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LETTER TO THE EDITOR

Early liver complications after allogeneic haematopoietic stem cell transplantation in patients with myelofibrosis: A study on behalf of the Chronic Malignancies Working Party of the EBMT

Patients with myelofibrosis (MF) have established liver myeloid metaplasia and are more susceptible to additional hepatic disorders such as fibrosis or vascular complications.[1–3] This characteristic should be taken into account for patients undergoing allogeneic haematopoietic stem cell transplantation (HSCT), which may lead to decompensation of these disorders. A Canadian group previously reported that 78% of patients with MF have hyperbilirubinaemia shortly after HSCT and sinusoidal obstruction syndrome (SOS) occurred frequently (36%).[4] Utilizing the EBMT registry, our study evaluated the incidence of liver biological abnormalities occurring within the first 100 days following HSCT and potential impact on outcomes. Two hundred and eighty-three consecutive patients with a diagnosis of primary or secondary MF undergoing first HSCT between 2007 and 2015 from eight centres that volunteered to participate were included. Liver adverse events (AEs) were defined as at least one elevated biological marker: aspartate transaminase (AST), serum alkaline phosphatase (ALP), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT) or bilirubin occurring from the start of the conditioning regimen up to 100 days after HSCT according to Common Terminology Criteria for Adverse Events (CTCAE

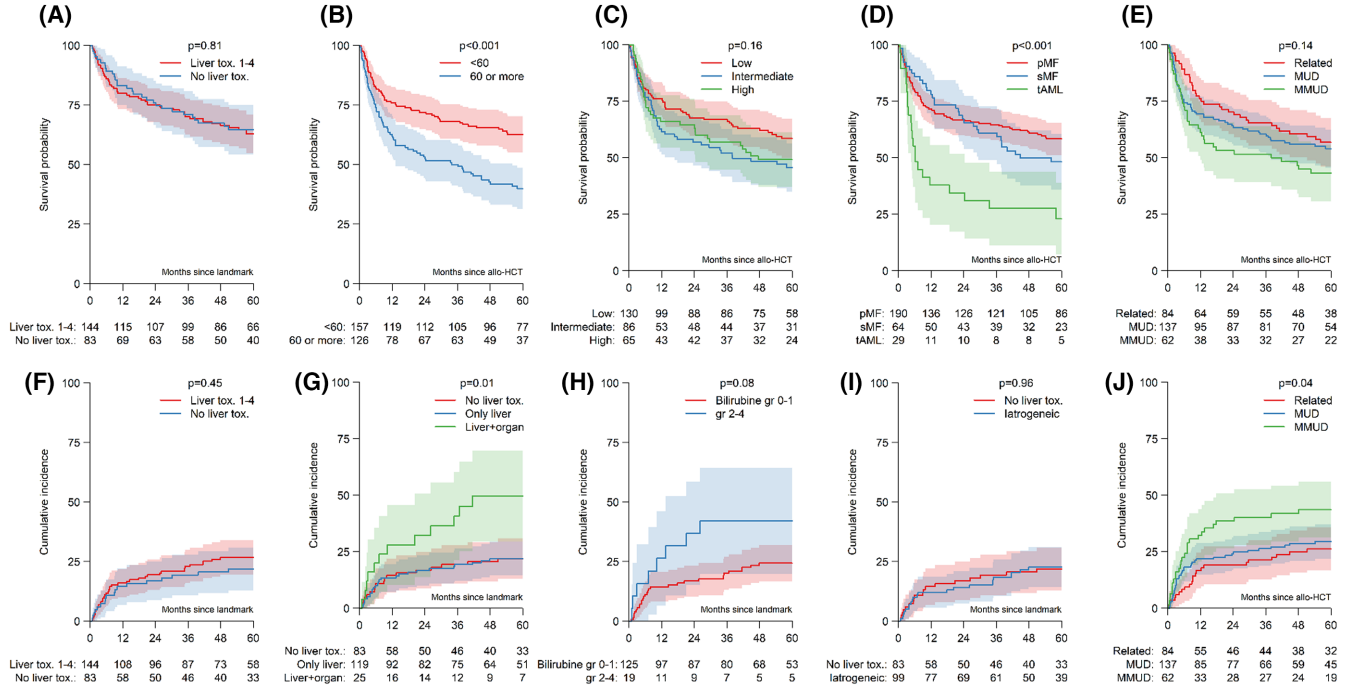

FIGURE 1 Outcome after HSCT, (A–E): probability of overall survival (OS) by (A) liver AE grade, (B) age at HSCT (years), (C) HCT-CI risk category, (D) type of disease, (E) type of donor and (F–J): cumulative incidence of non-relapse mortality (NRM) by (F) liver AE grade, (G) liver AE + organ involvement, (H) bilirubin toxicity, (I) iatrogenic liver AE (as reported on questionnaire) and (J) type of donor. Figure (A) and (F–I) are landmark analyses starting from 100 days after HSCT, all other figures start from HSCT. Numbers below the graphs show the number at risk. Shaded areas show the 95% confidence intervals. *p*-values were obtained using the log-rank test from figure (A–E) and Gray's test for Figure (F–J). high, HCT-CI risk score 3 or more; HSCT, haematopoietic stem cell transplantation; Intermediate, HCT CI risk score 1–2; low, HCT-CI risk score 0; MMUD, mismatched unrelated donor; MUD, matched unrelated donor; pMF, primary myelofibrosis; sMF, secondary myelofibrosis; tAML, transformed to AML.

version 4). Statistical analysis followed standard EBMT policies and are detailed in supplementary data.[5] Patient, disease and transplant characteristics are available in Table S1. A total of 32 patients had pre-existing hepatic disorders prior to HSCT. Liver AEs were more frequent than expected in a general cohort of transplanted patients, with 180/283 grade 1–4 liver AEs occurring within the first 100 days (64%). Liver AE onset was reported during conditioning therapy in 57% of patients, date of transplantation and day+30 in 29% and thereafter in 14%. Liver AE occurrence associated with at least one other concomitant organ failure in 44 patients: cardiac failure ($n=24$), renal failure ($n=39$) and respiratory failure ($n=29$). In contrast with the Canadian study, only a minority of patients had an increase in bilirubin (12% of the whole cohort), most often grade 1–2 (8%). GGT was frequently increased (63%), including grade 3–4 (55% of the whole cohort). Maximal grade 1–2 in either ALT, AST or ALP was observed in 40% and maximal grade 3–4 in 23% of the whole cohort (Figure S1). Most frequently, liver AEs were iatrogenic (80%), attributed to the conditioning regimen in all but one case. Anti-thymocyte globulin (ATG) was the most frequent causative agent, and despite being well described, related hepatic AE appeared to occur more frequently in MF HSCT.[6] Other causes (sometimes associated) were hepatic graft-versus-host disease (GvHD; 19%), infection with or without organ failure (10%) and SOS (20%), confirming that SOS was more frequently diagnosed in MF patients (Table S2).[4,7,12] However, only 5/36 patients had SOS as the single cause of liver AE. Of note, 63 patients had two of three criteria compatible with SOS diagnosis (bilirubin >34 μmol/L, the presence of hepatomegaly or weight gain) but for 40 the diagnosis was not met, highlighting that these patients may have symptoms mimicking SOS. These findings favour consideration to a diagnostic liver biopsy in MF HSCT patients but only five patients in this cohort underwent a biopsy, possibly due to clinician choice/institutional policy and avoidance of invasive procedures.[13]

Regarding risk factors for development of liver toxicity in MF HSCT, on multivariable analysis (MVA) using logistic regression, worse performance status (odd ratio [OR]: 2.53, 95% confidence interval [CI]: 1.30–5.16), Hematopoietic stem cell transplantation - comorbidity index (HCT-CI) ≥3 (OR: 1.81, 95% CI: 1.81, 95% CI: 1.02–3.26) and a higher Dynamic International Prognostic Scoring System (DIPSS) (high risk vs. low and intermediate risk, OR: 2.42, 95% CI: 2.42, 95% CI: 1.03–6.35) score associated with higher risk for liver AE (Table S3). Use of ATG was associated with an elevated risk of liver AE, albeit not significantly (OR: 2.33, 95% CI: 0.90–6.24). Busulfan usually used in Reduced intensity conditioning regimen (RIC) and associated with ATG in this study, was not an independent risk factor following adjustment (HR: 0.81, 95% CI: 0.34–1.84). The type of donor and the sex of recipient did not increase the risk to develop liver toxicity (data not shown). History of liver disease did not increase post-transplant liver AE occurrence but the retrospective nature of the study may

TABLE 1 Risk estimates of the association between liver AE according to different definitions and overall survival (OS) and non-relapse mortality (NRM) obtained using multivariable Cox (cause-specific) proportional hazards models.

	OS		NRM	
	HR (95% CI)	***p***	**HR (95% CI)**	***p***
Toxicity as a time-dependent variable[a]				
Liver AE grade 1–4 versus no grade 1–4 liver AE	1.11 (0.75–1.64)	0.60	1.06 (0.65–1.71)	0.82
Liver AE grade 2–4 versus no grade 2–4 liver AE	1.25 (0.87–1.78)	0.22	1.45 (0.94–2.26)	0.10
Liver AE due to medications versus no liver AE[c]	0.95 (0.61–1.47)	0.81	0.74 (0.42–1.27)	0.27
Liver AE due to liver GvHD versus no liver AE[c]	1.77 (1.02–3.06)	0.04	2.07 (1.09–3.93)	0.03
Liver AE due to SOS versus no liver AE[c]	0.95 (0.61–1.47)	0.89	1.09 (0.55–2.15)	0.82
Toxicity in 100-day landmark analyses[b]				
Bilirubin grade 2–4 versus no bilirubin grade 2–4 AE	1.75 (0.88–3.46)	0.11	2.39 (1.07–5.34)	0.03
AST grade 2–4 versus no AST grade 2–4 AE	1.21 (0.69–2.11)	0.51	1.23 (0.65–2.34)	0.53
ALT grade 2–4 versus no ALT grade 2–4 AE	1.10 (0.69–1.76)	0.68	1.23 (0.71–2.13)	0.47
GGT grade 2–4 versus no GGT grade 2–4 AE	0.95 (0.57–1.56)	0.83	1.02–0.55-1.90)	0.95
ALP grade 2–4 versus no ALP grade 2–4 AE	1.43 (0.85–2.39)	0.18	1.45 (0.79–2.65)	0.23
No grade 1–4 liver AE	1		1	
Liver AE with organ failures	1.86 (0.93–3.74)	0.08	2.14 (0.94–4.85)	0.07
Liver AE without organ failures	0.76 (0.45–1.29)	0.31	0.78 (0.41–1.50)	0.46

Note: Apart from liver AE, all models further included age at allo-HCT, conditioning regimen, Karnofsky performance score, stage of disease at allo-HCT, donor type and MPN classification. Association between these variables and outcome after allo-HCT for the model on the first row is shown in Table S2.

Abbreviations: AE, adverse event; ALP, serum alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate transaminase; ATG, anti-thymocyte globulin; GGT, gamma-glutamyl transferase; NRM, non-relapse mortality; OS, overall survival; SOS, sinusoidal obstruction syndrome.

[a]Estimates were obtained by modelling toxicity as a time-dependent variable in analyses including 270 patients without missing data.

[b]Estimates obtained using day 100 landmark analyses including 227 patients alive and relapse/progression free at day 100.

[c]Reason as recorded on the questionnaire. Each model also included 'toxicity for other reasons' (not shown).

have underestimated the prevalence of liver disease prior HSCT due to a potential underreporting. Outcomes were consistent with previous series: 5-year cumulative incidence of secondary graft failure was 11% (95% CI: 7–14); grades 2 to 4 acute GvHD cumulative incidence was 35% (95% CI: 29–40) at day 100; chronic GvHD cumulative incidence was 56% (95% CI: 51–62) at 5 years. OS was 52% (95% CI: 47–58) at 5 years. Five-year OS was lower in patients >60 years (63%, 95% CI: 55–70 vs. 40%, 95% CI: 31–49, log-rank $p < 0.001$) and age was the only independent risk factor for mortality (HR: 1.02 [1.00–1.04], $p = 0.05$). Five-year relapse-free survival was 44% (95% CI: 38–50), 5-year relapse cumulative incidence was 25% (95% CI 20–30) and 5-year non-relapse mortality (NRM) was 32% (26–37) (Figure 1).

We analysed the association of liver AEs with outcomes according to a number of different liver AE definitions: grades 2–4 or grades 3–4 ALT, AST, ALP, GGT, bilirubin rises and according to the cause of liver AEs documented by clinician questionnaire responses (Table 1). Grades 1–4 or 2–4 AEs for hepatic enzymes did not associate with increased mortality, in keeping with liver AE resolution by Day 100 in the majority of patients (70%). This suggests predominantly transient mild abnormalities, possibly drug induced, which do not appear to influence longer term outcomes. However, grades 2–4 hyperbilirubinaemia was significantly associated with higher NRM (HR: 2.39, 95% CI: 1.07–5.34), confirming results from previous studies.[4,8,9] In addition, when liver AEs had one or more concomitant organ failures, there was a trend towards increased mortality (HR: 2.14, 95% CI: 0.94–4.85). When hepatic GvHD was recorded as the underlying cause, mortality risk was increased (HR: 1.77, 95% CI: 1.02–3.06), confirming previous studies reporting that hepatic GvHD increased the risk of death in patients with acute GvHD.[10,11] Our hypothesis is that the majority of liver AEs are induced by ATG which itself is protective for key early complications like GvHD, potentially counterbalancing the deleterious effect on the liver. However, an increase in bilirubin may be an alert for more severe liver insult. Careful monitoring of MF HSCT patients is mandated to document liver complications, if possible, by enhanced use of imaging and biopsies to increase determination of aetiology, and guide SOS treatment if it occurs.

AUTHOR CONTRIBUTIONS

Marie Robin, Donal P. McLornan and Luuk Gras performed the research. Marie Robin designed the research study. Marie Robin, Nico Gagelmann, Nicolaus Kröger, Gwendolyn van Gorkom, Matthias Ederr, Maija Itälä-Remes, Tsila Zuckerman, Yves Beguin and MS provided patients. Luuk Gras and Liesbeth C. de Wreede analysed the data. Marie Robin wrote the paper. All co-authors discussed the results and analysis and approved the manuscript.

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CONFLICT OF INTEREST STATEMENT

No relevant conflict of interest with the current study.

ETHICS STATEMENT

Approved by the CMWP/EBMT.

PATIENT CONSENT STATEMENT

EBMT informed consent for all included participants.

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[Correction added on 13 December 2023 after first online publication: Affiliation 16 was corrected.]

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