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LETTER TO THE EDITOR

Strong impact of extramedullary involvement in high-risk AML patients with active disease receiving the FLAMSA conditioning regimen for HSCT

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Despite a growing number of new molecular targets, allogeneic hematopoietic cell transplantation remains the most relevant treatment for adverse risk AML.[1] In order to balance a low therapy-related mortality with high anti-leukemic efficacy relying on the GvL effect, Schmid *et al.* introduced a sequential therapy approach consisting of cytoreductive chemotherapy with fludarabine, high-dose cytarabine and amsacrine (FLAMSA), followed by reduced-intensity conditioning (RIC) with 4-Gy TBI, high-dose cyclophosphamide and antithymocyte globulin, and prophylactic donor lymphocyte infusions if indicated. With this regimen, long-term remissions are achieved in up to 40% of patients with high-risk AML.[2] Considering the current controversy about the clinical relevance of extramedullary disease (EMD)[3,4] and tumor burden as one of the strongest predictors for treatment outcome after hematopoietic stem cell transplantation (HSCT), we performed a retrospective analysis of high-risk AML patients treated with FLAMSA-RIC followed by HSCT with respect to the impact of medullary as well as EMD manifestations.

Eighty-four patients diagnosed with *de novo* AML ($n = 67$) or secondary AML ($n = 17$) treated at our institution between 2000 and 2012 were included. High-risk disease was defined as AML with high-risk cytogenetics,[5] secondary AML, AML in second CR, primary induction failure and chemo-refractory relapse (Table 1). Disease staging before transplant included a lumbar puncture and the prophylactic administration of 12 mg of methotrexate in all patients. Outcome was analyzed with respect to overall survival (OS), cumulative incidence of death (CID) or cumulative incidence of relapse (CIR).

In 17 patients (20%), EMD was present at the time of HSCT; 10 CNS, 3 chloroma (1 skin, 1 axillary lymph nodes and 1 intraorbital) and 4 with multiple sites (1 CNS, skin and pleural effusion, 1 CNS and cervical lymph nodes, 1 lymph nodes and skin, and 1 CNS and skin). In seven patients, EMD persisted in spite of prior intrathecal (i.th.) therapy or i.th. therapy plus irradiation (two patients), in the remaining 10 patients EMD (7 CNS, 3 skin) was detected immediately before the initiation of the conditioning regimen so that no additional therapy directed toward the extramedullary manifestation was given.

All patients with EMD at HSCT also presented with active bone marrow disease (Table 1). After HSCT, 8 of 13 patients with CNS involvement (two died during HSCT, one had intracerebral bleeding during HSCT) received i.th. therapy with either 12 mg methotrexate or 40 mg cytarabine or 50 mg liposomal cytarabine ranging from 1 to 5 administrations.

The median OS after HSCT was 12.1 months (confidence interval (CI) 95%; range, 6.4–17.6 months) with survival rates at 1, 2 and 4 years of 51%, 35% and 24% respectively, which is in line with previous publications[6] (Figure 1a). There was no significant difference in OS (Table 1), CIR and CID (data not shown) according to sex, age, donor type, *de novo* AML or sAML and cytogenetics. The hematopoietic CR rate of refractory (including primary

Table 1. Patient characteristics

Patient characteristics	*Number (%)*	*Univariate analysis*	*Multivariate analysis*
No. of patients	84 (100)		
Age (years)		$P = 0.886$	
Median	48.7		
>60	8 (9)		
<60	76 (91)		
Sex		$P = 0.538$	
Male	46 (55)		
Female	38 (45)		
Diagnosis		$P = 0.786$	
De novo AML	67 (80)		
sAML	17 (20)		
Cytogenetic risk (ELN)		$P = 0.125$	
Favorable	9 (11)		
Intermediate I	16 (19)		
Intermediate II	25 (30)		
Adverse	34 (40)		
Stage at transplantation		$P = \mathbf{0.005}$	$P = 0.292$
First CR	13 (15)		
Second CR	12 (14)		
Primary refractory	31 (37)		
Refractory relapse	28 (34)		
Extramedullary disease	24 (29)	$P < \mathbf{0.001}$	$P = 0.981$
Time			
Present at transplantation	17	$P < \mathbf{0.001}$	$P = \mathbf{0.008}$
Present at relapse after transplantation	4		
Present at first relapse before transplantation	1		
Only present at diagnosis	1		
Localized			
Chloroma	7 (25)		
Meningeosis	16 (67)		
Chloroma and meningeosis	2 (8)		
GvHD			
cGvHD	32 (38)		
Skin	21 (25)		
Gastrointestinal	11 (13)		
aGvHD	44 (52)		
Skin	19 (22)		
Gastrointestinal	25 (30)		
Donor		$P = 0.984$	
Family donor	16 (19)		
Unrelated donor	56 (67)		
Unrelated HLA-mismatch donor	12 (14)		
Prior transplantation	5		
Allogeneic HSCT	4		
Autologous HSCT	1		
Cause of death			
Leukemia related	34 (57)		
Non-leukemia mortality	22 (37)		
Unknown	4 (6)		

Abbreviation: ELN, European Leukemia Network. Bold entries represent $P < 0.05$.

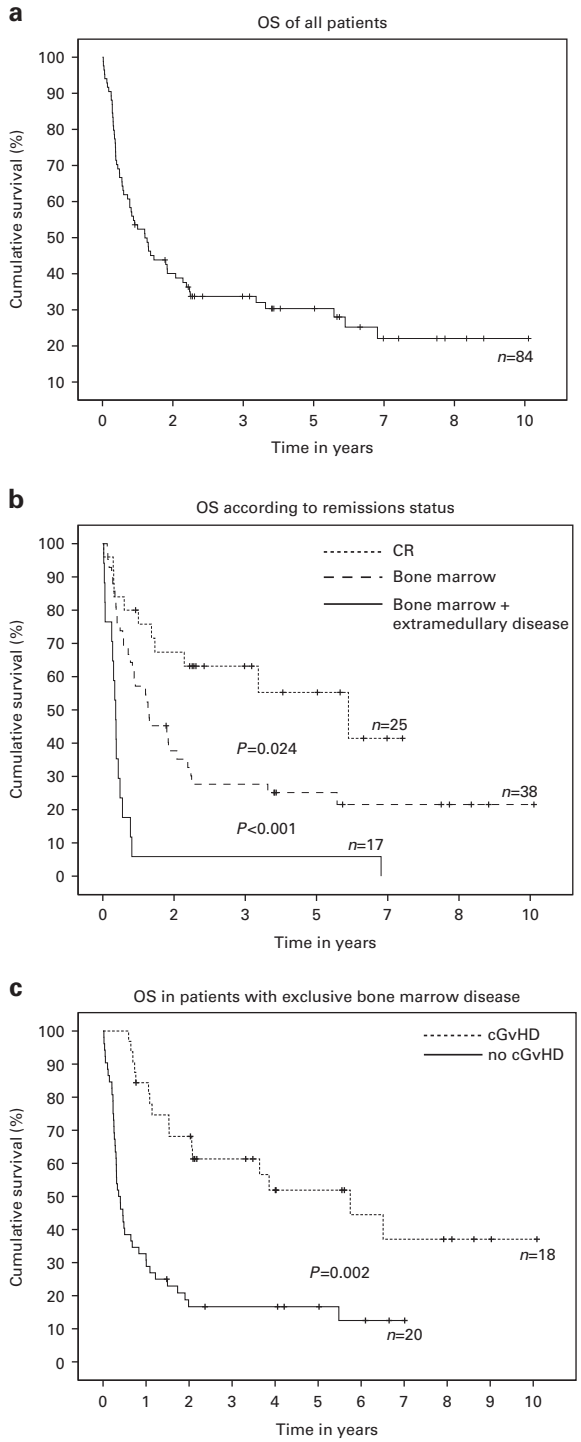

Figure 1. (**a**) Overall survival (OS) of all analyzed patients. (**b**) OS according to remission status. (**c**) OS of patients who developed cGvHD with bone marrow disease but no extramedullary disease.

refractory and refractory relapse) patients after HSCT was 81% (four patients died during HSCT, seven showed persistent bone marrow disease). Six of seven patients who presented with persistent bone marrow disease had exclusive bone marrow disease before HSCT with no extramedullary involvement.

CID for patients in CR ($n = 25$) and no-CR ($n = 59$) before transplant after 12 months was 25% and 59%, respectively; whereas CIR was 19% and 60%, respectively. Patients transplanted in CR had a 2-year OS rate of 63% in comparison with 24% for refractory patients (Figure 1b). With regard to tumor load, in a multivariable analysis the strongest predictive factor for inferior prognosis was absence of CR at the time of HSCT with concurrent EMD ($P = 0.008$; HR 0.31; CI 95%: 0.131–0.732). Due to the small number of patients, no differences were seen in location of the EMD site.

The median OS of these patients was 3.6 months in comparison with patients with exclusively active bone marrow disease with a median OS of 13 months ($P < 0.0001$) (Figure 1b). With regard to GvHD, cGvHD positively modulated relapse-free survival ($P < 0.001$) for all patients who were alive at day +100 (Figure 1c). However, in a subgroup analysis this was not seen for patients with extramedullary and concurrent bone marrow disease at HSCT.

FLAMSA-RIC followed by allogeneic HSCT offers acceptable OS rates for high-risk AML patients without concurrent active bone marrow and EMD. This confirms prior studies that did not specifically evaluate the impact of EMD.[6,7] In the retrospective analysis by Goyal *et al.*[4] no impact of pre-transplant EMD was observed with regard to outcome. However, patients with active medullary disease and EMD were excluded from the multivariate analysis due to their dismal outcome. Here, we made a similar observation that concurrent EMD is highly associated with a negative outcome in AML patients and that FLAMSA-RIC followed by HSCT is not effective in this patient group. The study by Bommer *et al.* exclusively focused on AML patients with CNS involvement underlining an adverse outcome in this patient group despite intrathecal blast clearance.[3] In our cohort of patients with residual disease, we could demonstrate a strong GvL effect associated with cGvHD but again this applied only to the subgroup without extramedullary involvement. There are several potential reasons for the lack of an effective GvL, such as the higher tumor load at transplant or the poor accessibility of extramedullary sites to alloreactive lymphocytes.[8,9]

Taken together, our data suggest that allogeneic HSCT as currently performed is futile in this subgroup of patients. Unfortunately, only insufficient data is available to evaluate a potential beneficial effect of an earlier diagnosis of extramedullary involvement by routine lumbar puncture and/or PET-CT and systematic treatment of extramedullary manifestations.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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S Bohl, S von Harsdorf, M Mulaw, S Hofmann, A Babiak, CP Maier, J Schnell, L-M Hütter-Krönke, K Scholl, V Wais, RF Schlenk, L Bullinger, M Ringhoffer, H Döhner, D Bunjes, M Bommer[1] and F Kuchenbauer[1]
Department of Internal Medicine III, University Hospital of Ulm, Ulm, Germany
[1]These authors contributed equally to this work.
E-mail: florian.kuchenbauer@uni-ulm.de

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