Extra-medullary recurrence of myeloid leukemia after allogeneic stem cell transplantation

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in Memory of Prof. Parvaneh Vossough

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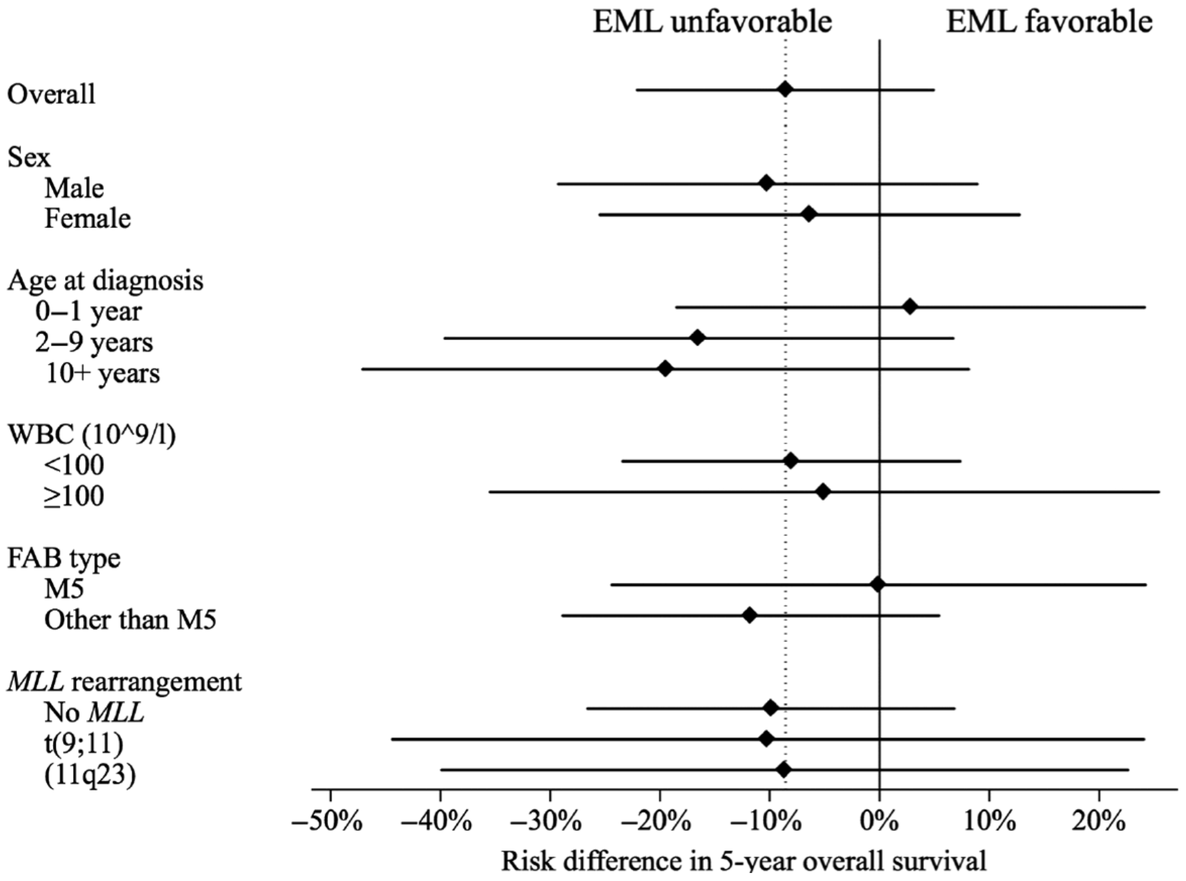
Extramedullary Leukemia

- Leukemic blast cells in the cerebrospinal fluid (CSF) or as a myeloid sarcoma (MS)
- Common finding in pediatric AML, frequencies varying from **18 to 25%.**
- Incidence of **CNSL** among pediatric patients with AML is **7% to 29%.**

- Developing in isolation and de novo
- Preceding systemic disease, or as a concomitant manifestation of
  - Acute myeloid leukemia (AML)/ common manifestation in the M4 and M5 subtypes
  - Myeloproliferative neoplasms (MPN) including blast phase chronic myeloid leukemia (CML)
  - Myelodysplastic syndromes (MDS)
- Manifest as relapse, especially in recipients of allogeneic hematopoietic stem cell transplantation (HSCT), A rare event

Extramedullary Leukemia presenting concurrently with marrow involvement requires systemic treatment directed at the underlying AML, including allogeneic hematopoietic cell transplantation (HSCT)

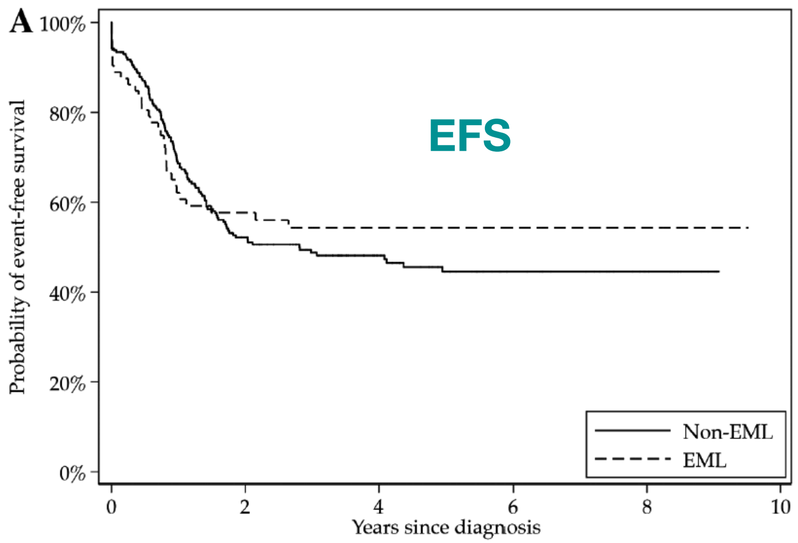
Extramedullary leukemia in children with acute myeloid leukemia



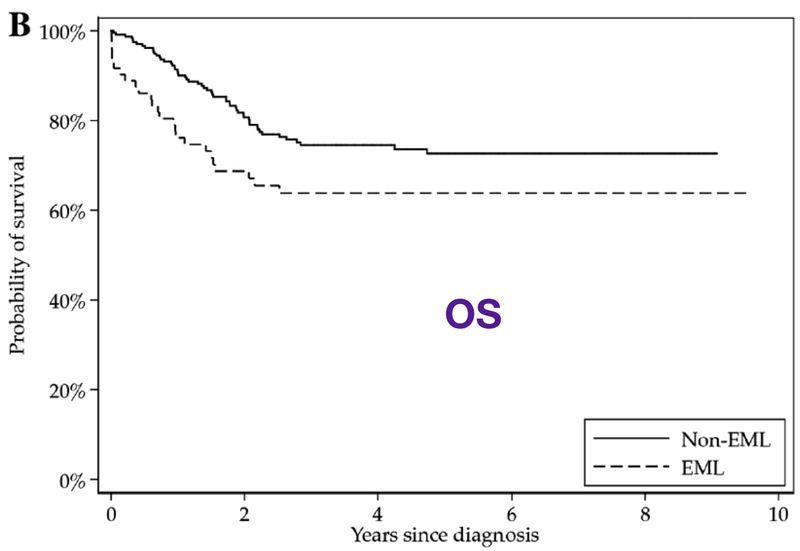
- **Myeloid sarcoma: younger and more often FAB M5 and t(9;11).**
- **CNS disease: significantly higher initial WBC and more often M4 morphology.**
- **Skin EML: young with 11q23 aberrations.**
- **Orbital EML: older with t(8;21).**

STØVE et al. Pediatr Blood Cancer. 2017;e26520.

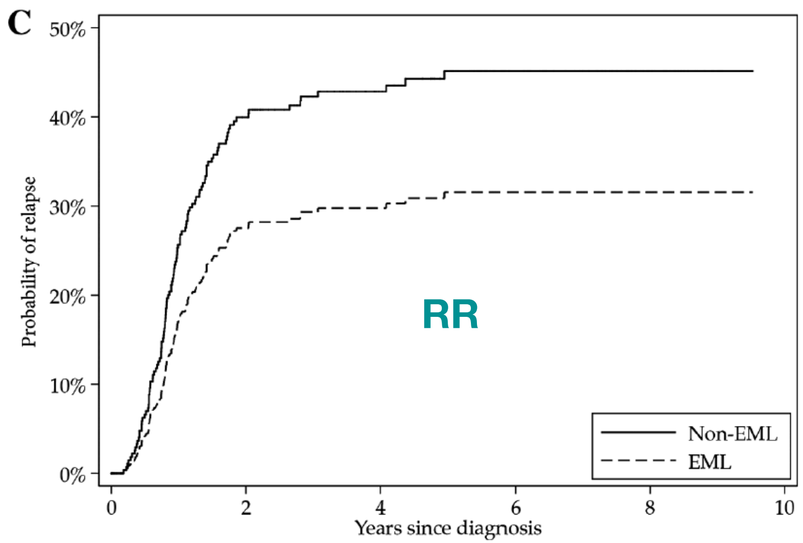
Extramedullary leukemia in children with acute myeloid leukemia



EML 5-year estimated event-free survival 54%
non-EML 5-year estimated event-free survival 45%
(Plog rank = 0.57).



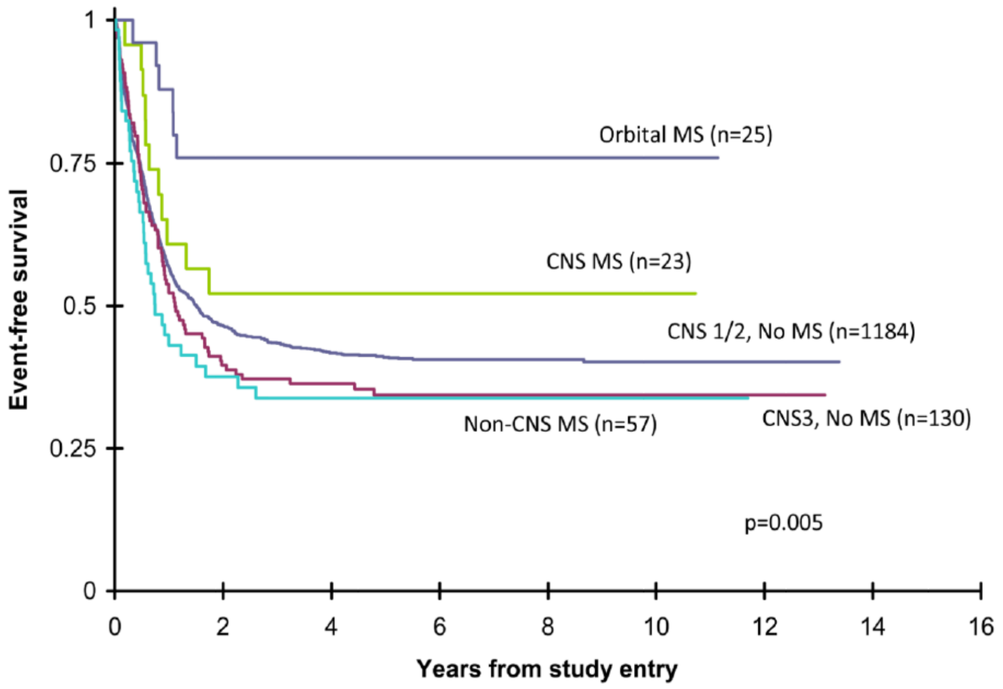
EML 5-year estimated overall survival 64%
non-EML 5-year estimated overall survival 73%
(Plog rank = 0.04).

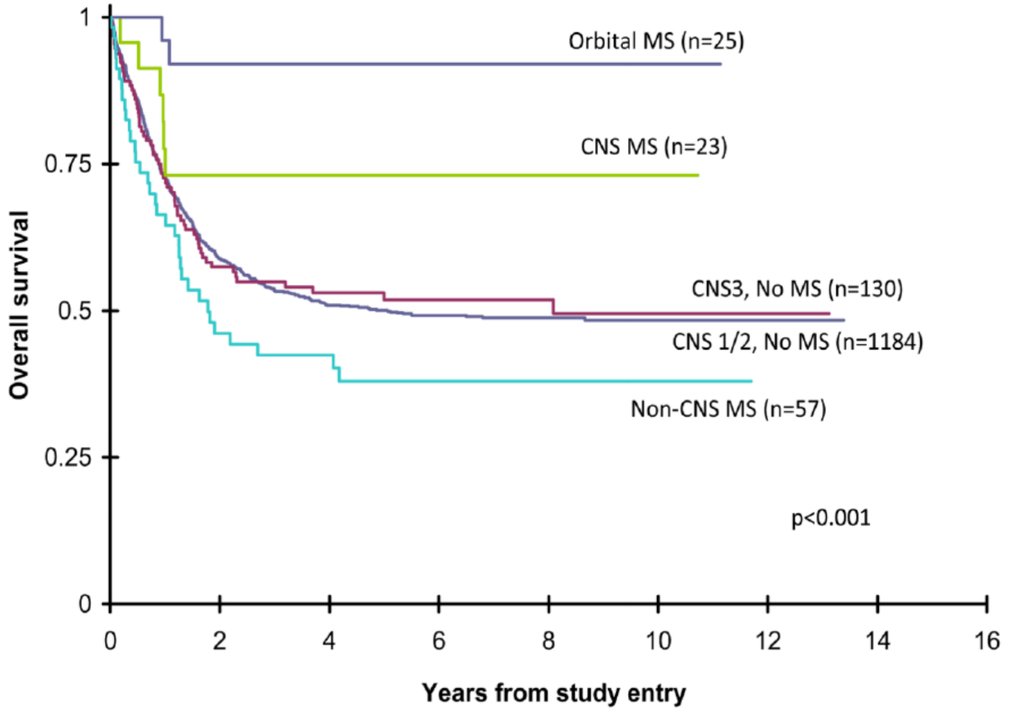


EML5-year estimated relapse risk 33%
non-EML 5-year estimated relapse risk
49% (Plog rank = 0.16)

STØVE et al. Pediatr Blood & Cancer. 2017;e26520.

Superior Outcome of Pediatric AML Patients with Orbital and CNS Myeloid Sarcoma

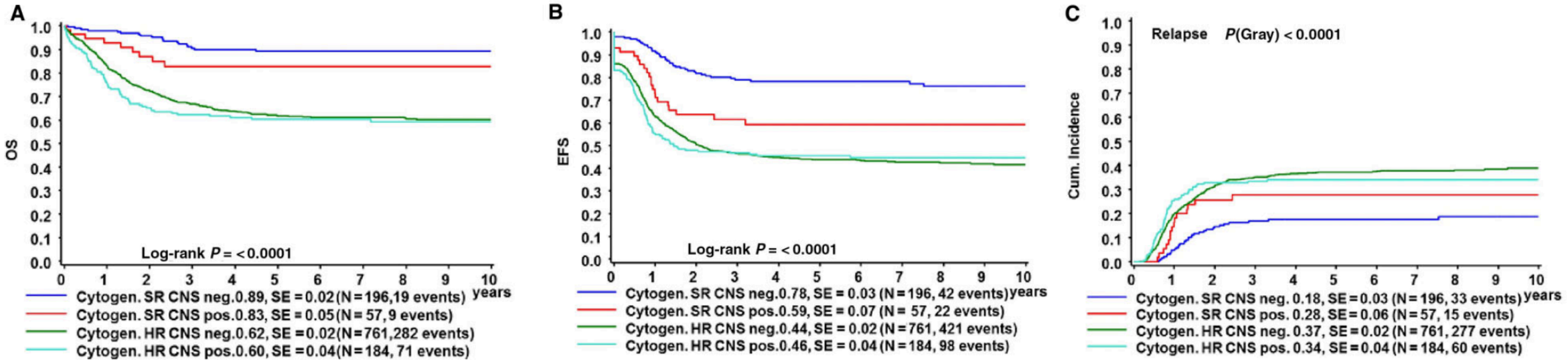




Patients with myeloid sarcoma involving orbital and CNS sites had a significantly better survival than patients with non-CNS MS, with CSF leukemia, or with no extramedullary leukemia.

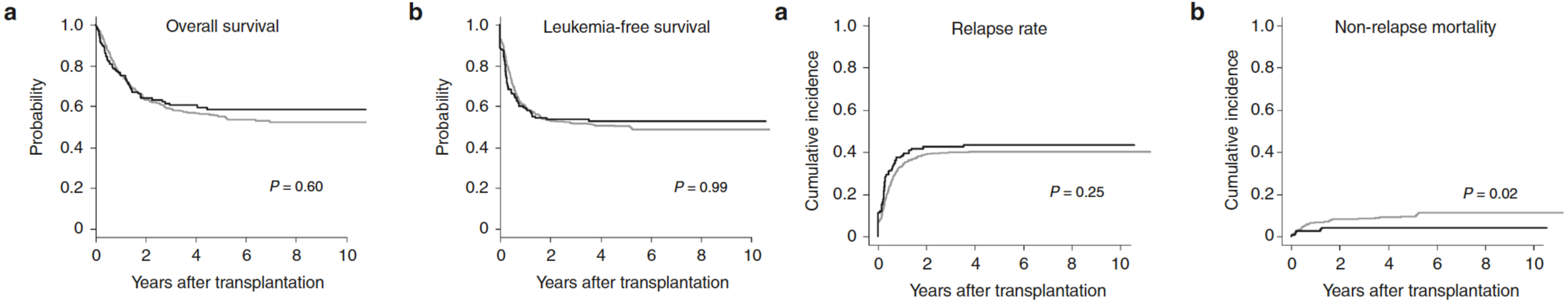
Johnston et al.Pediatr Blood Cancer . 2012 April ; 58(4): 519–524.

Outcomes of pediatric AML patients with CNS involvement



Creutzig et al. Pediatric blood & cancer. 2017 Dec 64(12):e26664.

Effect of extramedullary disease on HSCT for pediatric acute myeloid leukemia (AML)



Overall survival and leukemia-free survival

Probability of overall survival and leukemia-free survival by the EMD (black line) versus non-EMD (gray line) groups.

Relapse rate and nonrelapse mortality

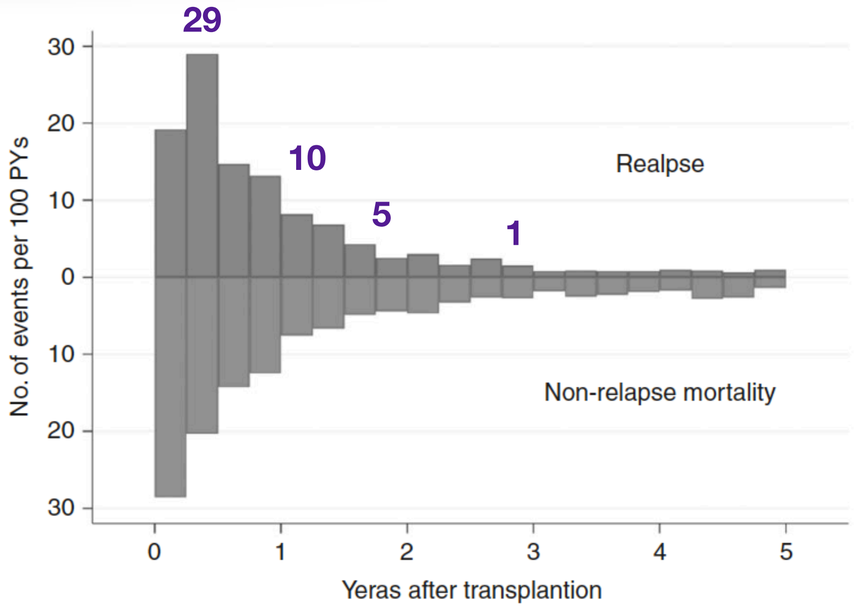
Cumulative incidence of relapse and nonrelapse mortality by the EMD (black line) versus non-EMD (gray line) groups.

H. Sakaguchi et al. Bone marrow transplantation. 2021 Mar 10:1-7.

Extramedullary relapse after Allogeneic hematopoietic stem cell transplantation

- Allogeneic hematopoietic stem cell transplantation ; an effective treatment modality in patients with AML.
- Allo-SCT improves survival in patients with unfavorable-risk AML in remission by reducing the risk of relapse/provide long-term survival in a certain proportion of patients with advanced AML.
- Recent improvements in supportive care and graft-versus-host disease (GvHD) prophylaxis regimens:
  - Reduced transplant-related mortality
  - Disease **relapse** has now emerged as the principle cause of **treatment failure after alloSCT**

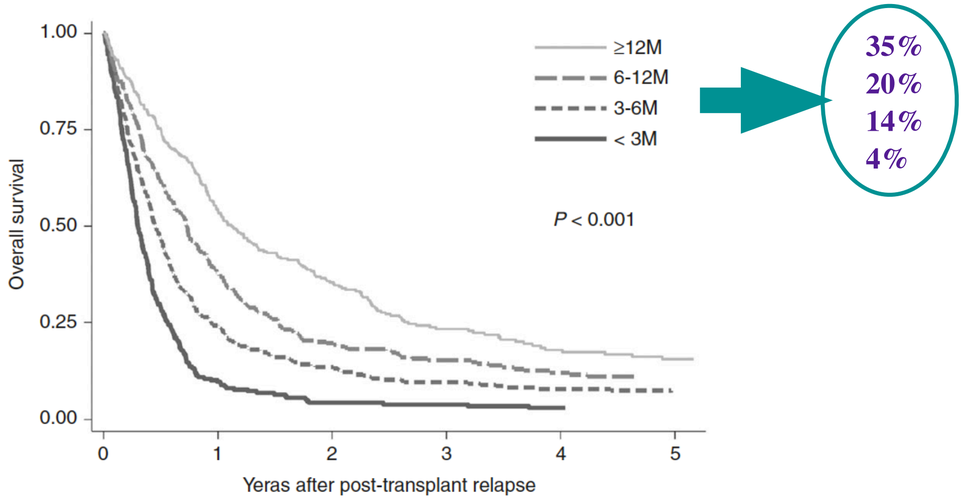
Relapse of acute myeloid leukemia after allogeneic hematopoietic cell transplantation



The incidence rate of relapse:
peaked at **29.0 per 100 PYs** during the period of **3– 6 months**
below **10 per 100 PYs** after **one year**
below **5 per 100 PYs** after **one and a half years**
remained consistently at **less than 1 per 100 PYs** after **3 years**.

Overall survival after posttransplant relapse

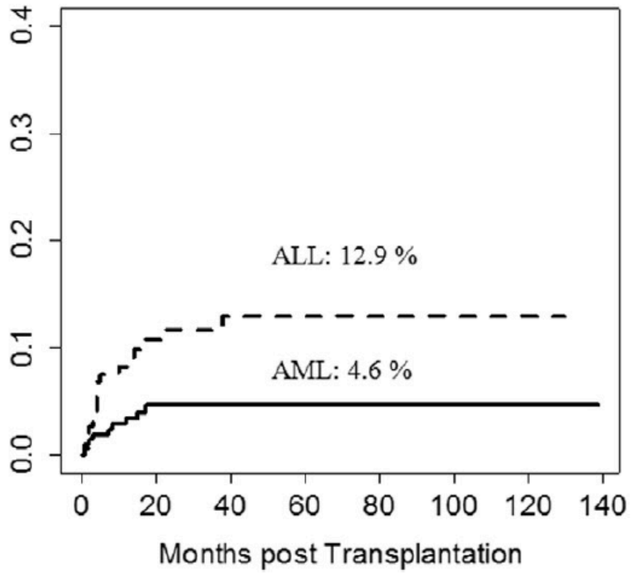
	HR	(95% CI)	*P* value
Time of posttransplant relapse			–
<3 vs. ≥12 months	3.02	(2.51–3.63)	<0.001
3–6 vs. ≥12 months	1.91	(1.61–2.27)	<0.001
6–12 vs. ≥12 months	1.38	(1.15–1.65)	<0.001



M. Yanada et al.Bone Marrow Transplantation. 2021 May;56(5):1126-33.

Extramedullary relapse after Allogeneic hematopoietic stem cell transplantation

- Isolated EM relapse after HSCT is a rare event, with incidence rates between **0.65–30%**.
- Up to **95%** of patients progress from isolated EM to **systemic relapse** after HSCT.
- Three-fourths of EM relapses happen within the **first 2 years** after HSCT.



L. Ge et al. / Biol Blood Marrow Transplant xxx (2014) 1e8

Incidence of EM Relapse after HSCT in AML

Author and Citation	Disease	Disease Status at SCT	Donor	Conditioning	Incidence of EM Relapse	EM Relapse/Total Relapse
Békássy et al. [5]	AML (n = 3,071)	ND	ND	ND	0.65%	ND
Simpson et al. [7]	AML (n = 81)	CR 64% Non-CR 36%	MRD 94% MMRD 4%	BU/CY	12%	45%
Lee et al. [9]	AML (n = 78)	CR 92% Non-CR 8%	MRD 83% MUD 15% MMUD 1%	BU/CY 95% Flu/BU/ATG 5%	10%	33%
Blum et al. [10]	AML (n = 228)	CR 54% IF 17% Rel 29%	Allo 84% Auto 16%	BU/CY-based 89% BU/VP16 11%[a]	7%	19%
Shimoni et al. [11]	MDS/AML (n = 277)	CR1 68%[b] Other 32%[b]	MRD 54%[b] Unrelated 39%[b] Haplo/cord 7%[b]	Myeloablative 68%[b] RIC 32%[b]	ND	8%
Harris et al. [12] and Porter et al. [13]	AML (n = 257)	ND	ND	ND	10%	26%
Kogut et al. [14]	AML (n = 246)	CR1/2 56% IF 16% Rel 28%	MRD 44% MUD 56%	RIC (Flu/Mel 92%)	10.4%	18%
Yoshihara et al. [15]	AML (n = 57; 38 in 1st and 19 in 2nd SCT)	CR 9% Non-CR 91%	Haploidentical	Myeloablative 25% RIC 75%	1st SCT: 11% 2nd SCT: 32%	1st SCT: 21% 2nd SCT: 51%
Solh et al. [16]	AML (n = 436)	ND	ND	ND	5.70%	20%

S. Yoshihara et al.Biol Blood Marrow Transplant 18:1800-1807, 2012

Extramedullary relapse after Allogeneic hematopoietic stem cell transplantation

- The median time from HSCT to EM relapse is longer than that from HSCT to BM-only relapse.

  Median time of **13.5 months** post-HSCT in patients with **EM relapse**
  6.1 months in those with **BM-only relapse**

- EM relapse of AML after HSCT can occur not only in **immunological sanctuary sites** (eg, CNS, testis, ovary) but also in any organ or site in the body, including the skin, muscle, bone, nasal sinuses, mammary glands, peritoneal cavity, pancreas, adrenal glands, gastrointestinal tract, kidney, and urinary tract .

Extramedullary relapse after Allogeneic hematopoietic stem cell transplantation/ Common sites

Location of extramedullary disease at relapse

Extramedullary site[a]	N. of patients (%)
Skin/soft tissue	20 (77%)
Lymph nodes	6 (23%)
Bone	6 (23%)
Central nervous system	5 (19%)
Pleura	5 (19%)
Visceral organs	4 (15%)
Testicle(s)	1 (4%)

[a]*10/26 (38%) patients presented with extramedullary disease in multiple sites.*

Skin and soft tissue were the most common sites of extramedullary relapse

A.C. Harris et al. Haematologica | 2013; 98(2)

Extramedullary relapse after Allogeneic hematopoietic stem cell transplantation

BM and EM relapses may occur as a result of immune escape from the GVL effect via various mechanisms.

Preferential occurrence of the GVL effect in the pathogenesis of EM relapse:

- Higher incidence of EM relapse after alloSCT than after autologous SCT
- An increased likelihood that patients with EM relapse have had preceding aGvHD and/or cGvHD when compared to those with BM relapse;

Patients with EM relapse were more likely to have had preceding acute GvHD (77% vs 49%; P=.03) or chronic GvHD (46% vs 15%; P=.02) compared with those with BM relapse.

- Longer time from SCT to EM relapse than the time to BM relapse
- High incidence of EM relapse in patients who received post transplantation immunomodulatory treatment, such as DLI
- High incidence of EM relapse after second SCT

M. Solh et al.Biol Blood Marrow Transplant 18:106-112, 2012.

Extramedullary relapse after Allogeneic hematopoietic stem cell transplantation

- **GVL effect** associated with an occurrence of GvHD is **less effective in preventing an EM relapse** than a BM relapse, by showing that the occurrence of aGvHD was significantly associated with better BM relapse free survival but that EM relapse-free survival was similar in patients with or without aGvHD.

- Major effector cells for the GVL response— that is, **CD8-positive T cells** and **natural killer cells (NK Cells)** are present in much higher numbers in BM than in EM tissues.

- In patients with extramedullary relapse (EMR), however, the **GVL effect is ineffective**, suggesting that leukemic cells may escape the GVL effect in sanctuary sites.

Extramedullary relapse after Allogeneic hematopoietic stem cell transplantation

- The **intrinsic characteristics of leukemic cells**, such as **CD56 expression**, may also be involved in the pathogenesis of EM relapse, particularly in the process of the homing of leukemic cells to the sites of relapse.

- The **CD56 antigen** has been identified as an isoform of the **neural cell adhesion molecule** and mediates cell-to-cell interactions via homophilic adhesion.

- CD56/neural cell adhesion molecule has been reported to be highly expressed in various tissues, including neural tissues, gut, pancreas, thyroid gland, adrenal gland, testis, ovary, visceral smooth muscle, and cardiac muscle.

- EM involvement at these sites may result from the homing of leukemic cells to these sites via homophilic adhesion of CD56 antigens.

Factors have been identified as being associated with EM relapse after HSCT

- GvHD：patients with EM relapse have been reported to be more likely to have had preceding acute GvHD and/or chronic GvHD compared to those with BM relapse.
- Donor lymphocyte infusion (DLI)
- Younger age
- EM manifestations before HSCT
- Advanced disease at HSCT
- Unfavorable cytogenetics
- M4/M5 subtypes according to FAB classification
- Intensity of conditioning; seems to play a role in the onset of EM relapse after HSCT:
  RIC protocols may be associated with a higher risk of EM relapse

Although chromosomal abnormalities such as t(8;21) and inv(16), and CD56 expression in leukemic cells have been suggested to be associated with EM infiltration of AML at diagnosis or at relapse after chemotherapy, the significance of these factors in EM relapse in the SCT settings remains unclear.

Risk Factors for EM relapse after Allogeneic hematopoietic stem cell transplantation

Variable	N	EMR						BMR only					
		Univariate Analysis			Multivariate Analysis			Univariate			Multivariate		
		HR	95% CI	*P* value	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Acute GVHD													
Grade 0–I	178	1.00			1.00			1.00					
Grade II–IV	115	.37	.12-1.11	.08	.36	.12-1.08	.07	.95	.57-1.59	.85	-	-	-
Chronic GVHD													
No	155	1.00						1.00			1.00		
Yes	138	1.10	.44-2.71	.84				.38	.22-.65	<.05	.34	.20-.57	<.05
Conditioning regimen													
TBI-MAC	94	1.00						1.00					
non-TBI-MAC	87	2.32	.72-7.44	.16	-	-	-	.94	.48-1.82	.85	-	-	-
RIC	112	1.25	.35-4.45	.73	-	-	-	1.13	.61-2.09	.69	-	-	-
Extramedullary lesions before allo-HSCT													
No	250	1.00						1.00					
Yes	43	1.77	.57-5.43	.32	-	-	-	.70	.30-1.63	.41	-	-	-
FAB classification													
M0-2, 6, 7, unknown MS	213	1.00						1.00					
M3-5	80	1.26	.48-3.30	.63	-	-	-	1.09	.62-1.91	.77	-	-	-
GVHD prophylaxis													
CSP-based	141	1.00						1.00					
TAC-based	152	.73	.29-1.88	.52	-	-	-	1.12	.67-1.87	.66	-	-	-
HCT-CI													
0	251	1.00						1.00					
≥1	42	1.87	.74-4.70	.18	-	-	-	.66	.35-1.26	.21	-	-	-
HLA disparity													
Matched	220	1.00						1.00					
Mismatched	73	.60	.18-2.09	.43	-	-	-	.72	.37-1.38	.32	-	-	-
Cytogenetic risk group													
Favorable	50	1.00						1.00			1.00		
Intermediate/poor	243	.46	.18-1.21	.12	-	-	-	2.53	1.01-6.34	<.05	2.60	1.02–6.66	< 0.05
Sex													
Male	177	1.00						1.00					
Female	116	1.03	.42-2.53	.96	-	-	-	1.29	.78-2.16	.32	-	-	-
Stem cell source													
BM	160	1.00			1.00			1.00					
PBSCs	118	2.68	1.00-7.13	<.05	2.77	1.04-7.34	<.05	.86	.51-1.45	.57	-	-	-
CB	15	2.40	.30-19.03	.41	2.39	.27-20.89	.43	.36	.05-2.37	.29	-	-	-
Disease status at allo-HSCT													
Any CR	192	1.00						1.00			1.00		
Non-CR	101	1.51	.60-3.80	.39	-	-	-	2.03	1.21-3.39	<.05	2.14	1.27-3.59	<.05

PBSCT ; an independent risk factor for EMR

S. Yuda et al. Biol Blood Marrow Transplant 25 (2019) 11521157.

Risk Factors for EM relapse after Allogeneic hematopoietic stem cell transplantation

	Any relapse, hazard ratio, (*P*)	Extramedullary relapse, hazard ratio[a], (*P*)
Pre-transplant risk factors		
Age ≤18 years at diagnosis	**1.7 (0.04)**	**3.3 (0.006)**
EM disease prior to transplant	**1.2 (0.6)**	**4.6 (<0.001)**
High risk cytogenetics[b]	**1.6 (0.03)**	**2.9 (0.006)**
FAB M4/M5	**1.6 (0.03)**	**2.5 (0.02)**
T-cell markers	0.8 (0.3)	1.4 (0.4)
CD56 expression	1.3 (0.4)	2.2 (0.08)
Related donor	1.1 (0.5)	0.9 (0.8)
HLA matched donor[c]	1.6 (0.08)	2.7 (0.1)
Gender mismatch	0.9 (0.7)	1.2 (0.6)
Stem cell source (peripheral blood *vs.* other)	0.9 (0.6)	1.0 (1.0)
Disease status CR3+/refractory at HSCT	**2.0 (0.001)**	**2.6 (0.02)**

	Any relapse, hazard ratio, (*P*)	Extramedullary relapse, hazard ratio[a], (*P*)
Transplant risk factors		
TBI in conditioning, n. (%)	0.6 (0.3)	1.3 (0.7)
Busulfan in conditioning, n. (%)	1.6 (0.3)	0.7 (0.6)
Full intensity conditioning, n. (%)	0.8 (0.5)	5.8 (0.08)
Tacrolimus/methotrexate in GVHD prophylaxis[d]	1.2 (0.5)	1.0 (0.9)
Any acute GVHD	1.3 (0.2)	1.4 (0.4)
Skin only	1.2 (0.5)	1.5 (0.4)
Visceral ± skin	1.5 (0.1)	2.2 (0.1)
Chronic GVHD	**0.5 (0.003)**	**1.6 (0.3)**

Unlike medullary relapse,chronic GvHD was not protective against extramedullary relapse.

A.C. Harris et al. Haematologica | 2013; 98(2)

Risk Factors for EM relapse after Allogeneic hematopoietic stem cell transplantation

Risk Factors for EMR and BMR in Patients with AL

Factor	EMR				BMR			
	Univariate RR (95% CI)	*P* Value	Multivariate RR (95% CI)	*P* Value	Univariate RR (95% CI)	*P* Value	Multivariate RR (95% CI)	*P* Value
Sex, male/female	3.486 (1.314-9.250)	.012	2.844 (1.060-7.631)	.038	1.543 (0.926-2.572)	.096		
Age, ≤18/>18 yr	2.224 (0.967-5.117)	.060			1.434 (0.780-2.636)	.247		
Disease								
AML	1.000				1.000			
ALL	2.911 (1.296-6.539)	.010			1.509 (0.916-2.484)	.106		
AMLL	0.000 (0.000-)	.977			2.005 (0.480-8.376)	.340		
Donor type								
Sibling	1.000				1.000			
URD	2.464 (1.025-5.926)	.044			1.249 (0.697-2.236)	.455		
Haploidentical	3.236 (1.170-8.950)	.024			2.098 (1.105-3.983)	.024		
HLA mismatch/match)	1.735 (0.727-4.140)	.214			1.737 (0.996-3.029)	.052		
Stem cell source								
BM	1.000				1.000			
PB	4.425 (1.605-12.199)	.004	5.495 (1.880-16.062)	.002	0.855 (0.484-1.510)	.589		
BM + PB	3.271 (0.998-10.719)	.050	2.583 (0.752-8.870)	.132	1.120 (0.588-2.135)	.730		
Hyperleukocytosis at diagnosis, yes/no	2.394 (1.107-5.176)	.027	3.382 (1.484-7.707)	.004	0.961 (0.566-1.630)	.881		
Cytogenetic risk, high/intermediate-low	2.999 (1.385-6.495)	.005	3.860 (1.647-9.045)	.002	2.013 (1.201-3.375)	.008		
Disease status at HSCT								
CR1	1.000				1.000		1.000	
≥CR2	2.770 (1.126-6.813)	.026	1.154 (0.431-3.087)	.775	2.598 (1.447-4.664)	.001	2.052 (1.098-3.835)	.024
NR	4.451 (1.467-13.505)	.008	6.663 (1.923-23.085)	.003	5.488 (2.728-11.043)	.000	7.387 (3.593-15.189)	.000
EM leukemia before HSCT, yes/no	3.427 (1.291-9.093)	.013	3.011 (1.064-8.521)	.038	1.029 (0.374-2.833)	.955		
Conditioning regimen								
Bu	1.000				1.000		1.000	
TBI	2.645 (1.210-5.780)	.015			1.959 (1.151-3.334)	.013	2.100 (1.179-3.739)	.012
NST	0.000 (0.000)	.979			2.247 (0.802-6.292)	.123	3.159 (1.114-8.956)	.031
aGVHD, no/yes	0.635 (0.294-1.371)	.248			0.958 (0.580-1.584)	.868		
cGVHD, no/yes	3.694 (1.108-12.320)	.033			5.085 (2.193-11.791)	.000	5.907 (2.531-13.784)	.000

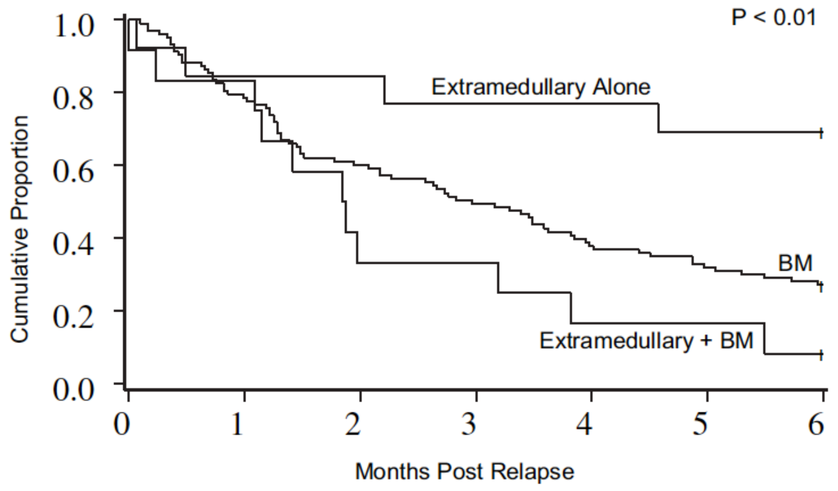
- Advanced disease status at HSCT
- Hyperleukocytosis at diagnosis
- History of extramedullary leukemia before HSCT
- Total body irradiation based conditioning regimen

Univariable and multivariable analysis of risk factors for CNS relapse after allo-HSCT

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P*	HR	95% CI	*P*
CNS involvement before HSCT						
No	1.000			1.000		
Yes	7.103	3.255–15.500	< .001	6.940	3.146–15.306	< .001
Conditioning regimen						
BU-based	1.000					
TBI-based	1.491	.452–4.917	.512			

Qi Chen et al. Ann Hematol (2021) 100:505–516

Extramedullary relapse after HSCT in AML ; Better prognosis than systemic relapse



6-month survival postrelapse was significantly better in patients with isolated EM relapse (69%) compared with those with combined EM and BM relapse (8%) or those with BM relapse alone (27%) (P<.01).

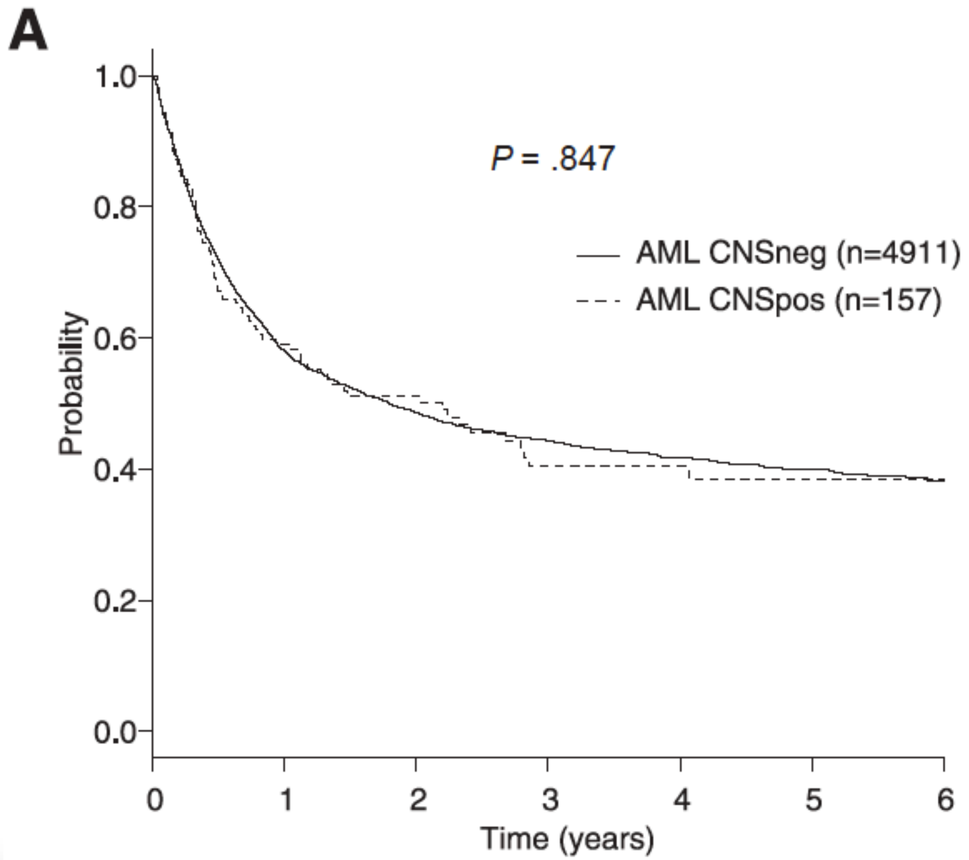
OS after HSCT in Patients with EM Relapse

Factors	Number of Patients	Number of Deaths	6-Month Survival (95% CI), %	*P* Value
Total	25	15	40 (21-58)	
Type of relapse				<.01
EM without concurrent BM	13	4	69 (37-87)	
EM with concurrent BM	12	11	8 (1-31)	
Relapse site				.62
CNS	5	4	20 (1-58)	
EM	19	10	47 (24-67)	
Testis	1	1		
EM leukemia before HSCT				.26
No	17	9	47 (23-68)	
Yes	8	6	25 (4-56)	
Therapy				<.01
Combined	5	3	40 (5-75)	
Local	9	6	33 (8-62)	
Systemic	9	4	56 (20-80)	
None	2	2		
Response to therapy				<.01
CR	13	3	77 (44-92)	
PD	9	9	0	
PR	3	3		

M. Solh et al.Biol Blood Marrow Transplant 18:106-112, 2012.

Outcome of Allo-HSCT for AML Patients with CNS Involvement

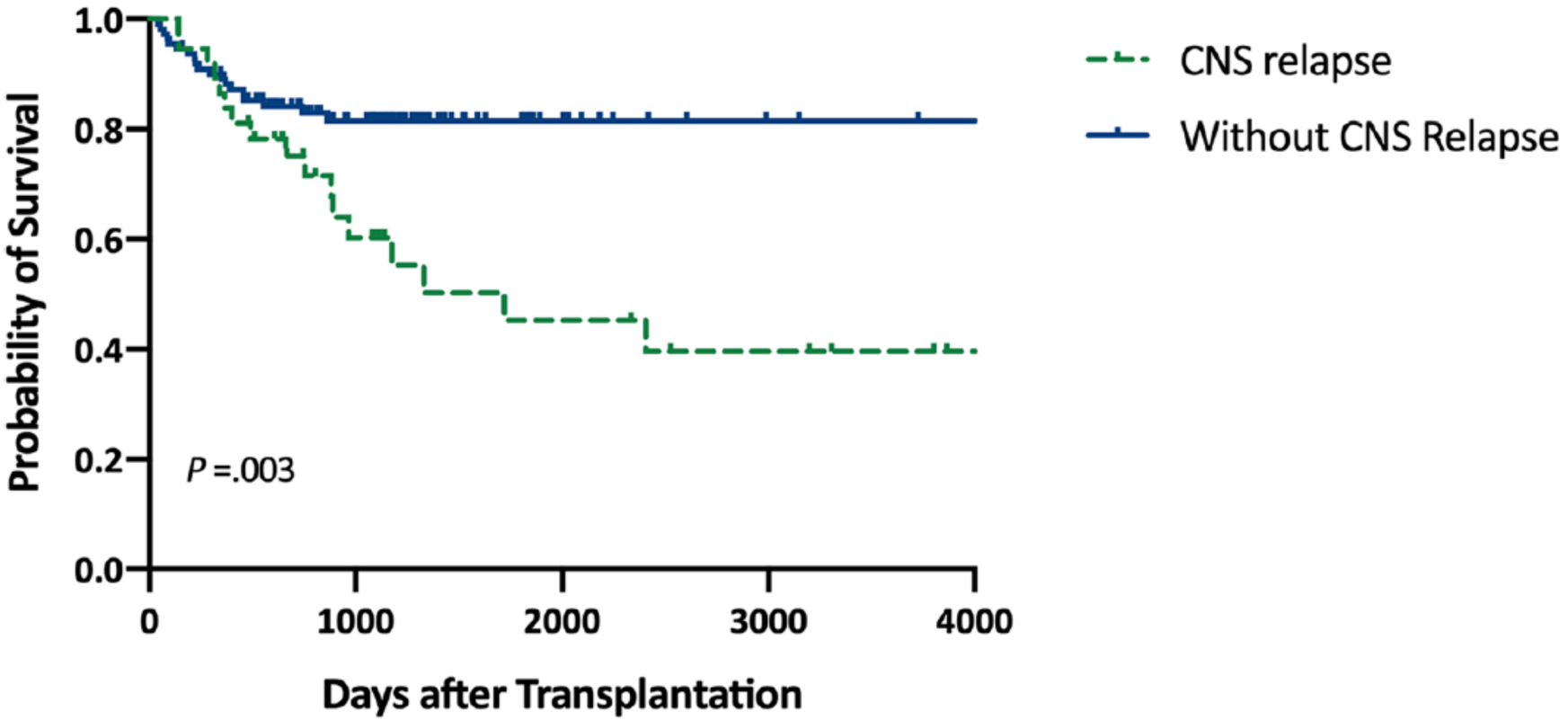
Although AML patients with EMD undergo allogeneic HCT because of poor outcomes, AML with EMD has a similar post-transplant outcome compared with AML without EMD



The estimated overall survival for CNS+AML (51.2%) were comparable with those for AML without CNS involvement (48.6%).

J. Aoki et al. / Biol Blood Marrow Transplant 20 (2014) 2029e2033

Clinical outcomes of patients with and without CNS relapse after allo-HSCT



Qi Chen et al. Ann Hematol (2021) 100:505–516

Diagnostic Modalities for EM relapse after Allo-HSCT

- No standardized strategy has been established for the **surveillance of EM relapse** after alloSCT.
- Most significant challenge in the early diagnosis of EM relapse is due to **diversity in relapse sites**.
- Diagnosis of an EM relapse is often **delayed** until patients develop the symptoms of a large mass.
- **FDG uptake** is **not specific** for leukemic infiltration/ the detection of EM relapse in areas with a physiologically high background of FDG uptake (eg, CNS, heart, and urinary tract) is difficult. cost-effectiveness may be an issue.

Diagnostic Modalities for EM relapse after Allo-HSCT

- **Histological confirmation** is necessary for the diagnosis of EM relapse.
- Minimal residual disease **(MRD) monitoring** using a chimeric gene or a WT1 transcript assay using Rq-PCR may predict EM relapse of AML.
- Minimal residual disease monitoring using a chimeric gene or WT1 transcripts in the PB may be useful for the prediction of relapse, and FDG-PET/CT may be useful for detecting the sites of relapse.

Optimal therapeutic approaches for EM relapse after Allo-HSCT

- The optimal therapy post-HSCT is a matter of debate.

- The choice of therapy depends on:
  - Time from transplant to MS onset
  - Patients' general health condition
  - Chimerism
  - Presence of GvHD

- Treatment options for post-transplant relapse include:
  - Chemotherapy
  - Radiotherapy
  - Donor lymphocyte infusion (DLI)
  - Second allo- HSCT (HSCT2)

Despite such treatments, however, the prognosis is usually dismal, making post-transplant relapse the greatest obstacle to the success of allogeneic HSCT.

Optimal therapeutic approaches for EM relapse after Allo-HSCT

- As a less effective GvL-effect is considered to be causative for the formation of MS, **DLI** and tapering of immunosuppression are recommended.
- **Hypomethylating agents**: enhance GvL by increasing HLA and tumor-associated antigen expression.
- Gemtuzumab ozogamizin.
- Targeted therapies, i.e. **tyrosine kinase inhibitors for FLT3-ITD**.

Optimal therapeutic approaches for EM relapse after Allo-HSCT

- Inhibition of CTL-4 may prevent immune escape / result in complete response of MS.
- In case of rapid tumor growth, surgery or palliative **radiotherapy**.
- combinational approach seems to be advantageous.
- Although, HSCT is a feasible option for the treatment of isolated or leukemic MS, the impact of a **secondary allogeneic HSCT**, remains unclear.

CNS involvement in AML/ Treatment Modalities

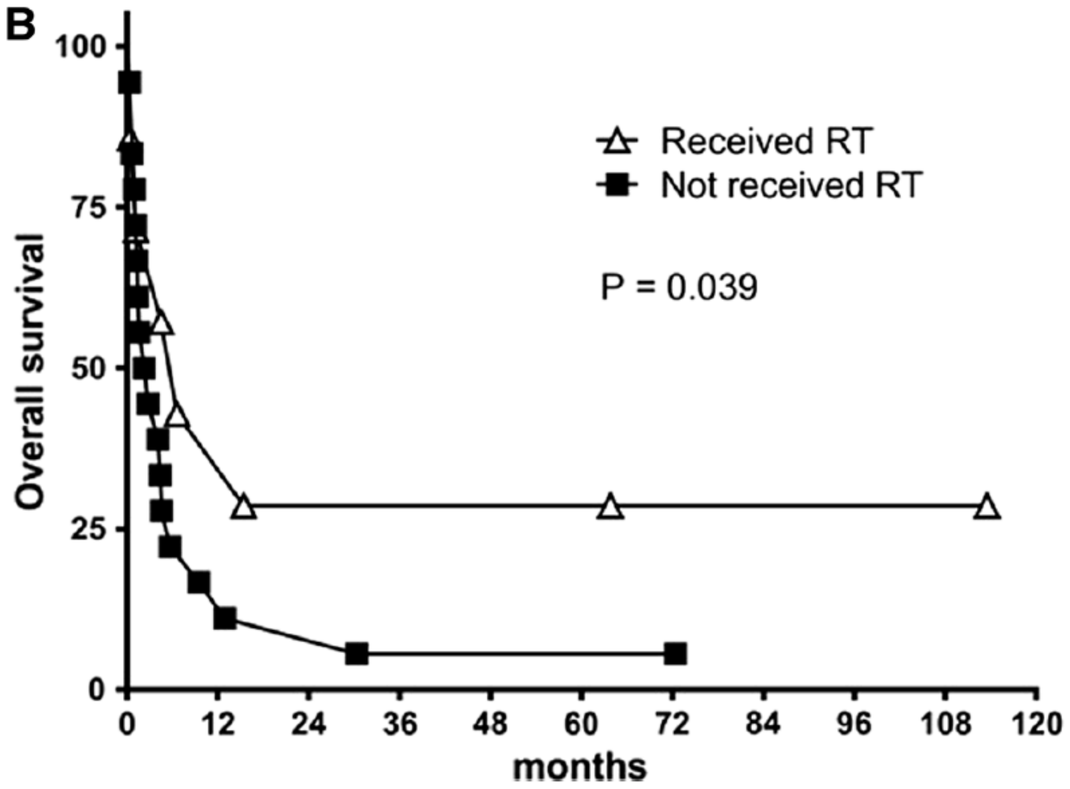
- There is **no consensus** with regard to the best treatment strategy for CNS involvement in AML.
- No standard treatment is available for CNS relapse after allo-HSCT for patients with AML
- **IT chemotherapy** alone is quite useful for the eradication of CNS blasts.
- In the cases of a heavy burden of leptomeningeal involvement or highly resistant leukemia, **RT** could be a more effective modality.

CNS involvement in AML/ Treatment Modalities

- **Allo-HSCT** has been proven to improve the outcomes of patients with CNS involvement.
- It has been shown that a **combined treatment of RT and IT chemotherapy**, compared with IT chemotherapy alone, improved the prognosis of patients who underwent allogeneic hematopoietic stem-cell transplantation.
- Patients with concomitant hematological or molecular relapse usually also received systemic chemotherapy followed by donor lymphocyte infusion (DLI).

Extramedullary relapse/ role of radiotherapy

The role of radiotherapy in the treatment of EML is controversial with lacking evidence for the benefit and the risk of long-term morbidity and mortality.



Whole-brain and/or craniospinal radiotherapy, received or not received disease.

J. H. Kwon et al.Int J Hematol (2016) 104:574–581

Case Presentation : A 6 year old girl with acute myeloid leukemia (AML)

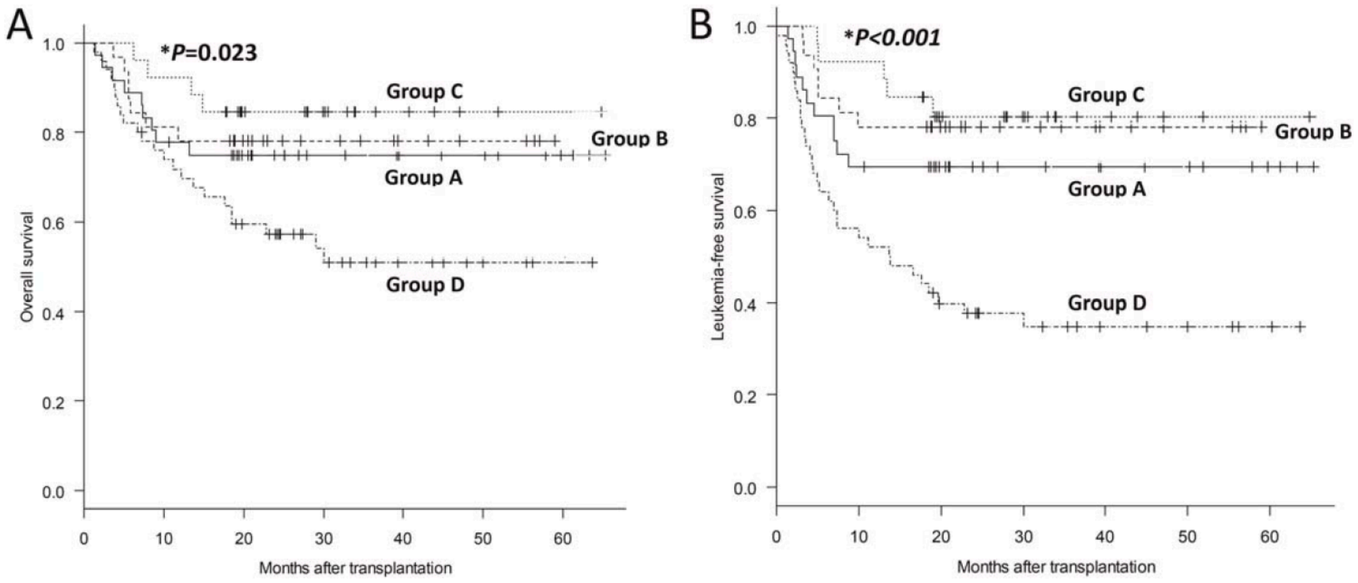
- AML-M5 subtype according to FAB classification
- Cytogenetic : Normal
- FLT3-ITD Mutated
- Allogenic HSCT from HLA matched related donor in first CR
- No acute & chronic GvHD
- BM relapse one year after transplant: Chemotherapy+ Sorafenib & DLI
- After the second DLI presented with Conjunctival hyperemia + skin GvHD
- Brain/orbit MRI: Normal
- No evidence of BM or CNS involvement

Smear from aqueous fluid:

Hypercellular and composed of many isolated blastoid cells with bean shaped nuclei, vesicular chromatin and moderate amount of pale pink cytoplasm indicative of **leukemic involvement.**

Intravitreal chemotherapy+ Sorafenib

Effect of sorafenib on the outcomes of patients with FLT3-ITD AML undergoing allo-HSCT



Group A: patients receiving sorafenib before transplantation
Group B: patients receiving sorafenib after transplantation
Group C: patients receiving sorafenib both before and after transplantation
Group D: patients receiving sorafenib neither before nor after transplantation

Sorafenib before transplantation, sorafenib maintenance after transplantation, and their combined application all could improve the outcomes for patients with FLT3-ITD AML.

Xuan et al.Cancer. 2018 May 1;124(9):1954-63.

TAKE HOME MESSAGE

- In patients with extramedullary relapse (EMR), however, the GVL effect is ineffective, suggesting that leukemic cells may escape the GVL effect in sanctuary sites.

- Younger age, EML before transplant , high risk cytogenetic , M4/5 morphology and disease status at transplant are associated with increased risk of EM relapse after transplant.

- Although AML patients with EMD undergo allogeneic HCT because of poor outcomes, AML with EMD has a similar post-transplant outcome compare with AML without EMD.

- 6-month survival postrelapse was significantly better in patients with isolated EM relapse (69%) compared with those with combined EM and BM relapse (8%) or those with BM relapse alone (27%) ($P<.01$).

- It has been shown that a combined treatment of RT and IT chemotherapy, compared with IT chemotherapy alone, improved the prognosis of patients with CNSL who underwent allogeneic hematopoietic stem-cell transplantation.

- Patients with concomitant hematological or molecular relapse usually also received systemic chemotherapy followed by donor lymphocyte infusion (DLI).

THANK YOU

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