylaxis. In vivo T cell depletion was performed in 4 patients with either antithymocyte globulin (n=3) or alemtuzumab (n=1). Engraftment with absolute neutrophil counts rising above $5 \times 10^9/L$ was achieved for all patients at a median of 19 days (range: 8 - 41) after allo-HSCT. Grade II-IV acute GVHD was observed in 4 patients. Seven patients survived more than 100 days after allo-HSCT and 2 developed extensive and 1 patient limited chronic GVHD. One patient relapsed early at day +24 after allo-HSCT and died soon afterwards due to disease progression. Four other allografted patients died because of severe infections. Viral infections were documented in 3 patients with concomitant GVHD in 2 of them. One

additional patient died from fungal respiratory tract infection. These 4 patients were heavily pretreated with a median of 3 chemotherapy lines. All of them had received alemtuzumab prior to or in preparation for allo-HSCT. Five patients are still alive and in remission after a median follow-up of 30 months (range: 19-95), resulting into a 2-year PFS and OS of 50% each (95%CI, 18% - 75%).

Auto-HSCT was performed in 5 patients at a median age of 49 years (range: 38-57). Three patients were in CR and 2 in PR at the time of transplantation. Conditioning regimens were BEAM (carmustine, etoposide, cytarabine and melphalan) in 4 patients and TAM6 (cytarabine, melphalan, TBI 12 Grays) in 1 patient. Two patients relapsed at 1 and 31 months post auto-HSCT and died. One patient could not achieve CR after auto-HSCT but is still alive after a follow-up of 40 months. No patient died due to auto-transplant related complications. Two patients remain alive and disease-free 27 and 52 months post auto-HSCT, respectively.

T-cell LGL leukemia is usually an indolent disease with a high sensitivity to immunosuppressive drugs.³ Contrasting with this classical presentation, some patients suffer from aggressive or refractory disease associated with an extremely poor prognosis.⁵ In this rare aggressive/refractory LGL leukemia, polychemotherapy has been tried with disappointed results raising the question of HSCT.^{5, 14} Autologous HSCT is a validated therapeutic option in many lymphoid malignancies.⁹ Disease control at the time of transplantation is crucial and associated with longer PFS in this setting.¹⁵ In our series, 3 patients who had received an autograft with advanced disease (2 patients in partial response and 1 patient in CR after 3 chemotherapy lines) at time of transplantation relapsed or progressed after auto-HSCT whereas the 2 patients autografted in first complete remission have not relapsed after a reasonable follow up. These results suggest that prolonged PFS might be achieved

by auto-HSCT in patients with a chemo-sensitive disease. Allogeneic HSCT represents the only curative treatment for several hematologic malignancies and "Graft versus lymphoma" (GVL) effects have been demonstrated in various lymphoid disorders.⁶ Due to the small number of patients included in this analysis, we were unable to evaluate the correlation between GVL and GVHD. However, it was remarkable that despite the inclusion of patients with advanced, non-remission disease, only one relapsed after allo-HSCT suggesting a "graft versus LGL" effect. Our finding of prolonged induction of remission in those patients supports additionally the possibility of an existing GvL effect in LGL leukemia. Thus our results suggest that allo-HSCT could be performed in chemo-refractory LGL-leukemia.

In conclusion, despite of the retrospective nature of our analysis and the small number of patients included not allowing the evaluation of prognosis factors, our results provide the first evidence of the feasibility of HSCT in refractory/aggressive LGL leukemia while an inside results showing efficacy in the treatment of a rare disease is provided. Thus, HSCT appears as a potential therapeutic option in rare aggressive and relapsing forms of T-LGL leukemia and should be further explored to define an optimal therapeutic strategy in this setting.

Conflicts of Interest

The authors declare no conflict of interest

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Authorship

TM and TL designed the study and performed statistical analysis. TM, TL, HF and PD were responsible for data collection, data analysis, data interpretation, manuscript preparation, writing and completion and final approval of manuscript. All authors approved the final version of the manuscript and the submission.

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Figure Legends :

Table 1. Patient characteristics and outcome

AraC, cytarabine; aGVHd, acute Graft versus Host disease; ATG, antithymocyte globulin; BEAM, Carmustine-etoposide-cytarabine-melphalan; cGVHd, chronic Graft versus Host disease; CHOP, cyclophosphamide-doxorubicine-vincristine-prednisone; CHVP, cyclophosphamide-adriamycine-etoposide-prednisolone; CR, complete remission; CY, cyclophosphamide; DHAP, dexamethasone-cytarabine-cisplatin; ESHAP, etoposide-prednisone-cytarabine-cisplatin; F, female; FLAG-Ida, fludarabine-cytarabine-granulocyte colony-stimulating factor-idarubicin; FLAMSA, fludarabine-cytarabine-amsacrine; Flu, fludarabine; FU, follow up; GMALL, German Multicenter Acute Lymphoblastic Leukemia group; ICE, ifosfamide-carboplatin-etoposide; M, male; MAC, myeloablative conditioning; Mel, melphalan; Mitox, mitoxantrone; MMF, mycophenolate mofetil; MOPP, mechlorethamine-vincristine-procarbazine-prednisone; MUD, match unrelated donor; MTX, methotrexate; NA, not applicable; OS, overall survival; PR, partial remission; Pred, prednisone; Prog, progression; RIC, reduced intensity conditioning; SCT indicates stem cell transplantation; Sib, sibling donor; Stanford V, doxorubicine-vinblastine-mechlorethamine-

252 etoposide-vincristine-bleomycine-prednisone; Syn, syngenic donor; Tacro, tacrolimus; TAM,
253 total body irradiation (TBI)-cytarabine-melphalan;
254