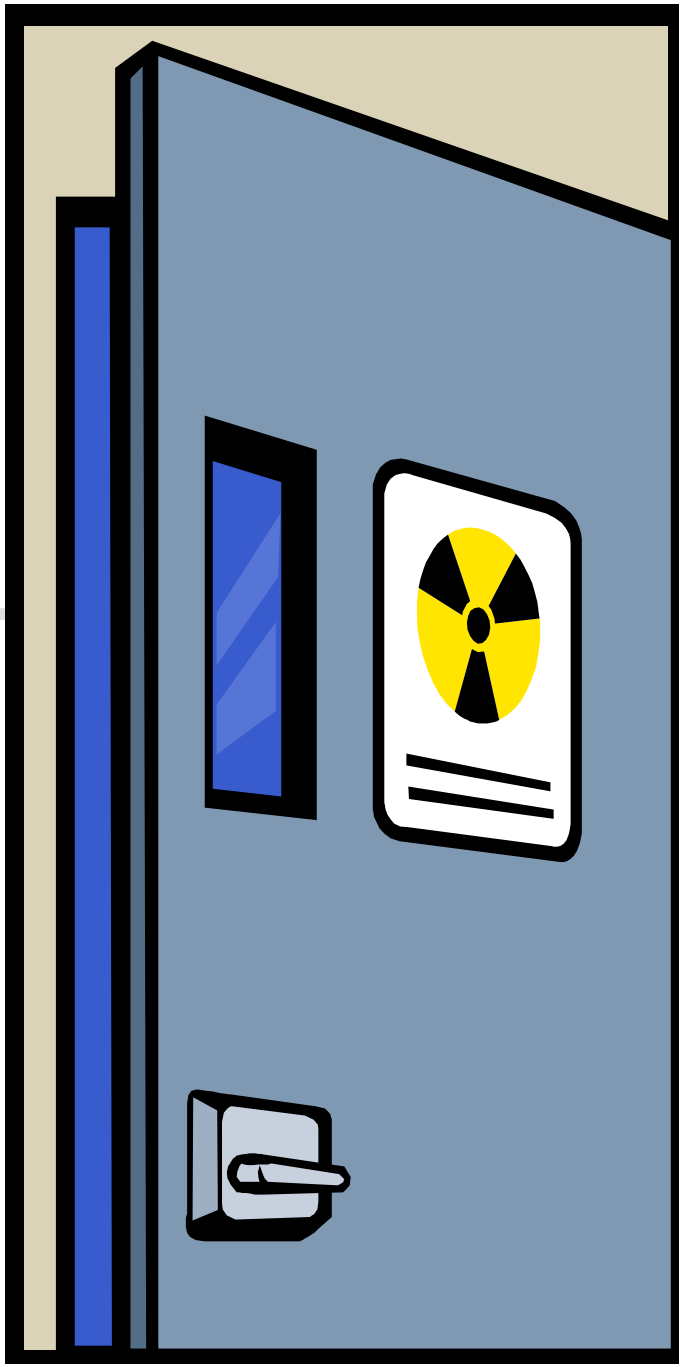
THE ROLE OF TBI IN STEM CELL TRANSPLANTATION



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Introduction

- Radiotherapy is the medical use of ionising radiation.
- TBI or Total Body Irradiation is the process by which a required amount of radiation is delivered to specific tissues to allow donor cell engraftment and kill abnormal cells.

OUTLINE

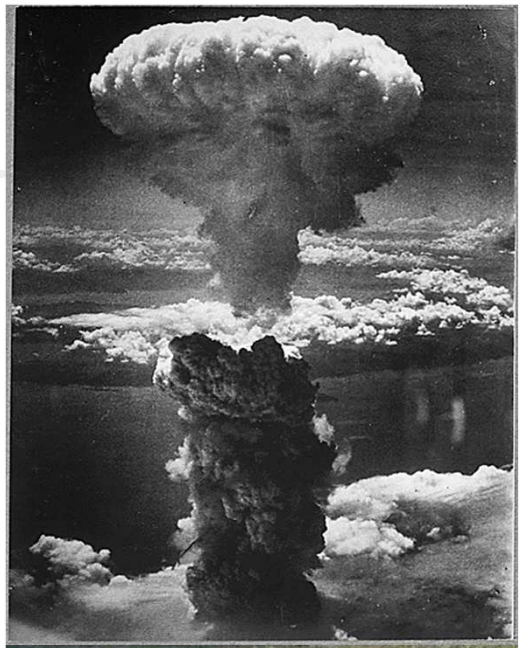
- Historical perspective
- Stem cell Transplant
- Role of TBI in SCT
- Indications for TBI
- Newer perspectives

HISTORICAL PERSPECTIVE

The use of TBI in conditioning for stem cell transplantation mirrors the start of SCT as a curative procedure.

This treatment concept was developed from findings in World War II that irradiation destroyed BM function.

Studies during the 1950s showed that irradiated animals could be saved from irreversible bone marrow failure by transfusion of bone marrow from another animal.



HISTORICAL PERSPECTIVE

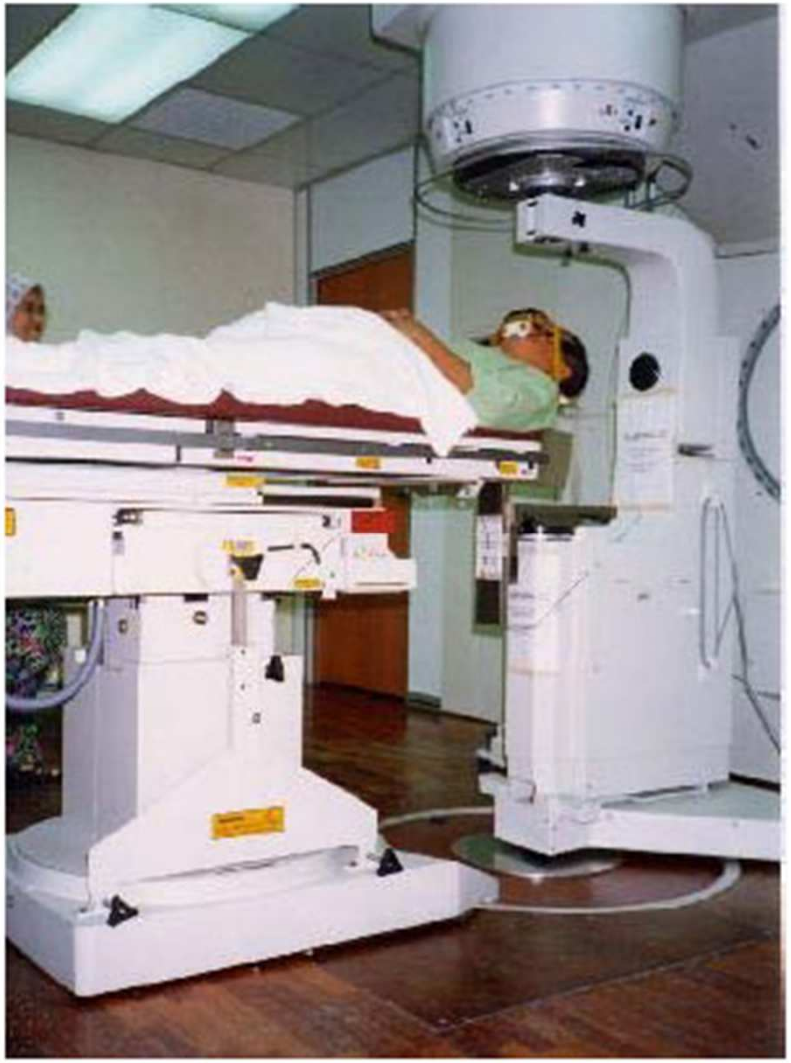
The use of TBI in conditioning for allo HSCT began in 1956 when Dr. Donnall Thomas used high dose chemoradiotherapy and alloSCT to treat patients with end stage leukemia.

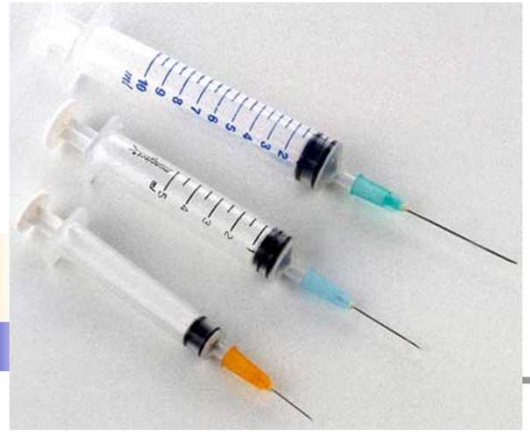
He was awarded the Nobel prize for Medicine in 1990

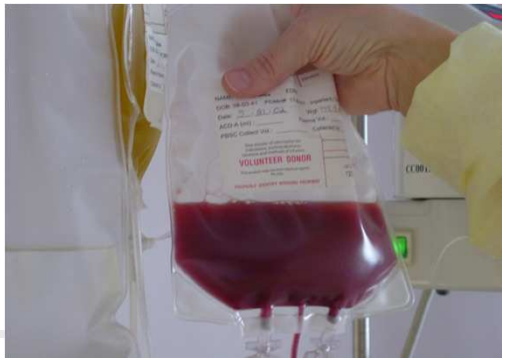
Research of the Curie's began a new era in medical treatment and research

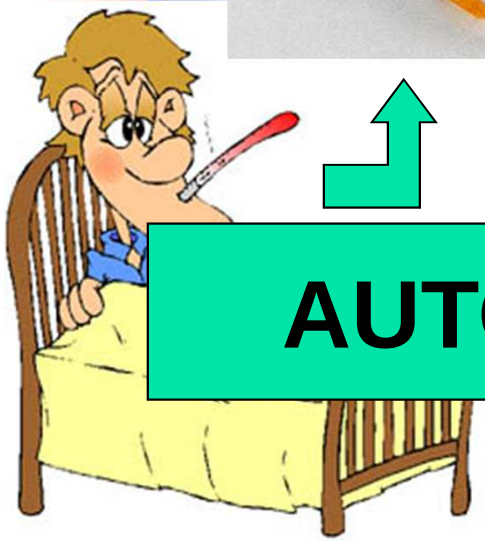
Radium was used in various forms until the mid-1900's when cobalt and cesium units came into use

Modern liner accelerators have been developed since the late 1940s

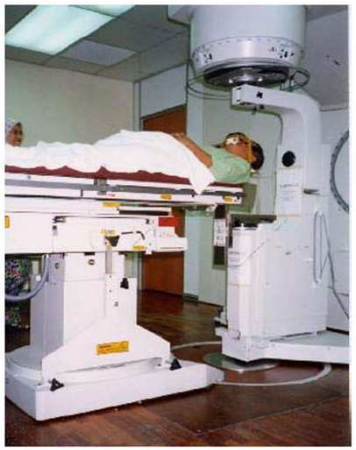




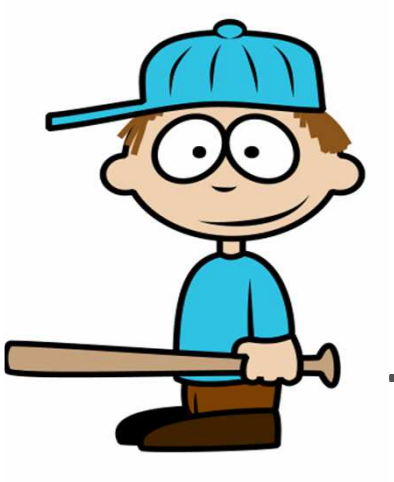


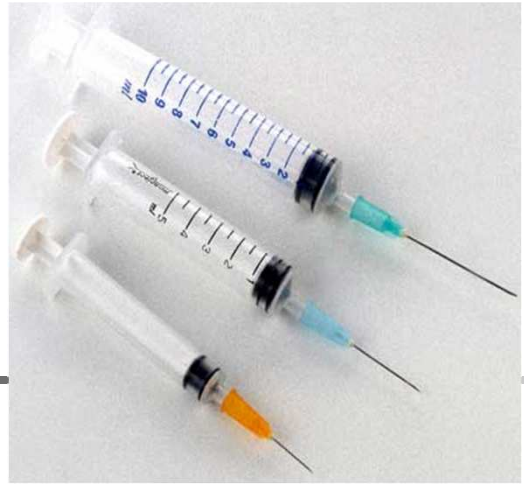


AUTOLOGOUS TRANSPLANT



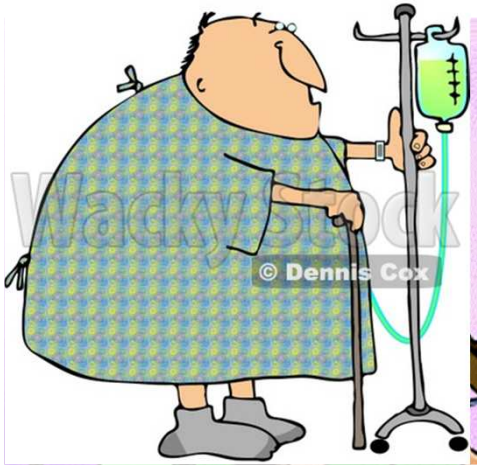
PBSC INFUSION





LOW DOSE

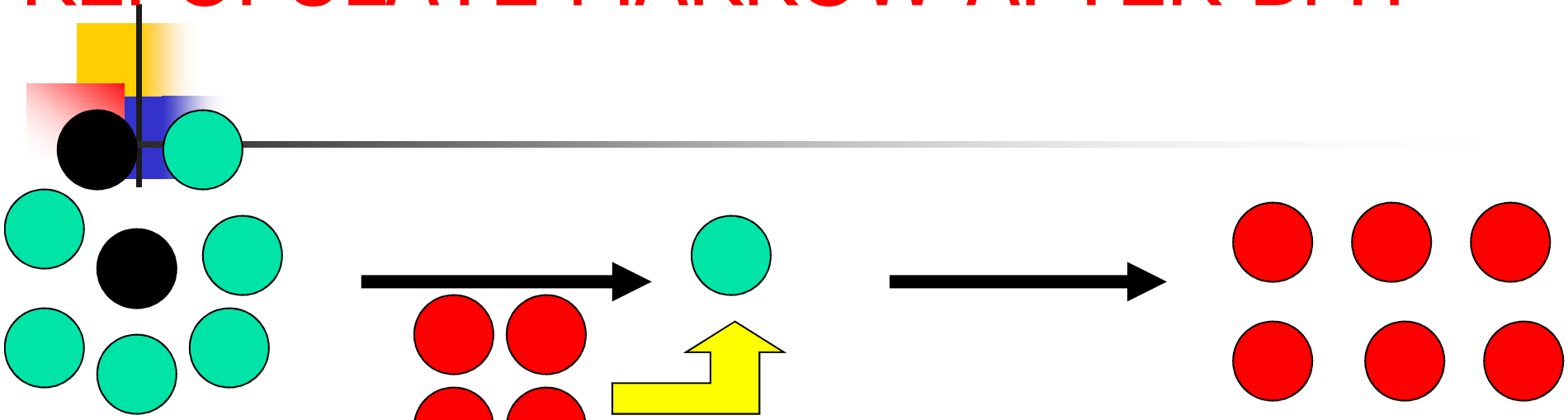
ALLOGENEIC TRANSPLANT



CHEMO ±
RT

INFUSION

DONOR STEM CELLS REPOPULATE MARROW AFTER BMT

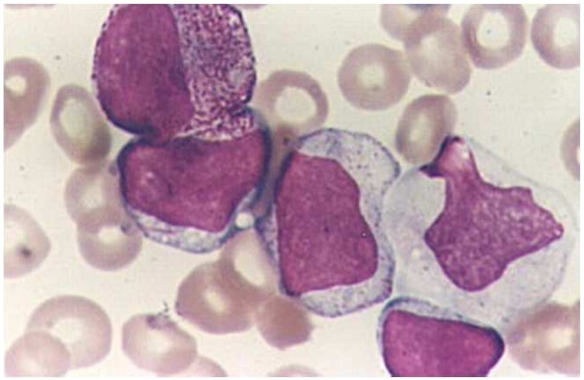


PATIENT CELLS

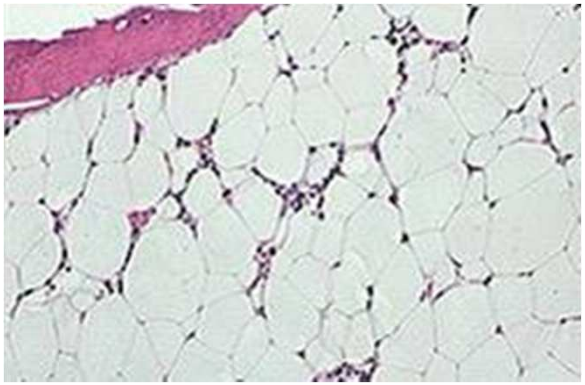
LEUKEMIC CLONE

DONOR CELLS

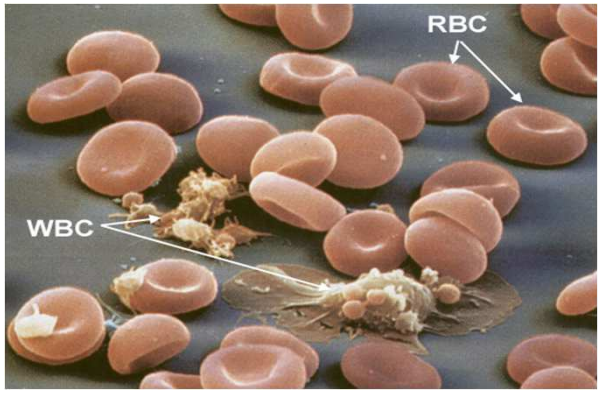
ONLY DONOR CELLS IN PT



PRE - BMT

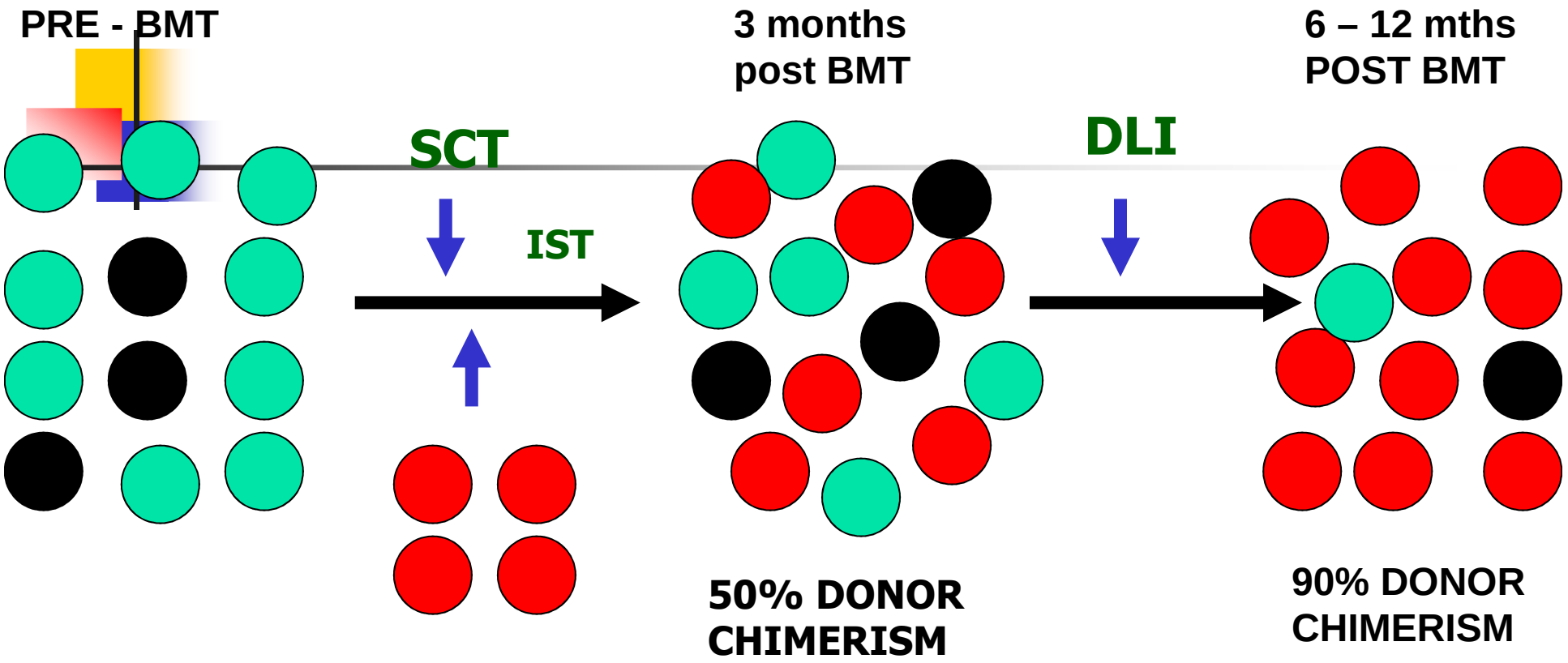


BMT



POST BMT

NON MYELOABLATIVE TRANSPLANTS



Host hematopoiesis

Donor Hematopoiesis

Leukemic clone

Goals of TBI

- Immunosuppression - lymphocyte elimination to allow grafting of donor bone marrow
- Eradication of malignant cells - leukemia, lymphoma, rarely solid tumors
- Eradication of cells with genetic disorders - Fanconi's anemia, thalassemia major, Wiskott-Aldrich syndrome

Severity of Radiation Injury

Dose Range (Gy)	Prodrome	Manifest - Illness	Prognosis (without therapy)
0.5-1.0	Mild	Slight decrease in blood cell counts	Almost certain survival
1.0-2.0	Mild to Moderate	Early signs of BM damage	Highly probable survival (>90% of victims)
2.0-3.5	Moderate	Moderate-severe BM damage	Probable survival
3.5-5.5	Severe	Severe BM damage; mild GI damage	Death within 3.5-6 weeks (50% of victims)
5.5-7.5	Severe	Pancytopenia and moderate GI damage	Death probable within 2-3 weeks
7.5-10.0	Severe	Marked GI and BM damage; hypotension	Death probable within 1-2.5 weeks
10.0-20.0	Severe	Severe GI damage, pneumonitis, altered mental status	Death certain within 5-12 days
20.0-30.0	Severe	CV collapse; fever; shock	Death certain within 2-5 days

12 Gy: TBI dose for clinical BMT

Abbreviations: Bone marrow (BM); Cerebrovascular (CV); Gastrointestinal (GI).

Modified from RI Walker and RJ Cerveny, eds.(reference 21); provided by Dr. J. Waselenko

The standard dose of irradiation used for total body irradiation (TBI) clinical BMT is 12 Gy (1200 rad), but….

- this total dose is administered in multiple fractions over several days to allow repair of normal cells and tissues

- the lungs are usually given a lower total exposure (e.g., 9 Gy) to reduce risks of pulmonary toxicity

ADVANTAGES OF TBI OVER SYSTEMIC CHEMOTHERAPY

1. No cross resistance with other agents.
2. Delivered dose independent of blood supply
3. No sanctuary sites (eg testes, brain)
4. After radiation is given, no detoxification or excretion required – hence delivered dose independent of renal and hepatic function.
5. Dose can be homogeneous, and tailored to "boost" areas at risk and "spare" more sensitive organs

INDICATIONS FOR TBI

- MALIGNANT
- Acute leukemia
- Chronic Leukemia
- Lymphoma
- Myeloma
- Solid tumors

- NON-MALIGNANT
- Aplastic anemia
- MDS
- Autoimmune disease
- Immunodeficiency syndromes

SIDE EFFECTS

- SHORT TERM
- Nausea, vomiting
- BM suppression
- Diarrhea
- Mucositis
- VOD liver
- Skin changes
- Interstitial pneumonitis

- LONG TERM
- Pulmonary
- Ocular
- Thyroid
- Infertility
- Secondary malignancies
- Radiation nephropathy
- Growth retardation
- Cognitive dysfunction

TBI vs CHEMOTHERAPY

- TBI combined with chemotherapy was the standard conditioning regimen used for all transplants.
- Acute side effects of TBI led to the replacement of TBI by other chemotherapy drugs like Busulfan.
- Majority of the trials are looking at comparing Cy/TBI and Bu/Cy in various diseases.

Busulfan plus cyclophosphamide compared with total-body irradiation plus cyclophosphamide before marrow transplantation for myeloid leukemia: long-term follow-up of 4 randomized studies

BLOOD, 15 DECEMBER 2001 • VOLUME 98, NUMBER 13

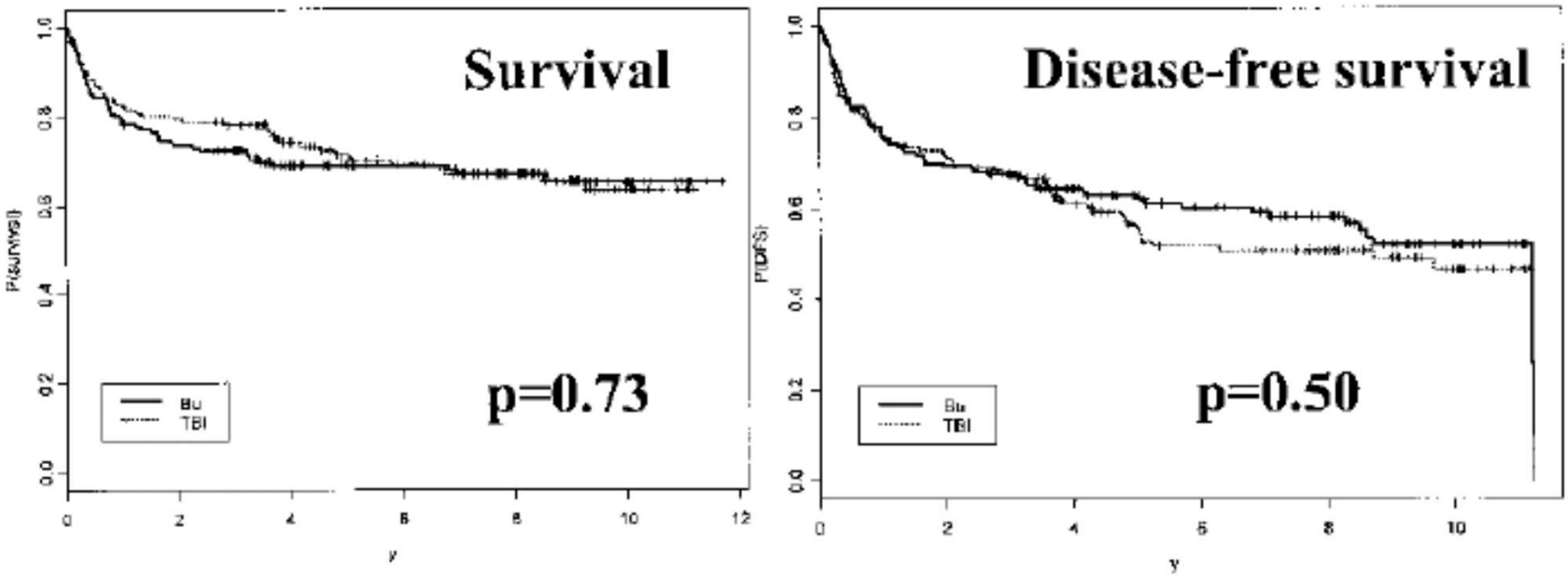
Table 1. Patient and disease characteristics in 4 randomized trials

	Disease	Stage	No. of patients (original report)	No. of patients with long-term follow-up (%)	Median age at transplant, y	Follow-up (original report, in mo)
Blaise et al	AML	First CR	101	100	32	23 ± 11
Clift et al	CML	CP	147	96.5	37	Minimum 12
Devergie et al	CML	CP	120	98.3	36	42
Ringden et al	CML/AML	CP/CR1	46/51	98.4	33	1-50
	CML/AML	Advanced	11/19			

Table 2. Transplantation characteristics in the 4 randomized trials

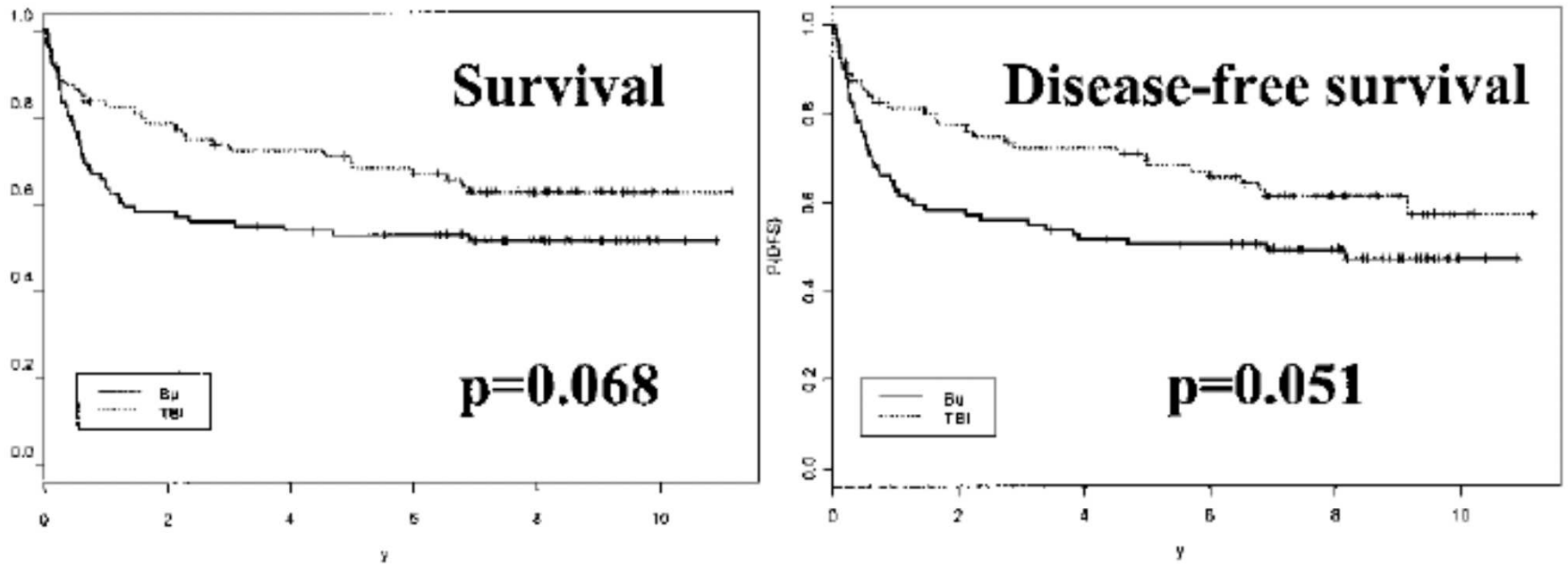
	AML (n = 172) Bu-CY/CY-TBI	CML (n = 316) Bu-CY/CY-TBI	Total (n = 488)
Trial			
FHCRC	—	73/69	142
SFGM-TC	55/49	65/53	222
Nordic group	37/31	30/26	124
Age at transplantation, y (range)	35 (2.5-42)/33 (26.5-39.5)	38 (31-44)/36 (29-41)	—
GVHD prophylaxis	MTX + CSA	MTX + CSA	100%
+ Anti–IL-2R	9:55/8:49	7:65/8:53	32:222 (14.4%)

IL-2R indicates interleukin-2 receptor; SFGM-TC, Société Française de Greffe de Moelle et de Therapie Cellulaire; MTX, methotrexate; CSA, cyclosporine.



CML

Figure 1. Survival and DFS of patients with CML receiving either Bu or TBI associated with CY as conditioning regimen before transplantation.



AML

Figure 2. Survival and DFS of patients with AML receiving either Bu or TBI associated with CY as conditioning regimen before transplantation.

Table 4. Estimation of conditioning effect in each diagnostic group on each end point

End point	AML (n = 172) (95% CI; *P*)	CML (n = 316) (95% CI; *P*)
Cataract	11 events	66 events
BUCY vs CY-TBI	1.05 (0.32-3.44; .94)	2.67 (1.56-4.57; **.0003**)
Multivariable model		
BUCY vs CY-TBI	1.05 (0.31-3.57; .94)	2.32 (1.32-4.07; **.0035**)
Acute GVHD	1.05 (0.30-3.69; .94)	1.37 (0.76-2.48; .30)
Chronic GVHD	0.27 (0.03-2.39; .24)	2.99 (1.64-5.44; **.0003**)
Age	1.02 (0.96-1.08; .51)	0.998 (0.975-1.023; .89)
Pulmonary complications	9 events	46 events
BUCY vs CY-TBI	0.75 (0.20-2.80; .67)	0.80 (0.44-1.48; .48)
Multivariable model		
BUCY vs CY-TBI	0.55 (0.14-2.11; .38)	0.70 (0.36-1.33; .27)
Acute GVHD	4.46 (0.85-23.5; .078)	1.32 (0.68-2.56; .41)
Chronic GVHD	1.60 (0.30-8.48; .58)	2.62 (1.31-5.27; **.0067**)
Age	0.995 (0.941-1.052; .86)	0.988 (0.958-1.019; **.45**)
Avascular osteonecrosis	10 events	19 events
BUCY vs CY-TBI	1.04 (0.30-3.62; .95)	3.09 (1.11-8.57; **.0307**)
Multivariable model		
BUCY vs CY-TBI	1.04 (0.30-3.64; .95)	2.52 (0.86-7.43; .094)
Acute GVHD	0.79 (0.21-3.03; .73)	1.33 (0.44-4.01; .61)
Chronic GVHD	3.18 (0.60-16.9; .17)	7.01 (1.85-26.5; **.0041**)
Age	0.972 (0.917-1.030; .34)	0.925 (0.880-0.972; **.0021**)
Hair loss	58 events/86	66 events/98
BUCY vs CY-TBI	0.30 (0.12-0.80; **.016**)	0.61 (0.26-1.43; .25)
Multivariable model		
BUCY vs CY-TBI	0.19 (0.06-0.58; **.0035**)	0.79 (0.32-1.95; .61)
Acute GVHD	2.53 (0.81-7.91; .11)	1.08 (0.43-2.70; .87)
Chronic GVHD	2.74 (0.50-15.0; .25)	3.26 (1.11-9.59; **.032**)
Age	1.046 (1.001-1.094; **.046**)	1.027 (0.972-1.077; .37)

Randomized trials

- **Fred Hutchinson** (1988-1992) - CML; CY/TBI vs. Bu/CY
  - Randomized. 142 patients with CML in chronic phase, treated with cyclophosphamide 120 mg/kg + TBI 12/6 vs. busulphan 64 mg/kg + cyclophosphamide 120 mg/kg
  - **9-years, 1999** -- "Long-term follow-up of a randomized study comparing cyclophosphamide and total body irradiation with busulfan and cyclophosphamide for patients receiving allogenic marrow transplants during chronic phase of chronic myeloid leukemia." (Clift RA, Blood. 1999 Dec 1;94(11):3960-2.). Median F/U 7.7 years
- 9-year outcome: OS: BUCY 73% vs. CY-TBI 65% (NS); relapse 19% vs. 22% (NS)
  - Non-relapse mortality: 20% vs. 25% (NS)
  - Conclusion: BU-CY better tolerated, and comparable efficacy

UNRELATED TRANSPLANTS IN AML

Comparative analysis of BU and CY versus CY and TBI in full intensity unrelated marrow donor transplantation for AML, CML and myelodysplasia

Bone Marrow Transplantation (2010), 1–10

Table 1 Characteristics of patients with hematologic malignancies who received an unrelated marrow transplant, facilitated by the National Marrow Donor Program, between 1991 and 1999, by conditioning regimen (BuCy, Cy/TBI standard dose (1000–1260 cGy), Cy/TBI high dose (1320–1500 cGyS)

Patient characteristics	*Total* N *(eval)*	*BuCy*	*Cy/TBI standard* *(⩾1000 and ⩽1260)*	*Cy/TBI high* *(>1320 and ⩽1500)*	P-*value*[a]
Total number of patients	1593	318	420	855	
Recipient age, median (range), years	37 (1–58)	40 (1–58)	38 (1–58)	36 (1–58)	<0.001
⩽20	192 (12)	32 (10)	36 (9)	124 (14)	
21–40	743 (47)	125 (39)	201 (48)	417 (49)	
41–60	658 (41)	161 (51)	183 (43)	314 (37)	
Performance score					0.06
<90	453 (28)	87 (27)	103 (24)	263 (31)	
⩾90	1140 (72)	231 (73)	317 (76)	592 (69)	
Disease					<0.001
AML	414 (26)	72 (23)	61 (15)	281 (33)	
CML	1038 (65)	188 (59)	340 (81)	510 (60)	
MDS	141 (9)	58 (18)	19 (5)	64 (7)	
Disease stage[b]					<0.001
Early	894 (56)	206 (66)	301 (72)	387 (45)	
Intermediate	430 (27)	56 (17)	76 (18)	298 (35)	
Advanced	269 (17)	56 (17)	43 (10)	170 (20)	
Year of infusion					0.35
1991–1993	399 (25)	68 (21)	111 (26)	220 (26)	
1994–1996	654 (41)	144 (46)	170 (41)	340 (40)	
1997–1999	540 (34)	106 (33)	139 (33)	295 (35)	
Recipient/donor sex match					0.07
Male/male	601 (38)	131 (42)	159 (38)	311 (36)	
Male/female	367 (23)	66 (21)	115 (27)	186 (22)	
Female/male	309 (19)	55 (17)	72 (17)	182 (21)	
Female/female	316 (20)	66 (21)	74 (18)	176 (21)	
Recipient/donor CMV match					0.08
Negative/negative	531 (33)	109 (34)	161 (38)	261 (30)	
Positive/positive	309 (19)	54 (17)	73 (17)	182 (21)	
Positive/negative	236 (15)	52 (16)	49 (12)	135 (16)	
Negative/positive	487 (31)	98 (31)	126 (30)	263 (31)	
Unknown	30 (2)	5 (2)	11 (3)	14 (2)	
Donor age, median (range), years	37 (18–58)	37 (19–58)	37 (19–58)	37 (18–57)	0.94
Interval from diagnosis to transplant, median (range), months	13 (1–263)	11 (1–225)	13 (3–219)	13 (1–263)	0.17
⩽12 months	750 (47)	167 (53)	192 (46)	391 (46)	
>12 months	837 (53)	151 (47)	226 (54)	460 (54)	
GVHD prophylaxis					<0.001
CSA + MTX ± other	1368 (86)	237 (75)	371 (88)	760 (89)	
CSA ± other	52 (3)	28 (9)	16 (4)	8 (1)	
FK506 ± other	159 (10)	48 (15)	30 (7)	81 (9)	
MTX ± other	9 (1)	3 (1)	1 (<1)	5 (1)	
Other[c]	5 (<1)	2 (1)	2 (<1)	1 (<1)	
HLA match status[d]					<0.001
Well matched	490 (31)	88 (28)	151 (36)	251 (29)	
Partially matched	608 (38)	152 (48)	167 (40)	289 (34)	
Mismatched	495 (31)	78 (24)	102 (24)	315 (37)	
Nucleated cell dose 10^8/kg, median (range)	3 (<1–52)	3 (<1–12)	3 (<1–29)	3 (<1–52)	0.0124
<1.7	263 (17)	36 (11)	69 (17)	158 (18)	
⩾1.7	1330 (83)	282 (89)	351 (83)	697 (82)	
Growth factor used to promote engraftment[e]					0.35
Yes	355 (22)	87 (27)	73 (17)	195 (23)	
No	1238 (78)	231 (73)	347 (83)	660 (77)	
Median follow-up of survivors median (range), months	97 (12–168)	100 (23–163)	103 (12–168)	96 (22–161)	<0.001

Table 2 Univariate probabilities of outcomes of patients with hematologic malignancies who received an unrelated marrow transplant, facilitated by the National Marrow Donor Program., between 1991 and 1999, by conditioning regimen (BuCy, Cy/TBI standard dose (1000–1260 cGY), Cy/TBI high dose (1320–1500 cGy))

Outcome event	N *(eval)*	*BuCY*	*CY/TBI standard dose*	*CY/TBI high dose*	P-*value*[a]
Transplant-related mortality[b]	1593				
@ 1 year		48 (43–54)%	43 (39–48)%	47 (43–50)%	0.37
Relapse[b]	1593				
@ 1 year		10 (7–13)%	9 (7–12)%	16 (14–18)%	<0.001
Neutrophil engraftment[b]	1590				
@ 28 days		80 (75–84)%	88 (84–91)%	81 (78–84)%	0.001
@ 60 days		88 (84–91)%	93 (90–95)%	88 (86–91)%	0.01
Platelet engraftment[b] *($20000 \times 10^9/L$)*	1303				
@ 100 days		63 (57–69)%	68 (63–73)%	57 (53–61)%	0.002
@ 1 year		66 (60–71)%	72 (67–76)%	61 (57–64)%	0.002
Acute GVHD[b]					
Grades II–IV @100 days	1581	48 (43–54)%	62 (57–66)%	59 (56–62)%	<0.001
Grades III–IV @100 days	1588	32 (27–38)%	35 (31–40)%	38 (34–41)%	0.20
Chronic GVHD[b]	1486				
@ 180 days		23 (18–28)%	35 (31–40)%	28 (25–31)%	0.001
@ 1 year		36 (31–41)%	44 (39–49)%	40 (37–44)%	0.07
@ 2 years		39 (34–45)%	48 (43–53)%	43 (40–47)%	0.06
Veno occlusive disease (VOD)[b]	1430				
@ 100 days		21 (16–26)%	13 (10–16)%	15 (13–18)%	0.02
Interstitial pneumonitis (IPN)[b]	1558				
@100 days		20 (16–25)%	22 (18–26)%	21 (19–24)%	0.91

Table 3 Multivariate analysis of patients with hematologic malignancies who received an unrelated marrow transplant facilitated by the NMDP between 1991 and 1999

Outcome of interest	*Main effect*[a]	N *(eval)*	*Relative risk (95% CI)*	P-*value*
Disease-free survival (DFS)	Conditioning regimen			
	BuCy	318	1.00[b]	$P^{c}_{overall} = 0.464$
	TBI standard	420	0.83 (0.60–1.15)	$P_{12} = 0.263$
	TBI high	855	0.99 (0.67–1.28)	$P_{13} = 0.649$
	Other significant covariates: HLA match status, total nucleated cell dose, recipient age, growth factor, disease*disease stage			
OS	Conditioning regimen			
	BuCy	318	1.00[b]	$P^{c}_{overall} = 0.236$
	TBI standard	420	0.81 (0.58–1.13)	$P_{12} = 0.218$
	TBI high	855	0.99 (0.72–1.36)	$P_{13} = 0.952$
	Other significant covariates: HLA match status, total nucleated cell dose, recipient age, growth factor, disease*disease stage			
Treatment-related mortality (TRM)	Conditioning regimen			
	BuCy	318	1.00[b]	$P^{c}_{overall} = 0.384$
	TBI standard	420	0.78 (0.54–1.12)	$P_{12} = 0.176$
	TBI high	855	0.87 (0.60–1.25)	$P_{13} = 0.442$
	Other significant covariates: donor/recipient CMV match, HLA match status, total nucleated cell dose, growth factor, disease*disease stage			
Relapse	Conditioning regimen			
	BuCy	318	1.00[b]	$P^{c}_{overall} = 0.155$
	TBI standard	420	1.08 (0.52–2.22)	$P_{12} = 0.837$
	TBI high	855	0.68 (0.36–1.29)	$P_{13} = 0.238$
	Other significant covariates: interval from diagnosis to transplant, months, disease*disease stage			
AGVHD (II–IV)	Conditioning regimen			
	BuCy	316	1.00[b]	$P^{c}_{overall} = 0.248$
	TBI standard	415	1.25 (0.92–1.71)	$P_{12} = 0.160$
	TBI high	850	1.31 (0.95–1.79)	$P_{13} = 0.096$
	Other significant covariates: HLA match status			
AGVHD (III–IV)	Conditioning regimen			
	BuCy	316	1.00[b]	$P^{c}_{overall} = <0.001$
	TBI standard	415	1.29 (0.82–2.00)	$P_{12} = 0.264$
	TBI high	850	1.79 (1.15–2.81)	$P_{13} = 0.011$
	Other significant covariates: HLA match status., year of transplant			
Neutrophil engraftment	Conditioning regimen			
	BuCy	318	1.00[b]	$P^{c}_{overall} = <0.001$
	TBI standard	418	2.36 (1.23–4.50)	$P_{12} = <0.001$
	TBI high	854	0.76 (0.41–1.40)	$P_{13} = 0.005$
	Other significant covariates: Karnofsky score, HLA match status, total nucleated cell dose			

Acute lymphoblastic leukemia

Comparison of Preparative Regimens in Transplants for Children With Acute Lymphoblastic Leukemia

J Clin Oncol 18:340-347.

Table 1. Characteristics of Children Who Received TBI/CY Versus Bu/CY for Pretransplant Conditioning

Variable	TBI/CY			Bu/CY			
	No. Assessable	No.†	%†	No. Assessable	No.	%	*P*
Age at transplant, years	451			176			.012
Median*		12.9			11.3		
Range*		0.7-19.9			0.5-19.9		
≤5 years		35	8		27	15	
5-10 years		130	29		52	30	
>10 years		286	63		97	55	
Sex	451			176			.550
Male		321	71		121	69	
Female		130	29		52	31	
Karnofsky score pretransplant	451			176			.068
Median*		90			100		
Range*		30-100			20-100		
≥90%		355	79		150	85	
<90%		96	21		26	15	
Immune phenotype	451			176			.246
Null cell		16	4		8	5	
cALLa		240	53		97	55	
Mature B cell		23	5		12	7	
T cell		93	21		24	13	
Unclassified/other		79	17		35	20	
Chromosomal abnormalities	388			145			.836
No abnormalities		87	22		36	25	
t(9;22)		14	4		4	3	
t(4;11)		6	2		4	3	
Other abnormalities		90	23		33	22	
Not tested		191	49		68	47	
WBC count at diagnosis $\times 10^9$/L	411			161			.859
Median*		14.7			13.5		
Range*		0.9-894			0.5-874		
$<10 \times 10^9$/L†		168	41		66	41	
10-100 $\times 10^9$/L†		159	39		66	41	
$>100 \times 10^9$/L†		84	20		29	18	
CNS involvement at diagnosis	451	26	6	176	17	10	.083
Interval from diagnosis to CR1, months	433			167			.994
Median*		1.15			1.15		
Range*		0.2-32.04			0.2-39.7		
<2 months		356	82		134	80	
>2 months		77	18		33	20	
Remission status pretransplant	451			176			.572
CR1		134	30		51	29	
CR2		194	43		73	41	
CR3-8		51	11		27	15	
Not in CR		72	16		25	14	
Interval between CR1 and tx (patients transplanted in CR1), months	134			51			.262
Median*		3.95			4.96		
Range*		0.66-28.88			0.46-17.27		
<3 months		38	28		14	27	
>3 months		96	72		37	73	
CR1 duration (patients transplanted beyond CR1), months	297			117			.247
Median*		18.98			23.16		
Range*		0.39-116.64			0.03-97.14		
≤18 months		143	48		45	38	
18-36 months		83	30		44	38	
>36 months		71	24		28	24	

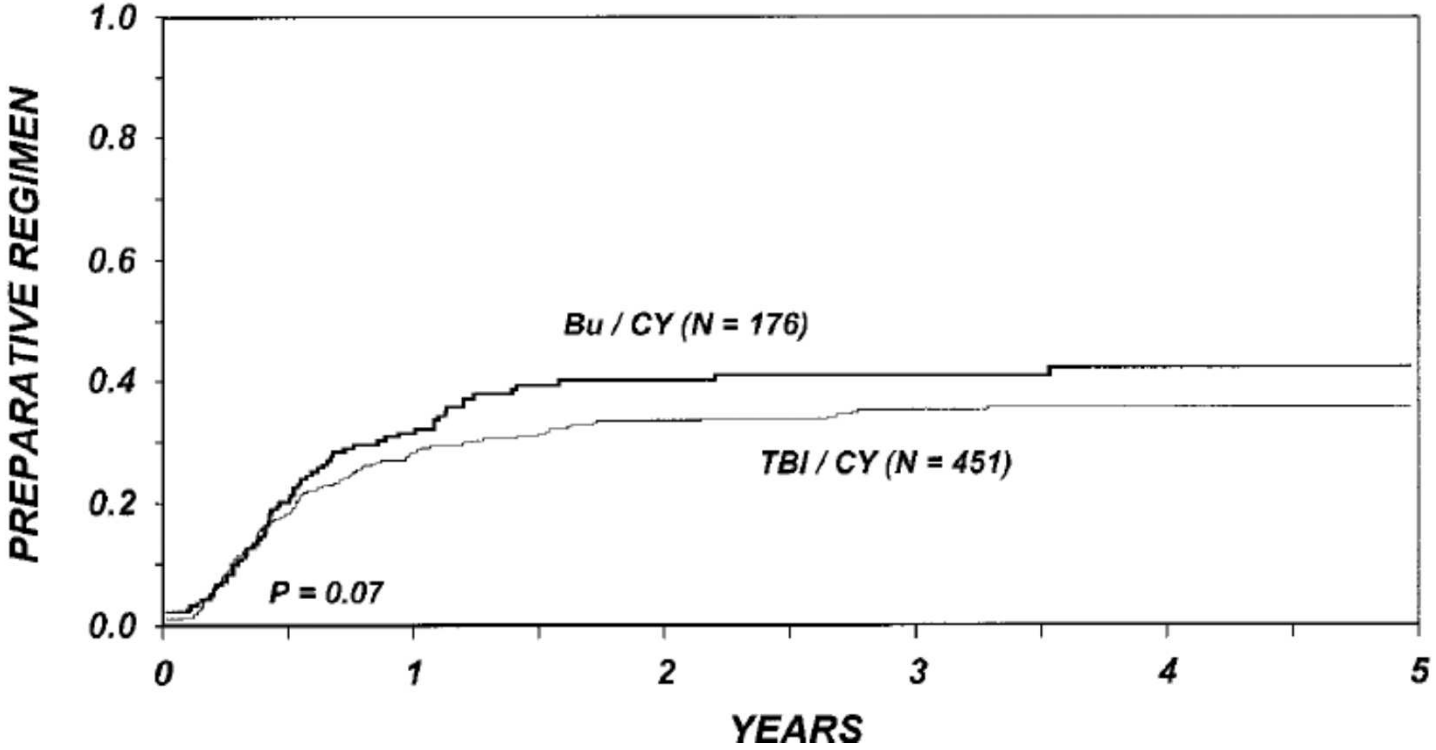


Fig 1. Actuarial probability of relapse after HLA-identical sibling bone marrow transplant for childhood ALL, by pretransplant conditioning regimen.

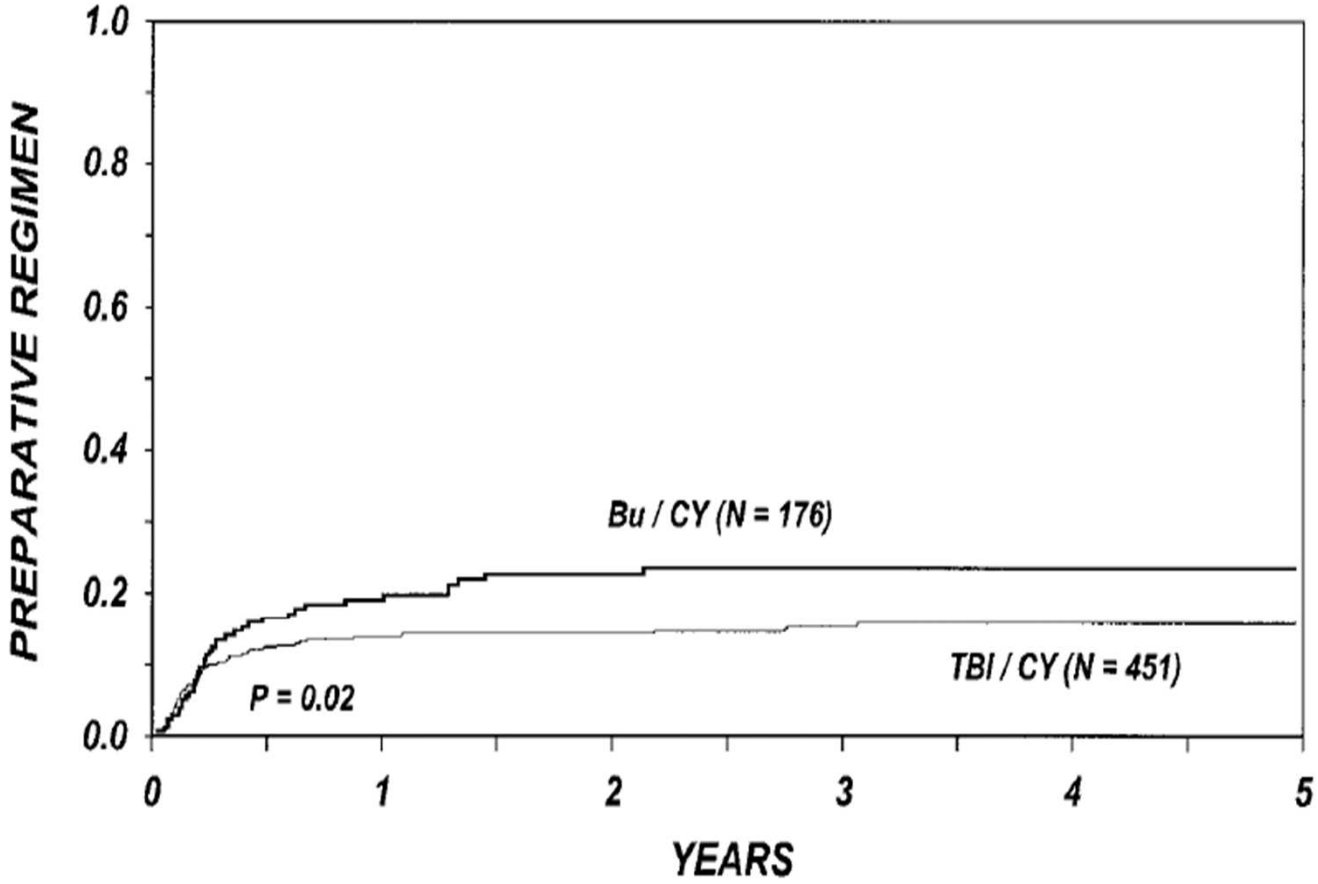


Fig 2. Actuarial probability of treatment-related mortality after HLA-identical sibling bone marrow transplants for childhood ALL, by pretransplant conditioning regimen.

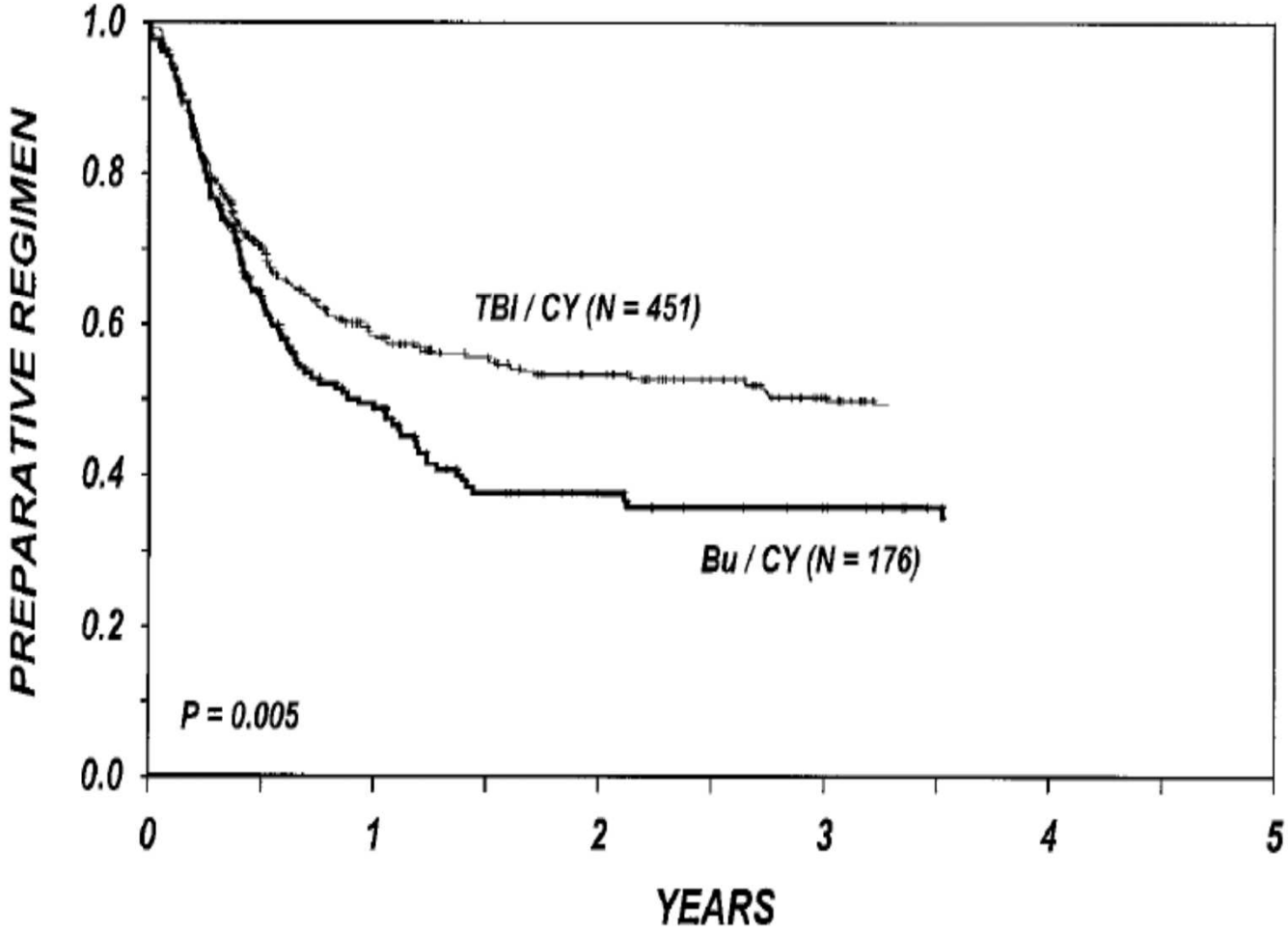


Fig 3. Actuarial probability of leukemia-free survival after HLA-identical sibling bone marrow transplants for childhood ALL, by pretransplant conditioning regimen.

NON-HODGKINS LYMPHOMA

- **Autologous stem cell transplantation for non-Hodgkin's lymphoma: comparison of radiation-based and chemotherapy-only preparative regimens.**
- ***Bone Marrow Transplant 2001 Sep***

- **Compared Cy/TBI/Etoposide with Bu/Mel/TT for NHL**

- **No difference in toxicities and outcome**

HODGKINS LYMPHOMA

- **Autologous stem cell transplantation for Hodgkin's disease: busulfan, melphalan and thiotepa compared to a radiation-based regimen.**
- ***Bone Marrow Transplant 2003 Aug***

- **Compared Cy/TBI/Etoposide with Bu/Mel/TT for NHL**

- **No difference in toxicities and outcome**

MULTIPLE MYELOMA

- Mel-140 and TBI vs Mel-200 Prior to Autologous Peripheral Blood Stem Cell Transplantation for Multiple Myeloma - a Single Institution Experience
- *ASH 2004*

- Mel TBI inferior to Mel 200 have higher toxicity with no improvement in DFS.

MULTIPLE MYELOMA

- **Analysis of outcome following allogeneic haemopoietic stem cell transplantation for myeloma using myeloablative conditioning--evidence for a superior outcome using melphalan combined with total body irradiation.**
- *Br J Haematol. 2005 Feb;128(4):496-502.*

- **Mel/TBI superior to Cy/TBI but still associated with high mortality rates following allogeneic stem cell transplantation.**

Dose of radiotherapy

- **Fred Hutchinson** -- CML
  - Randomized. CML in chronic phase. Cyclophosphamide 120 mg/kg, then randomized TBI 12/6 daily vs. 15.75/7 daily
  - **4-years, 1991** -- "Allogeneic marrow transplantation in patients with chronic myeloid leukemia in the chronic phase: a randomized trial of two irradiation regimens." (*Clift RA, Blood. 1991 Apr 15)*
    - 4-year outcome: RFS 12 Gy 58% vs. 15.75 Gy 66% (NS). OS 60% vs. 66% (NS).
    - Transplant mortality: 24% vs. 34% (NS)
    - Conclusion: Higher RFS with higher dose, but no difference in OS due to higher mortality from other causes

Dose of radiotherapy

- **Fred Hutchinson** (1985-1988) -- AML
  - Randomized. 71 patients with AML in first remission. Cyclophosphamide 120 mg/kg, then randomized TBI 12/6 daily vs. 17.75/7 daily
  - **11-years, 1998** - "Long-term follow-Up of a randomized trial of two irradiation regimens for patients receiving allogeneic marrow transplants during first remission of acute myeloid leukemia." (Clift RA, Blood. 1998 Aug 15;92(4):1455-6.) Min F/U 7.5 years
    - 11-year outcome: OS 51% in both arms (NS); cumulative relapse 12 Gy 39% vs. 17.75 Gy 14% (p=0.06); cumulative non-relapse mortality 19% vs. 38% (p=0.05)
    - Conclusion: OS similar, higher mortality in higher dose arm during first 6 months

Dose rate–dependent marrow toxicity of TBI in dogs and marrow sparing effect at high dose rate by dose fractionation

Storb et al; BBMT 1999

Evaluated giving single doses of 200 cGy TBI, delivered at either 10 or 60 cGy/min.
With 300 cGy TBI at 10 cGy/min, delivered as either single doses or three fractions of 100 cGy each.
Also few dogs received 300 cGy TBI at 60 cGy/min, administered either as single doses or three fractions of 100 cGy each.

Conclusions

- **With 200 and 300 cGy single-dose TBI, an increase of dose rate from 10 to 60 cGy/min, caused significant increases in marrow toxicity;**
- **At 60 cGy/min, dose fractionation resulted in a significant decrease in marrow toxicities whereas such a protective effect was not seen at 10 cGy/min; and**
- **With fractionated TBI, no significant differences in marrow toxicity were seen between dogs irradiated at 60 and 10 cGy/min.**

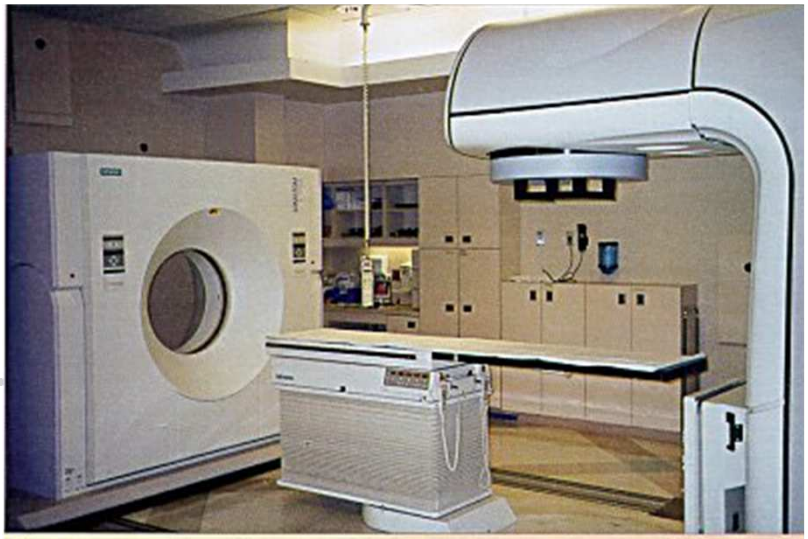
Cranial boost

- **U. Michigan** (1994-2003) - 2005 — "Utility of cranial boost in addition to total body irradiation in the treatment of high risk acute lymphoblastic leukemia." Alexander BM et al. Int J Radiat Oncol Biol Phys. 2005 Nov 15;63(4):1191-6.
  - Purpose: Evaluate role of cranial boost.
    - Retrospective. 67 pts. High-risk pts treated with or without a cranial boost in addition to TBI prior to BMT. All received chemotherapy for conditioning. TBI was most commonly 2 Gy BID to 12 Gy or 2.5 Gy qd to 10 Gy. Cranial boost given in 39% of pts, median dose 11 Gy
- Conclusion: **Cranial boost not associated with lower CNS relapse rate especially in patients with only hematologic disease at presentation**

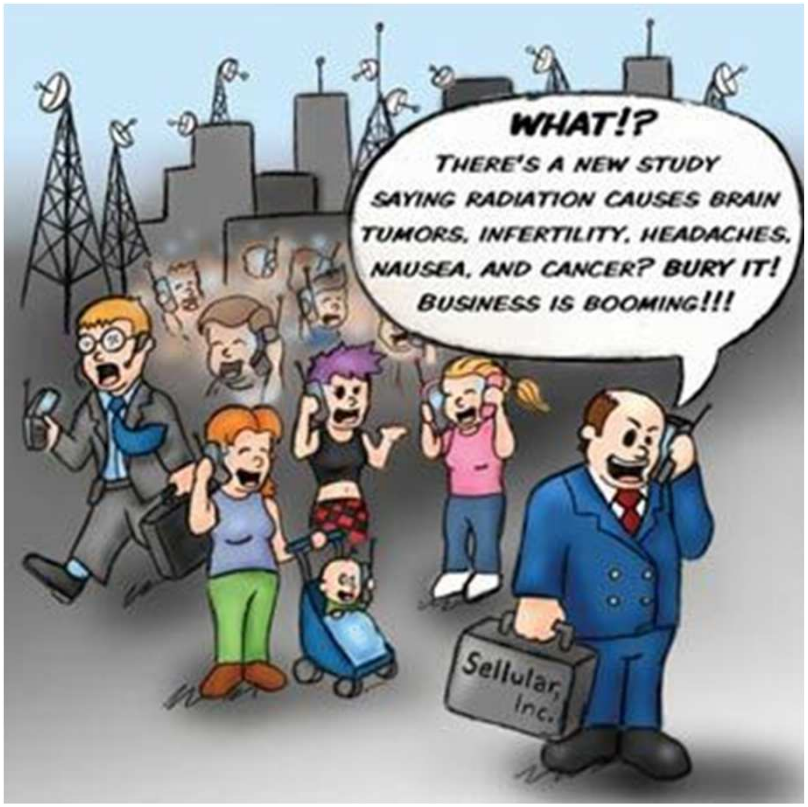
NEWER ADVANCES

- Reducing the dose of TBI
  - Single dose 200 cG
  - TBI 5 Gy
  - TBI 8 Gy

- Total Marrow irradiation (TMI)



With the PRIMATOM System, the gantry holding the CT scanner encircles the patient on the treatment table. During scanning, the gantry moves incrementally along high-precision rails, providing updated tumor localization data. The gantry retracts when scanning is complete.



Hematopoietic cell transplantation in older patients with hematologic malignancies: replacing high-dose cytotoxic therapy with graft-versus-tumor effects

BLOOD, 1 JUNE 2001 • VOLUME 97, NUMBER 11

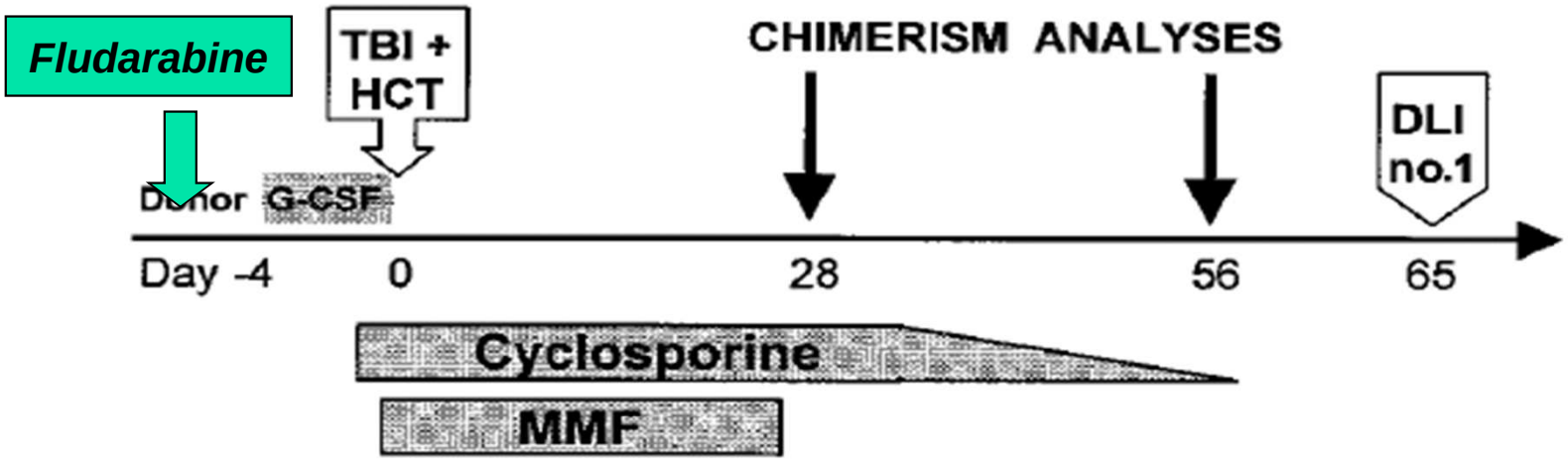
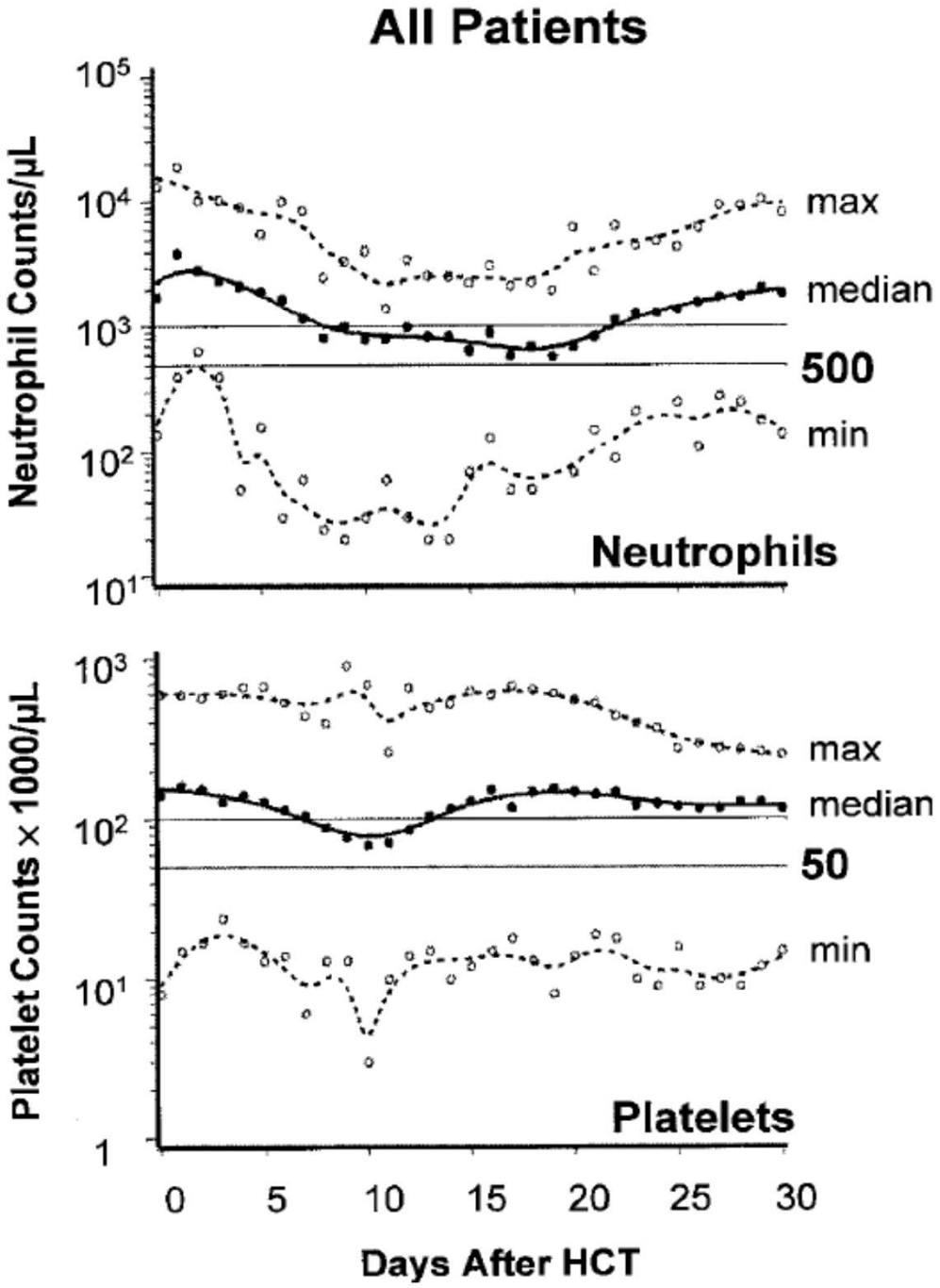
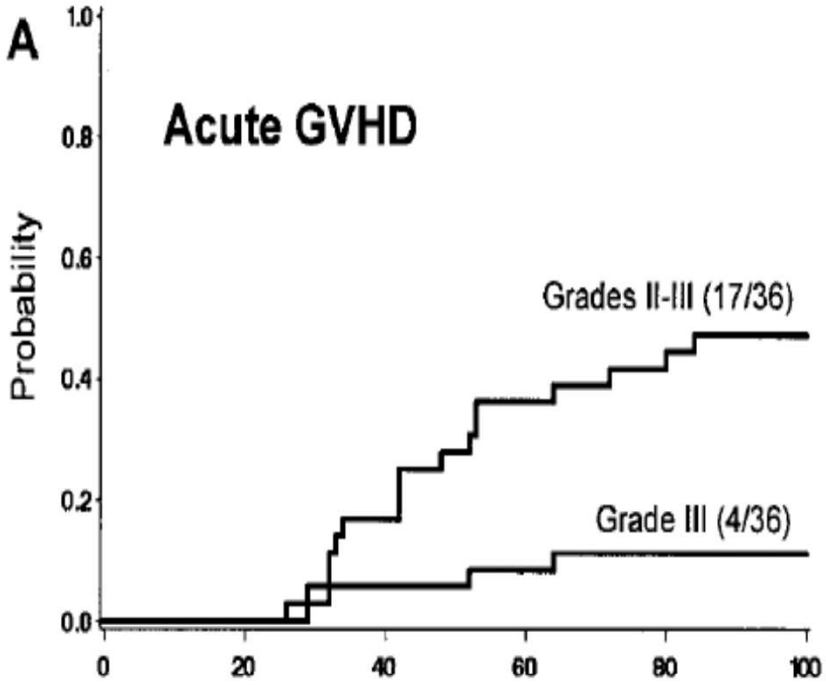
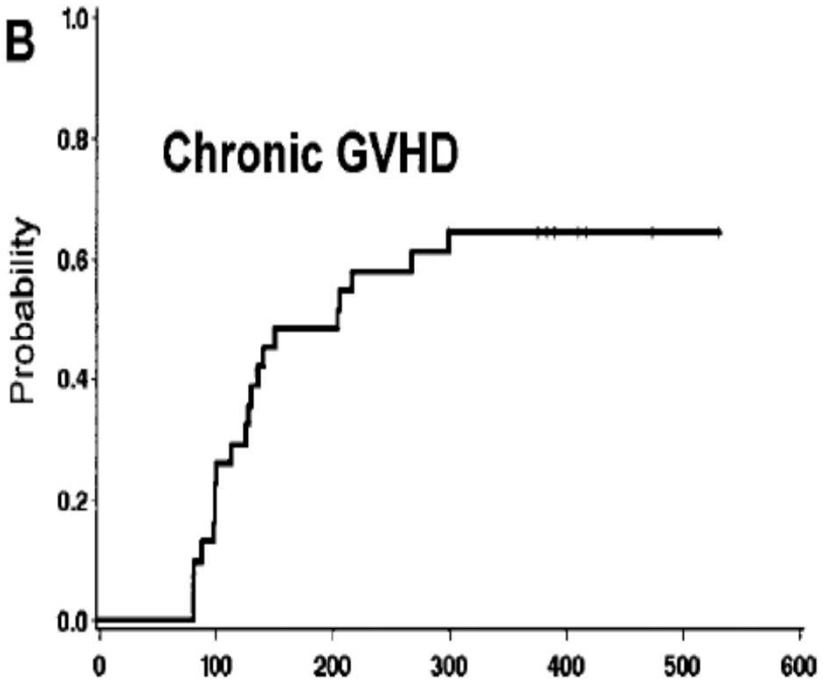
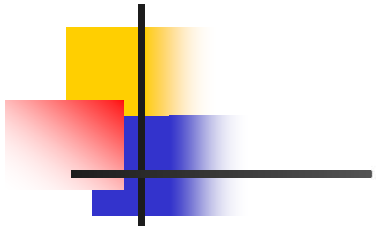


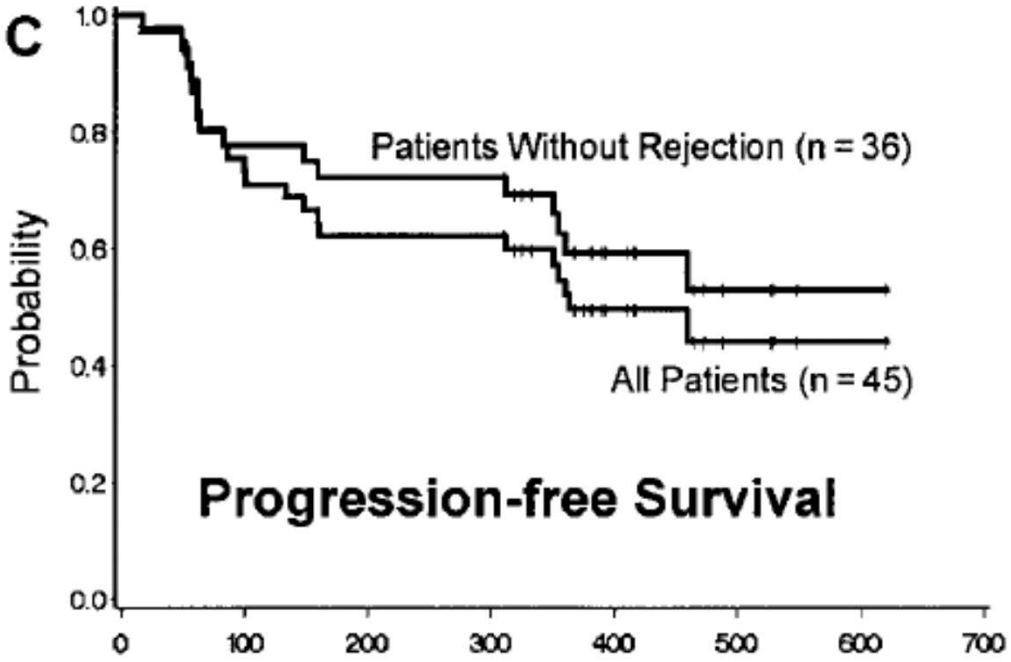
Figure 1. Treatment protocol for nonmyeloablative HCT. Granulocyte colony-stimulating factor (G-CSF)–mobilized peripheral blood stem cells (PBSCs) were infused after TBI on day 0. One patient (FH14726) received fludarabine 30 mg/m^2 ×3 intravenously on days −4, −3, and −2 before TBI/MMF/CSP. G-CSF: 16 μg per kg per day on days −4 to 0, aphereses on days −1, 0; TBI: 200 cGy (7 cGy/min) single fraction; HCT: PBSCs infused on day 0; CSP: 1.5 mg/kg intravenously twice daily on days −1 and 0, 6.25 mg/kg orally twice daily on days 1 to +35 (cohort 1), then taper to +56 (cohort 2); MMF: 15 mg/kg orally twice daily on days 0 to +27; DLI: no. 1 equals 10^7 CD3$^+$ cells/kg, no. 2 equals 3.3×10^7 CD3$^+$ cells/kg.

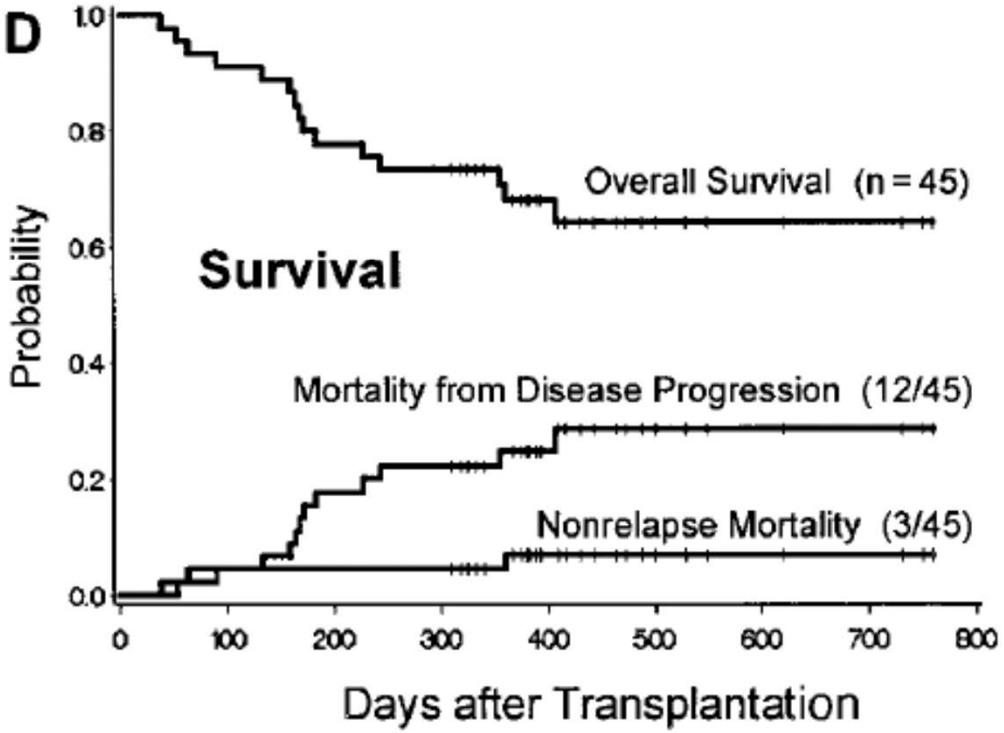

All Patients
Neutrophil Counts/μL
10^5
10^4
10^3
10^2
10^1
max
median
500
min
Neutrophils
Platelet Counts × 1000/μL
10^3
10^2
10^1
1
max
median
50
min
Platelets
0
5
10
15
20
25
30
Days After HCT


A
Acute GVHD
Probability
1.0
0.8
0.6
0.4
0.2
0.0
Grades II-III (17/36)
Grade III (4/36)
0
20
40
60
80
100


B
Chronic GVHD
Probability
1.0
0.8
0.6
0.4
0.2
0.0
0
100
200
300
400
500
600




C
1.0
0.8
0.6
0.4
0.2
0.0
Probability
Patients Without Rejection (n = 36)
All Patients (n = 45)
Progression-free Survival
0
100
200
300
400
500
600
700


D
1.0
0.8
0.6
0.4
0.2
0.0
Probability
Overall Survival (n = 45)
Survival
Mortality from Disease Progression (12/45)
Nonrelapse Mortality (3/45)
0
100
200
300
400
500
600
700
800
Days after Transplantation

Conditioning with 8-Gy total body irradiation and fludarabine for allogeneic hematopoietic stem cell transplantation in acute myeloid leukemia

Matthias Stelljes, Martin Bornhauser, Matthias Kroger, Joerg Beyer, Maria C. Sauerland, Achim Heinecke, Bjorna Berning, Christian Scheffold, Gerda Silling, Thomas Buchner, Andreas Neubauer, Axel A. Fauser, Gerhard Ehninger, Wolfgang E. Berdel, and Joachim Kienast, for the Cooperative German Transplant Study Group

Conditioning regimen consisted of
Fludarabine 120 mg/m^2 over 4 days
TBI 8 Gy over 2 days in 2 fractions

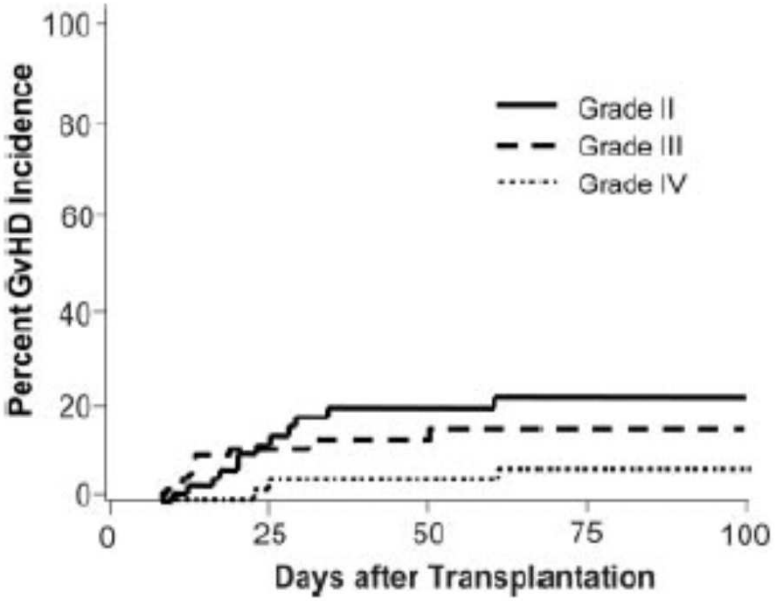


Figure 1. Acute GvHD. Estimates of cumulative incidences of acute GvHD by severity grading.

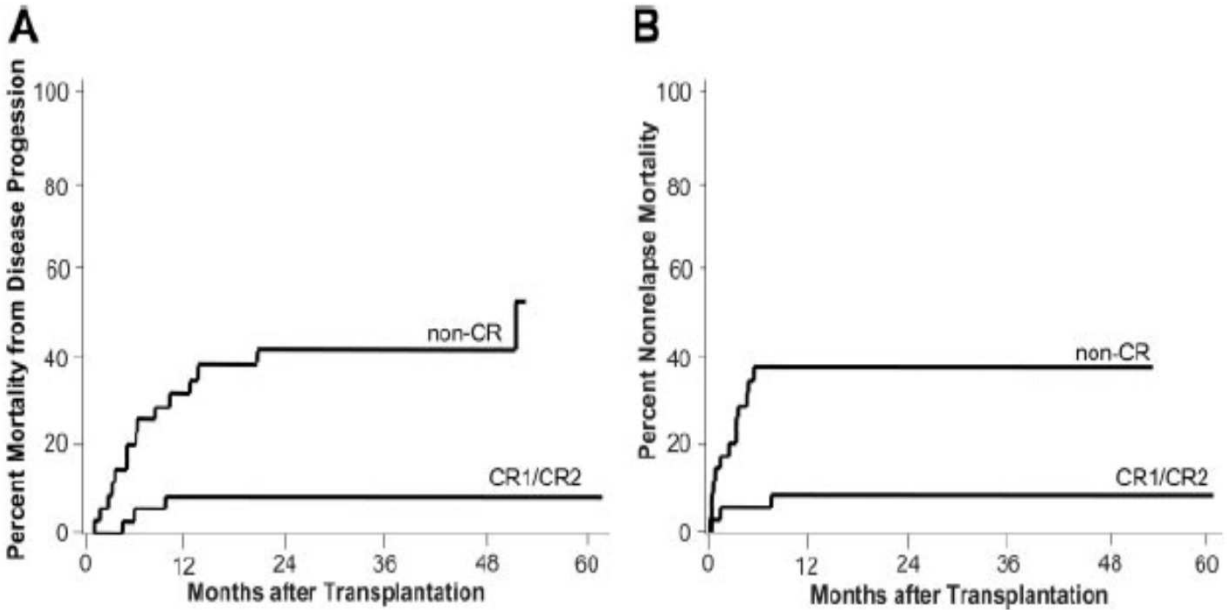


Figure 2. Mortality from disease progression and nonrelapse mortality. Estimates of the cumulative incidences of mortality from disease progression (A) and nonrelapse mortality (B) by disease status at transplantation are shown. CR1/CR2 indicates complete remission 1 (n = 22) or 2 (n = 14); non-CR, patients with refractory disease (n = 27), untreated relapse (n = 7), or untreated primary disease (n = 1).

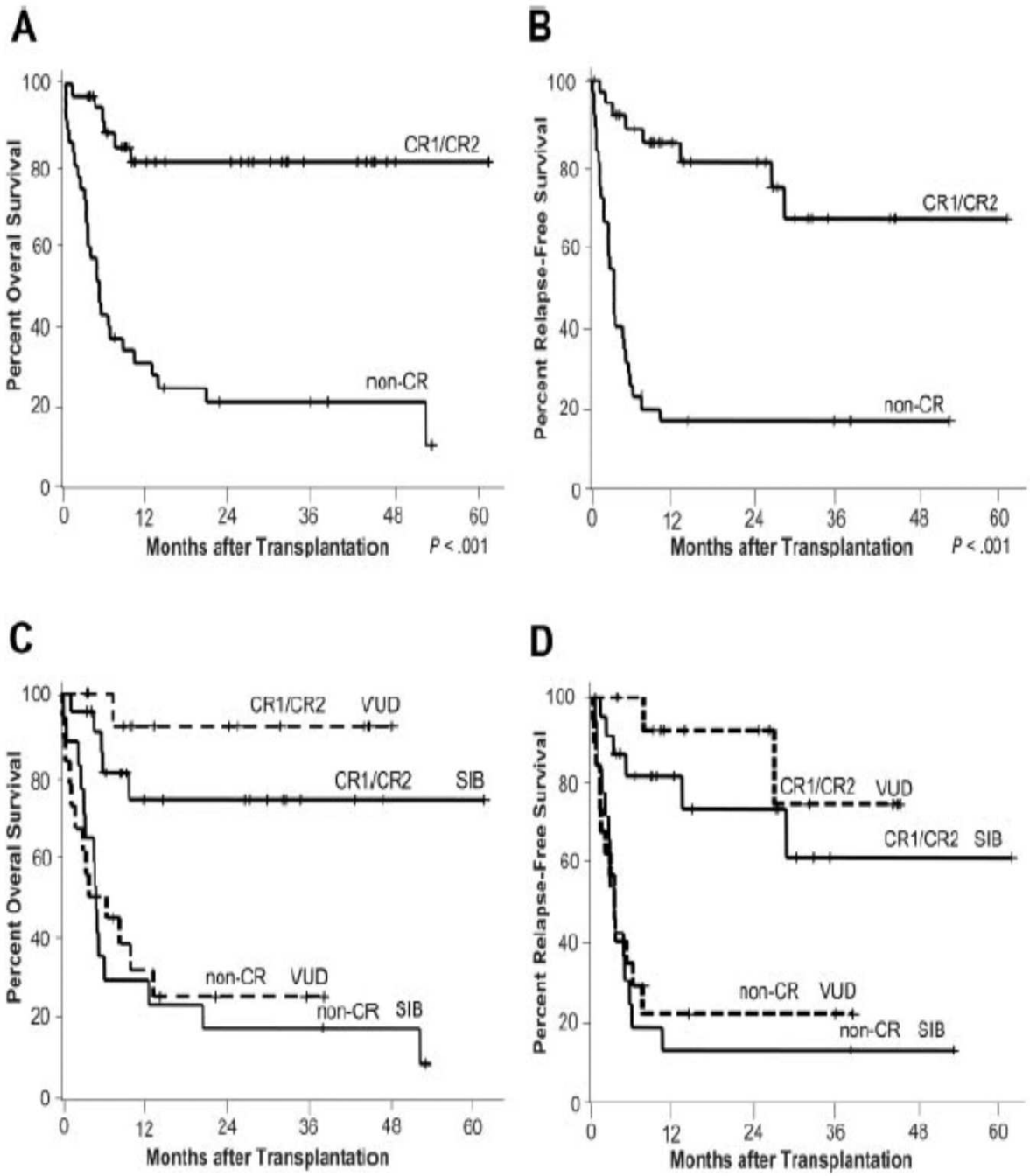


Figure 3. Overall and relapse-free survival. Kaplan-Meier estimates of overall (A) and relapse-free survival (B) by disease status at transplantation are depicted. CR1/CR2 indicates complete remission 1 (n = 22) or 2 (n = 14); non-CR, patients with refractory disease (n = 27), untreated relapse (n = 7), or untreated primary disease (n = 1). (C-D) Overall and relapse-free survival was similar for patients who received a transplant from siblings (SIB) or volunteer unrelated donors (VUD) (CR group: SIB n = 22, VUD n = 14; non-CR group: SIB n = 17, VUD n = 18).

TOTAL MARROW IRRADIATION

World's First Total Marrow Irradiation Using
HI-ART System (R) Performed at City of Hope
Thursday, 14 July 2005

TOTAL MARROW IRRADIATION

- TomoTherapy Highly Integrated Adaptive Radiotherapy (Hi-Art) system is a novel way of delivering IMRT and literally means “slice therapy.”
- It is the combination of a helical CT scanner and a linear accelerator.
- A helical dose delivery is achieved by a continuous gantry rotation over 360º while the patient is translated through the gantry bore similar to a CT scan.
- Other studies have looked at linac based TMI

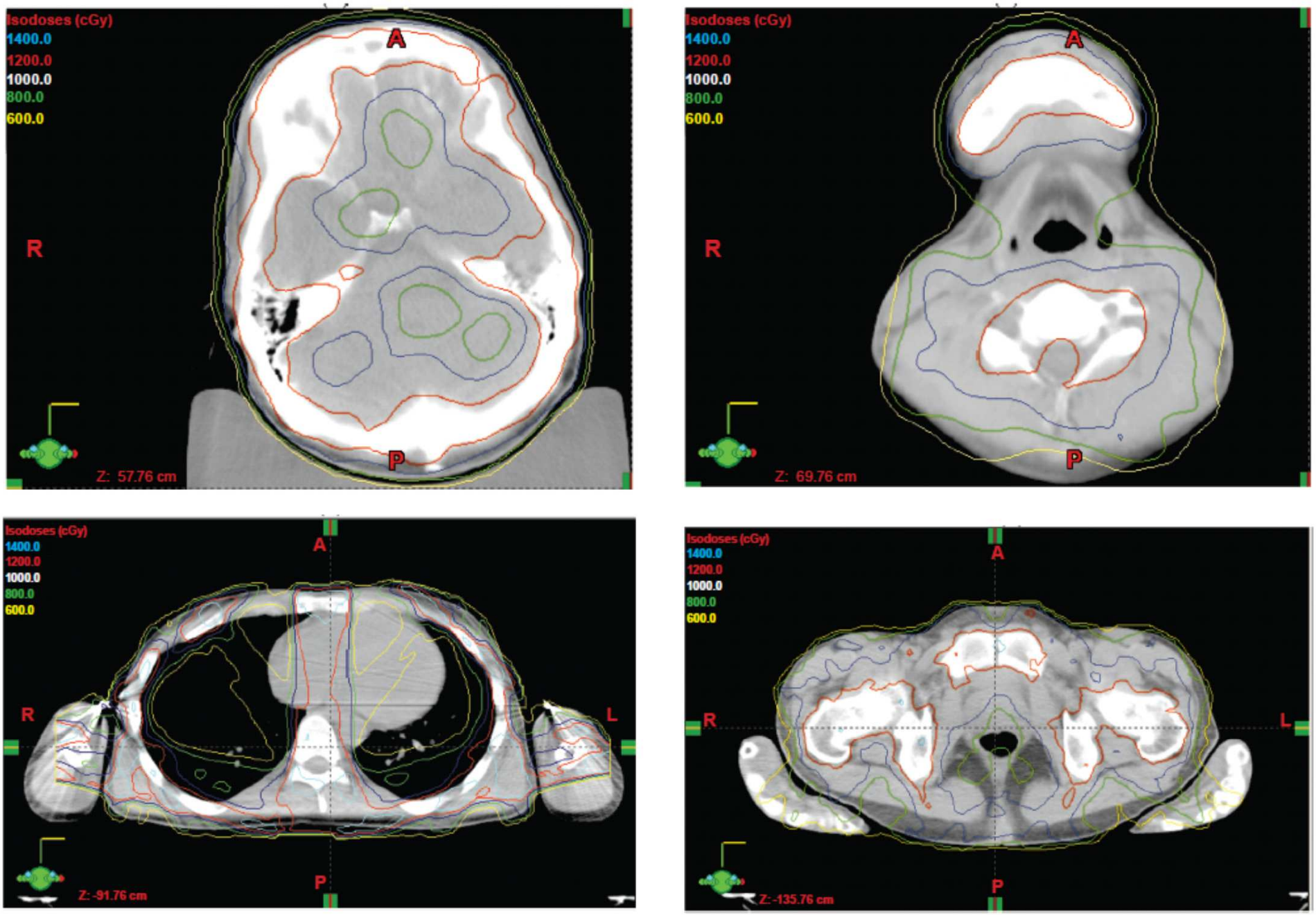


Figure 1: Example axial linac-based IM-TMI dose distributions in the head (A), neck (B), chest (C), and pelvis (D). The dose distribution is displayed in four isodose levels:1400 cGy (cyan), 1200cGy (red), 1000 cGy (blue), 800 cGy (green), 600 cGy (yellow).

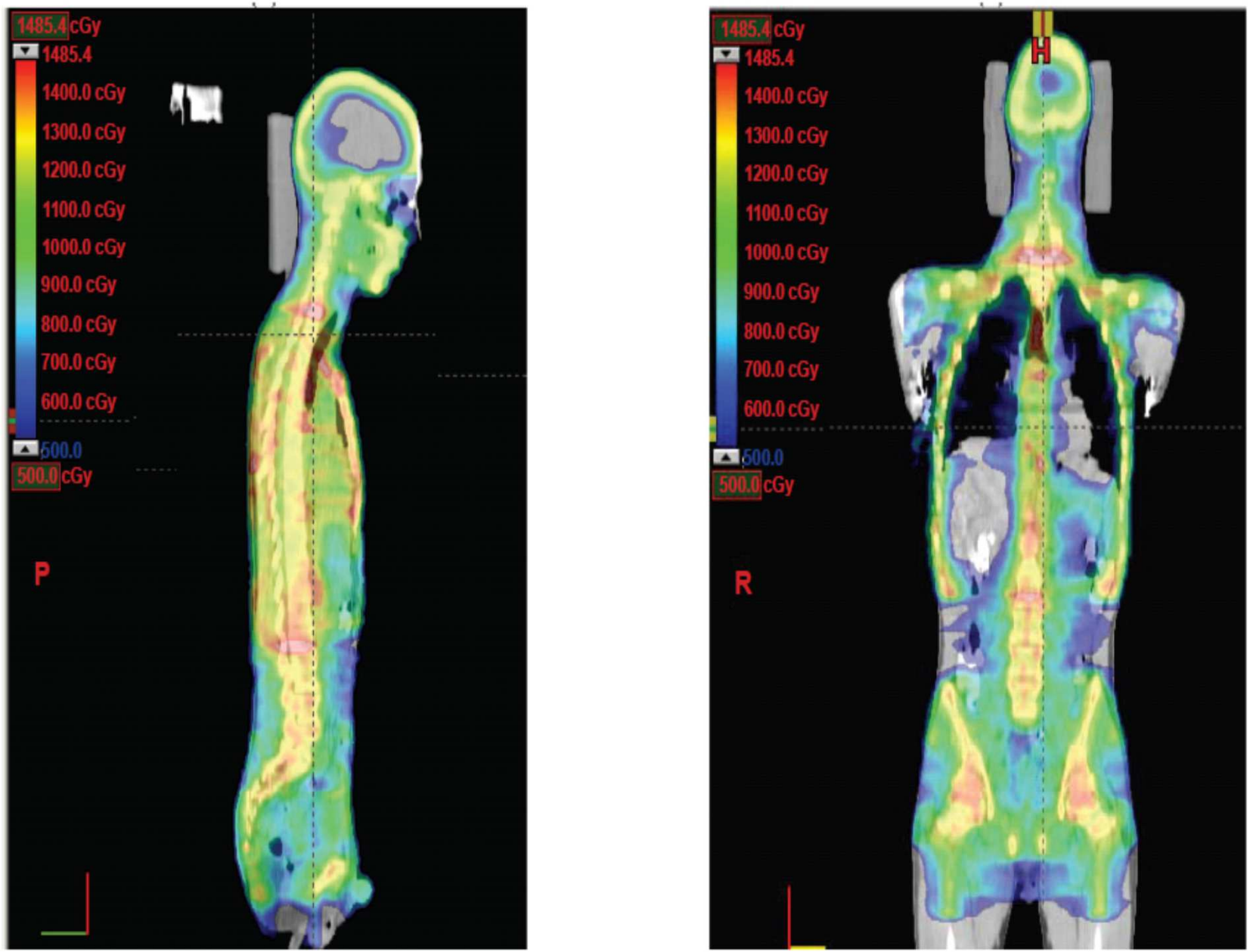


Figure 2: IM-TMI dose distribution in sagital (A) and frontal (B) planes. The dose distribution is displayed as color-wash with values ranging from 500 cGy (blue) to 1485 cGy (red). Shades of yellow color present doses ranging between 1200-1300 cGy. Prescription dose is 1200 cGy.

Table I

Comparison of median doses (Gy) to organs at risk for linac-based TMI and conventional TBI[11].

Organ	TMI	TBI	Ratio of TBI/TMI Median Doses
Lungs	7.0	8.8	1.3
Liver	6.5	12.3	1.9
Kidneys	6.8	12.2	1.8
Heart	7.1	12.1	1.7
Lenses	2.5	11.3	4.5
Eyes	3.0	11.3	3.8
Brain	7.3	12	1.6

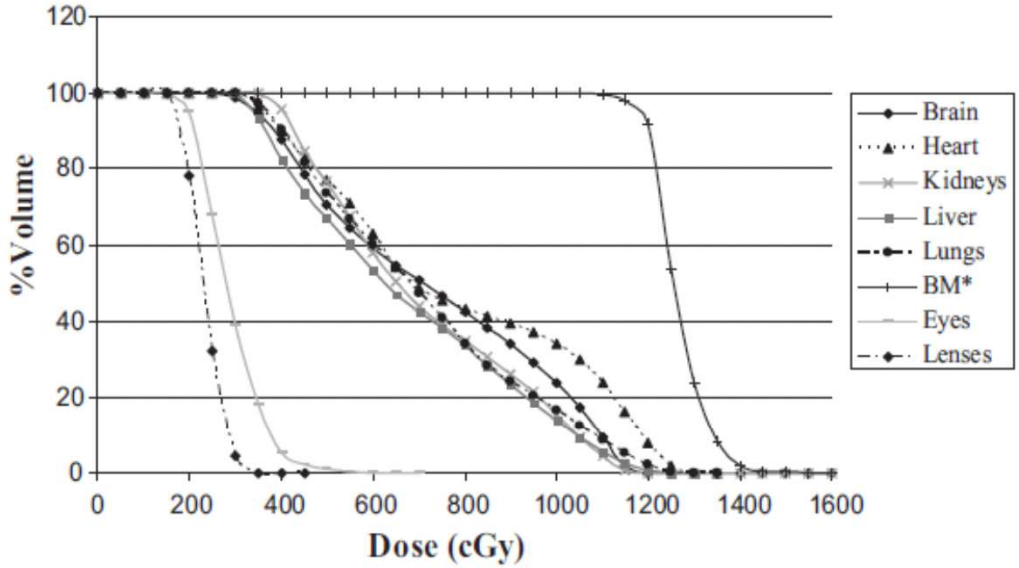
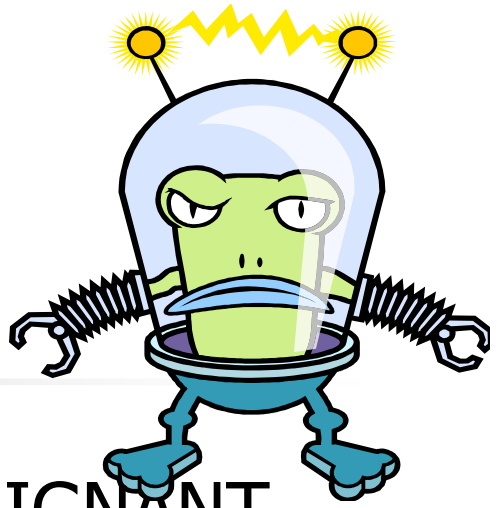


Figure 3: DVHs for the OARs and skeletal bone/marrow obtained in this pilot planning study for one patient. The DVH for the skeletal bone/marrow shows a good coverage while DVHs for all OARs are shifted to left indicating dose sparing. *Bone Marrow

CLINICAL DATA

- ***Total Marrow Irradiation (TMI) with Helical Tomotherapy and PBPC Following High-Dose Melphalan and PBPC as Part of Tandem Therapy for Patients with Multiple Myeloma.***
- ***Image-Guided Total-Marrow Irradiation Using Helical Tomotherapy in Patients With Multiple Myeloma and Acute Leukemia Undergoing Hematopoietic Cell Transplantation***
- ***Total Marrow Irradiation (TMI) using Helical Tomotherapy: Dosimetric analysis demonstrates reduced organ doses which correlate with reduction in acute toxicities and predict for escalation of dose to target marrow beyind that achievable by standard TBI***

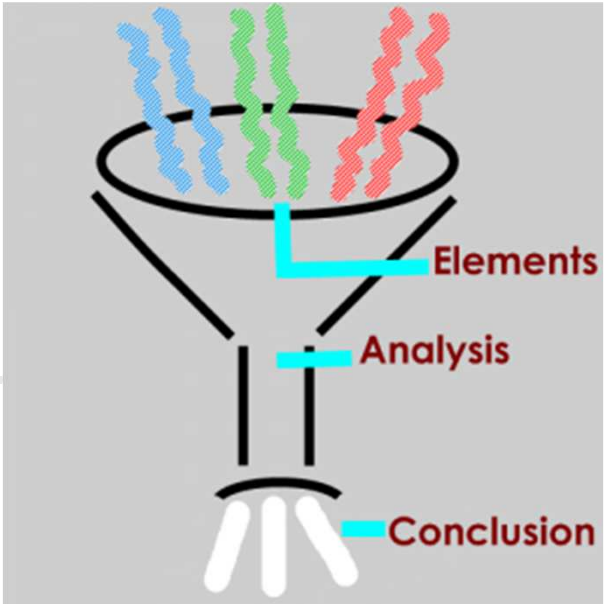
INDICATIONS FOR TBI AT CMC VELLORE



- MALIGNANT
- ALL
- AML – MUD
- CML – lymphoid BT
- NHL – young pt
- MDS – MUD
- Ph+ ALL - RIC

- NON-MALIGNANT
- Aplastic anemia – sick, rejection, MUD
- Fanconi's – rejection
- Autoimmune disease
- Haploidentical Tx

Conclusions



- TBI is an effective modality of treatment for patients requiring Allogeneic SCT
- Fractionation of doses and reduction of total dose has helped reduce side effects
- Used for acute and chronic leukemia, MDS and lymphomas
- Low dose TBI being increasingly used for immunosuppression with RIC protocols.

Thank You