Hematopoietic stem cell transplantation

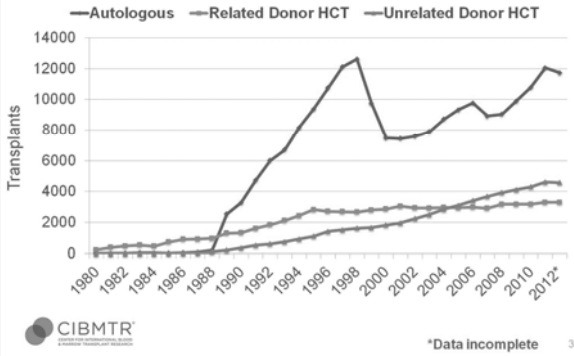
What to expect in the future ?

Wednesday 19th November 2014

Philippe Lewalle

BHS-MDPB committee

Transplant Activity in the US

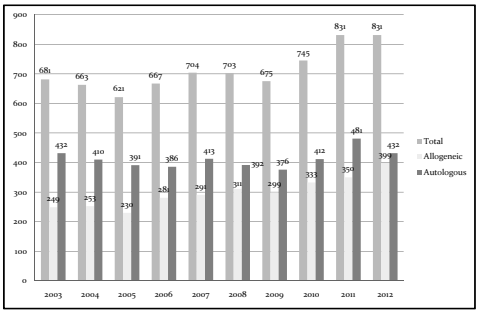


CIBMTR

*Data incomplete

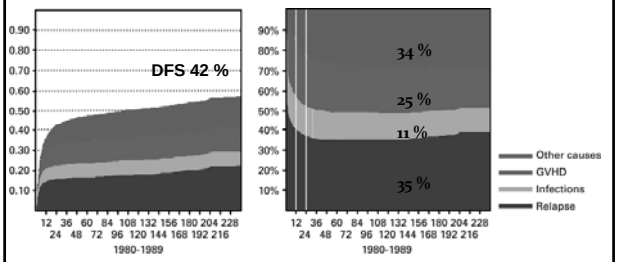
3

Number of stem cell transplants per year between 2003 and 2012 (BELGIUM).



Belgian Cancer Registry

Causes of Death after Allo-HSCT up to 20 years

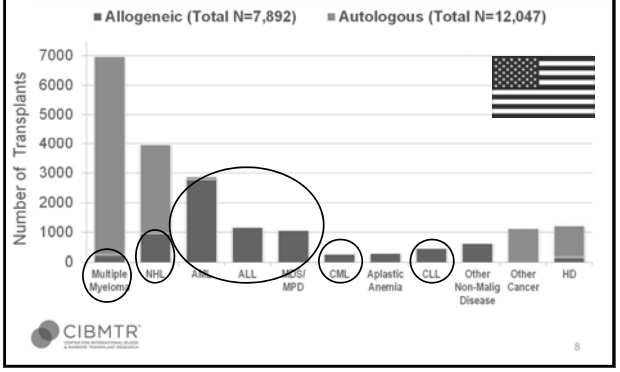


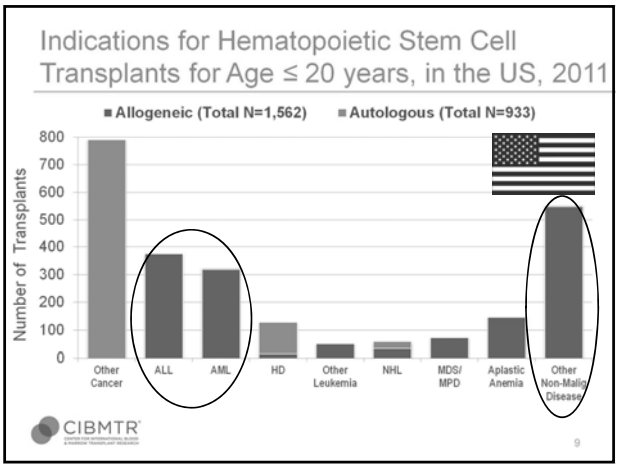
A Gratwohl, Bone Marrow Transplantation (2005)

Factors affecting Outcome and Immune Reconstitution

- Host factors: Age, conditionning regimen (ATG), initial pathology
- Donor factors: Age, sex, serology, ABO group, HSC mobilisation/harvest
- Genetic differences: HLA, mAgs, SNPs on genes linked to microbial responses.
- Source of HSC: Marrow, PBSC, CB, TCD,
- Post HSCT events: immunossupressive treatments, aGVHD, cGVHD

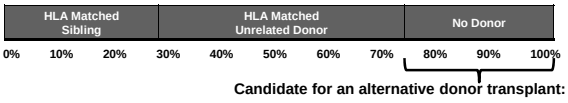
Indications for Hematopoietic Stem Cell Transplants in the US, 2011





Availability of a Stem Cell Donor Limits Applicability of Allogeneic Stem Cell Transplantation

Chances of Finding a Stem Cell Donor

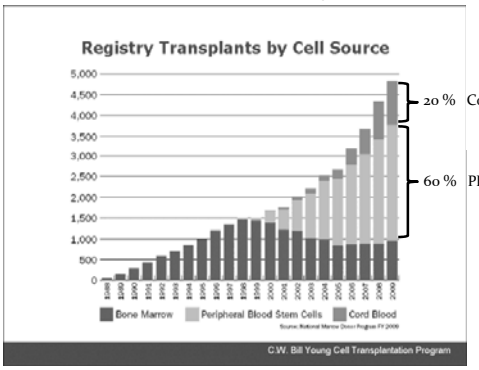


Candidate for an alternative donor transplant:

Report from the National Marrow Donor Program's registry indicates an 8/8 HLA-matched adult unrelated donor is available for
51% of Whites,
30% of Hispanics,
20% of Asians
17% of African-Americans

25-30% of all patients requiring HCT lack a suitable matched donor

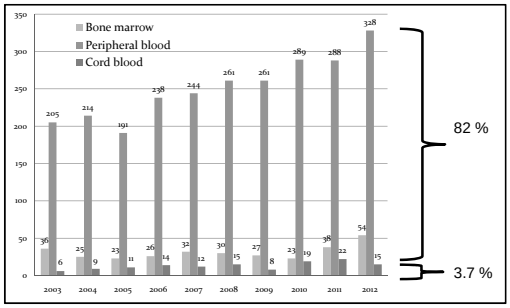
Increasing use of PBSC with a move away from BM for MUD recipients (USA)



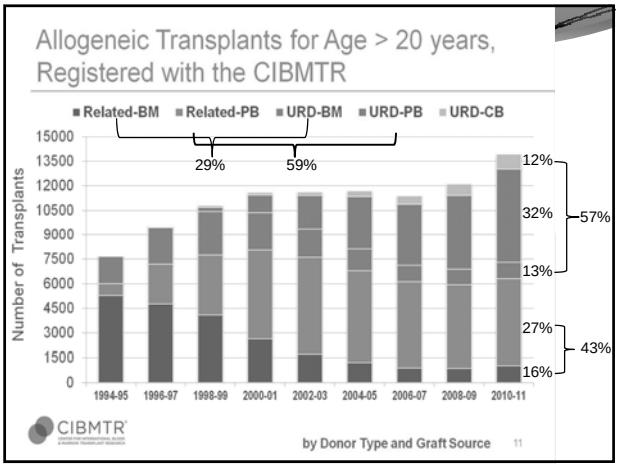
20 % Cord Blood

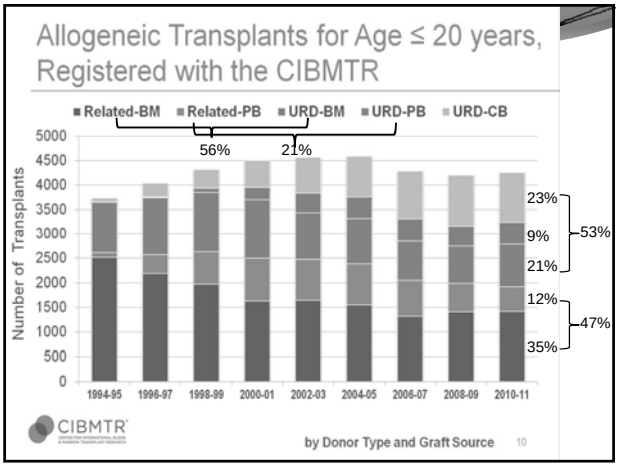
60 % PBSCs

Stem cell sources of allogeneic transplants between 2003 and 2012. (Belgium)



Belgian Cancer Registry





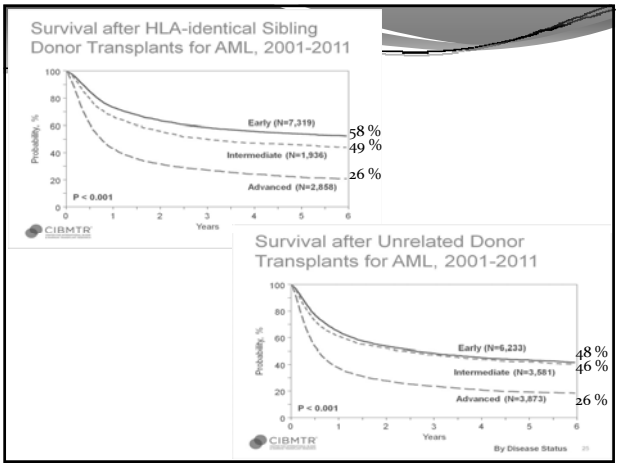
What Graft Source is Better: PBSC or BM ?

Peripheral Blood Stem Cell (first performed 1993)

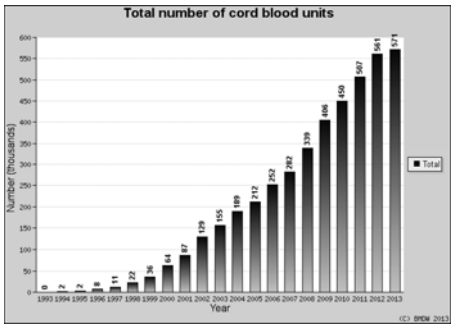
- Higher stem cell number (quicker engraftment)
- Higher T-cell number (Th2 polarized)
- Reduces risk of rejection
- Increases risk of chronic graft versus host disease (GVHD)

Bone Marrow

- Lower stem cell number (slower engraftment)
- Lower T-cell number
- Increased rejection rate
- Lower chronic graft versus host rate (GVHD)

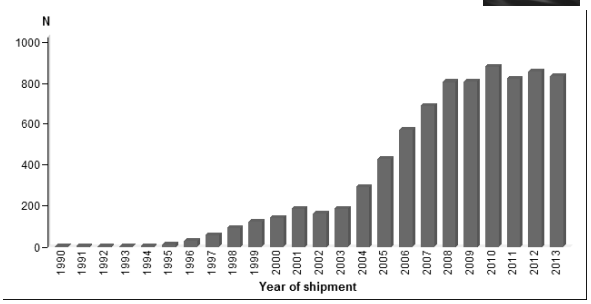


Alternative Graft : Haploidentical donor versus Cord Blood

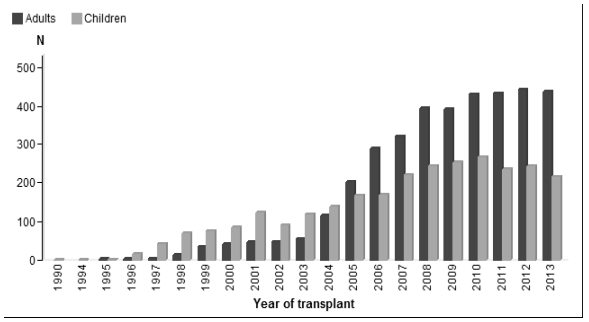


Data from BMDW - Bone Marrow Donors Worldwide

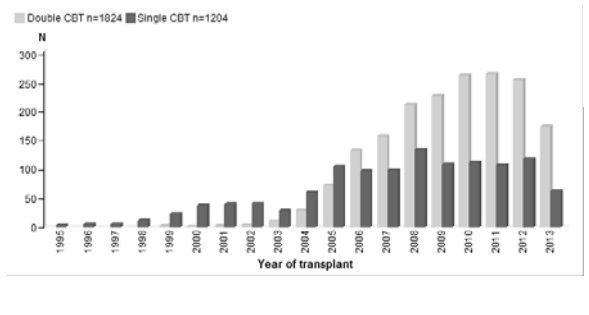
Eurocord registry at ABM
European CBUs shipped by year



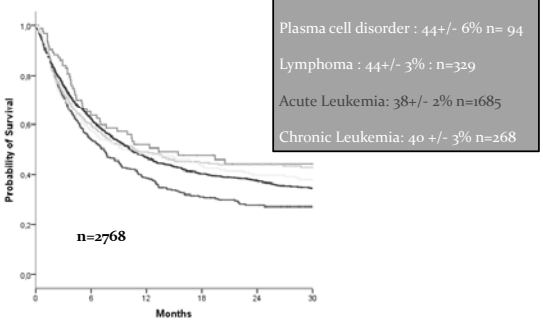
Eurocord Registry at ABM Unrelated European CBT by year and recipient's age



Eurocord Registry at ABM
Unrelated European CBT



Single and Double UCBT in EBMT centers, Adult, 2-y OS according to disease



MDS/MPS: 25+/- 3%: n=380

Plasma cell disorder : 44+/- 6% n= 94

Lymphoma : 44+/- 3% : n=329

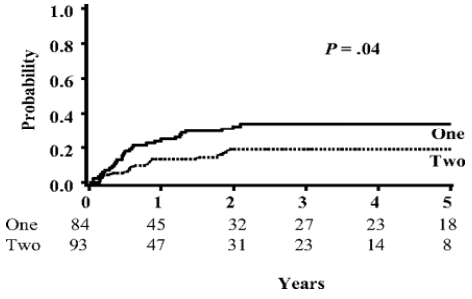
Acute Leukemia: 38+/- 2% n=1685

Chronic Leukemia: 40 +/- 3% n=268

Eurocord : 2y DFS single versus double cord

- DFS single cord : (6/6-5/6)
  33 % MDS
  37 % AML (46% CR1- 6% Relapse)
- Double cord : MAC 58% CR1 42% CR2 21% Adv
  MIDI/RIC 66% 54% 31%

DUCB HCT: lower risk of Relapse Acute Leukemia in CR1 & CR2



HSCT after myeloablative conditioning in adult patients comparing umbilical cord blood and other donor sources

Year	Graft type	Number of patients	Median age		aGVHD II-IV(%)	E cGVHD (%)	100 d TRM (%)	Relapse rate (%)	Survival (%)
2004[…]	UCB	150	16-60		41	51	63	17 (3 yr)	26 (3 yr)
	MUD BM	367	16-60		48	35	46	23	35
	MMUD BM	83	16-60		51	40	65	14	20
2004[…]	UCB	98	25		26	30	44	23 (2 yr)	36 (2 yr)
	MUD BM	584	32		39	46	38	13	42
2007[…]	UCB	100	38		60	23	8	17 (3 yr)	NA
	MRD (BM and PB)	71	40		55	30	4	26	
2008[…]	UCB	148	29		NA	NA	41	26 (2 yr)	35 (2 yr)
	MUD PB	518	35		NA	NA	27	30	45
	MMUD PB	210	NA		NA	NA	42	24	36
	MUD BM	243	29		NA	NA	26	28	48
	MMUD BM	111	NA		NA	NA	37	26	38
2009[…]	UCB AML	173	38		32	8	32 (2 yr)	31 (2 yr)	43 (2 yr)
	MUD BM	311	38		35	20	22	24	60
	UCB ALL	114	34		28	10	24	31	49
	MUD BM	222	32		42	17	25	24	57

Melhem Solh: World J Stem Cells. Sep 26, 2014; 6(4): 371–379.

UCBT

Pros

- CB banks: ~600,000 units, immediate availability, no donor risk, advantage for ethnic minorities, low risk of transmissible infections
- Applicability for children and adults with malignant and non malignant disorders
- Survival outcomes comparable to other sources of HSCs
- HLA mismatch accepted; ↓ GvHD and relapse (> GvL)
- Use extended in older populations with RIC and double UCBT

Cons

- Delayed engraftment and immune reconstitution; high risk of graft failure (> TRM)
- Unavailability of the donor for additional donations (i.e DLI)
- Sustainability of CB banks

Why UCBT in adults has been increasing over the years and is now a "plateau" ?

- Use of double cord to increase the TNC dose and facilitate engraftment
- Increased confidence in the procedure
- Several published reports showed similar outcomes of UCBT with HLA matched bone marrow or peripheral blood stem cell donors
- The use of reduced intensity conditioning (RIC) regimen that decreases the mortality related to transplantation

✓**Decreased use in recent years :**

- Competition with related haplo identical HSC
- Cost of graft acquisition especially for double unit of CB

Advantage of haploidentical transplant

- Family donor (minor Ag/SNPs/ HLA linked genes)
- Immediate donor availability
- Multiple donors available (age sex CMV ABO group)
- KIR mismatched : NK alloreactivity
- Control of graft composition
- Access to cellular immunotherapy and to DLI.
- Second graft possible if rejection.
- Cheaper

Conditioning Regimen

- **T Cell depletion**
  Partial T cell depletion(CD3/CD19 depletion)
  $5x10^4$ CD3/KG
  Post transplant immunosuppression
  ExtensiveT cell depletion (CD34+ selection)
  $1x10^4$ CD3/Kg
  Mega stem cell dose $10x10^6$ CD34/Kg
  No post transplant Immunossupression
- **Non T cell depletion**
  RIC – (Bone marrow)+ PBSC
  Heavy post-transplant Immunosuppression

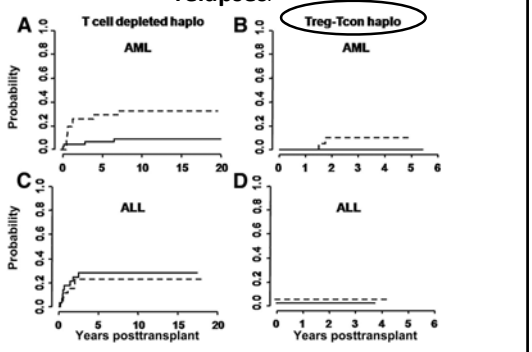
RESULTS of PERUGIA

- Grade II-IV aGVHD 5%
- TRM 36% patients in RC
  58% patients transplanted in relapse
- Relapse (transplanted in CR) AML 18%
  ALL 30%
- OS: AML+ ALL: CR1 55%, 33% CR2, 28% any CR

- NK mismatched LMA CR: Relapse : 3% versus 47%
  NK mismatched LMA + LLA : EFS : 67% versus 18%
  (EFS UNRELATED 44% CR1 et 37% CR2)

Aversa F, J Clin Oncol. 2005 May 20;23(15): 3447-54

Cumulative incidence of posttransplant leukemia relapses.



Martelli M F et al. Blood 2014;124:638-644

blood

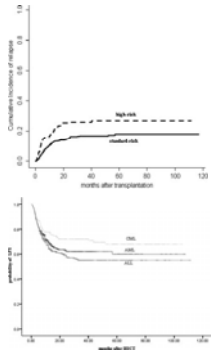
Haploidentical HSC transplantation without in vitro T cell depletion for leukemia

aGRADE II-IV 47% cGVHD 23%

Rechute 12% Standard Risk
39% High Risk

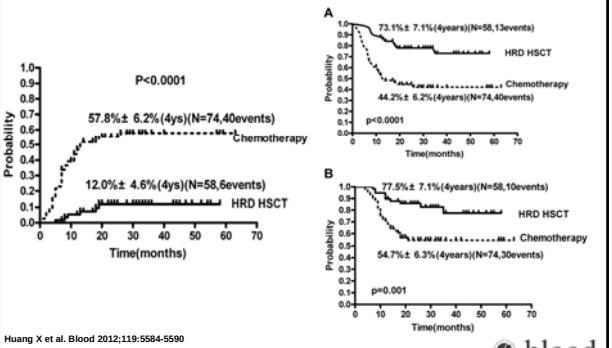
TRM 12% Standard Risk
39% High Risk

DFS LMA (RS) 78%, (HR) 57% et (A) 22%
LLA (RS) 74%, (HR) 35% et (A) 14%



Wang Y, Huang XJ, Cancer: Volume 119, Issue 5, pages 978-985, 23 OCT 2012
Huang XJ. Blood. 2012 Jun 7;119(23):5584-90.

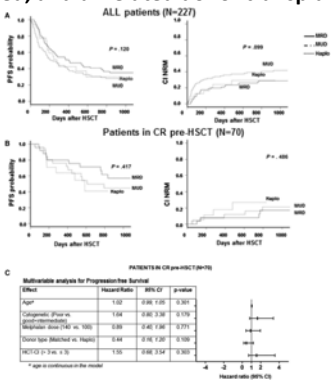
HRD-HSCT group and the chemotherapy-alone group of patients with intermediate- and high-risk AML. RR and DFS (A) and OS (B).



Huang X et al. Blood 2012;119:5584-5590

blood

Transplantation outcomes for haploidentical, matched related, and unrelated donor transplantations



Di Stasi A. Biol Blood Marrow Transplant. 2014 Sep 28

Haploidentical hematopoietic cell transplantation compared to transplantation from other graft sources

Year	Number of patients	aGVHD II-IV (%)	cGVHD (%)	100 d NRM (%)	Relapse (2 yr)	Survival (%)
2002[63]	MUD BM 81	42	57	23	25	58 (2 yr OS)
	MMUD BM 58	33	51	45	26	34
	Haplo 48	46	50	42	42	21
2005[53]	Haplo-ALL 74	8	NA	49	38	13 (2 yr LFS)
	UCB-ALL 91	26		41	23	36
	Haplo-AML 151	12		58	18	24
	UCB-AML 91	26		24	24	30
2009[48]	Haplo 56	27	23	13	22	68 (2 yr LFS)
	MRD 51	14	31	8	17	76

Melhem Solh: World J Stem Cells. Sep 26, 2014; 6(4): 371–379.

Single center (Genoa) comparative study Bacigalupo

GVHDa	Sibling/URD	31% (II-IV)	6%/7% (III-IV)
	CB	14%	1%
	HAPLO	19%	4%
GVHDc	Sibling/URD	63/65%	
	CB	53%	
	HAPLO	50%	
TRM	Sibling/URD	19%/34%	
	CB	36%	
	HAPLO	16%	
RR	Sibling/URD	22%/24%	
	CB	27%	
	HAPLO	25%	
DFS	Sibling/URD	41/40%	CR1 51/55%
	CB	36%	41%
	HAPLO	43%	62%

Take home message

- Today a matched donor is still the first choice
  - Perhaps not true for all situation.
- More and more matched unrelated donor are available
  - Effort for ethnic group other than Caucasian
- Transplantation with an alternative donor compares fairly with a matched donor.
  - Optimize the best donor choice strategy
- Results of UCB and Haplo are tight
  - Haplo is cheaper

Need for randomized study
The dream non allotransplant immunotherapy