

STEM CELL TRANSPLANTATION:

Redefining Optimal Timing of SCT for Malignant Hematologic Disorders in the Era of Novel Therapies



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Disclosure Information

I have no financial relationships to disclose
relevant to the content of this presentation.



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Timing of SCT for Acute Myeloid Leukemia

- Patients who fail to achieve complete remission with initial induction therapy
- Patients with AML who relapse should be transplanted in CR2
- **First Choice:** Myeloablative HLA-identical sibling SCT (up to age 55)
Second Choice: Myeloablative HLA-identical SCT from unrelated volunteer donor (up to age 50)
- **Third Choice:** Myeloablative unrelated cord blood SCT (up to age 50)
- Reduced-intensity SCT if patient not eligible for myeloablative SCT due to age or cardiac, pulmonary, liver or renal comorbidities (up to age 65)



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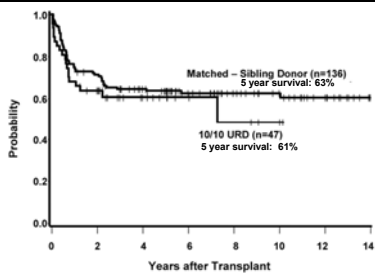
Who should be transplanted in CR1?

- Patients requiring more than 1 induction therapy
- Older age (>60 years)
- Secondary AML
- WBC >100,000/ μ l at diagnosis
- Unfavorable-risk cytogenetics:
 - t(9;22); t(6;9)
 - Complex (>3) abnormalities
 - Abnormalities of chromosomes 5 or 7; 3q-
- Internal tandem duplications of FLT-3; c-KIT mutations; MDR-1 expression:
 - e.g. all patients with normal cytogenetics who are FLT-3 ITD positive;
 - all patients with favorable-risk cytogenetics [t(8;21) or inv(16)] who have c-KIT mutations



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Survival following Transplantation for AML in CR1 with either Matched Sibling Donors or Matched Unrelated Donors (Retrospective Analysis from FHCRC)



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Appelbaum, F. R. Hematology 2008;412-417

Nonmyeloablative Allogeneic SCT For De Novo and Secondary AML (Seattle Consortium)

(ASH 2008, Abstract 149)

- 256 patients (CR1, n=100; >CR1, n=79; secondary AML, n=77)
- Median age = 59 years; (5-74 years)
- Conditioning tx: 2 Gy TBI; fludarabine
- GVHD prophylaxis: Cyclosporine or Tacrolimus and mycophenolate mofetil
- Median follow-up: 35 months (3-111 months)



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5-Year Probabilities of Outcomes after Nonmyeloablative Allogeneic SCT for AML

Disease Status	n	%OS	%PFS	RR	NRM
CR1	100	33	34	36	30
>CR1	79	38	35	40	25
sAML	77	20	23	45	32



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5-Year Probabilities of Outcomes after Nonmyeloablative SCT for AML According to Donor Type

Disease Status	n	%OS	% PFS	RR	NRM
HLA-identical related	109	34	34	47	18
HLA-matched unrelated	131	31	30	37	33
HLA-mismatched unrelated	16	24	24	6	70

Conclusion: Nonmyeloablative SCT from related or unrelated donors provide long-term remission in elderly or medically infirm patients with AML who are not candidates for myeloablative SCT.



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Timing of SCT for Acute Lymphoblastic Leukemia

- Patients who fail to achieve remission with initial induction therapy
- Patients with ALL who relapse should be transplanted in CR2.



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Who should be transplanted in CR1?

- Patients with Ph+ ALL after imatinib containing front-line therapy
- Patients with other unfavorable risk factors like:
 - B-lineage ALL with WBC >30,000/ μ l at diagnosis
 - age >35 years
 - Residual leukemic blasts by PCR or multiparameter flow cytometry after morphologic CR (>10⁴ MRD after induction and first consolidation)
 - Late CR (>3-4 weeks)
 - t(4;11)



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New Timing of SCT for Acute Lymphoblastic Leukemia

Two large studies on the treatment of ALL in adults (MRC UKALL XII/ECOG E2993 and LALA-94 trial) have recently confirmed that, in most cases, salvage after relapse by SCT is not successful. Adult patients with ALL should, therefore, undergo SCT in CR1 if a matched related or unrelated donor is available.



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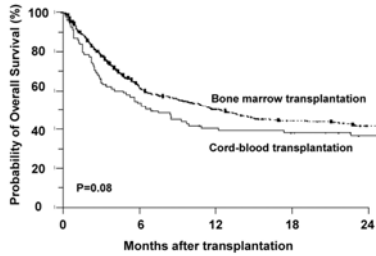
Role of Kinase Inhibitors before and/or after SCT for Ph+ ALL

- Current data support a role for TK inhibitors, both during induction and as maintenance therapy after SCT, especially with increased MRD and/or a decrease in donor chimerism.
- No randomized studies have been completed so far and the long-term benefit of TK inhibitors before and/or after SCT remains therefore unclear.
- Abnormal TK activity alone is not entirely responsible for the phenotype of Ph+ ALL (unlike CML); in ALL Src Kinase activity is also involved.
- Simultaneous inhibition of both tyrosine and Src kinases might be more beneficial. Dasatinib, an inhibitor of both bcr-abl and Src family kinases, is an obvious candidate drug for future studies of its possible benefit when given before and/or after SCT for Ph+ ALL.



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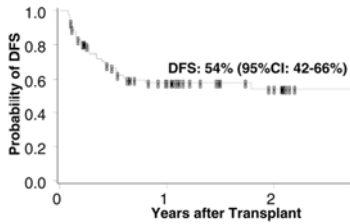
Retrospective Comparison of Overall Survival after Cord Blood versus Matched Unrelated Donor Transplantation in Adults with Acute Leukemia (Eurocord)



Rocha V et al. N Engl J Med 2004; 351:2276-2285

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Double-Unit Umbilical Cord Blood Transplantation after Myeloablative Conditioning in 83 Adult Patients with High-Risk Hematologic Malignancies

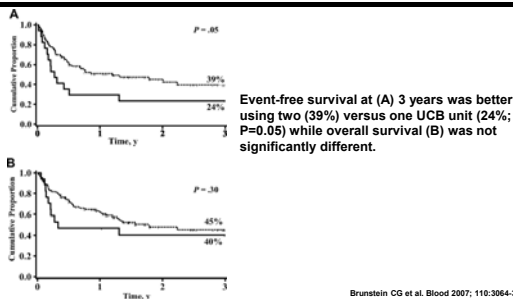


Probability of disease-free survival at 3 years was 54%.

Barker JN. Hematology 2007; 65-61

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Three-Year Event-Free Survival (A) and Overall Survival (B) in Adult Patients Receiving either 1 (—; N=17) Or 2 (---; N=93) UCB Unit Transplantation after a Reduced-Intensity Conditioning Regimen



Brunstein CG et al. Blood 2007; 110:3064-3070

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Timing of SCT for Myelodysplastic Syndromes

- Intermediate-2 risk MDS
- High-risk MDS
- Low-risk / intermediate-1 risk with high transfusion frequency
- Low-risk / intermediate-1 risk MDS: SCT at time of disease progression to intermediate-2 risk MDS

Cutler CS et al. Blood 2004; 104:579-585



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Retrospective Comparison of Myeloablative versus Reduced-Intensity and Non-Myeloablative Allogeneic SCT for AML or MDS (CIBMTR)

(ASH 2008, Abstract 348)

- Myeloablative SCT: 3,731 patients
- RIC/Non-myeloablative SCT: 1,500 patients
- Median Age: MA: 42 years (18-68 years);
RIC/NMA: 55 years (18-69 years)
- Median follow-up: MA 58 months;
RIC/NMA: 40 months



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5-Year Probabilities of Outcomes after Different Types of Allogeneic SCT for AML or MDS

(ASH 2008, Abstract 348)

	MA	RIC PBSC	RIC BM	NMA
Relapse, %	32	39	42	43
TRM, %	34	34	37	36
LFS, %	33	30	28	24
OS, %	34	33	32	26

- MA regimens were associated with significantly less relapse ($p < 0.001$)
- While early TRM was substantially less with RIC/NMA approaches, 5 year TRM was equivalent ($p=0.48$)
- This leads to marginally better 5 years LFS ($p=0.05$) but similar OS ($p=0.25$) with MA vs RIC/NMA
- Prospective trials are necessary to compare MA vs RIC/NMA transplants in patients eligible for either approach (EBMT and US – studies are ongoing)



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New Approaches to Improve Outcomes after SCT for Myelodysplastic Syndromes

- Improve depth of pretransplant remission status using new, less toxic MDS active drugs like:
 - Hypomethylating agents (decitabine, azacitidine)
 - Histone deacetylase inhibitors (valproic acid, vorinostat)
 - Immunomodulators (lenalidomide)
- Posttransplant prevention of relapse:
 - Adoptive immunotherapy with preemptive donor lymphocyte infusion
 - Maintenance therapy with hypomethylating agents, histone deacetylase inhibitors, lenalidomide.
- Currently available studies using these new approaches in small numbers of patients suggest benefit but they need to be confirmed by large, prospective clinical studies



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Timing of SCT for Chronic Myeloid Leukemia

- Tyrosine kinase inhibitors have displaced allogeneic SCT as first-line treatment for newly diagnosed adult patients with CML in chronic phase.
- Regular monitoring of patients with CML in chronic phase on treatment with tyrosine kinase inhibitors for disease progression is necessary to determine the optimal time for allogeneic SCT.
- Patients in chronic phase who have failed or are intolerant to tyrosine kinase inhibitors (~20%-30% of newly diagnosed patients) should undergo SCT in first chronic phase.
- Patients who have progressed to accelerated or blast phase should undergo allogeneic SCT in second chronic phase.



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Long-Term Efficacy of Allogeneic SCT in Patients with CML after Imatinib Failure (MD Anderson Results)

(ASH 2006, Abstract 979)

- Myeloablative SCT: 52 patients
- Reduced-intensity SCT: 40 patients
- Matched related donors: 49 patients
- Matched unrelated donor: 43 patients

- Median time on imatinib before SCT: 15 months (2-50 months)
- Median age at SCT: 43 years (14-69 years)
- Disease status at time of SCT:
 - 33% CP-1; 29% AP; 18% BP; 20% CP-2
- Median follow-up after SCT: 48 months (4-93 months)



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Indications for Allogeneic SCT in CLL (EBMT Guidelines)

Allogeneic SCT recommended for younger patients early in the disease course who:

- fail to achieve CR with chemoimmunotherapy
- progress within 12 months after treatment with purine analogs
- relapse within 24 months after having achieved a response with purine analog-based combination therapy

Dreger P, Leukemia 2007; 21:12-17



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Retrospective Comparison between Myeloablative and Reduced-Intensity Allogeneic SCT for CLL (EBMT)

(ASH 2008, Abstract 566)

- Myeloablative SCT: 292 patients
- Reduced-intensity SCT: 82 patients
- HLA-identical sibling donor: 202 patients
- HLA-MM related donor: 2 patients
- HLA-matched unrelated donor: 170 patients

- Interval between diagnosis and SCT: 53 months (3-308 months)
- Disease status at time of SCT: 14% CR; 45% PR; 12% SD; 29% PD

- Median follow-up after SCT: 38 months

- Probability of 5-year overall survival:
 - Myeloablative SCT: 52% (42-66%)
 - Reduced-intensity SCT: 47% (40-55%) > P=0.44

Conclusion: High percentage of long-term overall survival either after myeloablative or reduced-intensity SCT without significant difference between the two types of SCT



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Timing of SCT for Aggressive Non-Hodgkin Lymphoma

- Relapsed chemosensitive patients should undergo autologous SCT (Parma trial: 5 year EFS 46% after autologous SCT vs 12% after chemotherapy).
- Autologous SCT in 1st CR for patients with two or three risk factors on age-adjusted international prognostic index (≥Stage III; LDH > nl; KS <80%) is superior to CHOP (ASH 2008, Abstract 770; Update of GOELAMS 072 trial with median follow-up of 9.8 years)
- But autologous SCT in 1st CR for patients with aggressive NHL remains controversial. Although some studies have suggested benefit, they were performed in the pre-rituximab era. Ongoing studies are comparing CHOP plus rituximab with high-dose chemotherapy plus rituximab followed by autologous SCT (S9704 and GOELAMS 075)



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Timing of SCT for Aggressive Non-Hodgkin Lymphoma

(Continued)

- Patients with primary refractory disease, relapsed disease not responding to salvage therapy, or patients who relapsed after autologous SCT should undergo reduced-intensity allogeneic SCT or possibly myeloablative allogeneic SCT if patient is young (<35 years) and in good performance status. Vigorous debulking with chemo and/or radiotherapy before SCT is important.
- The role of posttransplant rituximab is currently being evaluated in a prospective EBMT study.



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Timing of SCT for Indolent Non-Hodgkin Lymphoma

- Autologous SCT as consolidation in first CR did not show improved overall survival compared to conventional chemotherapy in several phase III randomized studies (German Low-Grade Lymphoma Study Group trial; GOELAMS trial; GITMO trial).
- Autologous SCT for relapsed indolent NHL has been shown to achieve improved OS and PFS rates compared to chemotherapy (European CUP trial, J Clin Oncol 2003; 21:3918-3927).
- Of concern is the increased incidence of second malignancies after autologous SCT with a cumulative incidence of 15-20% at 15 years after SCT, especially in older patients (>45 years) and patients with more than two prior lines of chemotherapy.
- Myeloablative allogeneic SCT is limited by high treatment-related mortality, therefore, lower risk of relapse does not translate into a survival benefit and OS and DFS are similar to those after autologous SCT.



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Retrospective Comparison of Reduced-Intensity Allogeneic SCT with Autologous SCT for Follicular Lymphoma (EBMT)

(ASH 2008, Abstract 458)

	Auto SCT	RIC SCT
Number of Patients	1,394	110
Median Age	51 Years (20-73)	50 Years (32-65)
Median Time from Diagnosis to SCT	26 months	34 months
Disease Status at Time of SCT	43% CR, 56% PR, 5% RD	34% CR, 52% PR, 10% RD
>3 Lines of Therapy before SCT	34%	61%
NRM at 1 Year	3%	15%
5 Year Relapse Rate	47%	19%
PFS at 5 Years	48%	62%

Conclusion: 1) RIC SCT is associated with higher non-relapse mortality but a lower relapse rate when compared to autologous SCT resulting in improved DFS after RIC SCT. 2) Progression free survival in both groups was significantly worse for patients with chemorefractory disease, more lines of therapy before SCT or with poor performance status.



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Timing of SCT for Hodgkin Lymphoma

- Patients with late relapse later than 1 year after initial therapy can be successfully salvaged with autologous SCT (3 year DFS of 55% as compared to 34% with chemotherapy; Schmitz N et al; Lancet 2002; 359:2065-2071).
- Patients with early relapse (<1 year after initial therapy) or primary refractory disease should be considered for reduced-intensity allogeneic SCT or possibly myeloablative allogeneic SCT if patient is young (<35 years) and in good performance status.



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Retrospective Comparison of RIC Allogeneic SCT with Conventional Chemo-and/or Radiotherapy in Patients with Hodgkin Lymphoma Relapsing after Autologous SCT Based on Donor Availability (GITMO Study)

(ASH 2008, Abstract 460)

	Donor Group	No Donor Group
Number of Patients	68	57
Median Age	30 Years (17-62)	30 Years (17-62)
Median Follow-UP	24 Months	24 Months
TRM	12%	NA
2 Year OS	70%	39% (p=0.001)
2 Year PFS	42%	10% (p=0.03)

Conclusion: RIC SCT achieves significantly better OS and PFS compared to chemo- and/or radiotherapy. Achievement of CR before RIC SCT leads to improved OS and PFS.



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Timing of SCT for Multiple Myeloma

- Single autologous SCT is considered standard of care as part of frontline therapy in newly diagnosed patients with multiple myeloma at least up to the age of 65 years.
- A second autologous SCT 3 months after the first SCT improves OS and EFS in patients who do not achieve at least a very good partial remission (≥90% reduction of serum M-component) after the first SCT.



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Randomized Studies of Single Autologous Stem Cell Transplant versus Conventional Chemotherapy

Author	N	Event-Free Survival	Overall Survival
Attal et al	200	7-year: 16% vs 8% (P >.01)	7-year: 43% vs 27% (P <.03)
Child et al	401	Median: 32 mo vs 20 mo (P <.01)	Median: 54 mo vs 42 mo (P <.01)
Palumbo et al	194	3-year: 37% vs 16% (P <.001)	3-year: 77% vs 62% (P <.01)

Attal M et al. Hematology 2007; 311-316

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Comparison of Overall Survival after Single vs. Double Autologous Stem Cell Transplant in Patients with Multiple Myeloma Depending on Response Achieved Three Months after One Transplant

A: Very Good Partial Response after First Transplantation

Patients who had at least a very good partial response after one transplant did not benefit significantly from the second transplant (P=0.70).

B: Absence of Very Good Partial Response after First Transplantation

Seven-year overall survival in patients who did not have at least a very good partial response after one transplant was 11% in the single-transplant group and 43% in the double-transplant group (P<0.001).

Attal M et al. N Engl J Med 2003; 349:2495-2502

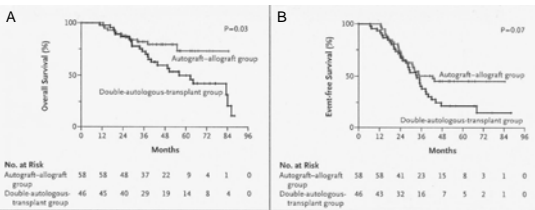
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Timing of SCT for Multiple Myeloma

- **Autologous** transplant followed by **RIC allogeneic** transplant may improve overall and event-free survival compared to double autologous SCT, but outcome data are currently controversial. Results of 2 recently completed prospective phase 3 trials comparing double autologous SCT with auto/RIC SCT are pending.
- **Maintenance** therapy with thalidomide improves overall and event-free survival after autologous SCT except for patients who achieve CR or VGPR after SCT or who have deletion of chromosome 13.

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Comparison of Tandem Autografts (N=46) with Autograft followed by RIC Allograft (N=58) in Patients with Newly Diagnosed Myeloma



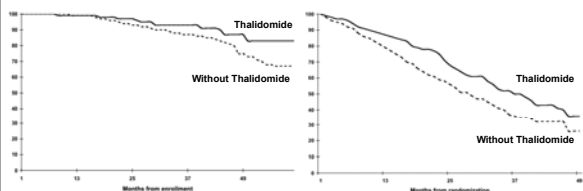
Kaplan-Meier estimates of overall (A) and event-free survival (B) from time of diagnosis

Bruno B et al. N Engl J Med 2007; 356:1110-1120



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Overall and Event-Free Survival with or without Maintenance Therapy with Thalidomide (Mean: 200 MG/Day) in Patients with Myeloma after Autologous Stem Cell Transplant



Four-year overall survival was 77% without Thalidomide and 87% with Thalidomide (P<.04).

Three-year event-free survival was 36% without Thalidomide and 52% with Thalidomide (P<.009)

Attal M et al. Blood 2006; 108:3289-3294



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SCT for Multiple Myeloma

- Novel agents like thalidomide, bortezomib and lenalidomide have changed frontline therapy in the context of autologous SCT.
- Current research is investigating the use of these novel agents prior to and after autologous SCT to further improve outcome.



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