Allogeneic HCT in leukemia and lymphoma

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Annales Pædiatrici
International Review of Pediatrics — Revue internationale de Pédiatrie
Jahrbuch für Kinderheilkunde
Redactor E. FREUDENBERG-Basel

Basel (Schweiz) S. KARGER New York

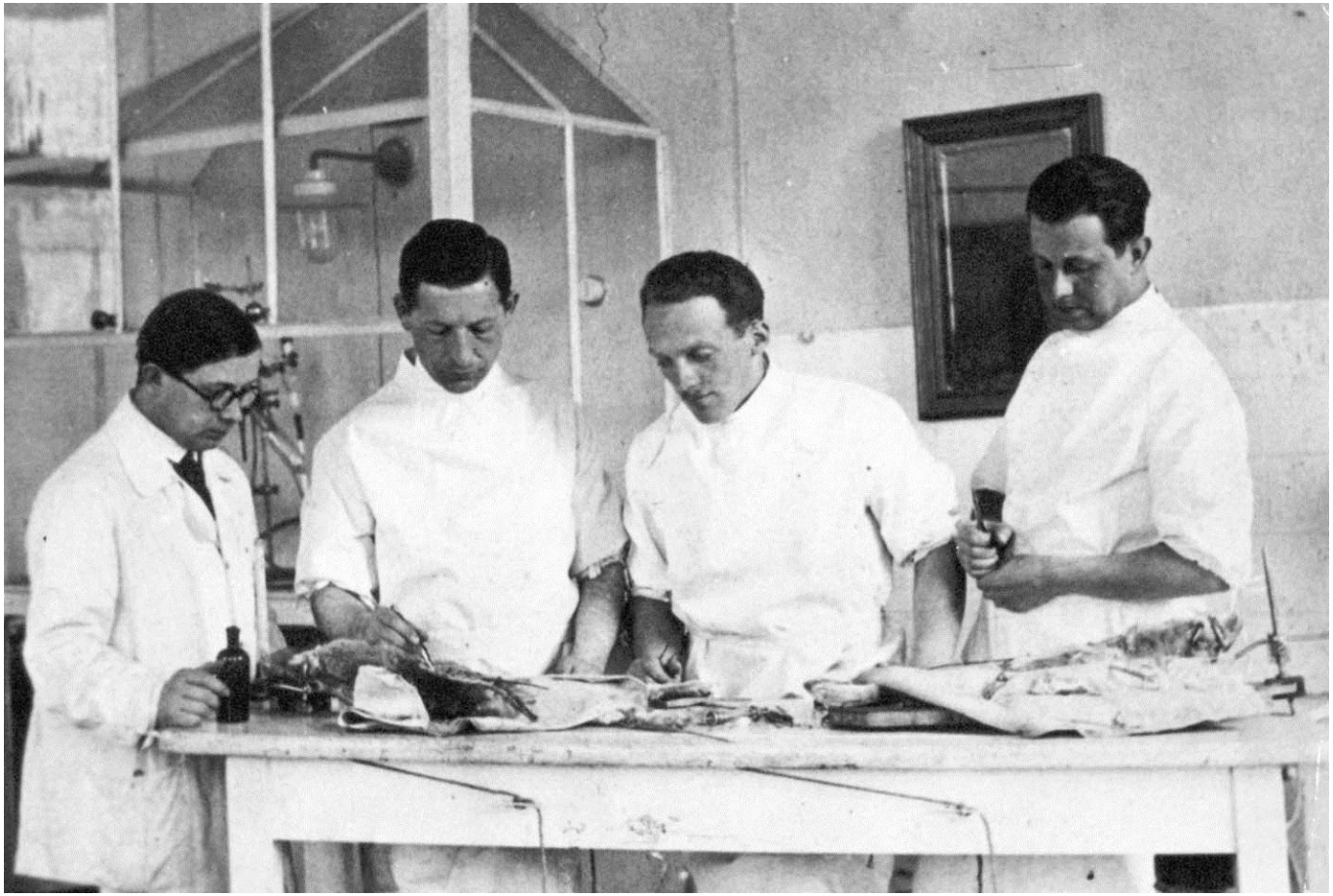
Separatum Vol. 173, No. 2 (1949) Printed in Switzerland

(From the Pediatric Department of the former Medical College in the John Casimir University of Lvov [Prof. Fr. V. Groër].)

Technique and Indications of the Therapeutic Intramedullar Transfusion of the Bone Marrow in Children.

By JAN RASZEK-ROSENBUSCH.

First attempts to transplant bone marrow performed in Lvov, Jan Kazimierz University, 1938, the third from the left **Jan Raszek**.



Intensive treatment of leukemia and lymphoma as

- A **bridge** to allogeneic transplantation
- If in particular center acute myelocytic leukemia patients survive induction remission treatment such as 3+7 (3 days of daunorubicin + 7 days cytarabine) or CODOX/IVAC treatment of Burkitt lymphoma then in the same conditions patients would survive allogeneic transplantation from sibling donor.
- The main added problem is acute graft versus host disease that at present in majority of cases may be managed.

Actually patient with newly diagnosed acute leukemia or Burkitt lymphoma…

- Has the higher risk of death from infectious complications than patient undergoing allogeneic transplantation from HLA-identical sibling donor.
- This is due to the fact the patient usually requires immediate administration of intensive chemotherapy despite the fact that he/she may have number of local and even systemic infections.
- Routine candidate for allogeneic transplantation from HLA-dentical sibling is in complete remission of leukemia and has all local sources of infection cleared.

Indications

- Indications are constantly evolving. There are indications that are introduced and some that are withdrawn.
- Final decision is made by transplant team leader based on both consideration of patient and consideration of actual team experience.
- Last EBMT publication: **Gratwohl A, Baldomero H, Sureda A: Indications for and current practice of allogeneic and autologous HSCT. In EBMT Handbook 2012, pp. 304-306.**
- For the purpose of presentation recommendations are slightly simplified. Please, compare the original publication for details.

Achievable results

- They are extracted mainly from:

- **Munker R, Hildebrandt GC, Lazarus HM, Atkinson K: The BMT Data Book, Including Cellular Therapy. Cambridge Univ. Press 2013, 3rd Edition**

Types of procedures and conventional upper age limits

- **MRD-MAC**: matched related donor – myeloablative conditioning: 55 ± 5 yrs
- **MUD-MAC**: matched unrelated donor – myeloablative conditioning: 45 ± 5 yrs
- **MD-RIC**: matched donor – reduced intensity conditioning: 60 ± 10 yrs.

Categories of indications for the transplantation of hematopoietic stem cells according to EBMT

- **Routine (R/S)** (standard, therapeutic method of choice)
- **Clinical option (CO)** (standard method of treatment for selected patients, reporting to EBMT required – in Poland required for all transplantations)
- **Developmental (D)**: performed within clinical trials
- **Not generally recommended (NR)**: data suggest either low efficacy or very high risk of procedure, however, patient without other therapeutic options together with his or her doctor may decide to perform procedure as „salvage therapy”.

Categories of indications for the transplantation of hematopoietic stem cells according to EBMT

- **Routine (R/S)** chance of cure: 50-90%, risk of death: 10-50% (combined transplant related mortality and relapse of disease despite transplantation)
- **Clinical option (CO)** chance of cure: 30-60%, risk of death: 40-70%
- **Developmental (D)**: chance of cure: 20-40%, risk of death 80-60%
- **Not generally recommended (NR)**: chance of cure 10-20% (other methods 0%). Risk of death 80-90%

EBMT risk score

Risk Factor	Score points
Age of the patient, years	
<20	0
20-40	1
>40	2
Disease stage	
Early	0
Intermediate	1
Late	2
Time interval from diagnosis to transplant, months	
<12	0
>12	1
Donor type	
HLA-identical sibling	0
Unrelated donor, other	1
Donor recipient gender combination	
All other	0
Female donor, male recipient	1

Age and performance status

- Current upper limit for allogeneic transplantation after myeloablative conditioning reaches 60-65 years, and for non-myeloablative conditioning 70 years but only if HLA-identical donor is available and patient is in good performance status.
- Less compatible donors – lower age limit.
- Consider „biological”, and not administrative age..

Cooperation of patient

- Success of the procedure hinges not only on doctors but also on patient ability to comply with all instructions concerning personal hygiene and life style during all phases of therapy.
- Patient discharged from the hospital to homelessness has no chances to survive.
- Particularly after non-myeloablative conditioning patient chances depend on the quality of care at later phases after transplantation.

Comorbidities

- Pressure of patients and their families is such, that particularly more experienced teams constantly attempt to transplant high risk patients including patients with comorbidities.
- However, at this stage in Africa I would suggest to concentrate on patients having matched related donors, and primary disease in complete remission being without significant comorbidities that is
- Patients who have the highest chance to benefit from the procedure.

Acute myeloblastic leukemia (AML)

Disease	Stage of disease	MRD-MAC	MUD-MAC	MD-RIC
AML excl. M3, inv16, i t8:21	CR1 CR2,3, inc. relapse Relapse	R/S R/S CO/D	CO CO D	over 60 yrs CO D
AML M3	Resistance to ATRA and As2O3	R/S	D	over 60 yrs CO
AML inv16 i t8:21	CR2	R/S	D	over 60 yrs CO

AML achievable results

MRD-MAC - indications	**DFS (%)**
AML (with risk factors) in CR1	50-70
AML in first relapse or CR2 or subsequent CR	15-35
Primary refractory AML	10-30
MUD-MAC - indications	
AML (with risk factors) in CR1	45-50
AML (beyond CR)	15-30

Acute lymphoblastic leukemia (preferably TBI in conditioning)

Disease	Stage	MRD-MAC	MUD-MAC	MD-RIC
ALL t(9:22)	CR1 CR2,3, inc. relapse, Relapse	R/S R/S D	R/S CO D	Over 55 yrs CO D
ALL t(4:11)	CR1 CR2,3, inc. relapse, Relapse	R/S R/S D	R/S CO D	over 55 yrs CO D
Other ALL	CR1 CR2,3	CO R/S	NR CO	Over 50 yrs CO

ALL – achievable results

MRD-MAC - indications	**DFS (%)**
ALL (adverse factors present) in CR1	45-75
ALL in CR2 or subsequent CR	10-30
Primary refractory ALL	10-20
BCR/ABL positive ALL in CR	30-40
MUD-MAC - indications	
BCR/ABL positive ALL in CR1	20-40
ALL beyond CR1	20-30

Chronic myelocytic leukemia imatinib-resistant chronic phase

- Patients without hematological remission after 3 months of therapy
- Patients without any cytogenetic remission after 6 months of therapy
- Patients without complete cytogenetic remission after 12 months of therapy
- Patients loosing any type of remission while receiving imatinib
- Dasatynib and nilotynib resistant patients
- Patients with additional chromosomal aberrations in Ph+ clone.
- Patients with T315i mutation.

Chronic myelocytic leukemia

Disease	Stage.	MRD-MAC	MUD-MAC	MD-RIC
CML	Imatinib - failure chronic phase	R/S	R/S	Over 55 yrs CO
CML	Accelerated phase	R/S R/S	R/S CO	Over 55 yrs. CO
CML	Blast crisis	CO	CO	Over 50 yrs CO

CML: achievable results: disease free long term survival

- Chronic phase: 65%
- Accelerated phase: 45%
- Blast crisis: 10-30% (depends on whether in CR at transplantation time or not)

Myeloproliferative neoplasms (not recommended for starting teams)

Disease	Stage	MRD-MAC	MUD-MAC	MD-RIC
Primary myelofibrosis	Progressive disease	R/S	CO	Over 55 yrs CO
Hypereos. syndrome	Imatinib-resistant	CO	CO	Over 55 yrs CO
Other	Resistance to other therapies Other phases	CO NR	CO NR	Over 50 yrs CO NR

Myelodysplastic syndromes

Disease	Stage	MRD-MAC	MUD-MAC	MD-RIC
RA, RC		Until 55 yrs R/S,	Until 55 yrs CO	Over 55 yrs CO
5q-	Lenalidomide -resistant	CO	CO	Over 55 yrs CO
RAEB		R/S	CO	Over 55 yrs CO

MDS: achievable results

MRD-MAC	DFS
RA (if significant neutropenia)	60%
RAS (or thrombocytopenia)	60%
RAEB	30-50%
RAEBt	30-50%

For MUD-MAC subtract 10%

Chronic lymphocytic leukemia

- Resistance to purine analogues
- Deletion p53

Disease	Stage	MRD-MAC	MUD-MAC	MD-RIC
CLL	Poor prognosis	R/S	CO	Over 55 yrs CO

Achievable 40% DFS

Non-Hodgkin's lymphoma

Disease	Stage	MRD-MAC	MUD-MAC	MD-RIC
NHL lymphoblastic, mantle and DLBCL	CR2	CO	D	over 55 yrs CO
NHL aggressive,	Primary resistance, marrow relapse	CO	CO	over 55. yrs CO
NHL intermediate	Pirimary resistance or relapse	CO	D	over 55 yrs CO
NHL indolent	Pirimary resistance or relapse	CO	D	over 50 yrs CO

NHL – achievable results

- Vary depending on specific type of NHL and on whether disease remained sensitive or resistant to chemotherapy.
- DFS may be as high as 70% in follicular lyphoma and as low as 20% in resistant diffuse large B cell lymphoma.

Hodgkin's lymphoma

Disease	Stage and type	MRD-MAC	MUD-MAC	MD-RIC
HL	First remission, lymphocyte predominance HL	NR	NR	Over 55 yrs. NR
HL	Relapse with marrow involvement, CR3,	CO	D	Over 55 yrs CO
HL	resistant	CO	D	over 50 yrs CO

HL – achievable results

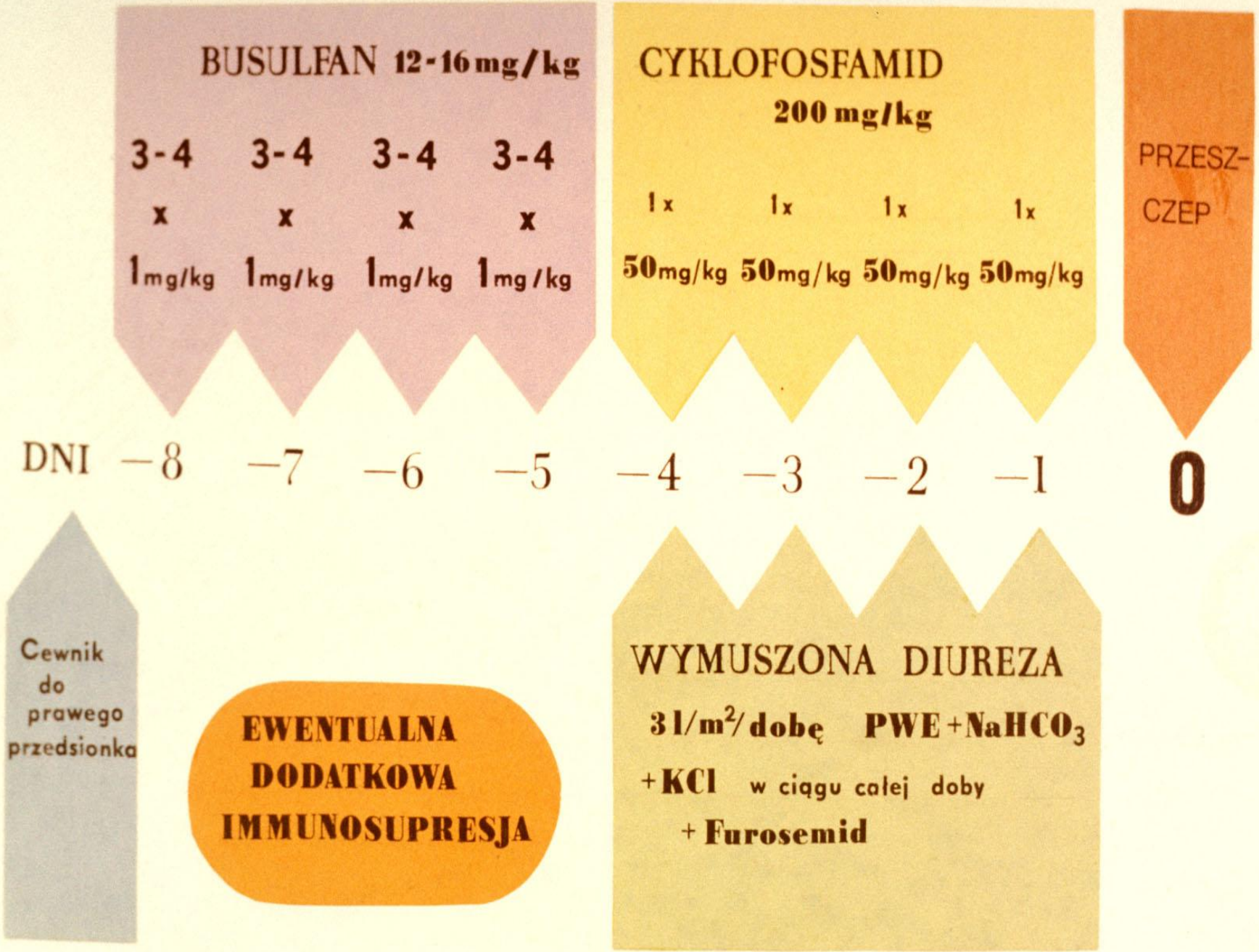
- Generally not better than autologous transplants
- Better with RIC than with MAC
- In patients relapsing after autologous transplant may offer up to 30% DFS.

Indications

- As starting indication I would recommend acute myeloblastic leukemia (intermediate or high risk) in 1CR in young patient having MRD.
- Alternatively high risk acute lymphoblastic leukemia in 1CR in young patient having MRD
- Other good choice is chronic myelocytic leukemia imatinib refractory in chronic phase in young patient having MRD.
- I would not suggest to go for older patients with primary myelofibrosis, and for patients with non-Hodgkin and Hodgkin lymphoma before accumulation of experience.

Conditioning

- While in ALL, many centers prefer total body irradiation (TBI) in conditioning it is acceptable to use chemotherapy only conditioning.
- Classical MAC chemotherapy only conditioning is BuCy200 that is being used also with modifications as BuCy120, CyBu200, BuFlu.
- And also with replacement of oral busulfan (cheap) with iv busulfan (expensive but dosage not influenced by absorption from GI tract).
- BuCy could be used for all leukemic indications.


BUSULFAN 12-16 mg/kg
3-4 x 1 mg/kg
3-4 x 1 mg/kg
3-4 x 1 mg/kg
3-4 x 1 mg/kg
CYKLOFOSFAMID
200 mg/kg
1x 50 mg/kg
1x 50 mg/kg
1x 50 mg/kg
1x 50 mg/kg
PRZESZ-CZEP
DNI −8 −7 −6 −5 −4 −3 −2 −1 0
Cewnik do prawego przedsionka
EWENTUALNA DODATKOWA IMMUNOSUPRESJA
WYMUSZONA DIUREZA
3 l/m²/dobę PWE + NaHCO3
+KCl w ciągu całej doby
+ Furosemid

Conditioning

- My recommendation is to limit initial program for leukemia only to MRD-MAC transplantation.
- The reason to omit RIC is that while it may be easier during early period after transplantation the difficulty is shifted to long term care.
- If good long term care is not established the outcome would be disastraous to the patient.
- Development of good long term care requires years of experience.

Warsaw Mermaid is chimera similarly as recipients of allogeneic transplants