Haploidentical HSCT from Family Members

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Haploidentical HSCT from family members

Rationale

- Lack of a compatible donor in a significant proportion of patient
- Pts with severe combined immunodeficiency have shown no GvHD by 3-log T-cell depletion even in non-matched BMT
- T-cell depletion and haploidentical SCT has high risk of graft failure
- Graft failure results from immunological rejection and/or competition between donor and residual host stem cells
- in experimental models immunological rejection of T-cell depleted non-identical BMT can be avoided by increasing Rx, by splenic irradiation or treatment with mAb. Stem cell competition can be avoided by increasing the size of the graft or by adding Bu or Thiotepa

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Early in vivo studies

blood 1994 84: 3948-3955

Successful engraftment of T-cell-depleted haploidentical "three-loci" incompatible transplants in leukemia patients by addition of recombinant human granulocyte colony-stimulating factor-mobilized peripheral blood progenitor cells to bone marrow inoculum

F Aversa, A Tabilio, A Terenzi, A Velardi, F Falzetti, C Giannoni, R Iacucci, T Zei, MP Martelli and C Gambelunghe

Haploidentical HSCT from family members

Early in vivo studies

- Conditioning including Irradiation, Thiotepa, ATG and Cyclophosphamid
- No immunosuppression
- BM collection and T-cell depletion
- G-CSF stimulated PBMNC harvested with leukapheresis and T-cell depleted
- Soybean agglutination and E-rosetting technique
- 3 – 3.5 log reduction of T-cells

Aversa F et al, Blood 1994

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Graft characteristics

Table 2. Characteristics of Transplanted BM and PB Cells After T-Cell Depletion

	Group I			Group II		
	BM	PBMC	Total	BM	PBMC	Total
MNC ($\times 10^8$/kg)*	0.31	5.96	6.27	0.27	2.98	3.25
CFU-GM ($\times 10^4$/kg)	12.77	71.55	84.32	4.56	35.80	40.36
$CD34^+$ ($\times 10^6$/kg)	1.9	12	13.9	ND	16	16
$CD3^+$ ($\times 10^5$/kg)	0.32	5.91	6.23	0.19	1.24	1.43

For group I, (7 donors), BM was T-cell–depleted by SBA and one-step E-rosette. PBMCs were T-cell–depleted by only two-step E-rosette. Donors underwent two to four leukaphereses. For group II (10 donors), BM and PBMCs were T-cell–depleted by SBA and two-step E-rosette. Donors underwent two to three leukaphereses.

Abbreviation: ND, not determined.

* Recipient body weight.

Aversa F et al, Blood 1994

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Engraftment characteristics

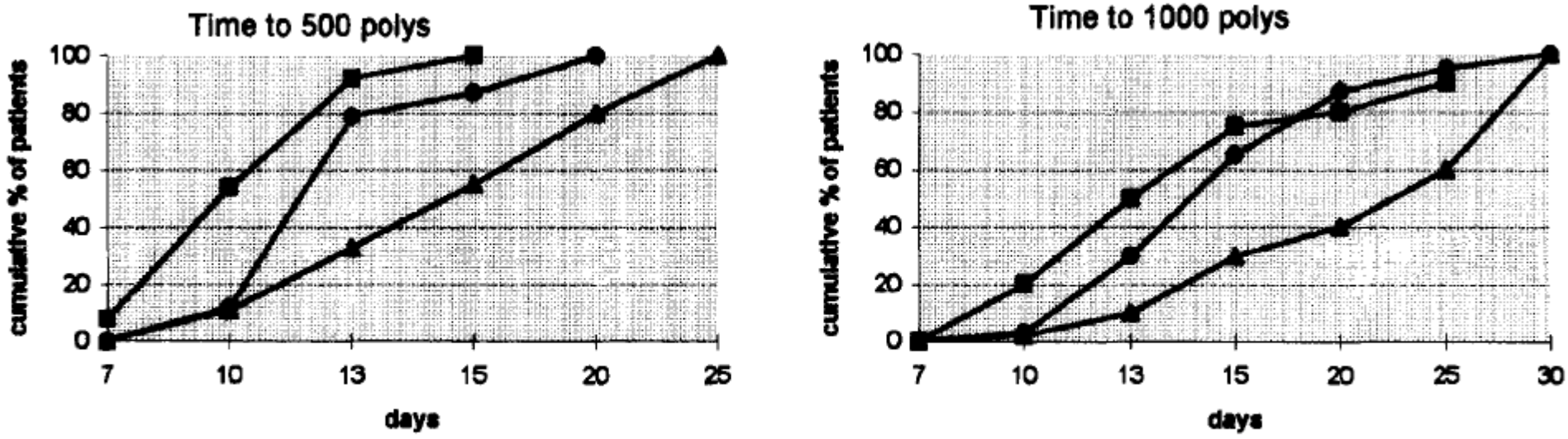

Fig 1. Curves represent cumulative proportions of patients reaching 500 and 1,000 neutrophils. (■), Present study; (▲), HLA-identical T-cell–depleted BMT; (●) autologous chemotherapy/cytokine-mobilized PBPC transplant.

Aversa F et al, Blood 1994

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Engraftment characteristics

Table 3. Clinical Outcome

UPN	Disease	Status at Transplant	Blasts (%) in BM	Engraftment	Acute GVHD (grade)	Current Status (June 30, 1994)
306	AML	2nd relapse	80	Yes	0	Alive in CCR on day +485
313	AML	Induction failure	100	Yes	0	Alive in CCR on day +413
315	ALL	3rd relapse	100	Yes	0	Died on day 120 from CMV-IP
317	ALL	2nd relapse	100	Yes	IV	Died on day 60 from GVHD
319	CML	2nd blast crisis	80	Yes	0	Died on day 90 from Idiopat-IP
320	CML	3rd blast crisis	15	Yes	0	Died on day 20 from CMV-IP
321	AML	3rd relapse	100	Yes	0	Died on day 18 from CMV-IP
329	ALL	3rd relapse	100	Yes	0	Relapsed on day 60, died on day 70
331	CML	2nd blast crisis	30	No	NE	Died on day 45 from sepsis
333	ALL	3rd relapse	15	Yes	0	Relapsed on day 50, died on day 60
334	ALL	2nd relapse	15	Yes	I	Died on day 180 from Idiopat-IP
401	AML	3rd relapse	100	Yes	0	Died on day 45 from sepsis
402	AML	Induction failure	100	Yes	I	Alive in CCR on day +157
404	ALL	2nd relapse	100	Yes	0	Died on day 62 from Idiopat-IP
407	ALL	2nd relapse	15	Yes	I	Alive in CCR on day +126
408	ALL	3rd relapse	15	Yes	I	Alive in CCR on day +110
409	ALL	3rd relapse	10	Yes	I	Alive in CCR on day +100

Abbreviations: NE, not evaluable; CCR, continuous complete remission; IP, interstitial pneumonia.

Aversa F et al, Blood 1994

Haploidentical HSCT from family members

Second generation transplants

VOLUME 23 · NUMBER 15 · MAY 20 2005

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Full Haplotype-Mismatched Hematopoietic Stem-Cell Transplantation: A Phase II Study in Patients With Acute Leukemia at High Risk of Relapse

Franco Aversa, Adelmo Terenzi, Antonio Tabilio, Franca Falzetti, Alessandra Carotti, Stelvio Ballanti, Rita Felicini, Flavio Falcinelli, Andrea Velardi, Loredana Ruggeri, Teresa Aloisi, Jean Pierre Saab, Antonella Santucci, Katia Perruccio, Maria Paola Martelli, Cristina Mecucci, Yair Reisner, and Massimo F. Martelli

Haploidentical HSCT from family members

Second generation transplants

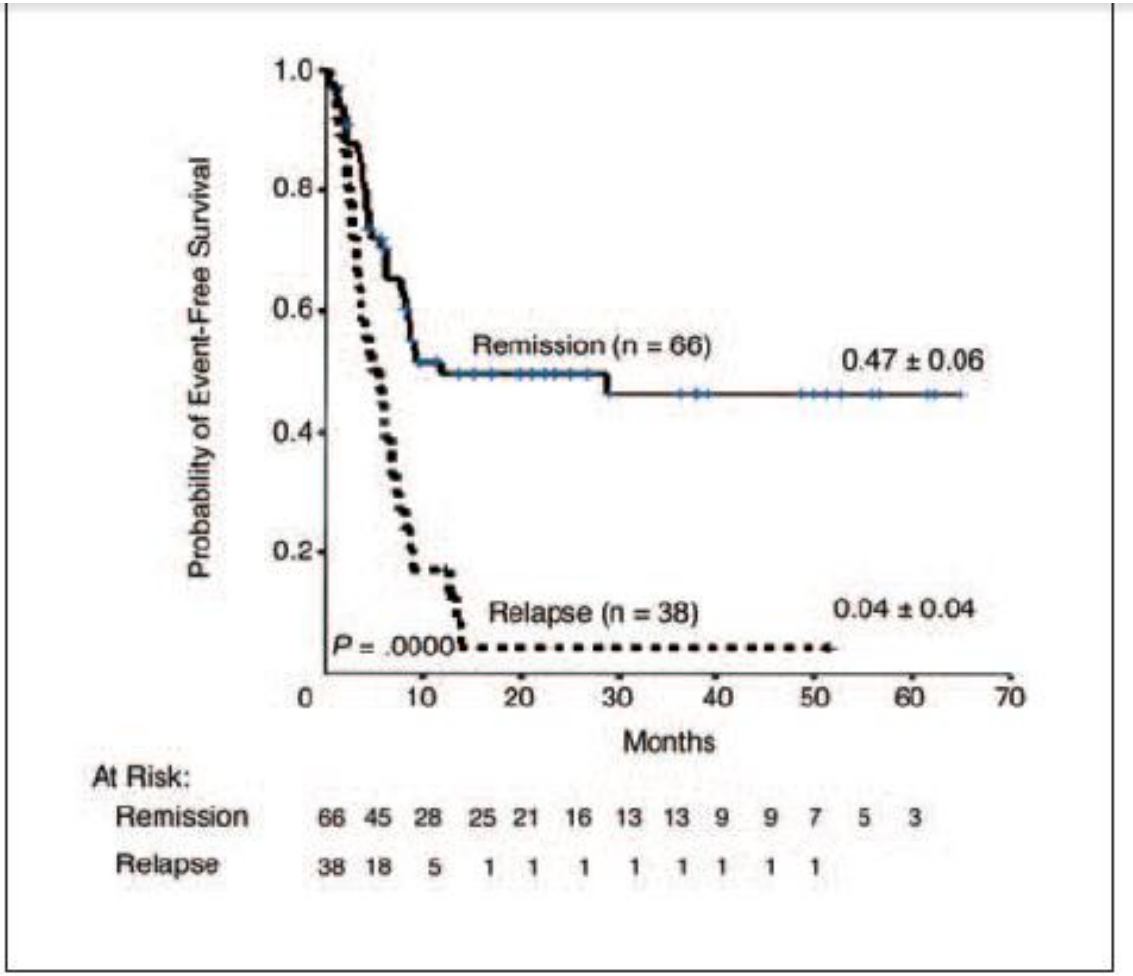

Fig 3. Probability of event-free survival in 66 patients who received transplantation in remission and 38 patients who received transplantation in relapse. Tick-marks indicate patients who were alive at the last check-up. Numbers under x-axis show surviving patients at each time-point after haploidentical transplantation.

Aversa F et al, JCO 2005

Haploidentical HSCT from family members

Second generation transplants

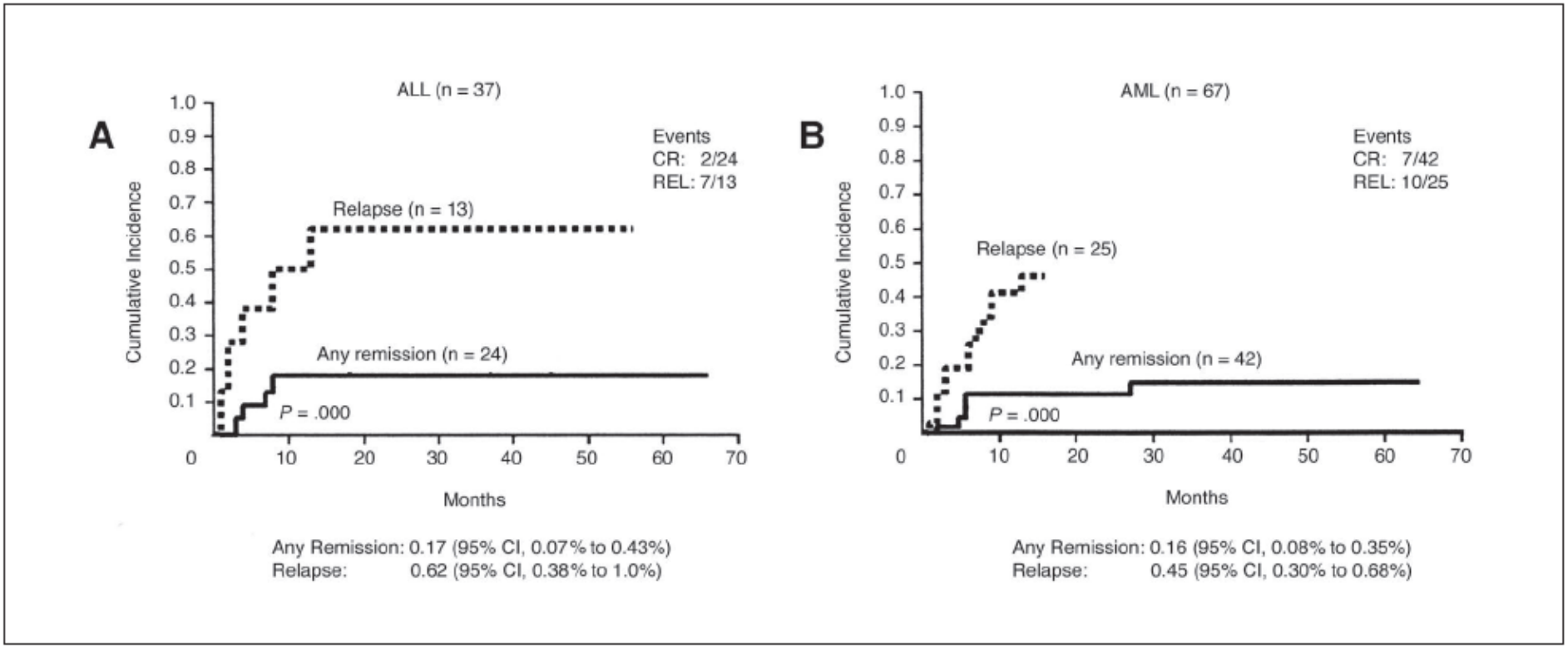

Fig 2. Cumulative incidence of leukemia relapse at 2 years for patients with acute lymphoblastic leukemia (ALL; A) or acute myeloid leukemia (AML; B) who were in either hematologic remission (CR; solid lines) or relapse (REL; dotted lines) at transplantation.

Aversa F et al, JCO 2005

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Second generation transplants

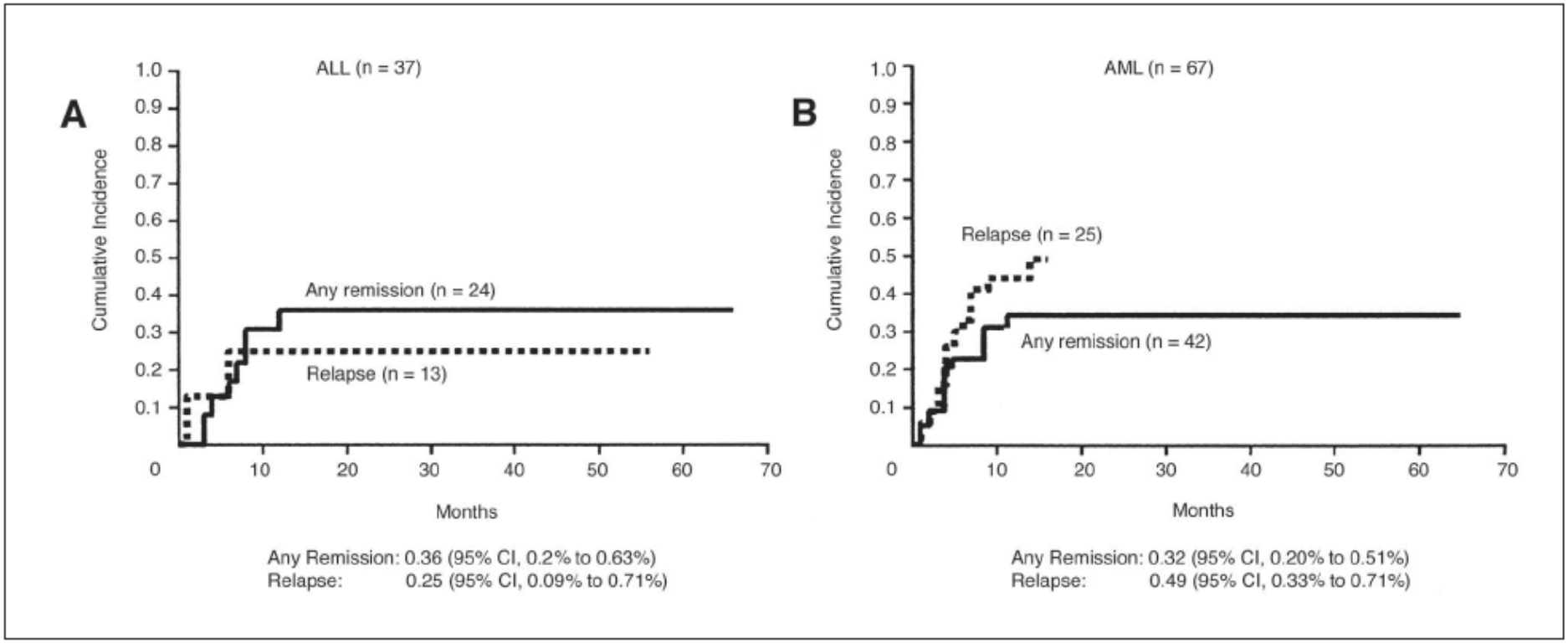


Fig 1. Cumulative incidence of transplant-related deaths at 2 years for patients with acute lymphoblastic leukemia (ALL; A) or acute myeloid leukemia (AML; B) who were in either hematologic remission (solid lines) or relapse (dotted lines) at transplantation.

Aversa F et al, JCO 2005

Haploidentical HSCT from family members

Improving results

Bone Marrow Transplantation (2001) 27, 777–783

www.nature.com/bmt

Allografting

Megadose transplantation of purified peripheral blood CD34+ progenitor cells from HLA-mismatched parental donors in children

R Handgretinger, T Klingebiel, P Lang, M Schumm, S Neu, A Geiselhart, P Bader, PG Schlegel, J Greil, D Stachel, RJ Herzog and D Niethammer

Department of Pediatric Hematology/Oncology and Blood Bank, University of Tübingen, Tübingen; von Haunersches Kinderspital, München; and Children's University Hospital, University of Erlangen-Nürnberg, Erlangen, Germany

Aversa F et al, JCO 2005

Haploidentical HSCT from family members

Improving results

Table 1 Patients' diagnosis

	No. of patients
Malignant diseases	31
ALL	16
CR1	4
CR2	4
CR3	2
NR	6
AML	5
CR1	1
CR2	1
NR	3
MDS (RAEB-T)	4
NR	4
CML (CP1)	3
Hodgkin's disease (NR)	1
NHL	2
CR2	1
NR	1
Nonmalignant diseases	8
Immunodeficiencies	6
SCID	4
WAS	1
Unclassified	1
SAA	1
Osteopetrosis	1

NR = not in remission; SCID = severe combined immunodeficiency; WAS = Wiskott–Aldrich syndrome; SAA = severe aplastic anemia.

Bone Marrow Transplantation

weight median 20 (range 5–66) kg
age median 7.25 (range 0.5 - 18) a
CD34+ mean 20.7±9.8 x 106/kg
CD3+ mean 15.5±20.4 x 103/kg

Handgretinger R et al, BMT 2001

Haploidentical HSCT from family members

Improving results

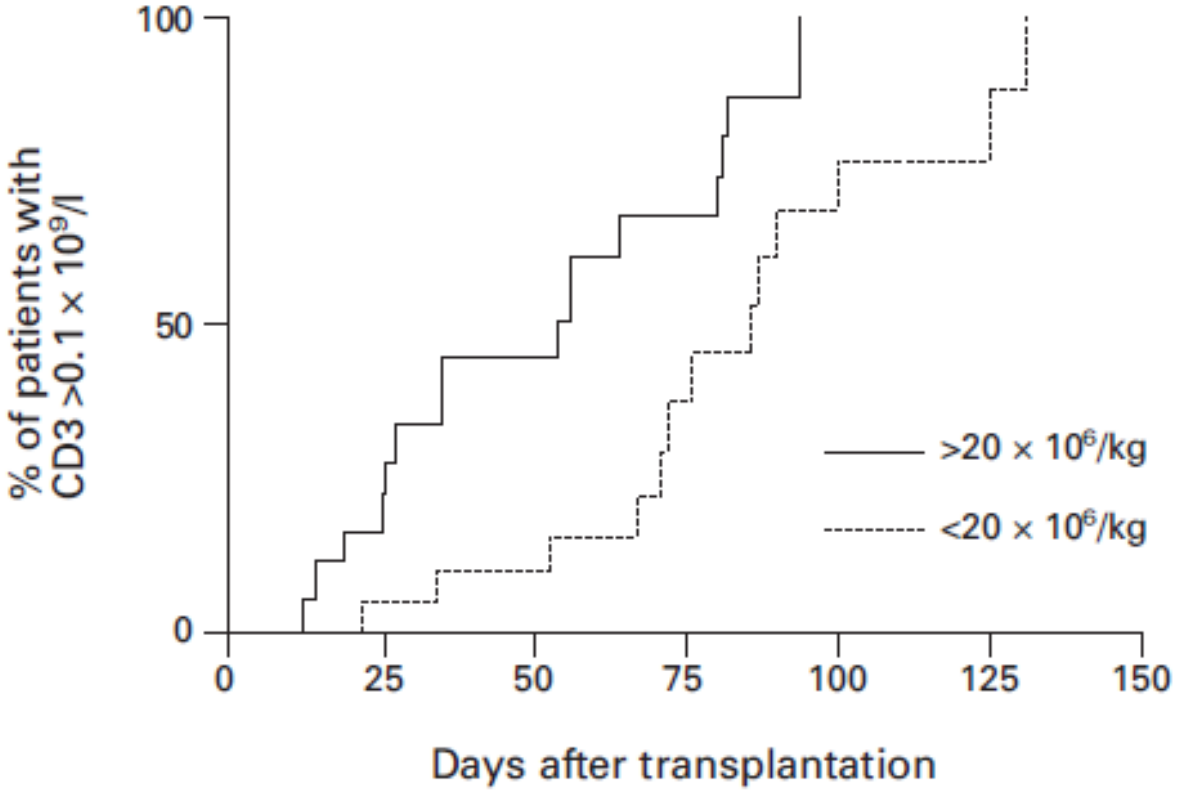


Figure 3 Time to reach $>0.1 \times 10^9$/l $CD3^+$ T lymphocytes in patients who were transplanted with $>20 \times 10^6$/kg and $<20 \times 10^6$/kg purified $CD34^+$ progenitor cells. A significantly faster reconstitution of $CD3^+$ T lymphocytes ($P = 0.0065$) was seen in patients who were transplanted with $>20 \times 10^6$/kg $CD34^+$ cells.

Handgretinger R et al, BMT 2001

Haploidentical HSCT from family members

Improving results

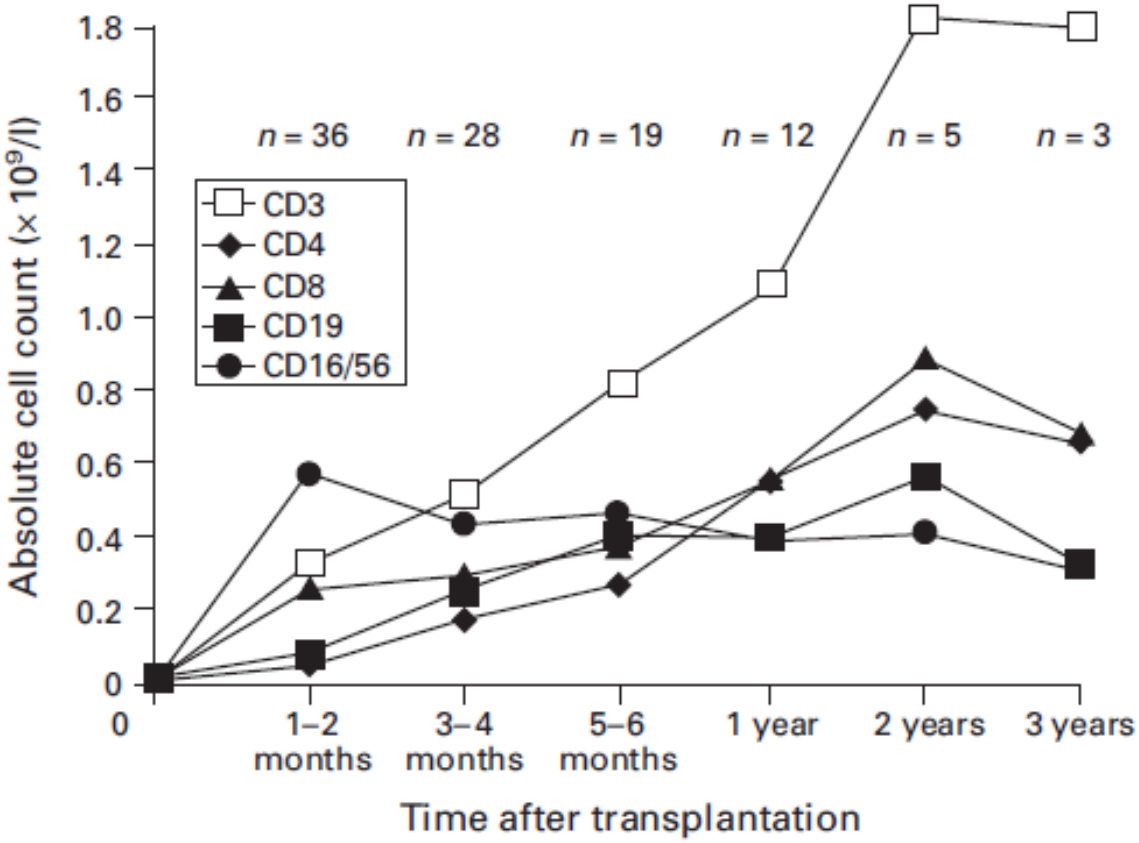


Figure 4 Long-term reconstitution of $CD3^+$ T lymphocytes, $CD4^+$ helper cells, $CD8^+$ cytotoxic/suppressor cells, $CD19^+$ B lymphocytes and $CD56^+$ natural killer (NK) cells in all evaluable patients. The mean absolute cell count for all evaluable patients is shown.

Handgretinger R et al, BMT 2001

Haploidentical HSCT from family members

Improving results

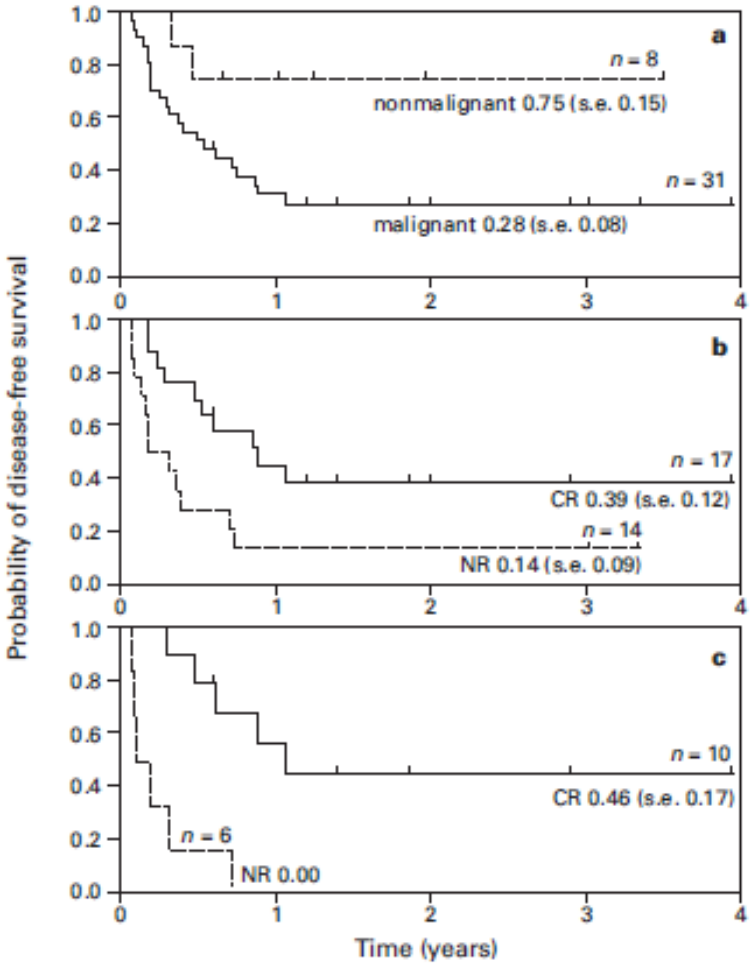


Figure 5 Disease-free survival of patients after haploidentical transplantation with malignant and nonmalignant diseases (a), malignant diseases in remission and not in remission (b) and in patients with ALL in remission or not in remission (c) at the time of transplant.

Handgretinger R et al, BMT 2001

Haploidentical HSCT from family members

T-cell depletion

bjh research paper

Transplantation of CD3/CD19 depleted allografts from haploidentical family donors in paediatric leukaemia

Peter Lang,[1]* Heiko-Manuel Teltschik,[1]* Tobias Feuchtinger,[1] Ingo Müller,[1] Matthias Pfeiffer,[1] Michael Schumm,[1] Martin Ebinger,[1] Carl P. Schwarze,[1] Bernd Gruhn,[2] Andre Schrauder,[3] Michael H. Albert,[4] Johann Greil,[5] Christian Urban[6] and Rupert Handgretinger[1]

Summary

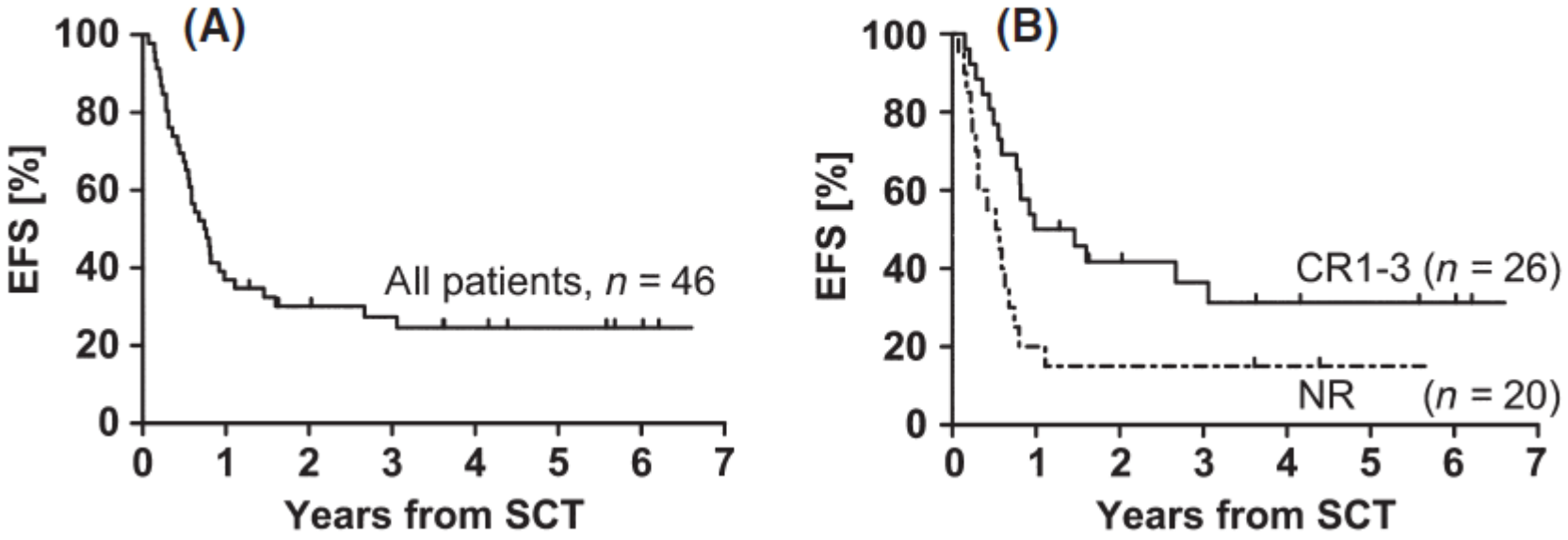
Transplantation of T- and B-cell depleted allografts from haploidentical family donors was evaluated within a prospective phase II trial in children with acute lymphoblastic leukaemia, acute myeloid leukaemia and advanced myelodysplastic syndrome ($n = 46$). 20 patients had active disease; 19 patients received a second or third stem cell transplantation (SCT). Toxicity-reduced conditioning regimens consisted of fludarabine or clofarabine

British Journal of Haematology, 2014, 165, 688–698

Haploidentical HSCT from family members

T-cell depletion

P. Lang *et al*



British Journal of Haematology, 2014, 165, 688–698

Haploidentical HSCT from family members

T-cell depletion

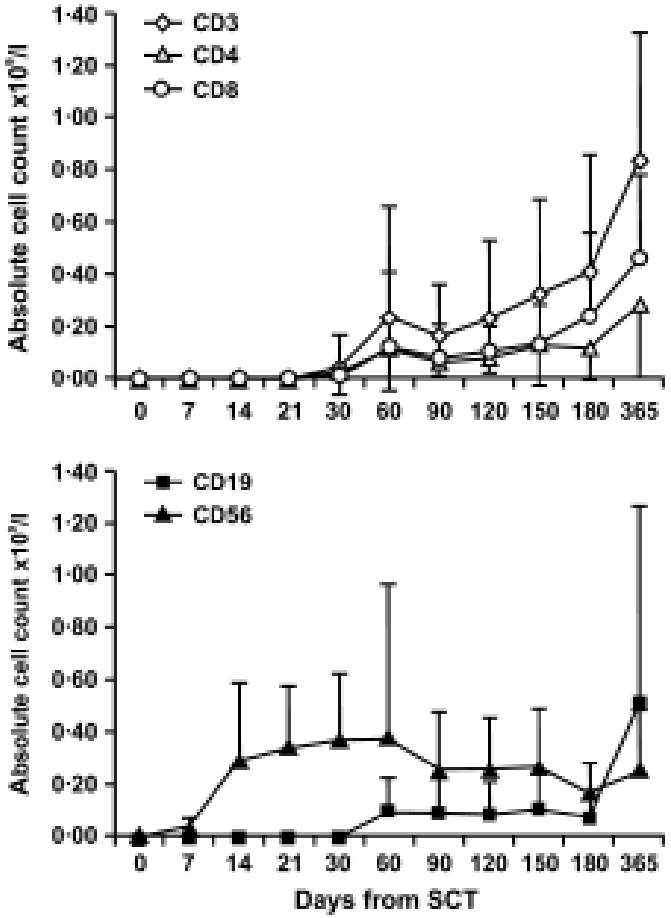


Fig 4. Immune reconstitution. Reconstitution of $CD3^+$, $CD3^+CD4^+$, $CD3^+CD8^+$, $CD19^+$, and $CD56^+$ T, B, and NK cells after transplantation of CD3/CD19-depleted allografts. Points represent the mean values and standard deviations at each time point.

British Journal of Haematology, 2014, 165, 688–698

Haploidentical HSCT from family members

specific T-cell depletion

Blood. 2014 Jul 31;124(5):822-6. doi: 10.1182/blood-2014-03-563817. Epub 2014 May 28.

HLA-haploidentical stem cell transplantation after removal of αβ+ T and B cells in children with nonmalignant disorders.

Bertaina A[1], Merli P[1], Rutella S[2], Pagliara D[1], Bernardo ME[1], Masetti R[3], Pende D[4], Falco M[5], Handgretinger R[6], Moretta F[1], Lucarelli B[1], Brescia LP[1], Li Pira G[1], Testi M[7], Cancrini C[8], Kabbara N[9], Carsetti R[1], Finocchi A[8], Moretta A[10], Moretta L[5], Locatelli F[11].

Author information

Abstract

Twenty-three children with nonmalignant disorders received HLA-haploidentical hematopoietic stem cell transplantation (haplo-HSCT) after ex vivo elimination of αβ(+) T cells and CD19(+) B cells. The median number of CD34(+), αβ(+)CD3(+), and B cells infused was 16.8 × 10(6), 40 × 10(3), and 40 × 10(3) cells/kg, respectively. No patient received any posttransplantation pharmacologic prophylaxis for graft-versus-host disease (GVHD). All but 4 patients engrafted, these latter being rescued by a second allograft. Three patients experienced skin-only grade 1 to 2 acute GVHD. No patient developed visceral acute or chronic GVHD. Cumulative incidence of transplantation-related mortality was 9.3%. With a median follow-up of 18 months, 21 of 23 children are alive and disease-free, the 2-year probability of disease-free survival being 91.1%. Recovery of γδ(+) T cells was prompt, but αβ(+) T cells progressively ensued over time. Our data suggest that this novel graft manipulation strategy is safe and effective for haplo-HSCT. This trial was registered at www.clinicaltrials.gov as #NCT01810120.

Haploidentical HSCT from family members

NK-add back

European Journal of Immunology

Regular Article

Tracking in vivo dynamics of NK cells transferred in patients undergoing stem cell transplantation

Monica Killig[1,§], Birte Friedrichs[2,§], Johannes Meisig[3,4], Chiara Gentilini[2], Nils Blüthgen[3,4], Christoph Loddenkemper[5,†], Myriam Labopin[6], Nadezda Basara[7,‡], Christian Pfrepper[7], Dietger W. Niederwieser[7], Lutz Uharek[2] and Chiara Romagnani[1,*]

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Issue

European Journal of Immunology

Volume 44, Issue 9, pages 2822–2834, September 2014

Haploidentical HSCT from family members

Killig M, E J Immunol 2014 Sep;44(9):2822-34

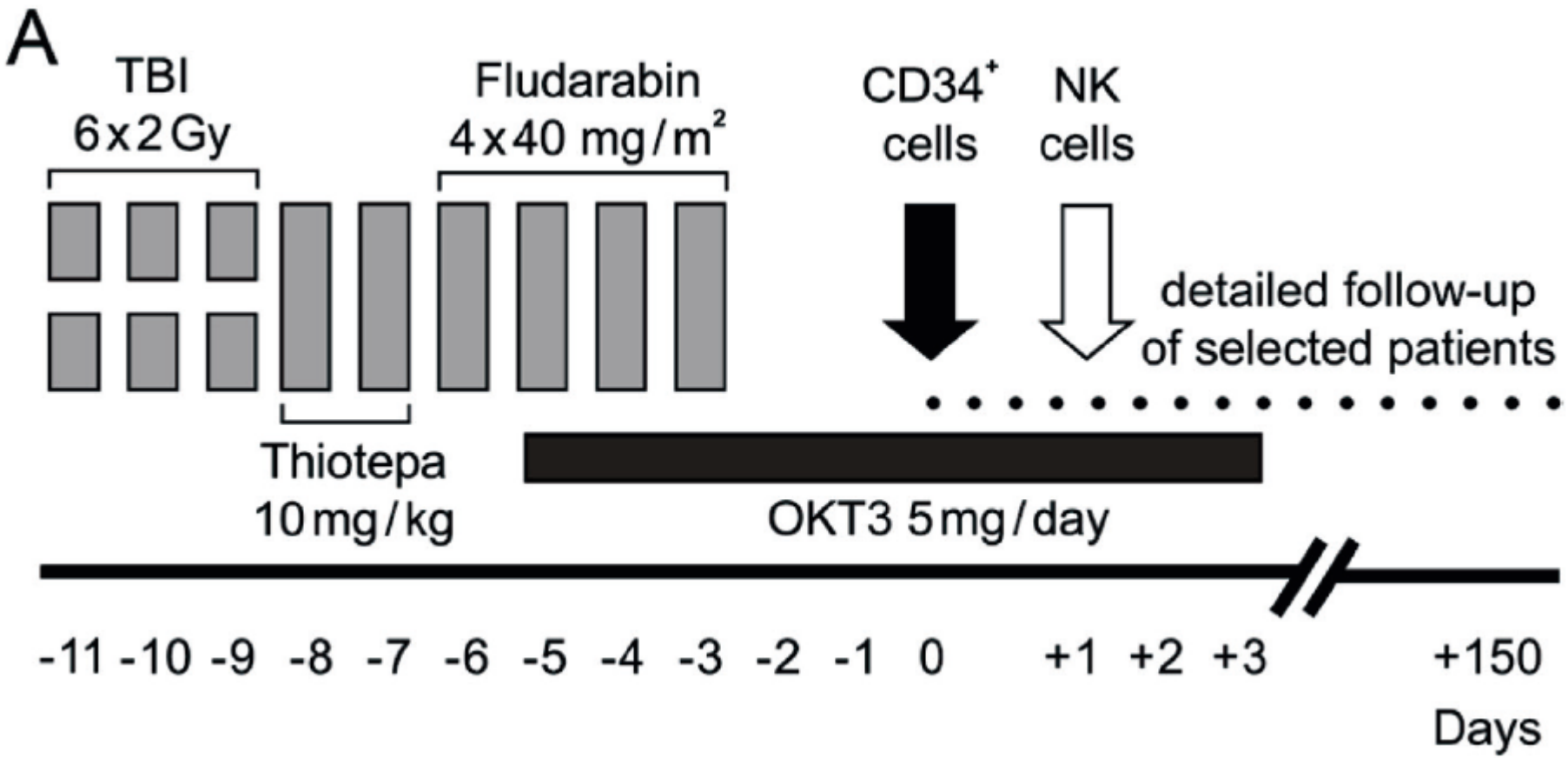
Table 1. Summary of patient characteristics

Pat.#	Age at haploSCT	Diagnosis	Disease status at haploSCT	prior Treatment	Donor	Conditioning	aGVHD grade (clinical stage of skin/gut GvHD)	Follow-up, months	Survival status
1	45	AML	CR2+	CT	brother	Myeloablative	I (skin II)	103.7	alive
2	48	AML	with disease	auto SCT	son	Myeloablative	I (skin I)	8.6	dead
3	45	AML	with disease	allo SCT	son	Myeloablative	I (skin II)	4.2	dead
4	19	AML	CR1	CT	father	Myeloablative	III (skin II, gut III)	95.3	alive
5	48	AML	with disease	CT	son	Myeloablative	III (skin III, gut II)	90.9	alive
6	26	AML	CR2+	CT	father	Myeloablative	II (skin II, gut I)	92.1	alive
7	43	AML	with disease	CT	son	Myeloablative	III (skin II, gut III)	5.2	dead
8	36	AML	CR1	CT	brother	Myeloablative	I (skin II)	14.4	dead
9	42	AML	with disease	auto SCT	daughter	Myeloablative	III (skin III, gut II)	3.2	dead
10	50	AML	with disease	CT	sister	Myeloablative	II (skin II, gut I)	14.6	dead
11	34	AML	with disease	CT	mother	Myeloablative	I (skin I)	52.3	alive
12	47	AML	with disease	allo SCT	mother	RIC	II (skin II, gut I)	17.7	dead
13	25	AML	with disease	syngenic SCT	mother	RIC	III (skin II, gut II)	10.2	dead
14	26	AML	with disease	CT	mother	Myeloablative	II (skin II, gut I)	1.7	dead
15	50	AML	with disease	CT	son	Myeloablative	II (skin II, gut I)	12.6	alive
16	37	AML	with disease	allo SCT	mother	Myeloablative	III (skin I, gut III)	13.5	dead
17	28	AML	with disease	CT	brother	Myeloablative	I (skin I)	12.4	alive
18	54	AML	with disease	CT	son	RIC	none	5.8	dead
19	20	AML	with disease	CT	mother	Myeloablative	III (skin III, gut II)	6.5	dead
20	54	AML	with disease	CT	son	Myeloablative	III (skin III, gut II)	5	dead
21	45	AML	with disease	CT	sister	Myeloablative	II (skin III)	23.2	alive
22	41	AML	with disease	allo SCT	father	RIC	none	1.1	dead
23	22	AML	CR2	auto	mother	Myeloablative	I (gut I)	17.3	alive
24	50	AML	with disease	CT	brother	Myeloablative	none	0.43	dead
25	48	AML	with disease	allo SCT	mother	RIC	none	1.22	dead

aGvHD = acute graft versus host disease; AML = acute myeloid leukemia; CR = complete remission; CT = chemotherapy; haploSCT = haploidentical stem cell transplantation; RIC = reduced intensity conditioning; SCT = stem cell transplantation

Haploidentical HSCT from family members

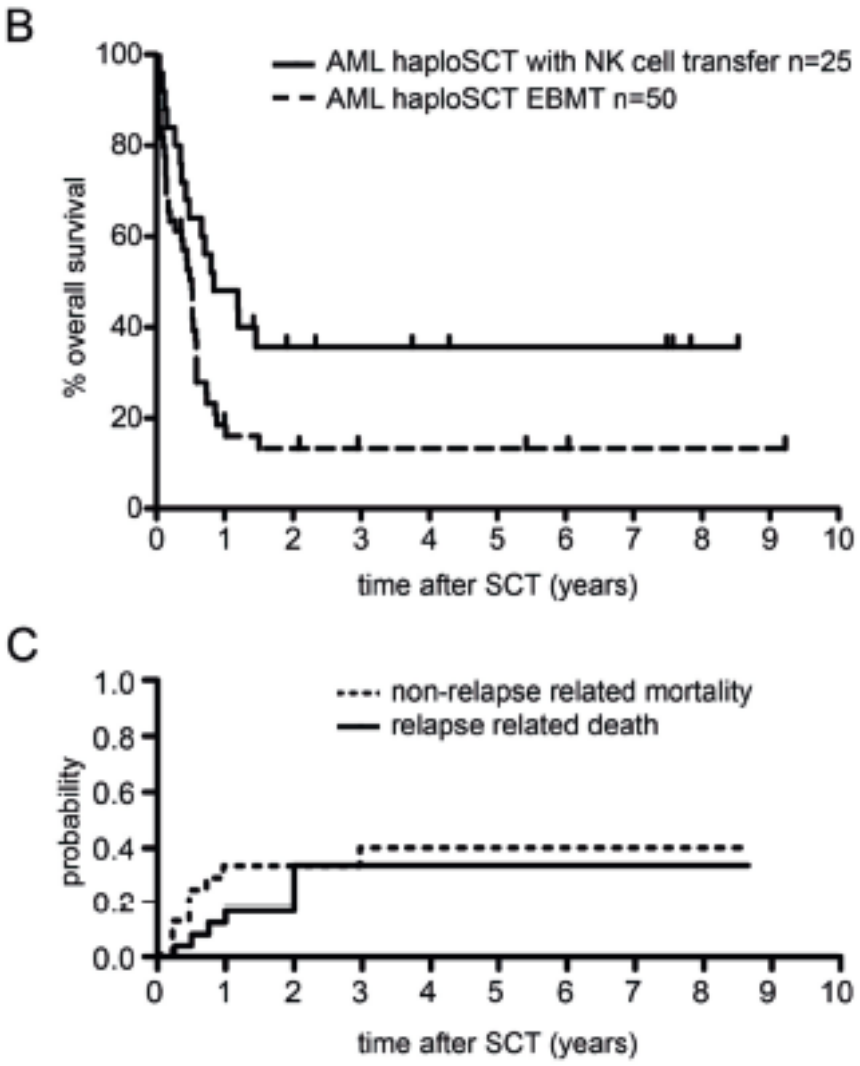
NK-add back



Killig M, E J Immunol 2014 Sep;44(9):2822-34

Haploidentical HSCT from family members

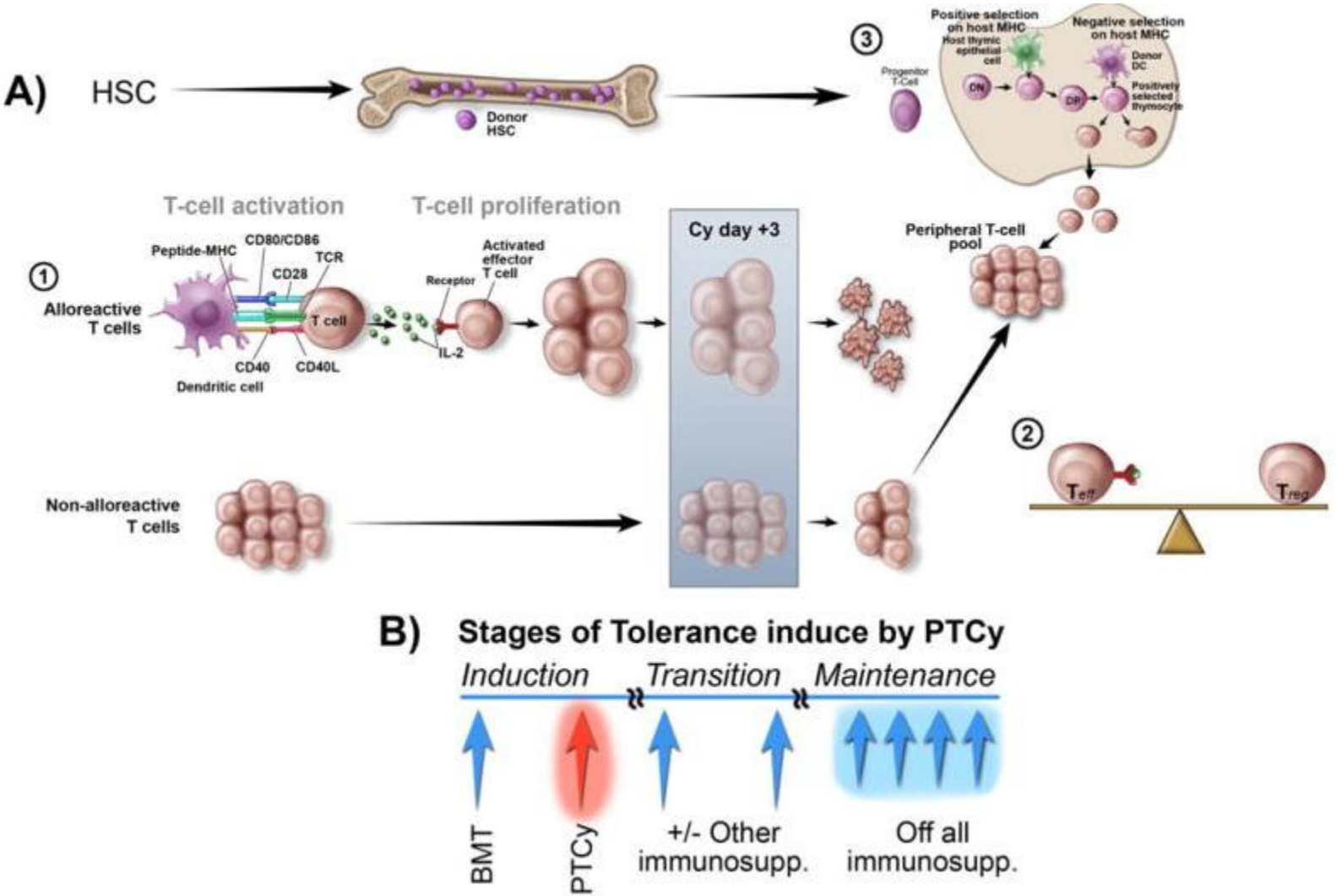
NK-add back



Killig M, E J Immunol 2014 Sep;44(9):2822-34

HSCT – present and limits

post-transplant cyclophosphamide induced tolerance



Luznik et al, Semin Oncol 2012

Haploidentical HSCT from family members

post-transplant cyclophosphamide induced tolerance

Blood. 2014 Oct 14. pii: blood-2014-07-587477. [Epub ahead of print]

Post-transplantation cyclophosphamide as single-agent GVHD prophylaxis after myeloablative conditioning and HLA-matched allografting for acute leukemias and myelodysplastic syndrome.

Kanakry CG[1], Tsai HL[1], Bolaños-Meade J[1], Smith BD[1], Gojo I[1], Kanakry JA[1], Kasamon YL[1], Gladstone DE[1], Matsui W[1], Borrello I[1], Huff CA[1], Swinnen LJ[1], Powell JD[1], Pratz KW[1], DeZern AE[1], Showel MM[1], McDevitt MA[1], Brodsky RA[1], Levis MJ[1], Ambinder RF[1], Fuchs EJ[1], Rosner GL[1], Jones RJ[1], Luznik L[2].

Author information

Abstract

High-dose, post-transplantation cyclophosphamide (PTCy) reduces severe graft-versus-host disease (GVHD) after allogeneic blood or marrow transplantation (alloBMT), but the impact of PTCy on long-term, disease-specific outcomes is unclear. We conducted a retrospective study of 209 consecutive adult patients transplanted for acute myeloid leukemia (AML, n=138), myelodysplastic syndrome (MDS, n=28), or acute lymphoblastic leukemia (ALL, n=43) using PTCy as sole GVHD prophylaxis after myeloablative conditioning and HLA-matched-related or -unrelated T-cell-replete allografting. At alloBMT, 30% of patients were not in morphologic complete remission. The cumulative incidences of grades II-IV and III-IV acute GVHD at 100 days and chronic GVHD at 2 years were 45%, 11%, and 13%, respectively. Forty-three percent of patients did not require immunosuppression for any reason beyond PTCy. At 3 years, relapse cumulative incidence was 36%, disease-free survival was 46%, survival free of disease and chronic GVHD was 39%, and overall survival was 58%. Lack of remission at alloBMT, adverse cytogenetics, and low allograft nucleated cell dose were associated with inferior survival for AML patients. Minimal residual disease but not t(9;22) was associated with inferior outcomes for ALL patients. The ability to limit post-transplantation immunosuppression makes PTCy a promising transplantation platform for the integration of post-grafting strategies to prevent relapse.

Haploidentical HSCT from family members
without in vitro T-cell depletion

Original Article

Long-Term Follow-Up of Haploidentical Hematopoietic Stem Cell Transplantation Without In Vitro T Cell Depletion for the Treatment of Leukemia

Nine Years of Experience at a Single Center

Yu Wang, MD; Dai-Hong Liu, MD; Kai-Yan Liu, MD; Lan-Ping Xu, MD; Xiao-Hui Zhang, MD; Wei Han, MD; Huan Chen, MD; Yu-Hong Chen, MD; Feng-Rong Wang, MD; Jing-Zhi Wang, MD; Yu-Qian Sun, MD; and Xiao-Jun Huang, MD

Cancer 2013;119:978-85

Haploidentical HSCT from family members

without in vitro T-cell depletion

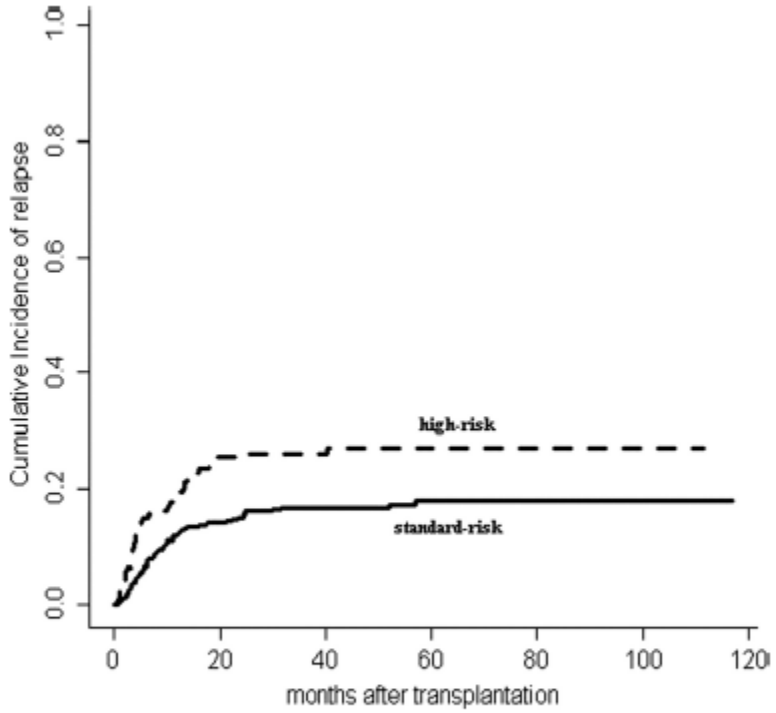


Figure 2. Cumulative incidence of relapse characterized by disease status is shown after haploidentical hematopoietic stem cell transplantation (P=.011).

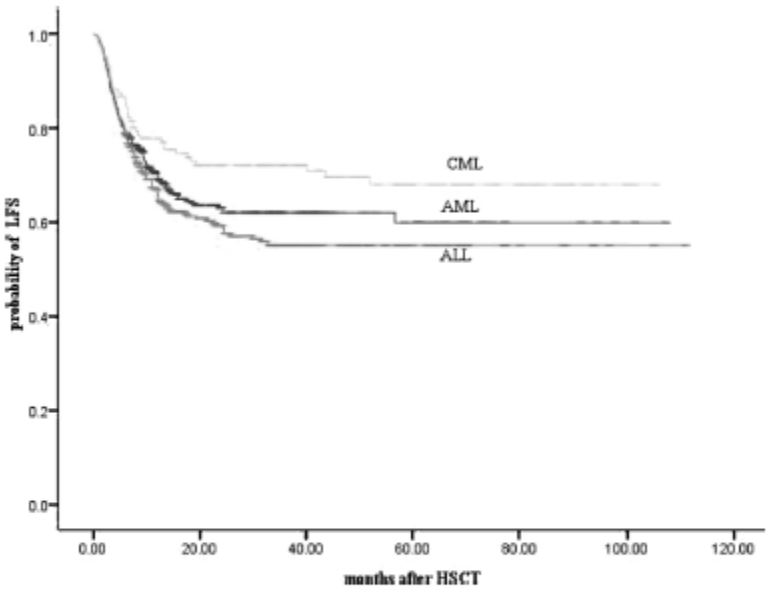


Figure 3. Probability of leukemia-free survival (LFS) is shown with respect to disease type after haploidentical hematopoietic stem cell transplantation (HSCT) (P=.049).

Cancer 2013;119:978-85

Haploidentical HSCT from family members

Conclusion

- Important option for patients without a matched related or unrelated donor
- Outcome of haploidentical HSCT improved considerably during the last decades
- Ideal technique still to be developed
- T-cell reconstitution still to be improved
- Comparative study have been initiated