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Summary

Allogeneic Haematopoietic Stem Cell Transplant (allo-HSCT) remains the only curative approach for Myelofibrosis (MF). Scarce information exists in the literature on the outcome and, indeed, management of those MF patients who relapse follow- ing transplant. We hereby report on the management and outcome of 202 patients who relapsed post allo-HSCT for MF.

Over the last decade, there has been a significant increase in the number of patients with Myelofibrosis (MF) undergoing Allogeneic Haematopoietic Stem Cell Transplantation (allo- HSCT). The European Society for Blood and Marrow Transplantation (EBMT) registry reported on 181 episodes in 2004 which had risen considerably to 559 episodes in 2014. Current practice often adheres to consensus European LeukaemiaNet (ELN)/EBMT guidelines that suggest consideration towards transplantation in intermediate-2- or high-risk disease, as defined by the International Prognostic Scoring System (IPSS), and for patients who are <70 years of age. Moreover, patients with intermediate-1-risk disease and age <65 years could be considered if they present with either refractory, transfusion- dependent anaemia, or a percentage of blasts in peripheral blood (PB) >2%, or adverse cytogenetics (Kröger *et al*, 2015).

Despite the advent of many novel agents in MF, allo-HSCT remains the only known curative approach (reviewed in McLornan *et al*, 2012). However, disease relapse remains a sig- nificant barrier to successful outcome. Long-term results from the first prospective study of reduced intensity conditioned (RIC) allo-HSCT co-ordinated by the EBMT suggested a sig- nificant relapse risk of up to 22% at 3 years and approximately 28% at 5 years, although historically relapse rates were higher (Kröger *et al*, 2009a). We hereby report on a retrospective analysis of 202 patients with MF registered in the EBMT data- base who have relapsed following allo-HSCT.

Methods

This was a retrospective, multicentre, EBMT registry-based analysis. All patients whose transplant data are reported to the EBMT by participating centres provide informed consent to use the information for anonymised research. Patient selection was performed by identifying adult patients who underwent first allo-HSCT for MF between the years 2000–2014, using either RIC or myeloablative conditioning (MAC). Those with documented and dated relapse (after Day +30) and sufficient clinical details were analysed. Statistical analyses were per- formed with SPSS 22 (IBM, Armonk, NY, USA). Patient-, dis- ease- and transplant-related variables were expressed as median and range for continuous variables and frequencies for categorical variables. Overall Survival (OS) was calculated from the date of documented relapse until death or last observation alive. Patients alive at their last follow-up were censored. This study was performed in accordance with the principles of the Declaration of Helsinki and approved by the Chronic Malig- nancies Working Party of the EBMT.

Results

From the registry, a total of 251 relapsed patients were identi- fied within an entire patient cohort of 1371, giving an esti- mated relapse incidence of 18·3%, albeit dependent on adequate reporting. For this analysis, we excluded cases with insufficient clinical information, umbilical cord blood and haploidentical transplants and, hence, a total of 202 patients were included (Table I). A total of 165 patients had a diagno- sis of primary MF and 37 secondary MF at the time of trans- plant. The cohort consisted of 133 males and 69 females with a median age at transplantation of 55 years (range, 22–69 years). Sixty-six (33%) patients underwent MAC and 136 (67%) patients had RIC. The most frequent conditioning reg- imens across the entire cohort were fludarabine/busulphan (Flu/Bu; 36%), fludarabine/melphalan (Flu/Mel; 13%) and busulphan/cyclophosphamide (BuCy; 6%). The most com- mon agent for *in vivo* T-cell depletion was antithymocyte

globulin (ATG). No *ex vivo* T-cell depletion was reported. The main source of haematopoietic stem cells (HSC) was peripheral blood (175 patients; 87%) whereas 27 (13%) received BM-derived HSC. Donors were human leucocyte antigen-matched related (n = 107) or unrelated [matched/ mismatched (n = 95)] (Table I).

The median time from diagnosis of MF to transplant was 28 months (range, 2–321 months). The median time to relapse was relatively short, at 7·1 months (range 1·4– 111 months), with a median OS from the time of relapse of 22·9 months for the entire cohort [95% confidence interval (CI) 16–29·6; Fig 1A]. Collectively, without treatment strati- fication, there was a significant difference in survival out- come for those relapsing <7·1 months post allo-HSCT [median survival 12·9 months (95% CI 27·2–44·6)] com- pared to those relapsing after 7·1 months following the initial allo-HSCT episode [median survival 36·9 months (95% CI 42·8–62·8); Log Rank Mantel Cox: $P < 0·002$]. Disease dura- tion prior to allo-HSCT did not significantly affect outcome post-relapse.

Heterogeneous practice existed regarding management of the relapse episode and was documented in 165 patients (82%). A total of 47 (23%) patients received a donor lymphocyte infusion (DLI) alone (median survival estimate, 76 months); 23 (11%) had chemotherapy alone (complete regimen details not documented; median survival approxi- mately 23 months) whereas 18 (20%) patients had DLI com- bined with chemotherapy. Fifty-one (25%) patients underwent 2nd allo-HSCT alone (median survival 26·9 months) and 26 (13%) underwent DLI and 2nd allo-HSCT (median survival estimate, 54 months). The median time to receive DLI in the entire cohort was relatively short at 43 days. Most frequent conditioning regimens for 2nd allografts were FluBu and fludarabine/ATG (Flu/ATG). Active management – if any- was not documented for 37 (18%) patients and hence was not analysed. Survival median estimates are highlighted in Table SI for all groups. The med- ian OS from the time of relapse for those receiving DLI alone, DLI followed by 2nd allo-HSCT or 2nd allo-HSCT is demonstrated in Fig 1B.

Discussion

Treatment of relapse evidently presents huge challenges and the heterogeneous management strategies highlighted reflects current practice. Direct comparison between

Table I. Patient characteristics (n = 202).

Characteristic	n
Median age, years (range)	55 (22–69)
Gender	
Male	133
Female	69
Diagnosis at time of transplant	
Primary myelofibrosis	165
Secondary myelofibrosis	37
Median time from diagnosis to transplant, months (range)	28 (2–321)
Median time to relapse post-transplant, months (range)	7·1 (1·4–111)
Median follow-up post-transplant for patients alive, months (range)	52·5 (4–116)
Donor type	
Matched related	107
Unrelated matched	35
Unrelated mismatched/degree of match not stated	60
Conditioning	
Myeloablative	66

Reduced intensity	136
Stem cell source	
Bone marrow	27
Peripheral blood	175
Graft-versus-host disease during first transplant	
Acute	
No graft-versus-host disease	122
Grade 1	34
Grade 2–4	37
Missing, ungraded or unknown	9
Chronic	
Limited	51
Extensive	33
Missing	118

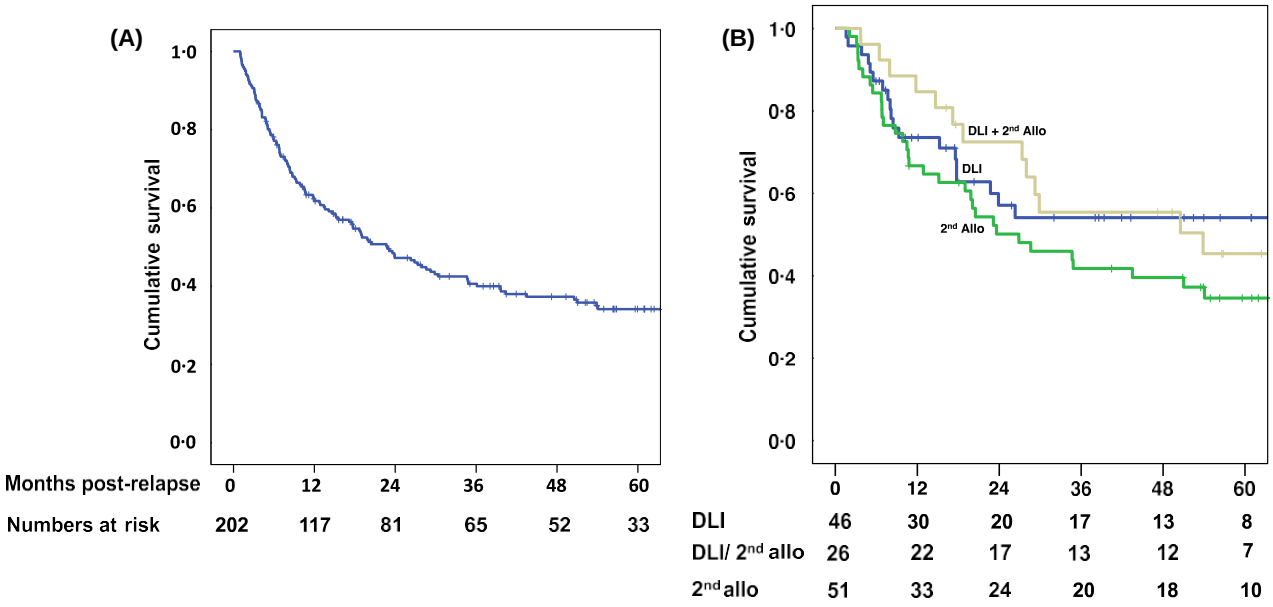

Fig 1. (A) Cumulative overall survival post-relapse of entire cohort as estimated by the Kaplan–Meier method. Median overall survival from the time of relapse of approximately 23 months for the entire cohort (95% Confidence Intervals 16–29 6). (B) Cumulative overall survival post- relapse of those patients receiving either DLI, DLI+2nd allo-HSCT or 2nd allo-HSCT alone as estimated by the Kaplan–Meier method. Median overall survival from the time of relapse was approximately 76 months for the DLI alone cohort, 54 months for the DLI+2nd allo-HSCT cohort and 27 months for the 2nd allo-HSCT. allo-HSCT, allogeneic haemopoietic stem cell transplant; DLI, donor lymphocyte infusion. [Colour figure can be viewed at wileyonlinelibrary.com]

therapeutic interventions to gauge efficacy is not feasible from this analysis as bias could well be influenced by patient performance status, heterogeneous timing of relapse, patient and physician choice and availability of either DLI or second allo-HSCT. No robust details were available concerning the dynamic IPSS or pre-transplant therapy and it is unknown if any of the patients transplanted in more recent years had received JAK inhibitors pre-transplant. Nonetheless, this retrospective analysis rep- resents the largest study to date which documents the out- come and management of MF patients who undergo relapse following allo-HSCT and, despite its limitations, provides important and clinically relevant information.

Survival varies markedly following relapse, in this study the median survival was just less than 2 years, i.e., approx- imately 23 months. It is clear that earlier relapse following MF allo-HSCT has a much worse prognosis than later relapses, akin to other myeloid disorders. Moreover, our data importantly suggests there is a beneficial role to be considered for adoptive immunotherapeutic approaches with DLI and/or 2nd allo-HSCT. DLI was administered to 45% of the entire cohort overall and almost 38% of patients underwent a second allograft either alone or following the use of DLI. Indeed, the efficacy and safety of dose escalating DLI in the post allo-HSCT setting for MF has previously been described (Kröger *et al*, 2009b; Klyuch- nikov *et al*, 2012). Survival following 2nd allo-HSCT (either alone or following DLI) is encouraging, although conclusions regarding absolute benefits of a 2nd transplant

procedure from this study are somewhat limited as this most often occurs in a highly selected group who survive long enough and are fit enough to undergo such interven- tion. Furthermore, 2nd allograft following DLI means that the recipient may not have responded to DLI alone and hence direct comparisons between the two modalities are not feasible. However, one should carefully evaluate the patient who has relapsed to decide whether a 2nd allo- HSCT is appropriate. Klyuchnikov *et al* (2012) previously reported on acceptable toxicity and outcomes in a cohort of relapsed patients who proceeded to 2nd allo-HSCT, utilising an alternative donor, the majority of whom received fludarabine, treosulphan and ATG-based condi- tioning.

The role of splenectomy and its effect on relapse risk and subsequent outcome remains unclear and was not analysed in this study due to a lack of complete information on splenectomy status. A recent study has suggested that expo- sure to JAK1/2 inhibitors did not adversely affect post-trans- plant outcomes and that there was superior survival and lower non-relapse mortality in patients who had clinical improvement with JAK1/2 inhibitors prior to allo-HSCT (Shanavas *et al*, 2016). The role of these agents in the man- agement of relapse remains intriguing, yet ill-defined. Janson *et al* (2016) recently reported on 10 patients from a single centre who had relapsed post MF allo-HSCT (median time to relapse 24 months; range 2·7–85·7) and who received rux- olitinib therapy (Novartis Pharmaceuticals, Basel, Switzer- land) at a median dose of 10 mg twice daily. The median treatment duration was 143•5 days (range, 12–369). Although transient amelioration of disease-related constitutional symp- toms, transfusion burden and spleen reduction was apparent in some, progressive disease eventually occurred in all patients. No significant improvement in chimerism or reduc- tion in JAK2 allelic burden quantification was evident. Of note, all patients who had concomitant graft-versus-host-dis- ease (GVHD), had an amelioration or resolution of their GVHD.

In conclusion, this retrospective study is, to the best of our knowledge, the first to describe the outcome and 'real-world' management of relapsed patients post MF allo- HSCT. Timing of relapse appears critical, with those relapsing early having worse outcomes. Close monitoring of chimerism and minimal residual disease would therefore be paramount. The role of DLI and, where required, 2nd allo-HSCT for relapsed MF should be studied collabora- tively as there is a suggestion of survival benefit for those fit enough to undergo such a procedure. How the era of JAK inhibitors for the therapy of MF will affect both relapse risk and management, however, remains unclear.

References

Janson, D., Ayuk, F.A., Wolschke, C., Christopeit, M., Badbaran, A., von Pein, U.M., van Randen- borgh, A. & Kroeger, N. (2016) Ruxolitinib for myelofibrosis patients relapsing after allogeneic hematopoietic transplantation. *Blood*, 128, 1948. Klyuchnikov, E., Holler, E., Bornhäuser, M., Kobbe, G., Nagler, A., Shimoni, A., Kröcnecke, C., Wolschke, C., Bacher, U., Zander, A.R. & Kröger, N. (2012) Donor lymphocyte infusions and second transplantation as salvage treatment for relapsed myelofibrosis after reduced-intensity allografting. *British Journal of Haematology*, 159, 172–181.

Kröger, N., Holler, E., Kobbe, G., Bornhäuser, M., Schwerdtfeger, R., Baurmann, H., Nagler, A., Bethge, W., Stelljes, M., Uharek, L., Wandt, H., Burchert, A., Corradini, P., Schubert, J., Kauf- mann, M., Dreger, P., Wulf, G.G., Einsele, H., Zabelina, T., Kvasnicka, H.M., Thiele, J., Brand, R., Zander, A.R., Niederwieser, D. & de Witte,

T.M. (2009a) Allogeneic stem cell transplanta- tion after reduced-intensity conditioning in patients with myelofibrosis: a prospective, multicenter study of the Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation. *Blood*, 114, 5264–5270.

Kröger, N., Alchalby, H., Klyuchnikov, E., Bad- baran, A., Hildebrandt, Y., Ayuk, F., Bacher, U., Bock, O., Kvasnicka, M., Fehse, B. & Zander, A. (2009b) JAK2-V617F-triggered preemptive and salvage adoptive immunotherapy with donor- lymphocyte infusion in patients with myelofi- brosis after allogeneic stem cell transplantation. *Blood*, 113, 1866–1868.

Kröger, N.M., Deeg, J.H., Olavarria, E., Nieder- wieser, D., Bacigalupo, A., Barbui, T., Rambaldi, A., Mesa, R., Tefferi, A., Griesshammer, M., Gupta, V., Harrison, C., Alchalby, H., Vannuc- chi, A.M., Cervantes, F., Robin, M., Ditsch- kowski, M., Fauble, V., McLornan, D., Ballen, K., Popat, U.R., Passamonti, F., Rondelli, D. &

Barosi, G. (2015) Indication and management of allogeneic stem cell transplantation in primary myelofibrosis: a consensus pro cess by an EBMT/ ELN international working group. *Leukemia*, 29, 2126–2133.

McLornan, D.P., Mead, A.J., Jackson, G. & Har- rison, C.N. (2012) Allogeneic stem cell trans- plantation for myelofibrosis in 2012. *British Journal of Haematology*, 157, 413–425.

Shanavas, M., Popat, U., Michaelis, L.C., Fau- ble, V., McLornan, D., Klisovic, R., Mas- carenhas, J., Tamari, R., Arcasoy, M.O., Davies, J., Gergis, U., Ukaegbu, O.C., Kam- ble, R.T., Storring, J.M., Majhail, N.S., Romee, R., Verstovsek, S., Pagliuca, A., Vasu, S., Ernst, B., Atenafu, E.G., Hanif, A., Champlin, R., Hari, P. & Gupta, V. (2016) Outcomes of allogeneic hematopoietic cell transplantation in patients with myelofibro- sis with prior exposure to Janus Kinase 1/2 inhibitors. *Biology of Blood Marrow Trans- plantation*, 22, 432–440.