LA TBI è ancora lo standard nel condizionamento delle leucemie acute linfoblastiche?

Angelo Michele Carella

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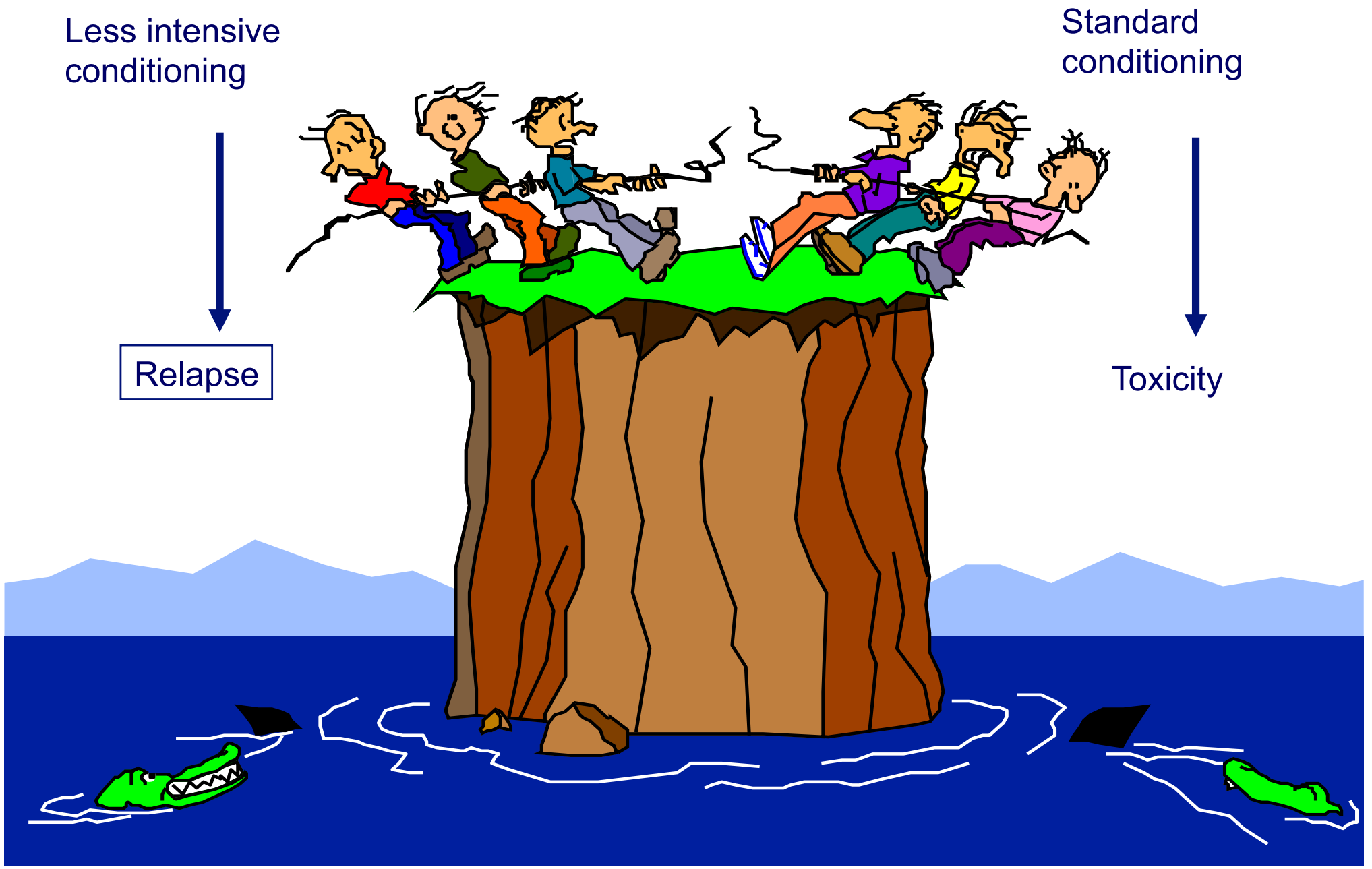
San Giovanni Rotondo (FG)


Less intensive conditioning
Relapse
Standard conditioning
Toxicity

La storia del trapianto di midollo osseo allogenico, da donatore a ricevente, inizia nel 1950, allorchè questa procedura fu impiegata in via sperimentale per il per il trattamento dei danni da radiazioni in modelli animali. *Il primo trapianto allogenico di midollo osseo nell'uomo viene eseguito nel 1959 da E. Donnal Thomas* in un paziente affetto da leucemia acuta. Il paziente fu sottoposto, prima, ad un trattamento radioterapico con irradiazione totale corporea (TBI) e poi alla reinfusione, per via endovenosa, del midollo osseo espiantato dal fratello gemello. Il paziente riuscì a tollerare la procedura del trapianto, ad ottenere l'attecchimento del midollo osseo donato e a raggiungere una condizione di remissione completa che durò alcuni mesi. L'identificazione del Sistema Maggiore di Istocompatibilità (HLA), ai primi anni '60, segna una tappa importantissima nell'applicazione e sviluppo del TMO per il quale *E. Donnal Thomas riceve il premio Nobel per la Medicna nel 1990*

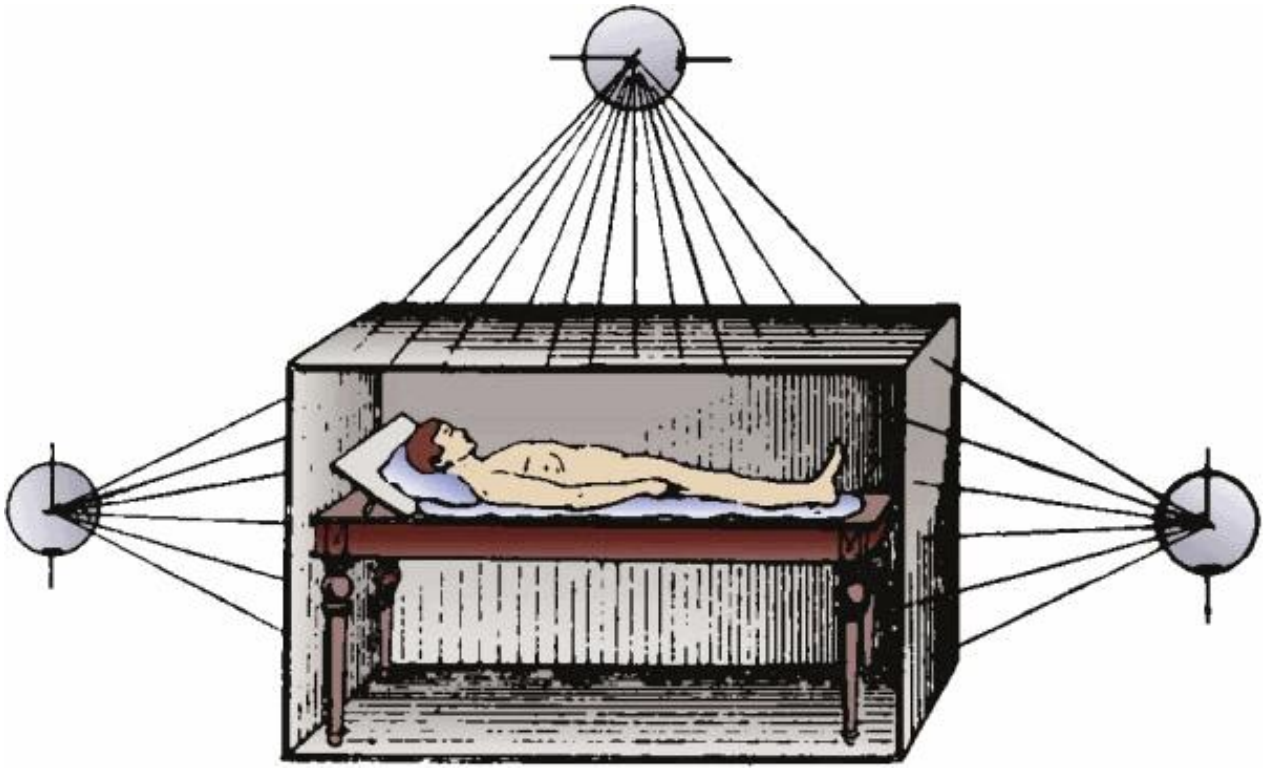


Figure 1: Filter housing for total body irradiation in 1903 (Dessauer, 1907)[43]

IRRADIAZIONE CORPOREA TOTALE: TBI

- **L'irradiazione corporea totale o Total Body Irradiation (TBI) consiste nell'irradiazione di tutto il corpo ed è parte integrante del condizionamento per il trapianto di midollo (TMO).**

INDICAZIONI CONDIZIONAMENTO TMO CON TBI

- **LLA, LMA, LMC, LH, LNH, talassemia major, MM, anemia aplastica, mielodisplasia.**
- **Tumori solidi: mammella M+, neuroblastoma, tumori germinali, PNET, tumore di Wilms, sarcomi, etc.**
- **Immunodeficienze ed errori genetici.**

CONDIZIONAMENTO TMO CON TBI

Razionale:

- **distruggere le cellule neoplastiche o geneticamente compromesse;**
- **eradicare il midollo osseo del paziente:**

1. **azione creante spazio al midollo infuso;**
2. **azione immunosoppressiva (per evitare il rigetto dovuto alle cellule immunocompetenti dell'ospite).**

La TBI è impiegata con finalità:

- ***Mieloablativa***
  Dosi sopraletali (7-15,75 Gy) somministrate in associazione a mono o polichemio-terapia per il condizionamento al trapianto di cellule staminali midollari e/o periferiche allogeniche o autologhe.
- ***Non mieloablativa***
  Basse dosi di TBI (1-2 Gy) erogate in seduta unica nel condizionamento al trapianto allogenico per pazienti di età avanzata o precedentemente sottoposti a trapianto.

IRRADIAZIONE CORPOREA TOTALE

- **Il volume bersaglio della TBI è rappresentato dall'intero organismo, compresa la cute.**

- **OARs: polmoni, reni, cristallini, fegato, cuore, ovaie, ecc.**

TBI VS CT: VANTAGGI

- **Non risparmia alcun sito “santuario” (testicolo, encefalo);**
- **la dose di irradiazione è omogenea ed è indipendente dalla vascolarizzazione;**
- **nessuna resistenza crociata con altri agenti citotossici non è necessaria alcuna detossificazione o escrezione di agenti tossici;**
- **nessuna alterazione della diffusione di farmaco se alterazione di funzionamento d’organo;**
- **distribuzione della dose ben definita e modellata dalle schermature secondo la necessità o incremento della dose con boost selettivo;**
- **non ciclo né fase-specifica.**

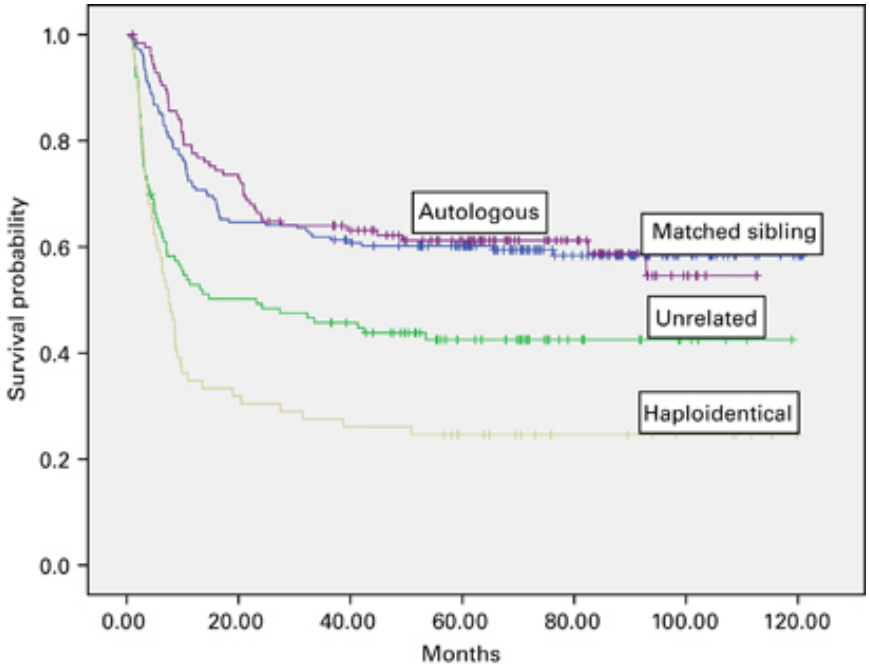
Bone Marrow Transplantation (2013) **48,** 908–914

www.nature.com/bmt

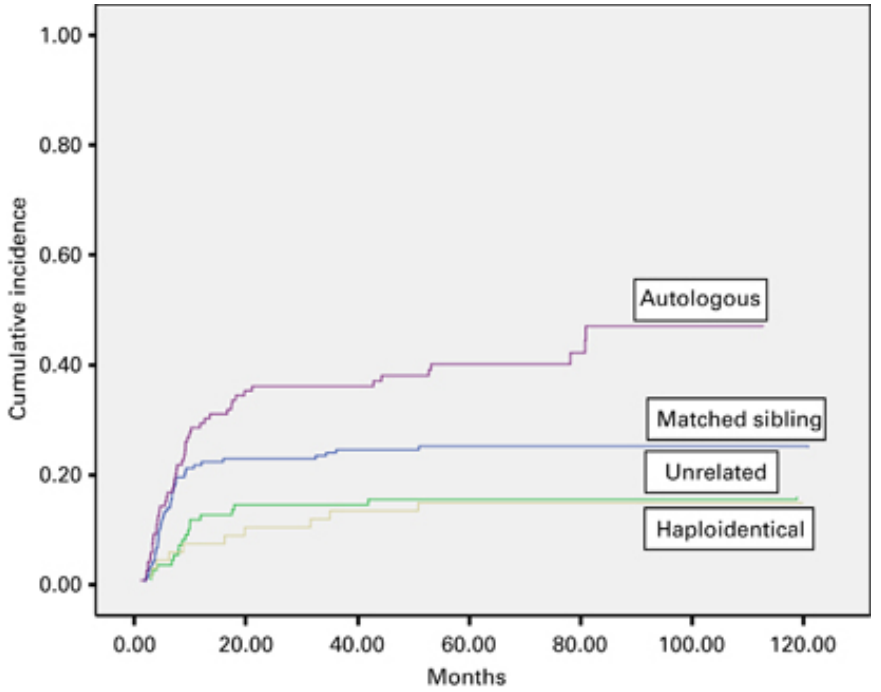
ORIGINAL ARTICLE

In haematopoietic SCT for acute leukemia TBI impacts on relapse but not survival: results of a multicentre observational study

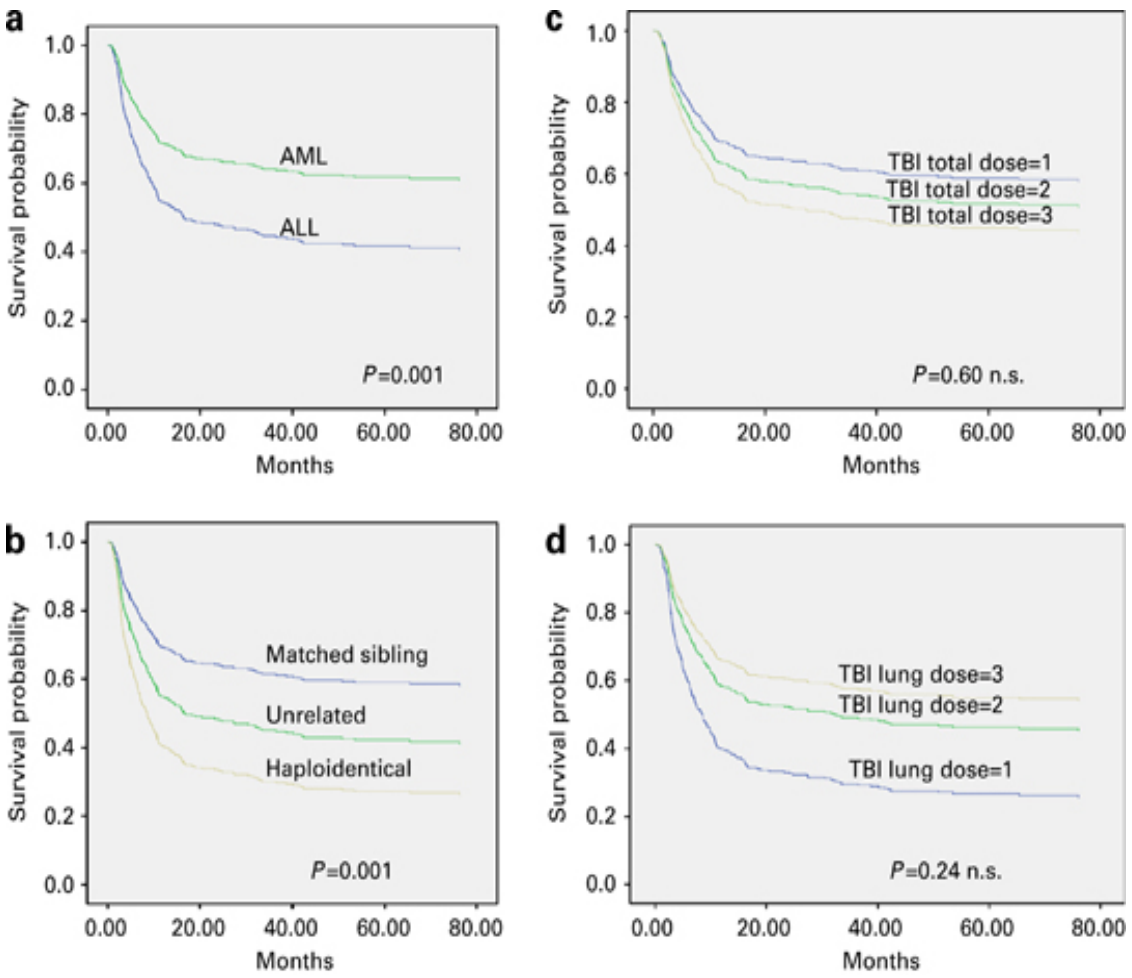
C Aristei[1], A Santucci[2], R Corvò[3], G Gardani[4], U Ricardi[5], G Scarzello[6], SM Magrini[7], V Donato[8], L Falcinelli[9], A Bacigalupo[10], F Locatelli[11], F Aversa[12], E Barbieri[13] and Italian TBI working group[14]



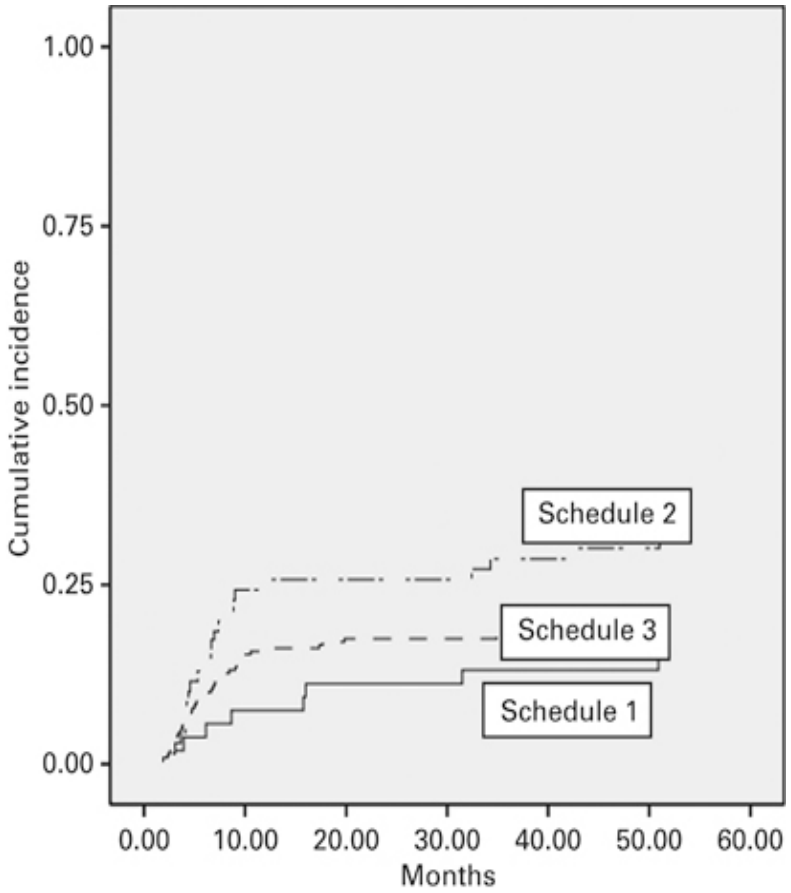
OS according to haematopoietic SCT.



Probability of relapse according to haematopoietic SCT.



Cox model. OS adjusted curves according to: disease (**a**); type of transplant (**b**); TBI total dose (**c**); TBI lung dose (**d**).



Probability of relapse according to TBI schedule. Schedule 1=7, 7.5, 8 and 10 Gy administered in single dose; schedule 2=3.3 Gy a day until 9.9 Gy; schedule 3=2 Gy twice a day for 3 days until 12 Gy and 1.2 Gy three times a day for 4 days until 14.4 Gy

Assume an α/β of 3	BED
750 cGy in 1 fraction	26
750 cGy in 3 fractions	14
1200 cGy in 6 fractions	20
1320 cGy in 8 fractions	20
1395 cGy in 12 fractions	19

Strahlenther Onkol. 2006 Nov;182(11):672-9.

Biologically effective dose in total-body irradiation and hematopoietic stem cell transplantation.

Kal HB, Loes van Kempen-Harteveld M, Heijenbrok-Kal MH, Struikmans H.

High BED values appear to cause less leukemia relapses and a higher disease-free and overall survival. With highly fractionated schemes a high BEDleukemia can be obtained....

Assume an α/β of 10	BED
750 cGy in 1 fraction	13
750 cGy in 3 fractions	9
1200 cGy in 6 fractions	14
1320 cGy in 8 fractions	15
1375 cGy in 12 fractions	16

Total Body Irradiation Conditioning Regimens in Stem Cell Transplantation
Kathryn E. Dusenbery and Bruce J. Gerbi

Esempi di regimi di TBI frazionata impiegati

Centro	Strumentazione	Intensità di dose (cGy/min)	Dose (Gy)	Frazioni
Royal Marsden Hospital, Surrey, UK	^{60}Co a duplice fascio	4	10.5	Singola
Hammersmith Hospital, Londra, UK	Acceleratore lineare	15	12	6 (2 al giorno)
Middlesex Hospital, Londra, UK	Acceleratore lineare	22	14.4	8 (2 al giorno)
Istituto Nazionale Ricerca Cancro, Genova, Italia	Acceleratore lineare	6	9.9	3 (1 al giorno)
Institut J Paoli Calmettes, Marsiglia, Francia	Acceleratore lineare	4	11	5 (1 al giorno)
University of Minnesota, Minneapolis, USA	Acceleratore lineare	10	13.2	8 (2 al giorno)
Fred Hutchinson Cancer Research Center, Seattle, USA	^{60}Co a duplice fascio	4	12	6 (1 al giorno)
Memorial Sloan-Kettering Cancer Center, New York, USA	Acceleratore lineare	12	13.2	11 (3 al giorno)

TOSSICITA' MULTIFATTORIALE
1.ACUTA SUBACUTA (ENTRO CENTO GIORNI)
2.CRONICA

Reazioni acute radioindotte che insorgono in corso di TBI (specialmente quando somministrata con dosi singole a basso rateo di dose):

astenia, nausea e vomito (a circa 3 Gy e possono restare intense per 24-48 ore);

diarrea, eritema cutaneo e mucosite (variabile e dipendente anche dai condizionamenti farmacologici);

alopecia (evento quasi costante);

tumefazione transitoria bilaterale delle parotidi (può insorgere entro 12 ore anche dopo basse dosi radiazione e perciò anche dopo TBI non mieloablativa e si esaurisce spontaneamente entro 48 ore; questo effetto è associato ad un innalzamento dell'amilasi serica)

1769 pazienti
CyTBI 948
TBICy 821

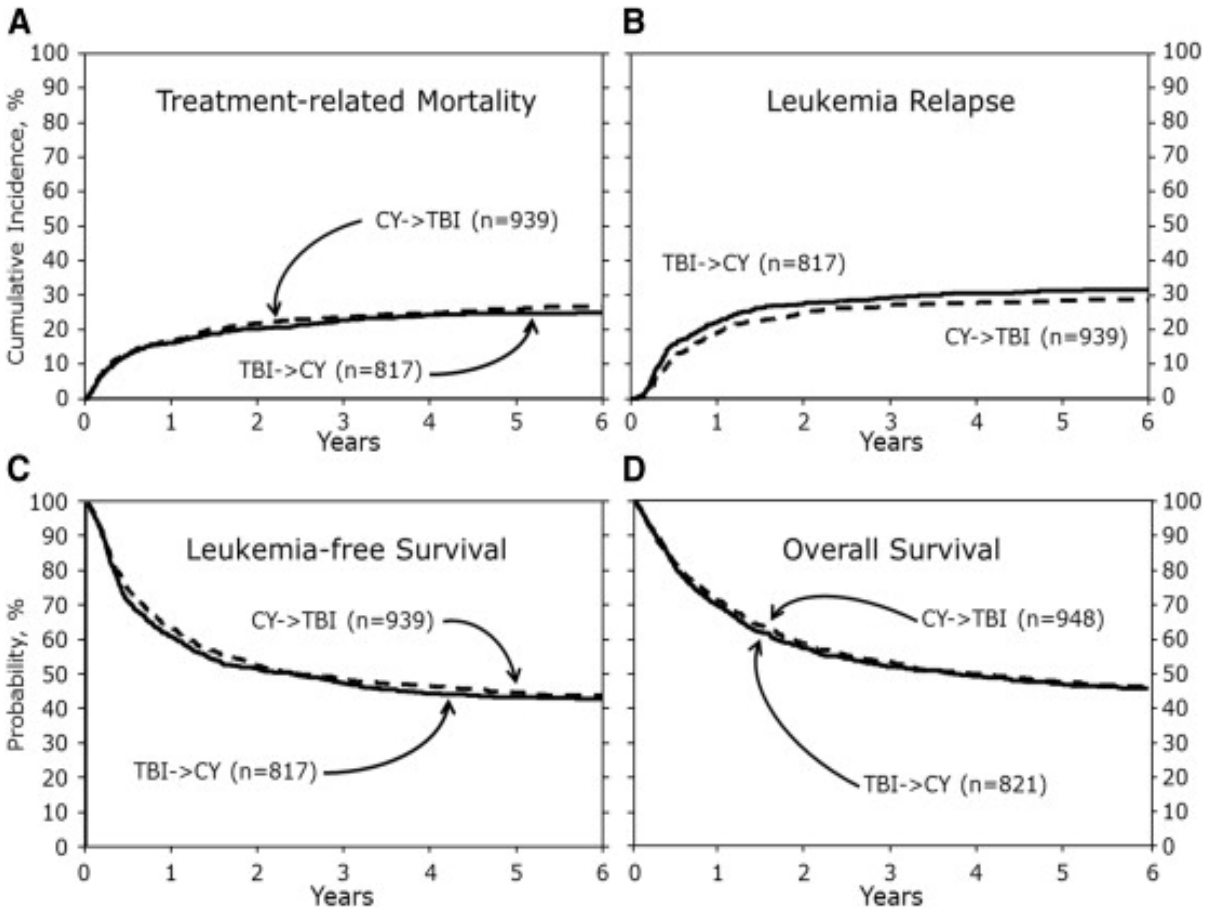


Figure 2. Cumulative incidence of transplantation-related mortality (A), cumulative incidence of leukemia relapse (B), probability of leukemia-free survival (C), and probability of overall survival (D) comparing CyTBI with TBICy before allogeneic transplantati...

Jennifer L. Holter-Chakrabarty, Namali Pierson, Mei-Jie Zhang, Xiaochun Zhu, Görgün Akpek, Mahmoud D. Aljurf, Andrew S. Artz, Frédéric Baron, Christopher N. Bredeson, Christopher C. Dvorak, Robert B. Epstein, Hillard M. Lazarus...

The Sequence of Cyclophosphamide and Myeloablative Total Body Irradiation in Hematopoietic Cell Transplantation for Patients with Acute Leukemia

Biology of Blood and Marrow Transplantation, Volume 21, Issue 7, 2015, 1251–1257

http://dx.doi.org/10.1016/j.bbmt.2015.03.017

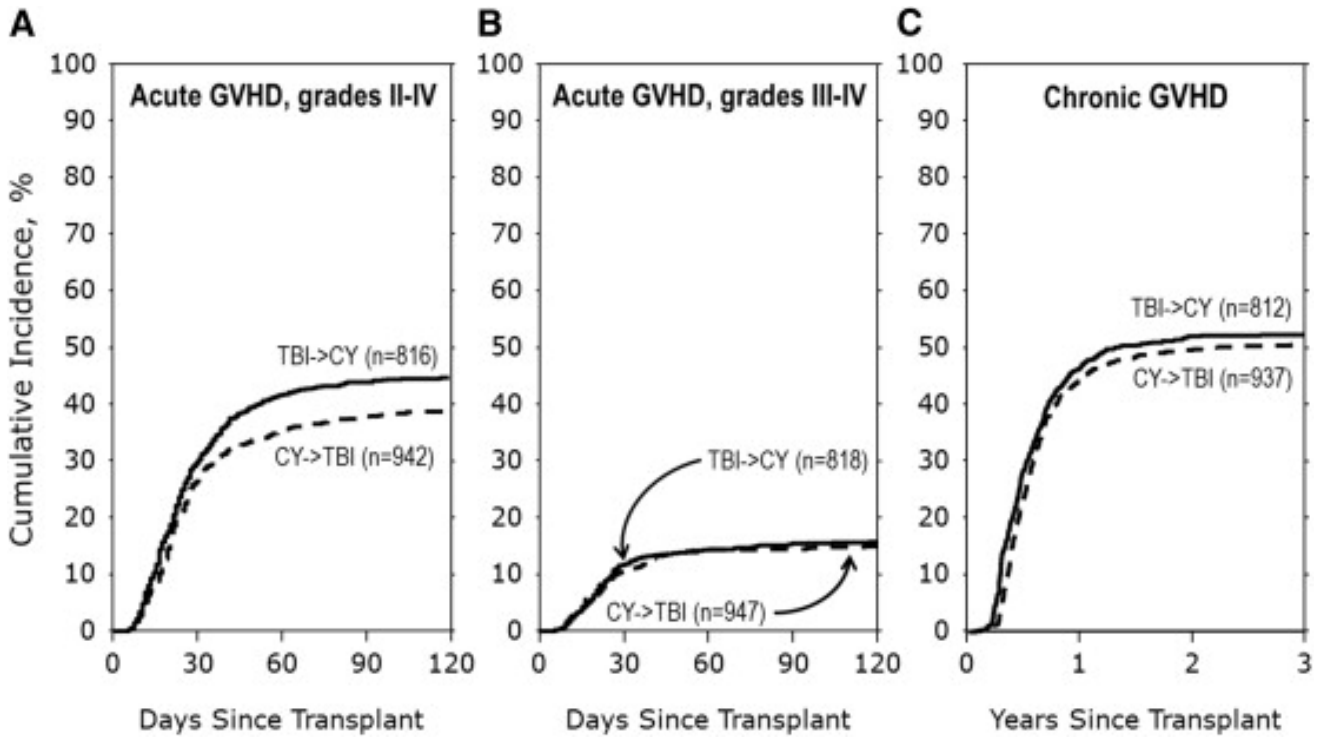


Figure 1. Cumulative incidences of II to IV (A) and III and IV (B) acute GVHD, and chronic GVHD (C) comparing CyTBI with TBICy before allogeneic transplantation for acute leukemia.

Jennifer L. Holter-Chakrabarty, Namali Pierson, Mei-Jie Zhang, Xiaochun Zhu, Görgün Akpek, Mahmoud D. Aljurf, Andrew S. Artz, Frédéric Baron, Christopher N. Bredeson, Christopher C. Dvorak, Robert B. Epstein, Hillard M. Lazarus...

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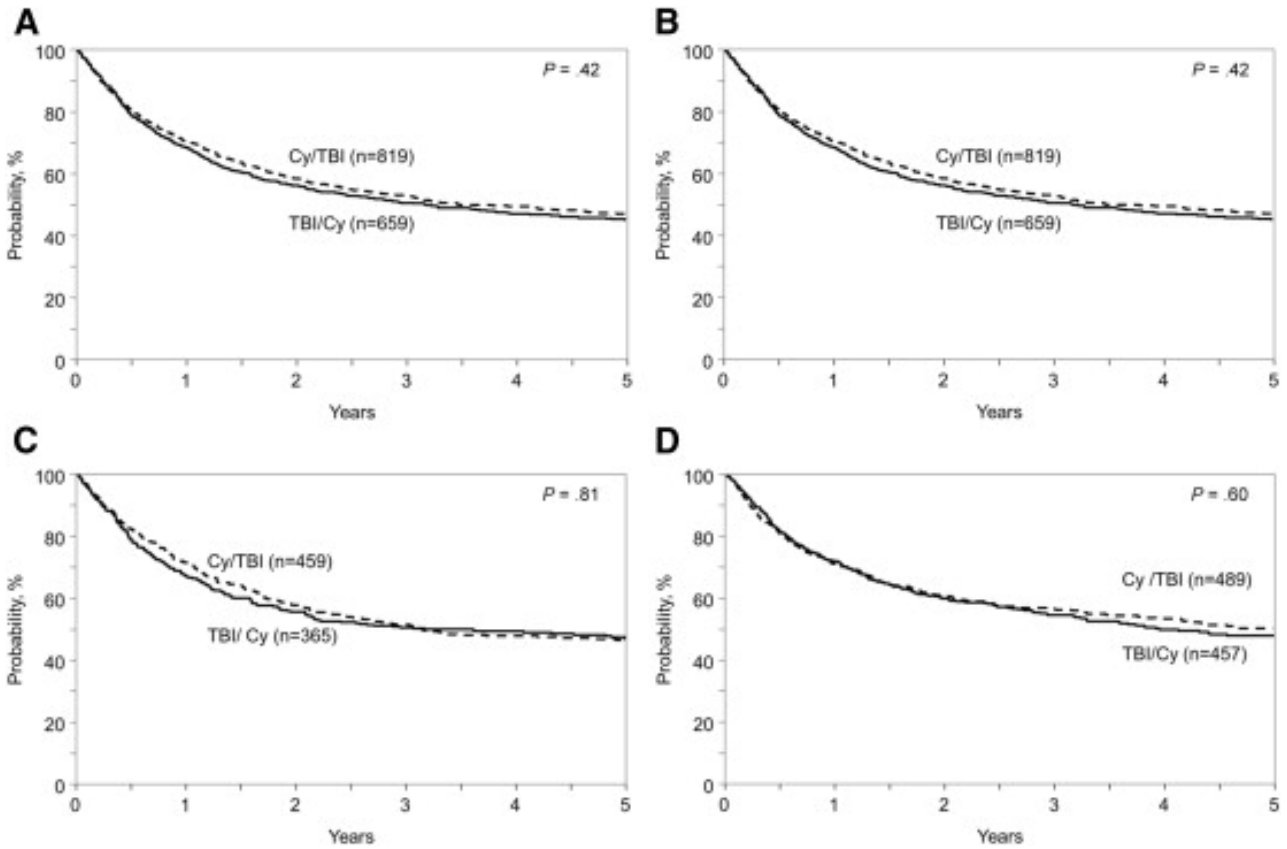


Figure 3. Overall survival among (A) adults patients, (B) children, (C) patients with acute lymphoid leukemia, and (D) with acute myeloid leukemia according to the sequence of cyclophosphamide and total body irradiation as part of a myeloablative conditioning ...

Jennifer L. Holter-Chakrabarty, Namali Pierson, Mei-Jie Zhang, Xiaochun Zhu, Görgün Akpek, Mahmoud D. Aljurf, Andrew S. Artz, Frédéric Baron, Christopher N. Bredeson, Christopher C. Dvorak, Robert B. Epstein, Hillard M. Lazarus...

The Sequence of Cyclophosphamide and Myeloablative Total Body Irradiation in Hematopoietic Cell Transplantation for Patients with Acute Leukemia

Biology of Blood and Marrow Transplantation, Volume 21, Issue 7, 2015, 1251–1257

http://dx.doi.org/10.1016/j.bbmt.2015.03.017

ARTICLE

Improving results of allogeneic hematopoietic cell transplantation for adults with acute lymphoblastic leukemia in first complete remission: an analysis from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation

Sebastian Giebel,[1] Myriam Labopin,[2,3] Gerard Socié,[4] Dietrich Beelen,[5] Paul Browne,[6] Liisa Volin,[7] Slawomira Kyrcz-Krzemien,[8] Ibrahim Yakoub-Agha,[9] Mahmoud Aljurf,[10] Depei Wu,[11] Mauricette Michallet,[12] Renate Arnold,[13] Mohamad Mohty[2*] and Arnon Nagler[3,14*]

Haematologica 2017
Volume 102(1):139-149

HLA matched sib. (n=2681)

Unrelated donors (n=2178)

Median age was 33.3 years (range 18-55 years).

Type of conditioning		
Busulfan + cyclophosphamide	433 (8.9%)	35 (6.2%)
Busulfan + fludarabine	78 (1.6%)	16 (2.8%)
Melphalan-based	49 (1%)	–
Other chemotherapy-based	247 (5.1%)	7 (1.2%)
TBI-based	4052 (83.4%)	504 (89.7%)
Source of stem cells		
Bone marrow	1660 (34.2%)	216 (38.4%)
Peripheral blood	3174 (65.8%)	346 (61.6%)

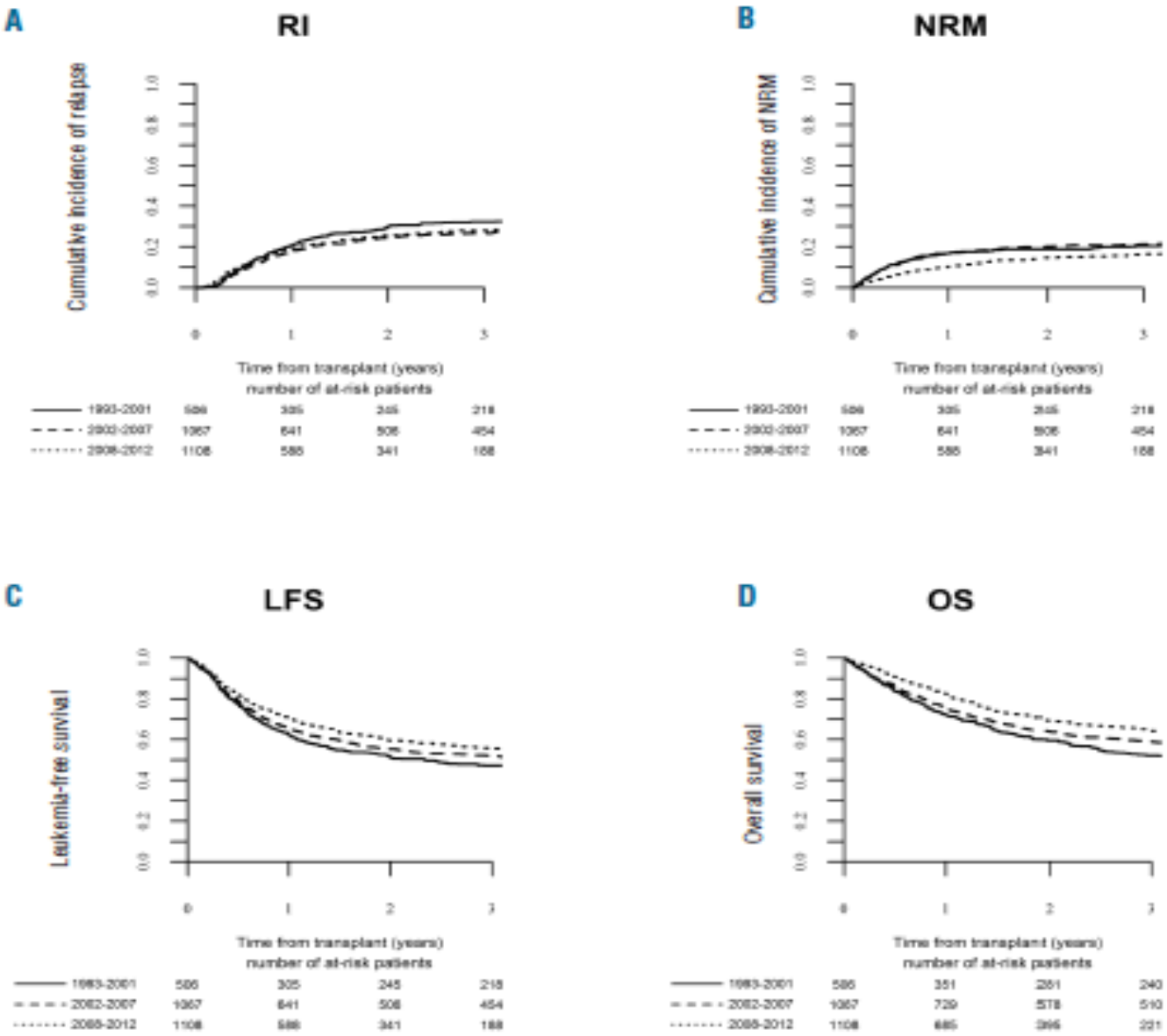


Figure 1. Outcome of matched sibling donor – hematopoietic cell transplantation for adults with acute lymphoblastic leukemia (ALL) in first complete remission (CR1). Changes over time in the period 1993-2012. (A) Relapse incidence (RI), (B) non-relapse mortality (NRM), (C) leukemia free survival (LFS), (D) overall survival (OS).

Glebel S et all Haematologica 2017

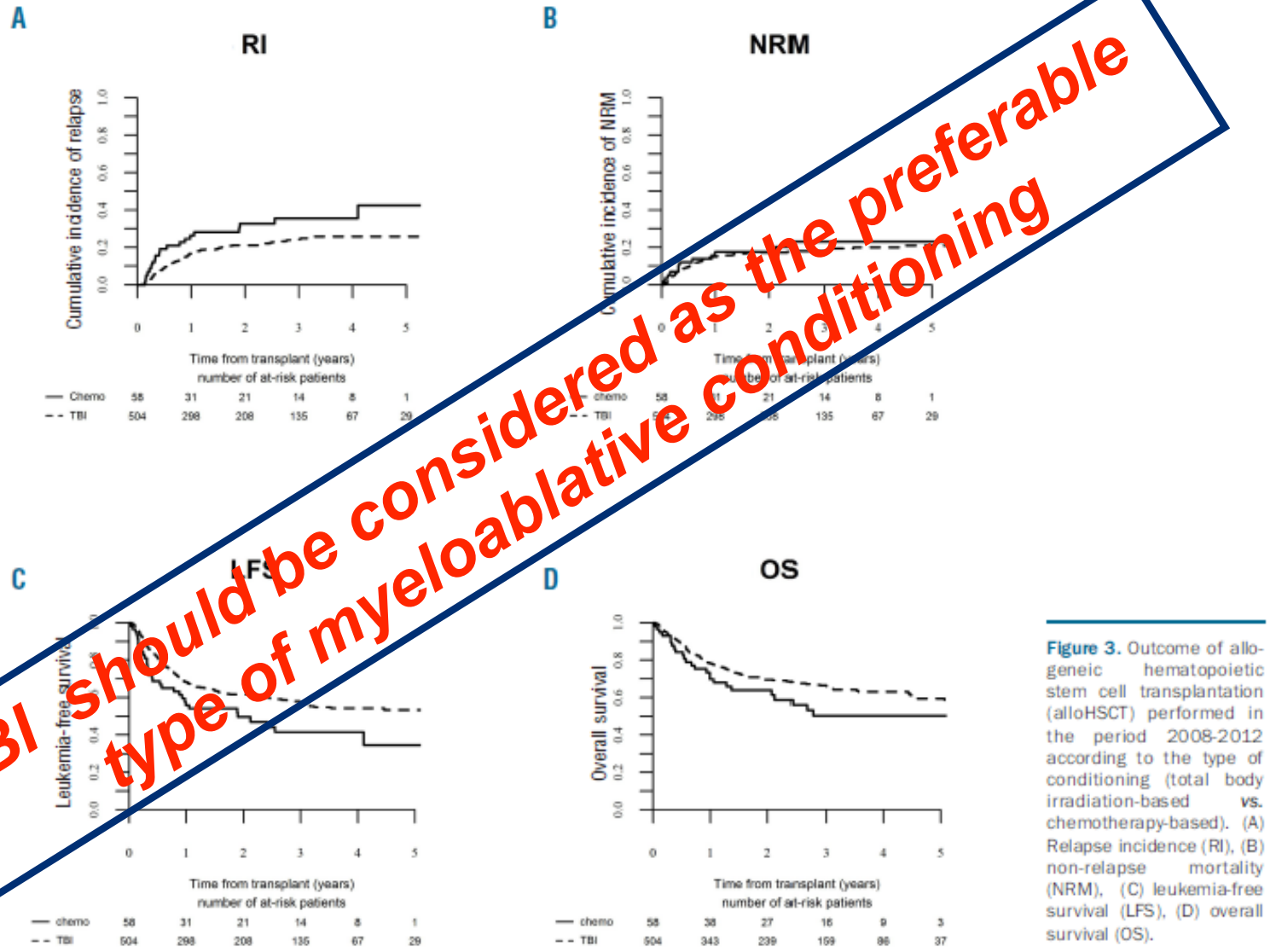


Figure 3. Outcome of allogeneic hematopoietic stem cell transplantation (alloHSCT) performed in the period 2008-2012 according to the type of conditioning (total body irradiation-based *vs.* chemotherapy-based). (A) Relapse incidence (RI), (B) non-relapse mortality (NRM), (C) leukemia-free survival (LFS), (D) overall survival (OS).

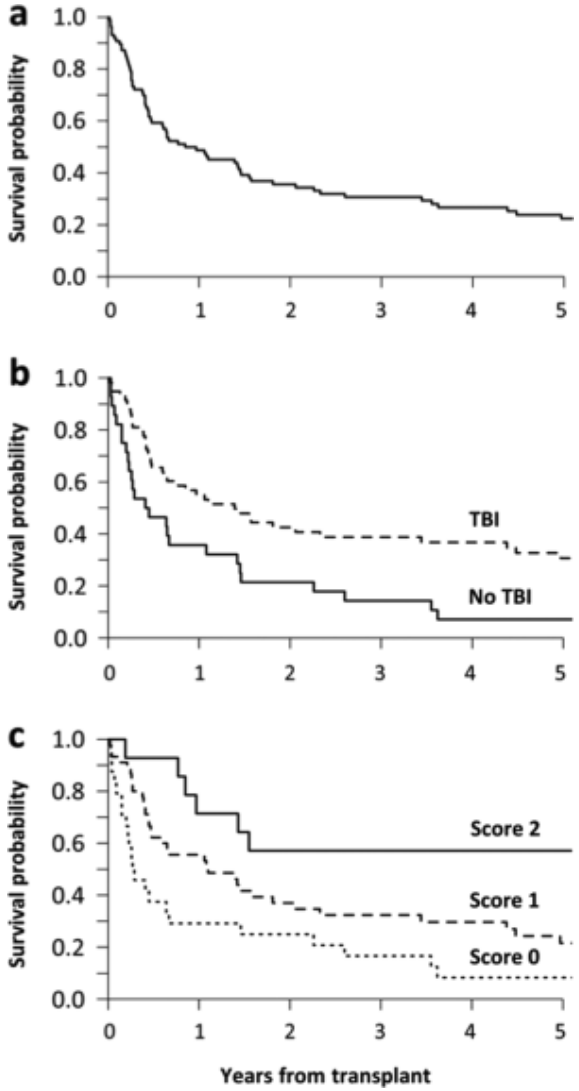
Allogeneic Hematopoietic Cell Transplantation for Primary Refractory ALL: A Report from the ALWP of the EBMT

- 86 adult patients
- Median follow-up 106 months
- OS was 36% at 2 years and 23% at 5 years
- LFS was 28% at 2 years and 17% at 5 years
- TRM was 20% at 2 years and 29% at 5 years

In multivariate analysis, use of TBI was found to be associated with improved survival

Pavlu J, Cancer June 2017

Allogeneic hematopoietic cell transplantation for primary refractory acute lymphoblastic leukemia: A report from the Acute Leukemia Working Party of the EBMT



Cancer
Volume 123, Issue 11, pages 1965-1970, 17 FEB 2017 DOI: 10.1002/cncr.30604
http://onlinelibrary.wiley.com/doi/10.1002/cncr.30604/full#cncr30604-fig-0001

Haematologica 2000; 85:1060-1067
original paper

Transplantation and Cell Therapy

Hematopoietic cell transplantation in acute lymphoblastic leukemia: better long-term event-free survival with conditioning regimens containing total body irradiation

ENRIQUE GRANADOS,* RAFAEL DE LA CÁMARA,* LUIS MADERO,° MIGUEL ANGEL DIAZ,° PATRICIA MARTÍN-REGUEIRA,* JUAN LUIS STEEGMANN,* REYES ARRANZ,* ANGELA FIGUERA,* JOSÉ MARÍA FERNÁNDEZ-RAÑADA*

*Hematology Department, Hospital Universitario de La Princesa, Madrid; °Oncology Department, Hospital del Niño Jesús, Madrid, Spain

156 pazienti
TBI n= 114
BuCy n=42

EFS at 6 years was 43% versus 22% in the TBI and BU subsets, respectively (p=0.01).

TRM at 18 months* was 22% and 17% in the BU and TBI groups (*p=0.24), respectively.

At 3 years actuarial PR was* 71% in the BU group and 47% in the TBI group (*p=0.01).

VOD developed in 9% and 16% of TBI and Bu treated patients respectively (p=NS)

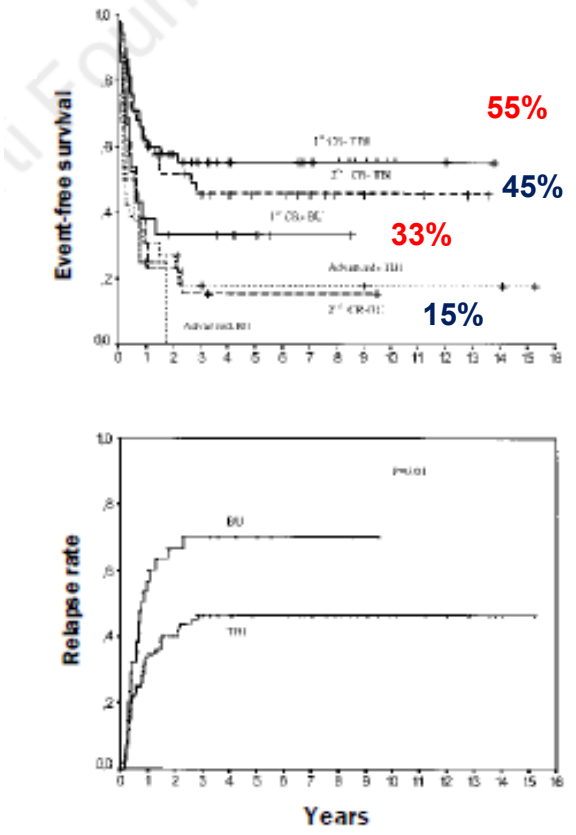


Figure 1. Kaplan-Meier curves representing the data of: A) comparison of the event-free survival between conditioning regimen (TBI versus BU) for the different status at transplant; B) comparison of the relapse rate between conditioning regimen (TBI versus BU) in the whole group. Comparisons were made with the log-rank test.

Bone Marrow Transplantation (2016) 51, 351–357

www.nature.com/bmt

601 pazienti
TBI 523
CT 78

ORIGINAL ARTICLE

Impact of conditioning with TBI in adult patients with T-cell ALL who receive a myeloablative allogeneic stem cell transplantation: a report from the acute leukemia working party of EBMT

X Cahu[1], M Labopin[2,3,4], S Giebel[5], M Aljurf[6], S Kyrcz-Krzemien[7], G Socié[8], M Eder[9], F Bonifazi[10], D Bunjes[11], S Vigouroux[12], M Michallet[13], M Stelljes[14], T Zuckerman[15], J Finke[16], J Passweg[17], I Yakoub-Agha[18], D Niederwieser[19], G Sucak[20], H Sengeløv[21], E Polge[2,3,4], A Nagler[22], J Esteve[23] and M Mohty[2,3,4] on behalf of the Acute Leukemia Working Party of EBMT

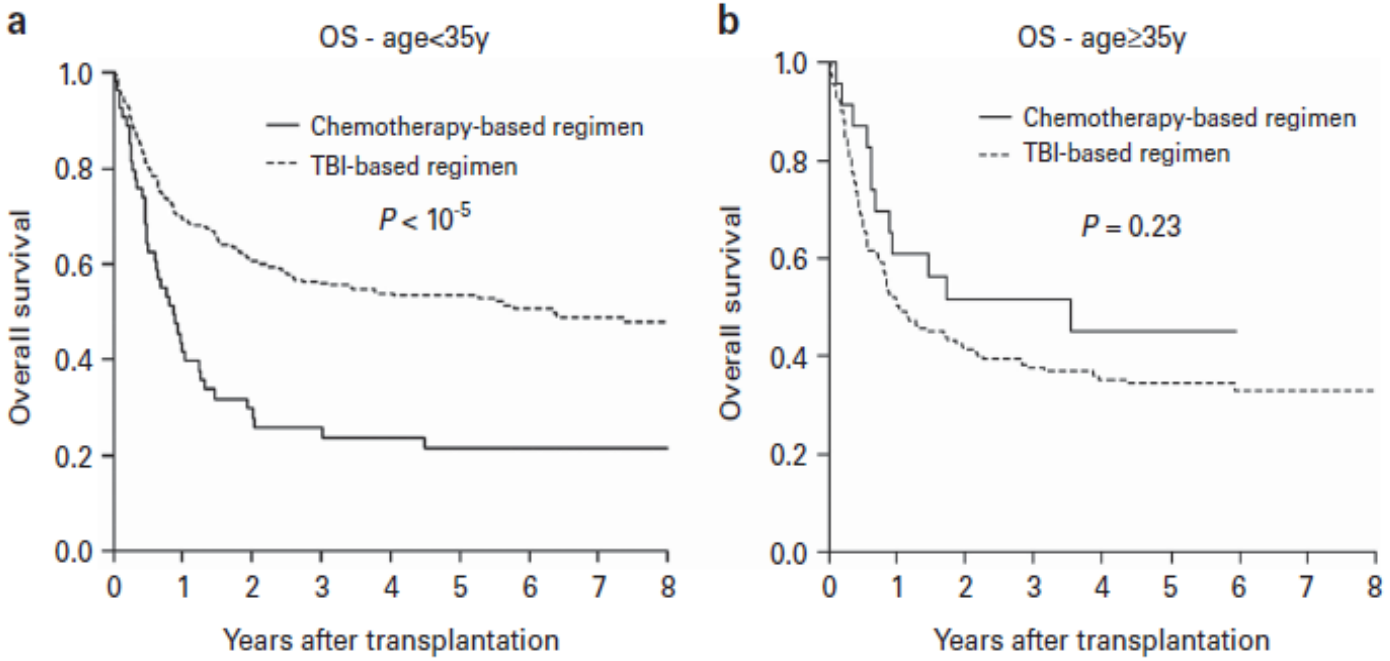


Figure 1. OS in patients <35 years (**a**) or ⩾35 years of age (**b**) according to the use of TBI.

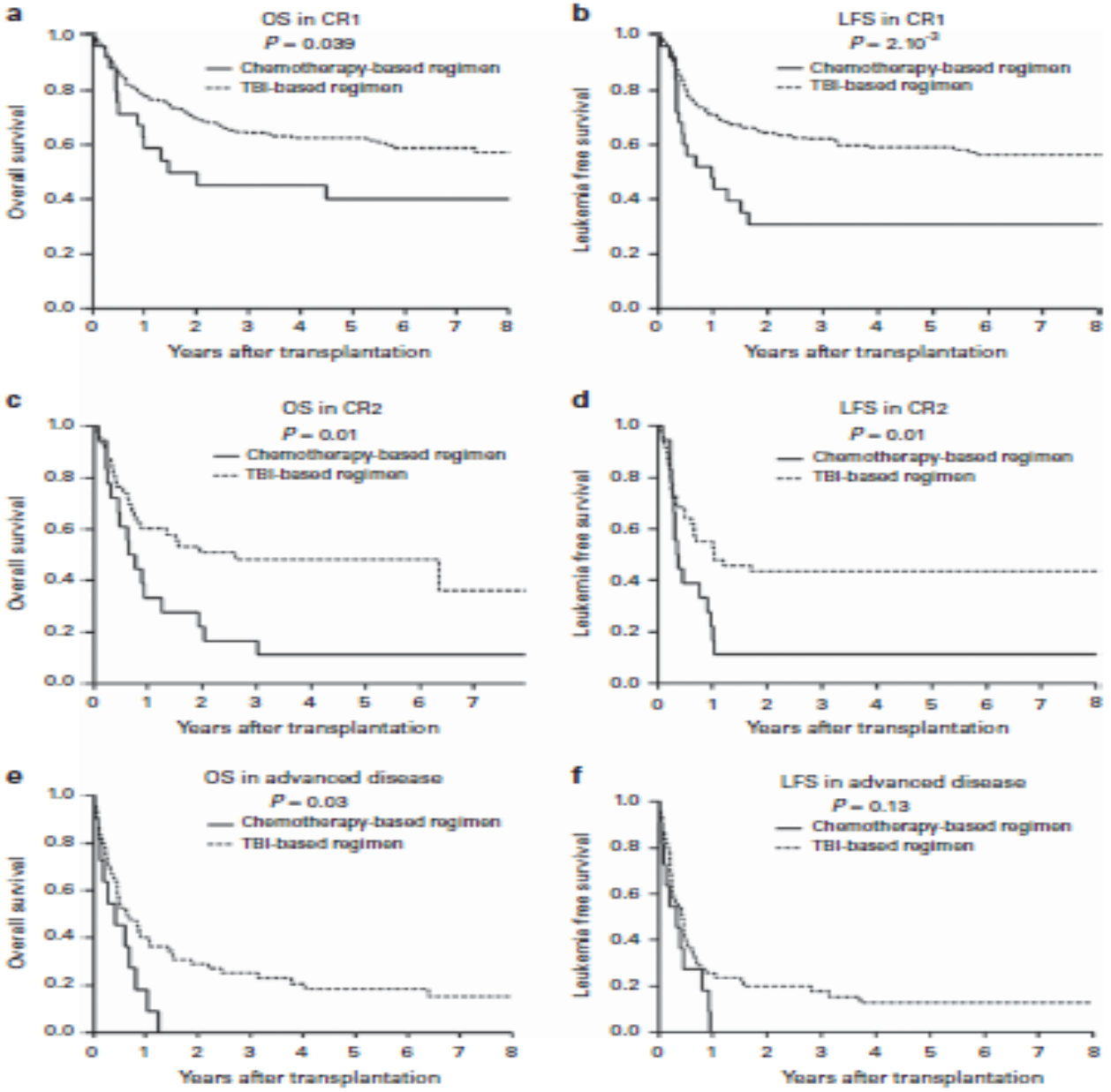
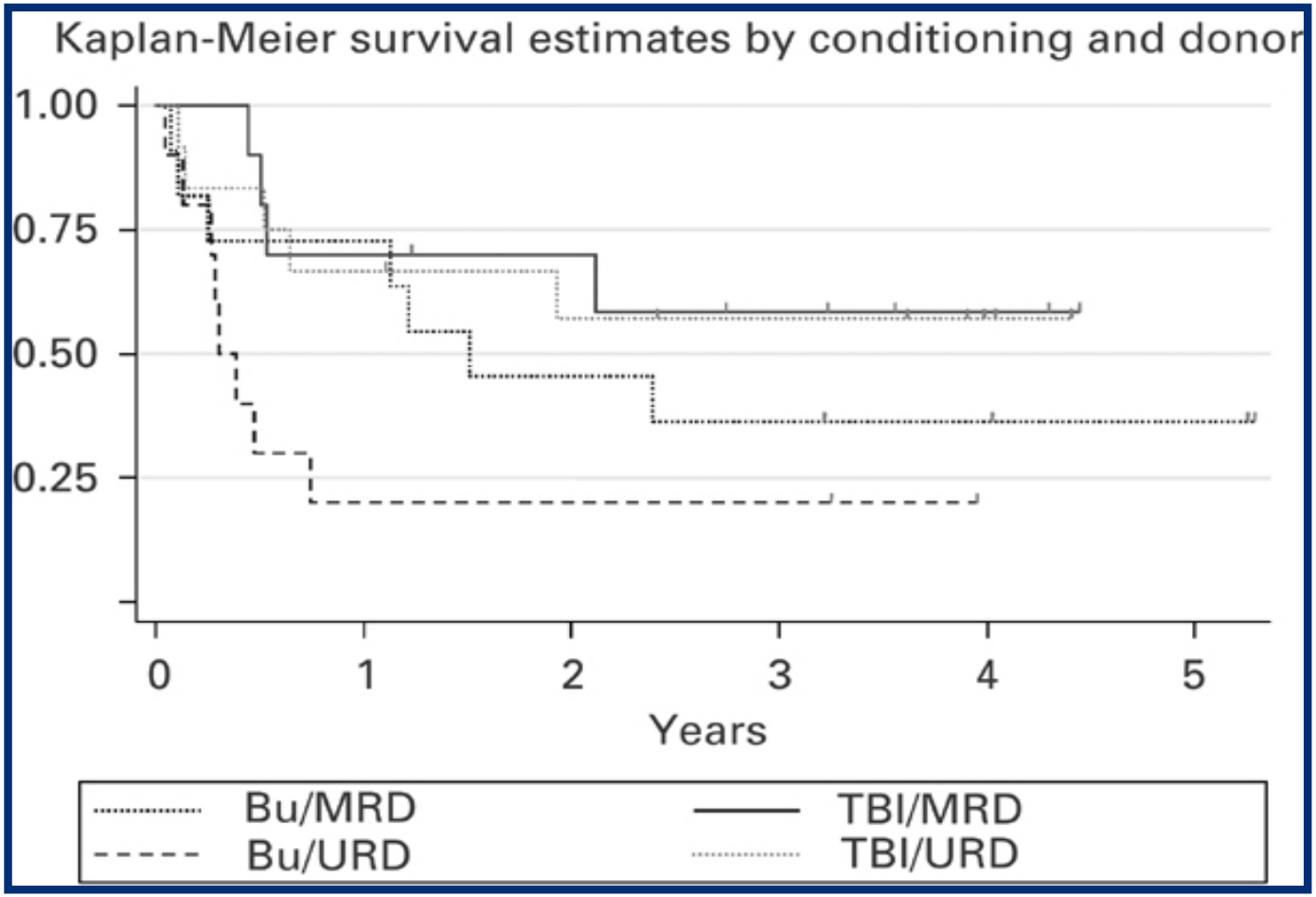


Figure 2. OS (**a**, **c**, **e**) and LFS (**b**, **d**, **f**) in younger patients (< 35 years old) who received allo-SCT in CR1 (**a**, **b**), CR2 (**c**, **d**) or advanced disease (**e**, **f**).

X Cahu et all Bone Marrow Transplantation 2016

Randomized trial of busulfan *vs* total body irradiation containing conditioning regimens for children with acute lymphoblastic leukemia: A Pediatric Blood and Marrow Transplant Consortium study

N Bunin, R Aplenc, N Kamani, K Shaw, A Cnaan and S Simms



43 pazienti
21 Bu+Cy+Eto 40 mg/kg
22 TBI+Cy+Eto 40 mg/kg

Biology of Blood and Marrow Transplantation 14:568-575 (2008)

1083-8791/08/1405-0001$32.00/0
doi:10.1016/j.bbmt.2008.02.018

ASBMT
American Society for Blood and Marrow Transplantation

Excellent Outcome of Allogeneic Hematopoietic Stem Cell Transplantation Using a Conditioning Regimen with Medium-Dose VP-16, Cyclophosphamide and Total-Body Irradiation for Adult Patients with Acute Lymphoblastic Leukemia

Akio Shigematsu,[1] Takeshi Kondo,[2] Satoshi Yamamoto,[3] Junichi Sugita,[1] Masahiro Onozawa,[2] Kaoru Kahata,[2] Tomoyuki Endo,[3] Soichi Shiratori,[1] Shuichi Ota,[2] Masato Obara,[3] Kentaro Wakasa,[1] Mutsumi Takahata,[2] Yukari Takeda,[3] Junji Tanaka,[1] Satoshi Hashino,[2] Mitsufumi Nishio,[3] Takao Koike,[3] Masahiro Asaka,[2] Masahiro Imamura[1]

37 pazienti

Table 2. *Organ Toxicities and GVHD*

	No (%)
Organ toxicity*	
Any grade 3 toxicity	27 (81.8%)
Stomatitis	19 (57.6%)
Diarrhea	11 (33.3%)
Cardiovascular	2 (6.1%)
Pulmonary/DAH	1 (3.0%)
Hepatic	3 (9.1%)
VOD	2 (6.1%)
TMA	2 (6.1%)
Death due to organ toxicity	2 (5.4%)
Febrile episode before engraftment	23 (69.7%)
GVHD†	
Acute GVHD total	29 (78.4%)
Acute GVHD grade II-IV	15 (40.5%)
Chronic GVHD total	18 (54.5%)
Chronic GVHD extensive	12 (36.4%)
Death due to GVHD	0 (0.0%)

DAH indicates diffuse alveolar hemorrhage; VOD, veno-occlusive disease of the liver, TMA, thrombotic microangiopathy.
*Toxicity is graded by NCI common toxicity criteria. Only patients with grade 3 toxicity are presented. Some patients had toxicity in more than one organ system. Organ toxicity was evaluated in 33 patients.
†Acute GVHD and chronic GVHD were evaluted in 37 and 33 patients, respectively.

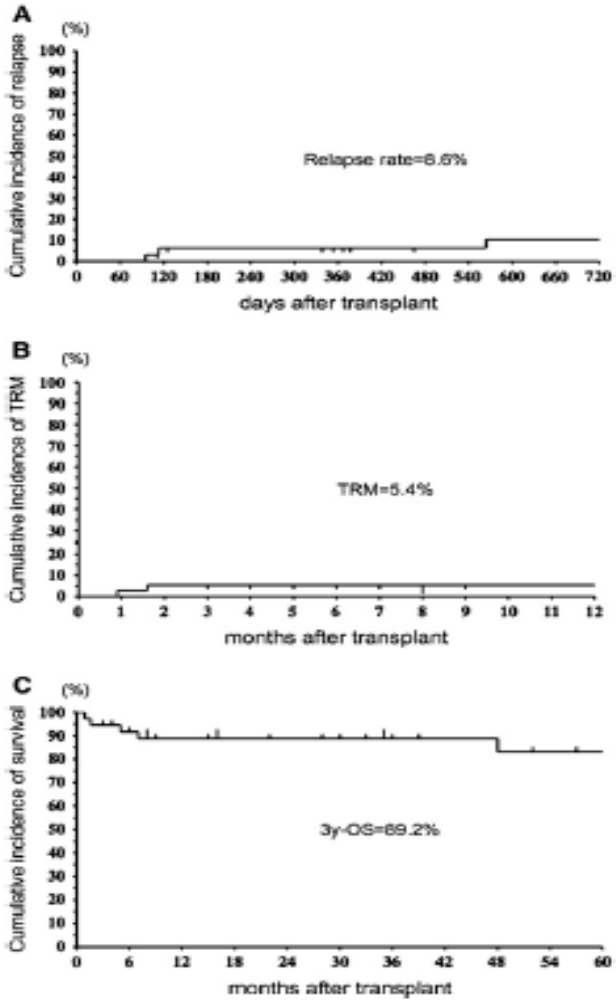


Figure 1. Cumulative incidence of relapse (a), TRM (b), and OS (c). TRM indicates transplant-related mortality; OS, overall survival.

Biology of Blood and Marrow Transplantation 12:438–453 (2006)

1083-8791/06/1204-0007$32.00/0
doi:10.1016/j.bbmt.2005.12.029

A Comparison of Cyclophosphamide and Total Body Irradiation with Etoposide and Total Body Irradiation as Conditioning Regimens for Patients Undergoing Sibling Allografting for Acute Lymphoblastic Leukemia in First or Second Complete Remission

David I. Marks,[1] Stephen J. Forman,[2] Karl G. Blume,[3] Waleska S. Pérez,[4] Daniel J. Weisdorf,[5] Armand Keating,[6] Robert Peter Gale,[7] Mitchell S. Cairo,[8] Edward A. Copelan,[9] John T. Horan,[10] Hillard M. Lazarus,[11] Mark R. Litzow,[12] Philip L. McCarthy,[13] Kirk R. Schultz,[14] David D. Smith,[2] Michael E. Trigg,[15] Mei-Jie Zhang,[4] Mary M. Horowitz[4]

298 TBICy
204 TBIETO
MSD

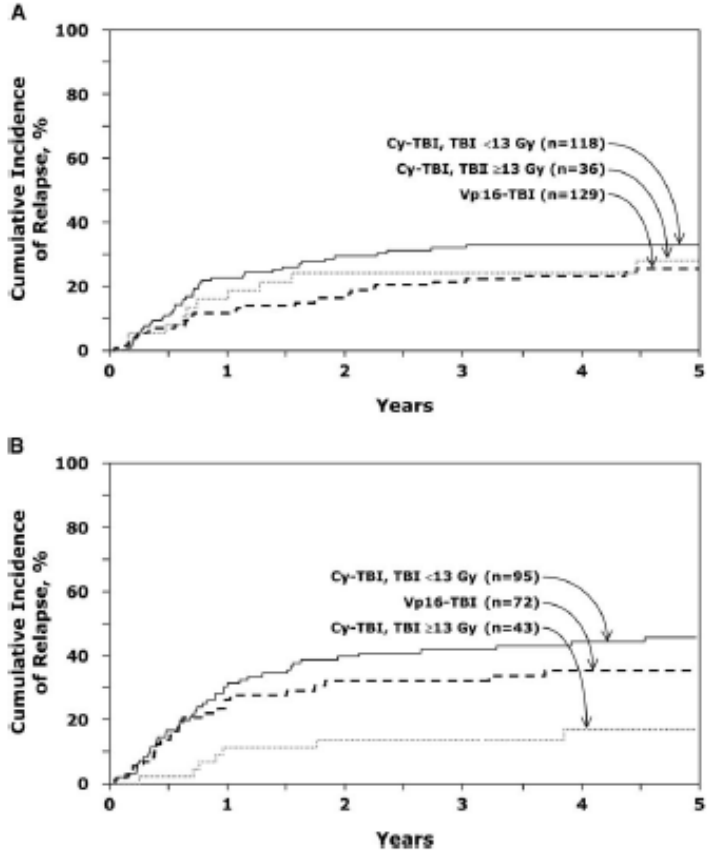


Figure 2. Cumulative incidence of relapse after HLA-identical sibling transplantations for ALL in first (A) or second (B) complete remission, according to the pretransplantation conditioning regimen (pointwise *P* value at 5 years for CR1 patients: etoposide-TBI versus Cy-TBI <13 Gy, $P = .23$; etoposide-TBI versus Cy-TBI ≥13 Gy, $P = .78$; Cy-TBI <13 Gy versus Cy-TBI ≥13 Gy, $P = .60$; pointwise *P* value at 5 years for CR2 patients: etoposide-TBI versus Cy-TBI <13 Gy, $P = .22$; etoposide-TBI versus Cy-TBI ≥13 Gy, $P = .033$; Cy-TBI <13 Gy versus Cy-TBI ≥13 Gy, $P = .001$). Vp16 indicates etoposide.

Biology of Blood and Marrow Transplantation 12:438-453 (2006)

1083-8791/06/1204-0007$32.00/0
doi:10.1016/j.bbmt.2005.12.029

A Comparison of Cyclophosphamide and Total Body Irradiation with Etoposide and Total Body Irradiation as Conditioning Regimens for Patients Undergoing Sibling Allografting for Acute Lymphoblastic Leukemia in First or Second Complete Remission

David I. Marks,[1] Stephen J. Forman,[2] Karl G. Blume,[3] Waleska S. Pérez,[4] Daniel J. Weisdorf,[5] Armand Keating,[6] Robert Peter Gale,[7] Mitchell S. Cairo,[8] Edward A. Copelan,[9] John T. Horan,[10] Hillard M. Lazarus,[11] Mark R. Litzow,[12] Philip L. McCarthy,[13] Kirk R. Schultz,[14] David D. Smith,[2] Michael E. Trigg,[15] Mei-Jie Zhang,[4] Mary M. Horowitz[4]

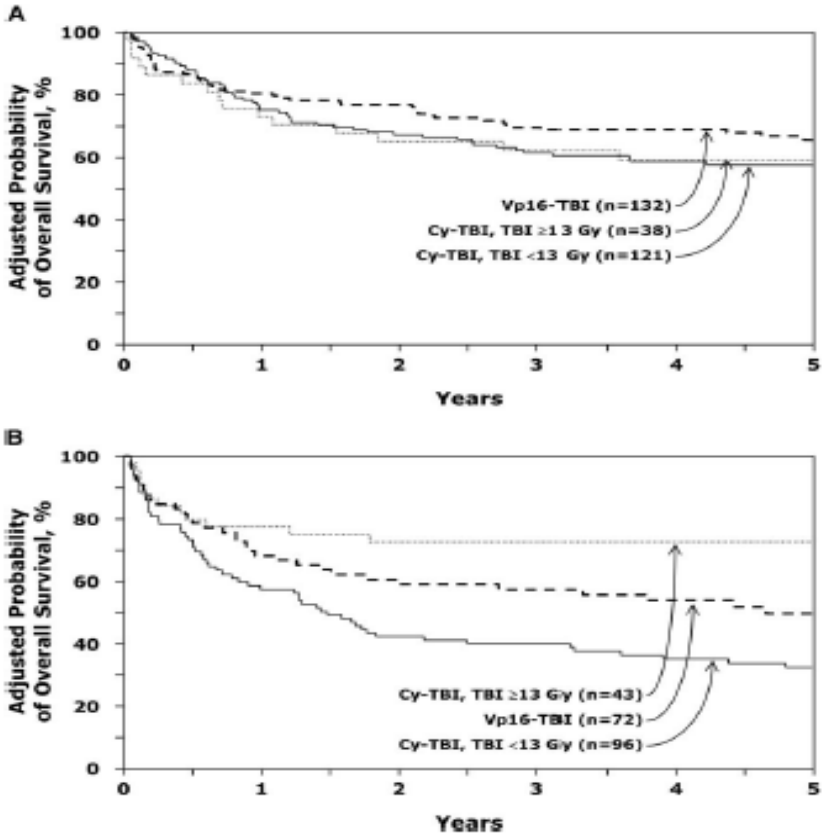


Figure 4. Adjusted probability (derived for multivariate regression models) of overall survival after HLA-identical sibling transplantations for ALL in first (A) or second (B) complete remission, according to the pretransplantation conditioning regimen (pointwise *P* value at 5 years for CR1 patients: etoposide-TBI versus Cy-TBI <13 Gy, $P = .18$; etoposide-TBI versus Cy-TBI ≥13 Gy, $P = .47$; Cy-TBI <13 Gy versus Cy-TBI ≥13 Gy, $P = .87$; pointwise *P* value at 5 years for CR2 patients: etoposide-TBI versus Cy-TBI <13 Gy, $P = .029$; etoposide-TBI versus Cy-TBI ≥13 Gy, $P = .012$; Cy-TBI <13 Gy versus Cy-TBI ≥13 Gy, $P < .001$). Vp16 indicates etoposide.

Leukemia Research 39 (2015) 1192–1200

Contents lists available at ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

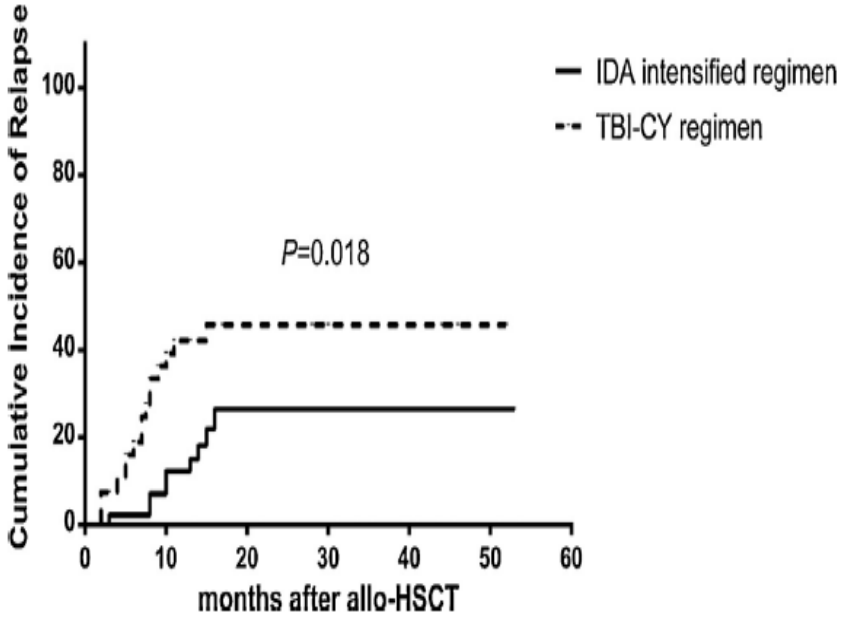
Comparison of outcomes of idarubicin intensified TBI–CY and traditional TBI–CY conditioning regimen for high-risk acute lymphoblastic leukemia undergoing allogeneic hematopoietic stem cell transplantation: A single center experience

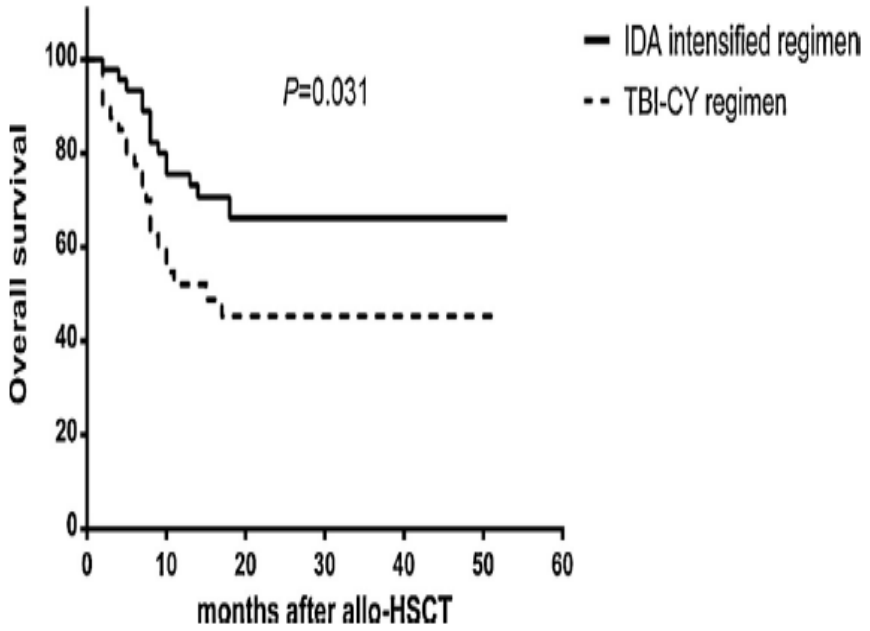
Qiuling Wu[a,1], Ran Zhang[a,1], Huafang Wang[a], Yong You[a], Zhaodong Zhong[a], Mei Hong[a], Jun Fang[a], Weiming Li[a], Wei Shi[a], Xuan Lu[a], Yu Hu[a], Linghui Xia[a,*]

[a] Institute of Hematology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan China

87 high-risk ALL patients
47patients received idarubicin (IDA) intensified TBI–CY
40 patients received traditional TBI–CY regimen.

Patients received TBI (8 Gy) on day-8, IDA of 15 mg/m2/d from day-6 to-5, followed by CY (60 mg/kg/d) on day-3 to -2.





Intravenous Busulfan-Cyclophosphamide as a Preparative Regimen Before Allogeneic Hematopoietic Stem Cell Transplantation for Adult Patients with Acute Lymphoblastic Leukemia

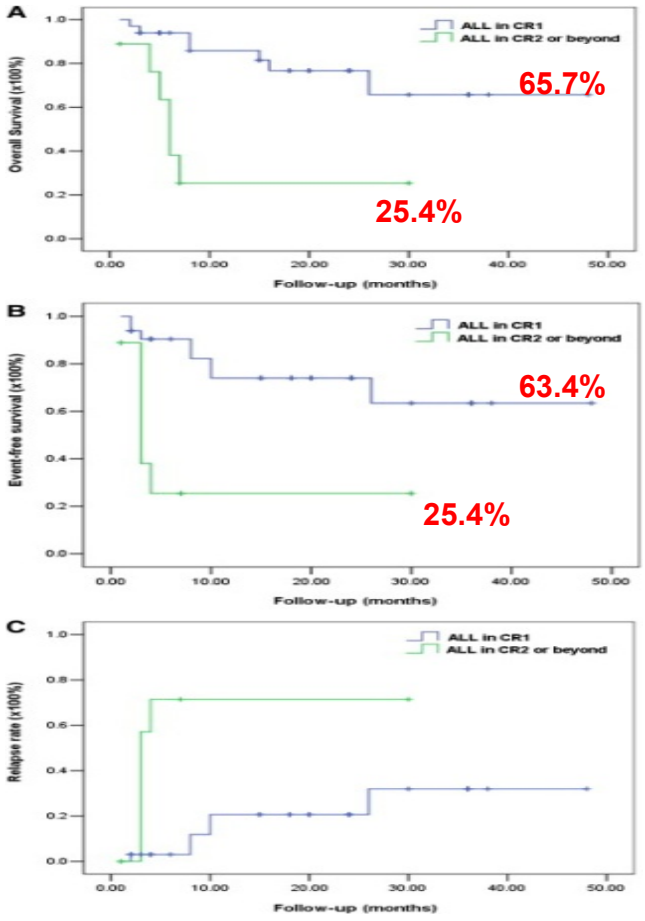
Wei Tang, Ling Wang, Wei-Li Zhao, Yu-Bao Chen, Zhi-Xiang Shen, Jiong Hu

Table 1. Patient Characteristics

Sex, n	
Male	28
Female	14
Age, years, median (range)	28 (17~55)
Donor type, n	
HLA-matched sibling	18
HLA-matched unrelated donor	24
Disease stage, n	
CR1	33 (Ph^+ ALL, 7)
CR2	2 (Ph^+ ALL, 1)
Relapsed/refractory	7 (Ph^+ ALL, 2)
HSC source, n	
Bone marrow	3
Peripheral blood	39
Follow-up, months, median (range)	15 (1~48)

OS 30-months 56.5%

aGvHD II-IV 40%
cGvHD 63.9%



Comparison of Cyclophosphamide Combined with Total Body Irradiation, Oral Busulfan, or Intravenous Busulfan for Allogeneic Hematopoietic Cell Transplantation in Adults with Acute Lymphoblastic Leukemia

Kenjiro Mitsuhashi [1,*], Shinichi Kako [2], Akio Shigematsu [3], Yoshiko Atsuta [4,5], Noriko Doki [6], Takahiro Fukuda [7], Heiwa Kanamori [8], Makoto Onizuka [9], Satoshi Takahashi [10], Yukiyasu Ozawa [11], Mineo Kurokawa [12], Yoshiko Inoue [13], Tokiko Nagamura-Inoue [14], Yasuo Morishima [15], Shuichi Mizuta [16], Junji Tanaka [1], on behalf of the Adult Acute Lymphoblastic Leukemia Working Group of the Japan Society for Hematopoietic Cell Transplantation

2130 TBI/CY
60 BU/CY (os)
42 BU/CY (iv)

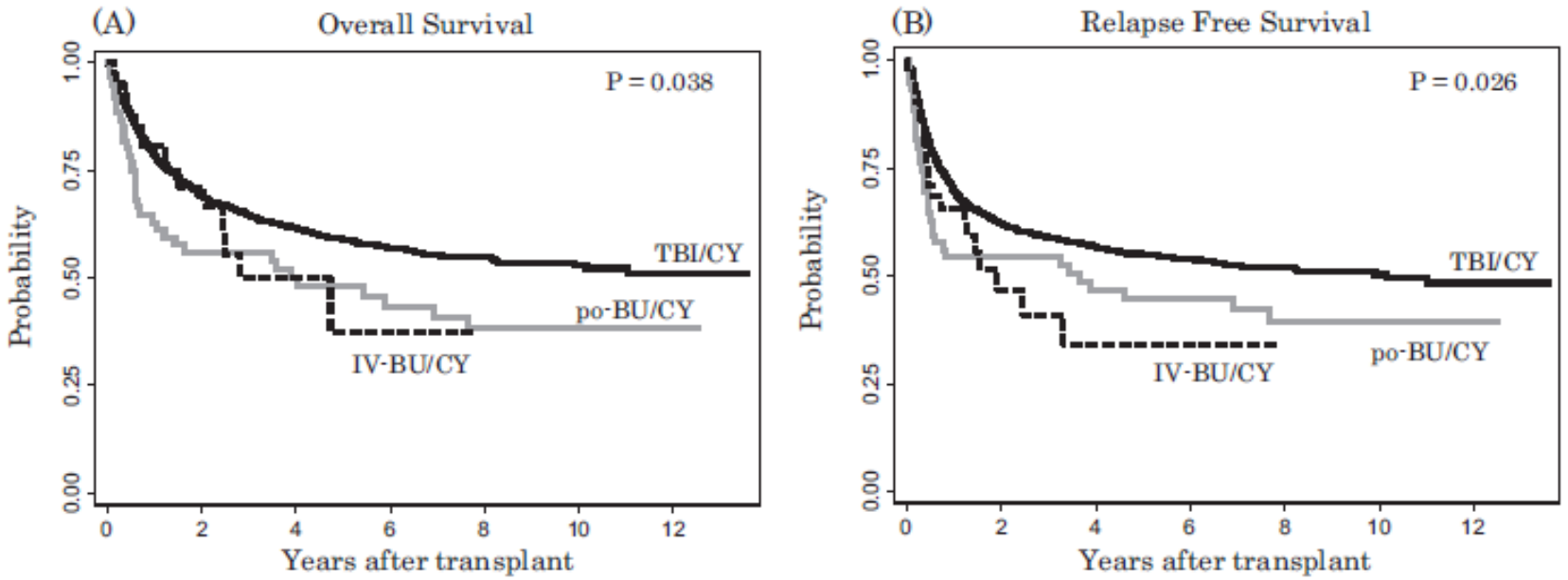


Figure 1. Univariate probabilities of OS (A) and RFS (B) according to conditioning regimen.

Leuk Lymphoma. 2013 Nov;54(11):2474-9.

Comparison of total body irradiation plus cyclophosphamide with busulfan plus cyclophosphamide as conditioning regimens in patients with acute lymphoblastic leukemia undergoing allogeneic hematopoietic stem cell transplant

In this study, we present a comparison of treatment results for 95 patients with ALL who underwent allogeneic hematopoietic stem cell transplant (AHSCT) with total body irradiation plus cyclophosphamide (TBI + Cy) or busulfan plus cyclophosphamide (Bu + Cy) as conditioning regimen.

Median age was 25 (range: 9-54) years.

Median follow-up was 24 (range: 3-107) months. Median overall survival (OS) was found to be 29 months. Median event-free survival (EFS) was 9 months.

Median OS was 37 months in the TBI + Cy arm, while it was 12 months in the Bu + Cy arm, suggesting a significant advantage favoring the TBI + Cy arm ($p = 0.003$).

Median EFS was 13 months in the TBI + Cy arm, while it was 4 months in the Bu + Cy arm, indicating a significant difference ($p = 0.006$).

In univariate and multivariate analysis, it was found that high OS and EFS were significantly correlated with TBI + Cy conditioning regimen and lack of transplant-related mortality ($p < 0.05$).

The TBI + Cy conditioning regimen was found to be superior to the Bu + Cy regimen in patients with ALL undergoing AHSCT regarding both OS and EFS

Bone Marrow Transplantation (2016) **51,** 1636–1639

www.nature.com/bmt

LETTER TO THE EDITOR

High-dose cytarabine added to CY/TBI improves the prognosis of cord blood transplantation for acute lymphoblastic leukemia in adults: a retrospective cohort study

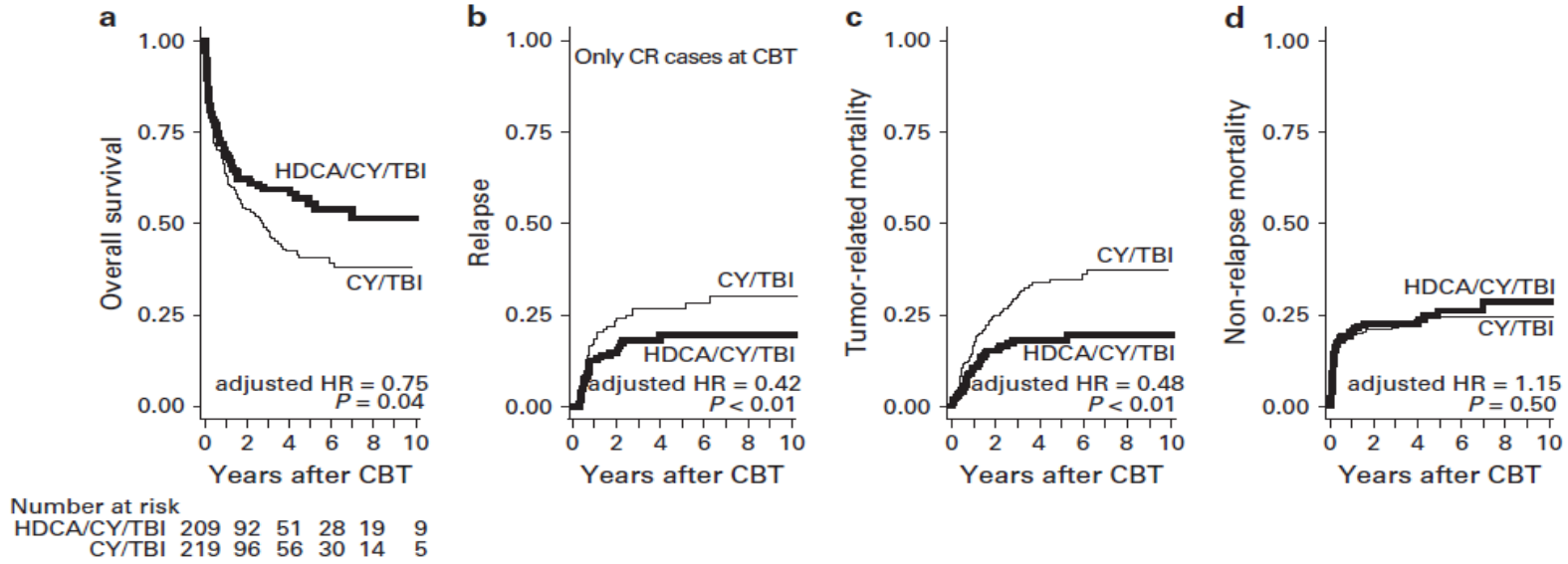
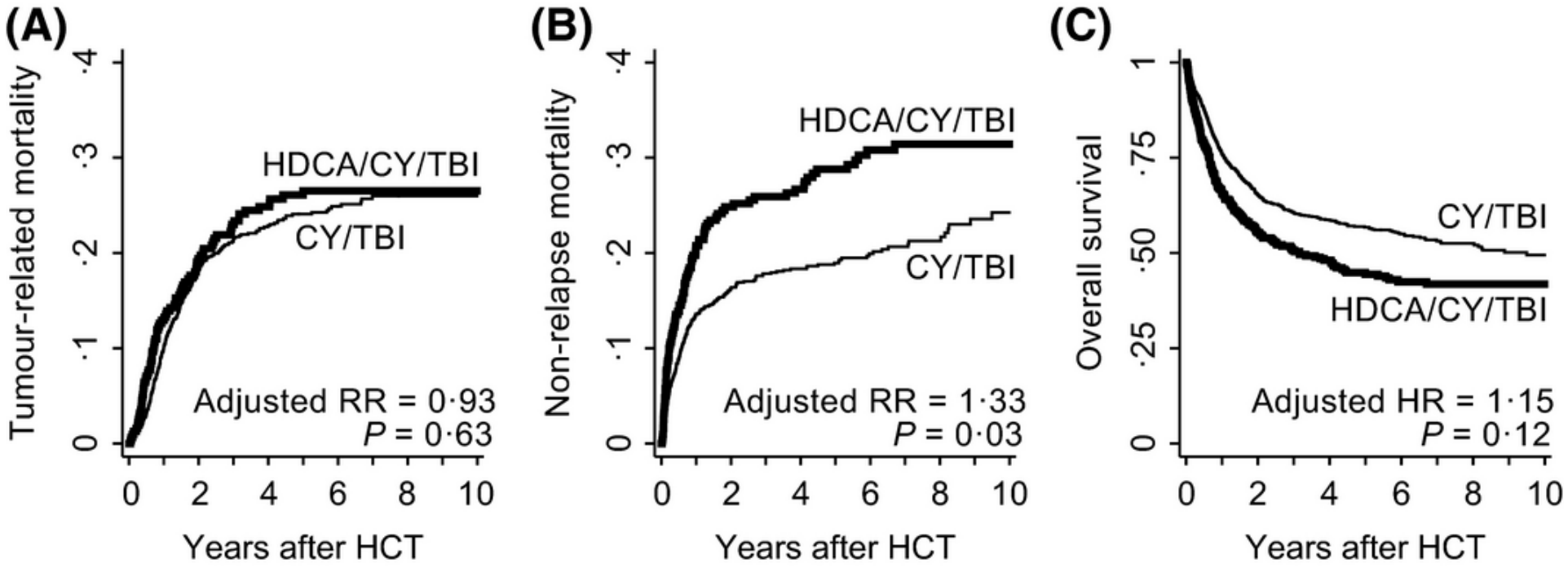


Figure 1. OS, relapse, tumor-related mortality and NRM after CBT in each group of the conditioning regimen. (**a**) OS was calculated with the Kaplan–Meier method in each group of HDCA/CY/TBI and CY/TBI. HR for overall mortality of HDCA/CY/TBI compared with CY/TBI was calculated by Cox proportional hazards model after being adjusted for confounding factors such as patient age, disease risk, GvHD prophylaxis and year of CBT. (**b**) Relapse after in CBT (only in patients transplanted at CR status), (**c**) tumor-related mortality (defined as death without remission or after relapse) and (**d**) NRM were calculated using Gray's method and compared with the Fine–Gray proportional hazards model.

Increased non-relapse mortality due to high-dose cytarabine plus CY/TBI in BMT/PBSCT for acute lymphoblastic leukaemia in adults



British Journal of Haematology
25 APR 2017 DOI: 10.1111/bjh.14652
http://onlinelibrary.wiley.com/doi/10.1111/bjh.14652/full#bjh14652-fig-0001

Biol Blood Marrow Transplant 23 (2017) 285–292

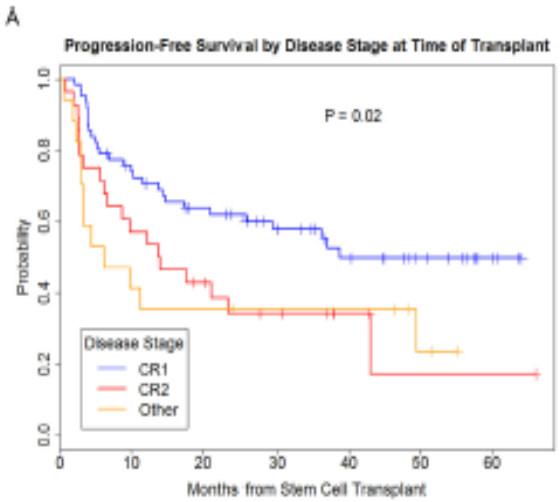
Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Clofarabine Plus Busulfan is an Effective Conditioning Regimen for Allogeneic Hematopoietic Stem Cell Transplantation in Patients with Acute Lymphoblastic Leukemia: Long-Term Study Results

Partow Kebriaei [1,*], Roland Bassett [2], Genevieve Lyons [2], Ben Valdez [1], Celina Ledesma [1], Gabriela Rondon [1], Betul Oran [1], Stefan Ciurea [1], Amin Alousi [1], Uday Popat [1], Krina Patel [1], Sairah Ahmed [1], Amanda Olson [1], Qaiser Bashir [1], Nina Shah [1], Roy Jones [1], David Marin [1], Katayoun Rezvani [1], Yago Nieto [1], Issa Khouri [1], Muzaffar Qazilbash [1], Chitra Hosing [1], Elizabeth Shpall [1], Richard E. Champlin [1], Borje S. Andersson [1]

107 pazienti
Età media 38 aa (19-64)
MSD 52
MUD 55



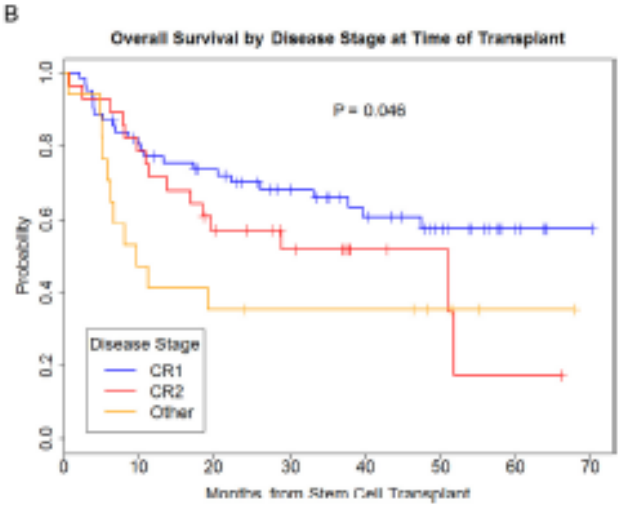
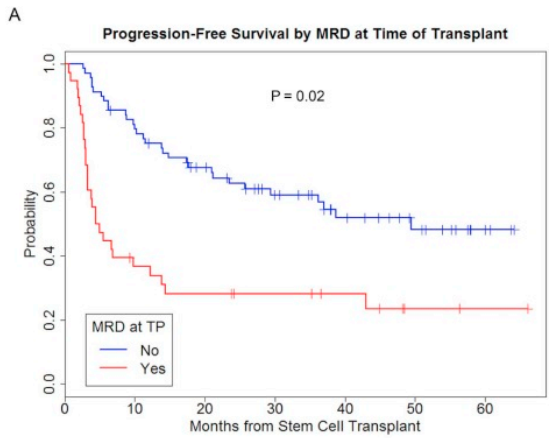
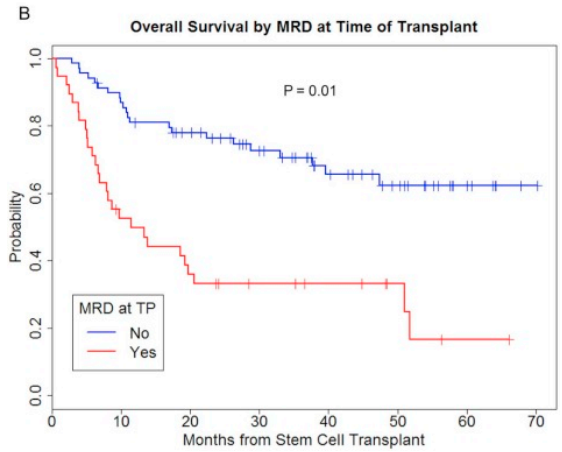


Figure 1. PFS (A) and OS (B) by disease stage at the time of HSCT.





Biol Blood Marrow Transplant 23 (2017) 285–292

Biology of Blood and Marrow Transplantation

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Clofarabine Plus Busulfan is an Effective Conditioning Regimen for Allogeneic Hematopoietic Stem Cell Transplantation in Patients with Acute Lymphoblastic Leukemia: Long-Term Study Results

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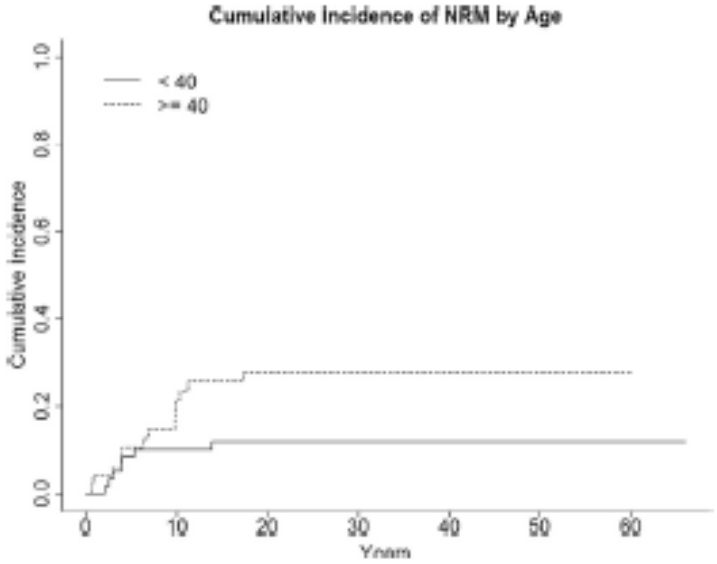


Figure 3. NRM by age at the time of HSCT.

Table 3
Regimen-Related Toxicity

Toxicity	Grade I	Grade II	Grade III	Grade IV	Grade V
Liver, n					
Bilirubin elevation	7	22	9	0	0
Transaminitis	36	23	32	0	0
VOD	0	0	5	0	1
Gastrointestinal tract, n					
Diarrhea	38	13	5	0	0
Nausea	6	61	1	0	0
Mucositis	9	70	26	0	0
Urinary tract/kidney, n					
Creatinine elevation	5	5	1	0	0
Skin, n					
Rash	11	7	3	1	0
Neurologic, n					
Headache	4	2	0	0	0

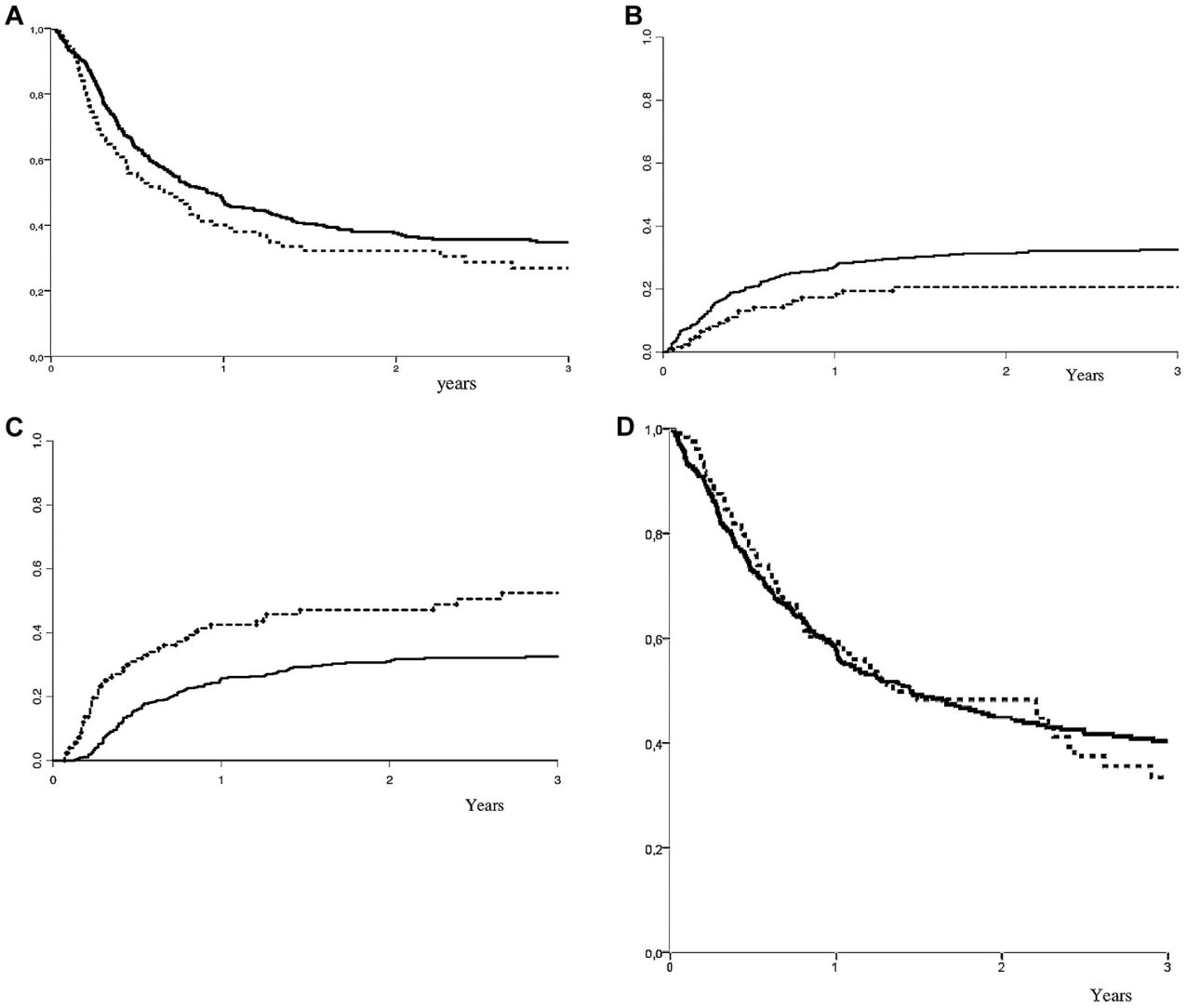
VOD indicates veno-occlusive disease.

Table 4
Cumulative Incidence of Acute and Chronic GVHD

Type of GVHD	n/N (%)
Acute GVHD	
Grade II-IV	19/54 (35)
Grade III-IV	5/50 (10)
Chronic GVHD	
Limited and/or extensive	8/28 (29)
Extensive	4/22 (18)

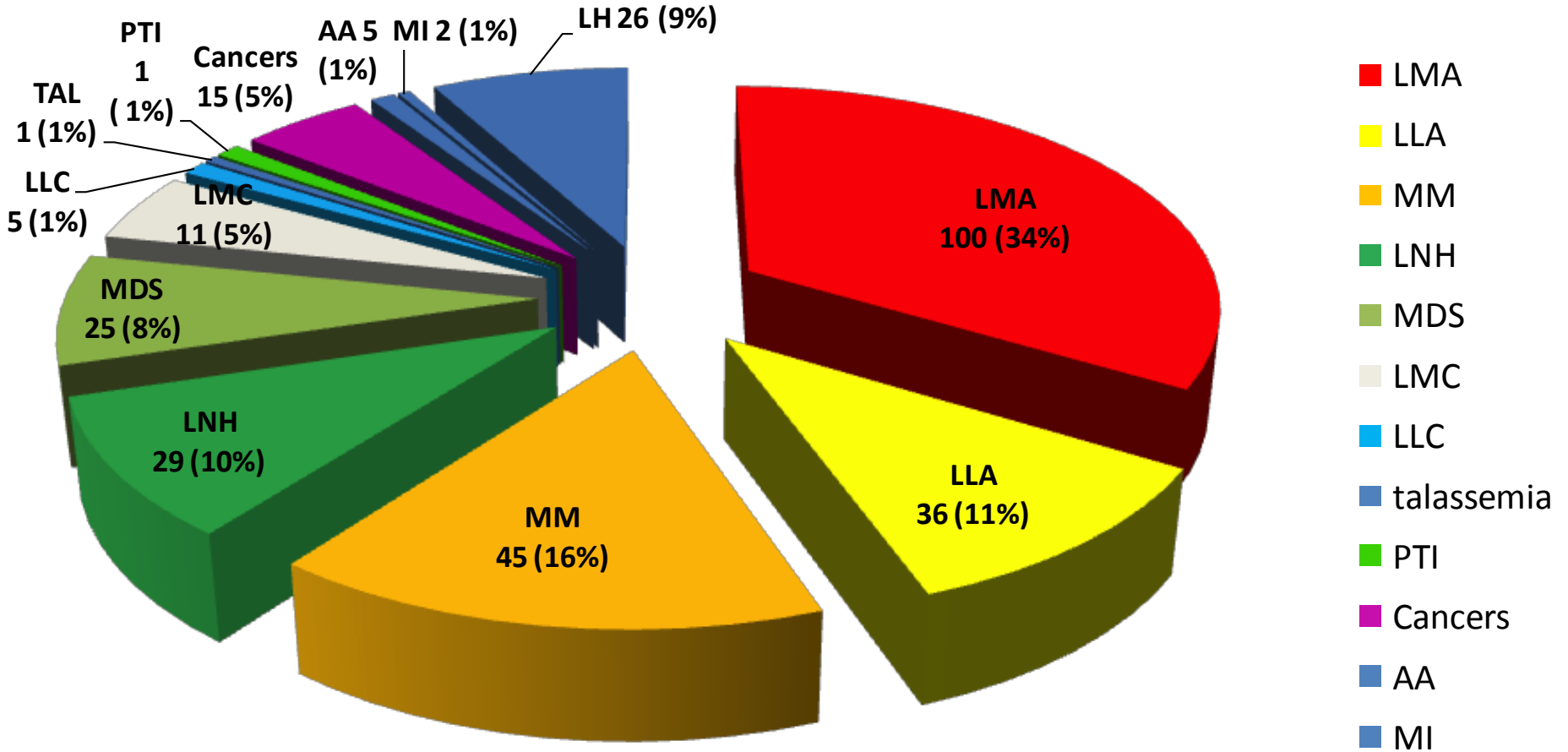
GVHD indicates graft-versus-host disease.

Survival probabilities.



Mohamad Mohty et al. Blood 2010;116:4439-4443

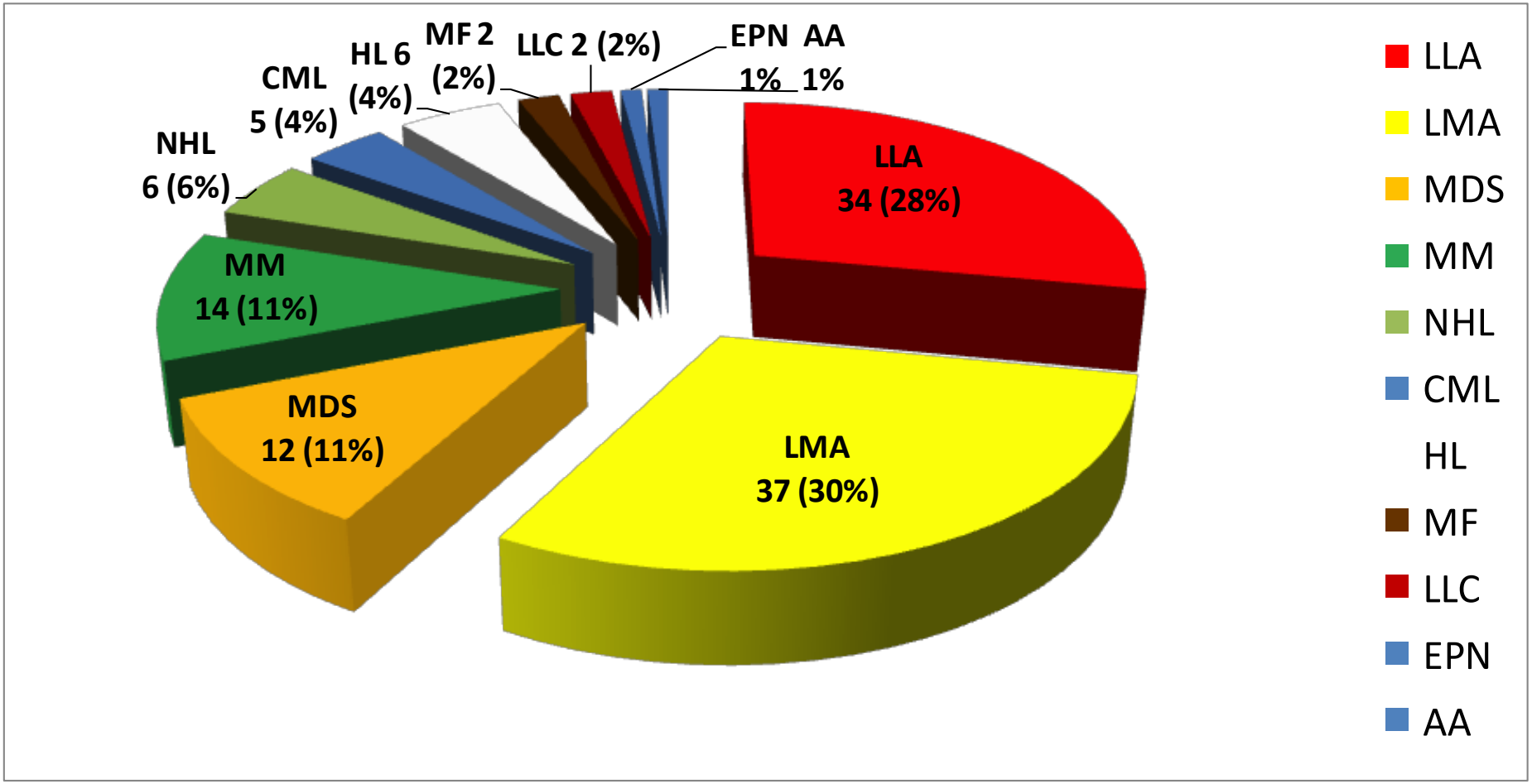
TRAPIANTO ALLOGENICO DA DONATORE FAMILIARE (n.301)



Ematologia SGR 05-2017

49 APLOIDENTICI

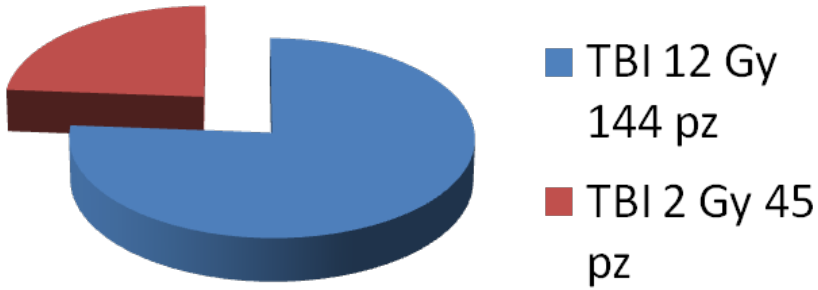
TRAPIANTO DA DONATORE VOLONTARIO (MUD) (n.120)



Ematologia SGR 05-2017

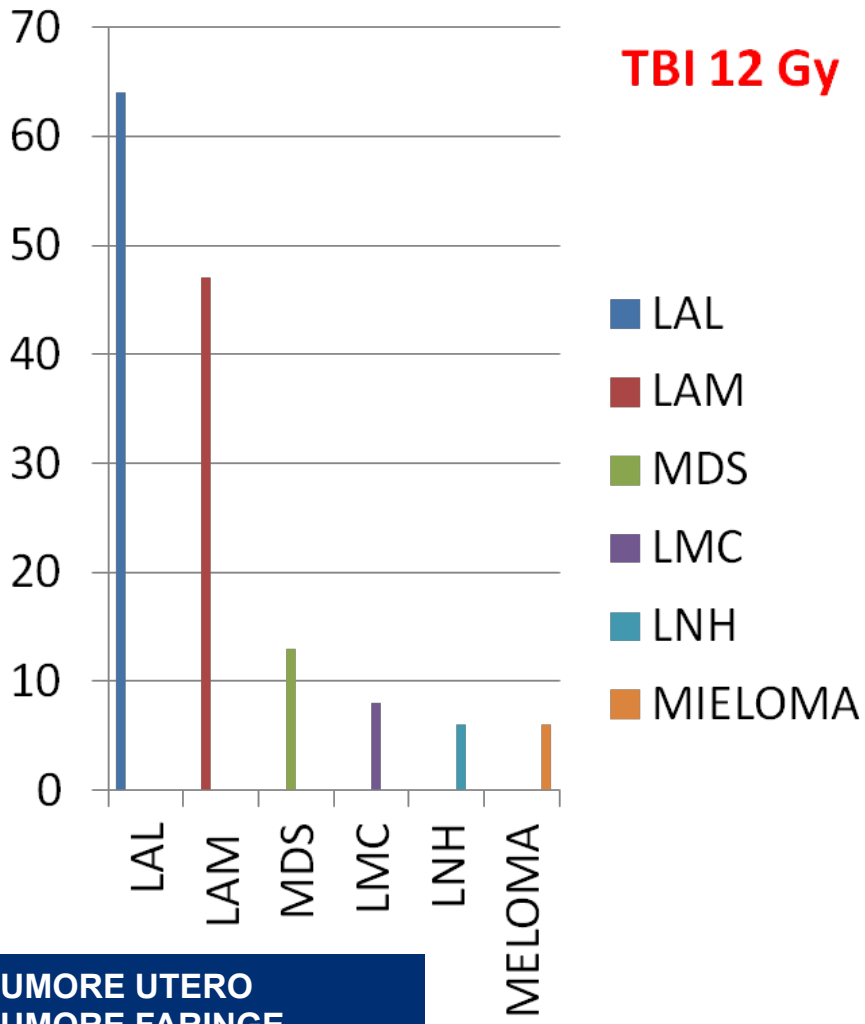
TBI Casistica San Giovanni Rotondo

TBI 189 pazienti

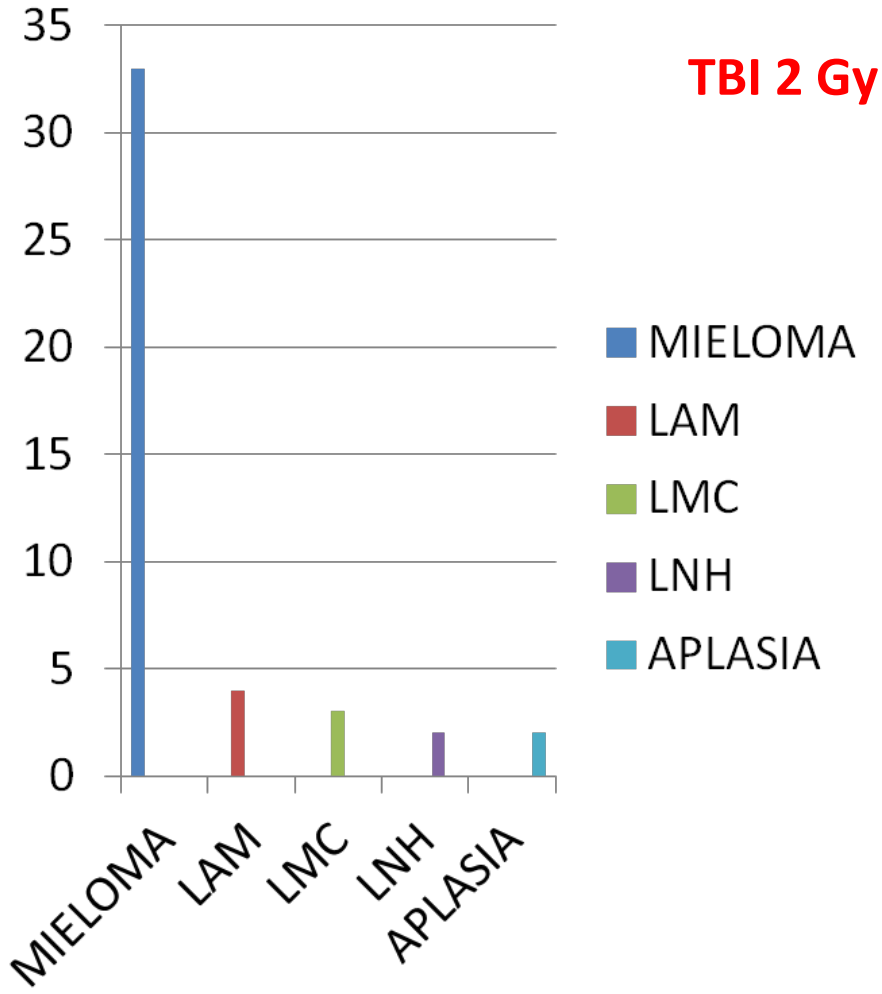


TBI vs CT

TBI Casistica San Giovanni Rotondo



1 TUMORE UTERO
1 TUMORE FARINGE
1 EPATOCARCINOMA
2%



1 TUMORE DELLA LINGUA
2%

Tabella 2. Effetti collaterali subacuti e tardivi più frequenti dopo impiego di TBI mieloablativa nel regime condizionante il trapianto: incidenza ed esami strumentali

Effetto	Incidenza	Esami strumentali
Insufficienza renale (sindrome emolitica/uremica, necrosi tubulare acuta, nefropatia acuta)	5-15%	test funzionalità renale
Polmonite interstiziale	5-15%	test diagnostica toracica
Cataratta	4-22%	esame oftalmologico
Ritardo della crescita	40-90%	ormone della crescita (GH)
Ritardo puberale	40-60%	testosterone-estradiolo
Amenorrea definitiva	90%	FSH-LH-funzionalità gonadica
Sterilità maschile	95%	testosterone/spermiogramma
Malattia veno-occlusiva epatica	<5%	Funzionalità epatica
Deficit cognitivi	<20%	test neuropsicologici
Tossicità neurologica	<5%	RM-TAC
Ipotiroidismo		
compensato	25-43%	TSH-T3-T4
manifesto	3-13%	

Acute toxicities associated with TBI

- Nausea and vomiting
  - Preventable with modern anti-emetic agents
- Parotitis
  - Occur after the first 1-2 fractions, subsided within 1 – 2 days
  - Unique to TBI
- Dry mouth and mucositis
  - 5 – 10 days after TBI

Morbidity associated with current regimens for TBI

- interstitial pneumonitis
  - In ~50% if single, large fraction of 8-10 Gy, with 50% fatal
  - 25% in fractioned and low-dose-rate TBI
  - CMV infection may take a role

Second malignant neoplasms

Two large, recent, analyses demonstrated the risk of solid tumor after BMT to range from 3 to 7% at 15 years following transplant

A recent multi-institutional analysis of 28 874 allogeneic transplant recipients allogeneic transplant recipients demonstrated a 3.3% incidence of development of a solid tumor 20 years

This risk was increased for the 67% of patients who received irradiation compared with those who did not

This excess risk was observed only in patients who received radiation ≦ 30 years old Blood 2009; 113: 1175–1183.

Curtis et al. 58 observed the risk of solid tumor to be 2.2% 10 years after BMT, and 6.7% 15 years

N Engl J Med. 1997; 336 (13): 8

Second malignant neoplasms

- Radiotherapy was observed to increase the risk of second cancers, this risk is significantly higher in receiving >10 Gy than <10Gy **RR: 0.9 < 10 Gy, 1.9>12 Gy, 4.1 > 13 Gy**
- Patients are also at risk for further hematological malignancies, including MDS and AML

J Clin Oncol 2000; 18: 348–357.

Bone Marrow Transplantation (2011) 46, 475–484

www.nature.com/bmt

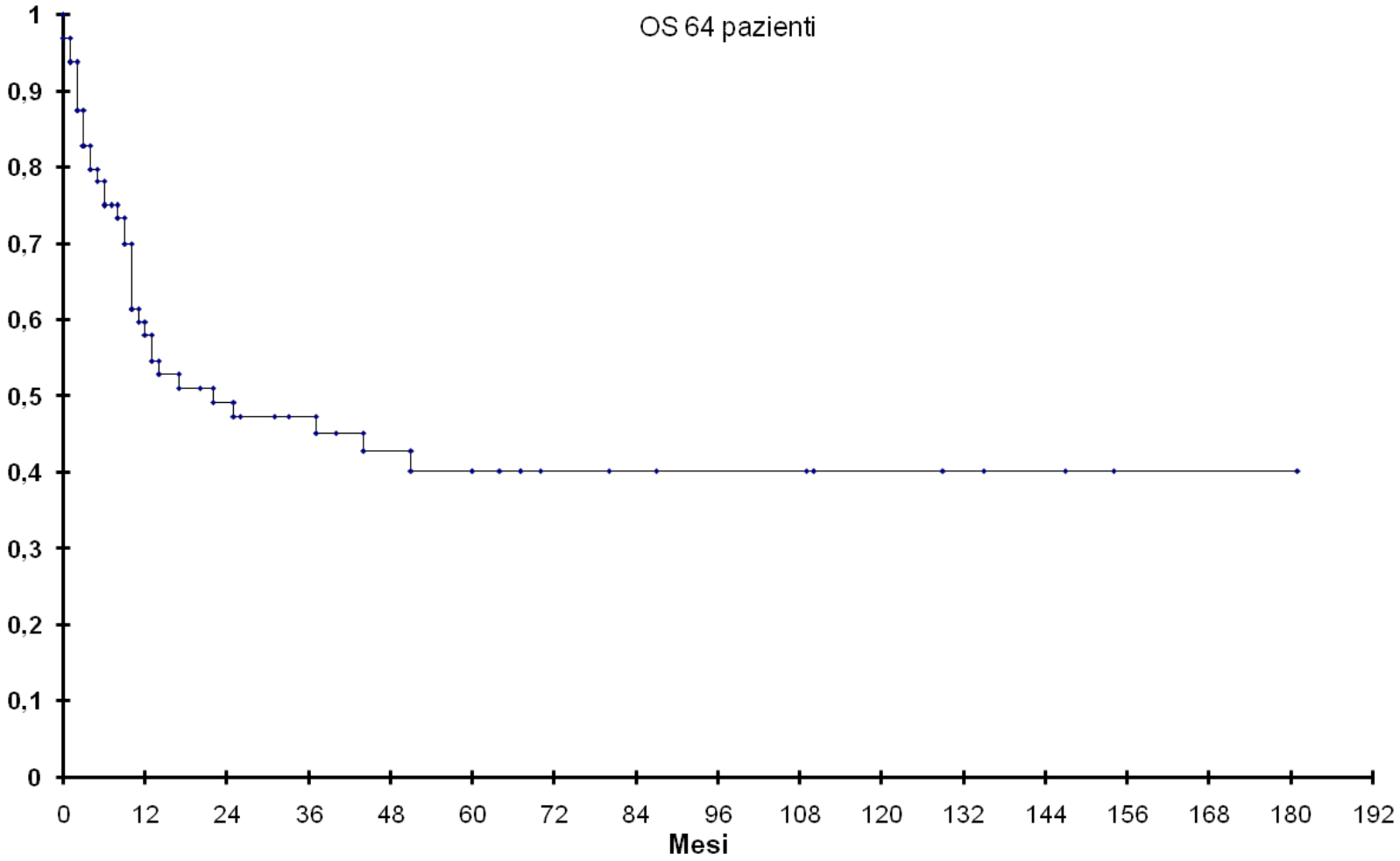
REVIEW

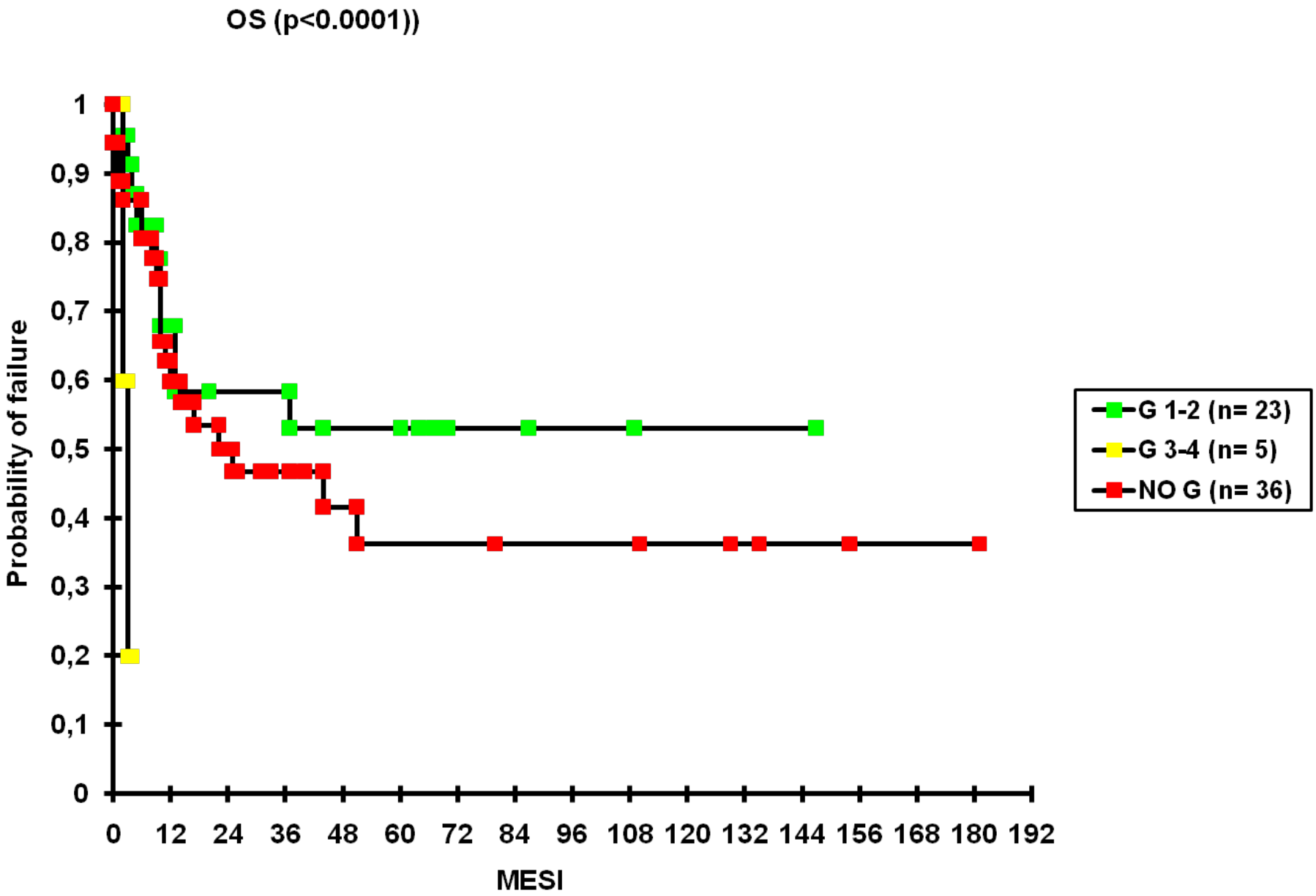
TBI during BM and SCT: review of the past, discussion of the present and consideration of future directions

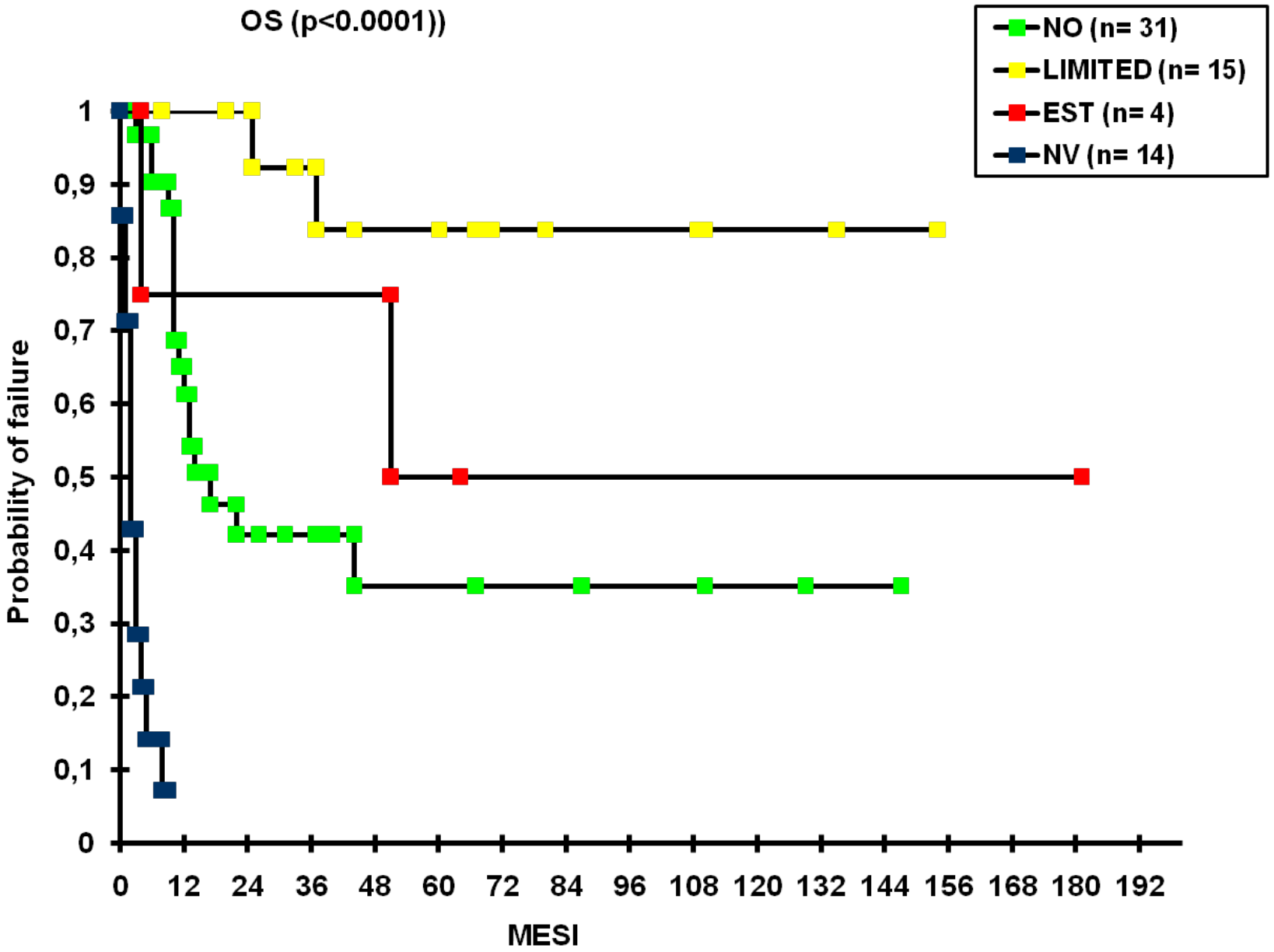
CE Hill-Kayser, JP Plastaras, Z Tochner and E Glatstein

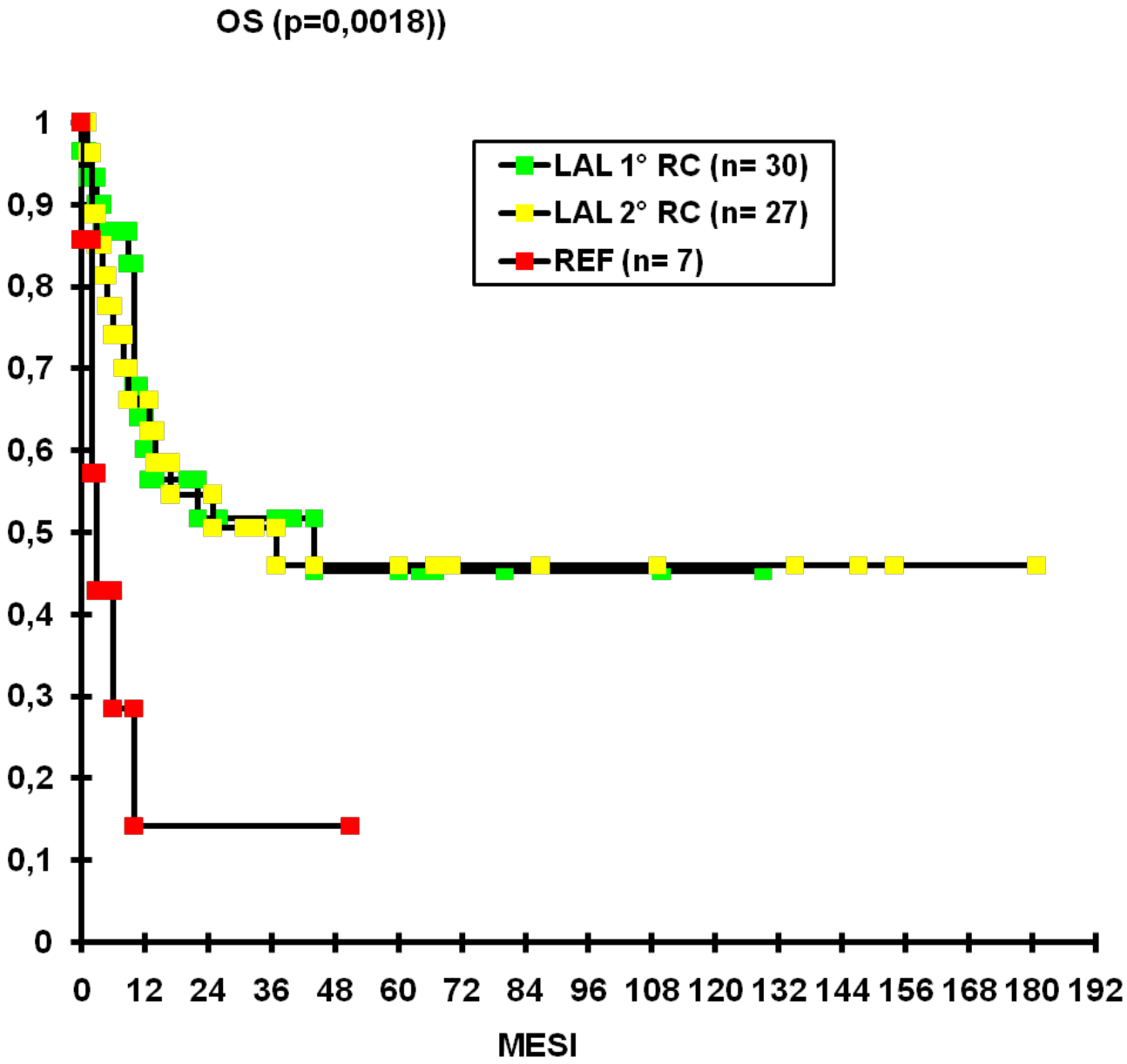
Department of Radiation Oncology, University of Pennsylvania School of Medicine, Philadelphia, PA, USA

nized. Toxicity associated with myeloablative TBI remains significant, and this treatment is generally reserved for younger patients with excellent performance status. Reduced intensity conditioning regimens may be useful to provide immunosuppression for patients who are not candidates for myeloablative treatment. Efforts to reduce toxicity through protection of normal tissue using methods of normal tissue blocking and use of TLI, rather than TBI, continue. In the future, modalities such as helical tomotherapy, proton radiotherapy and radioimmunotherapy, may have roles in delivery of radiation to the BM and lymphoid structures with reduced normal tissue toxicity. With further investigation, these


OS 64 pazienti
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
0
12
24
36
48
60
72
84
96
108
120
132
144
156
168
180
192
Mesi


OS (p<0.0001))
Probability of failure
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
0 12 24 36 48 60 72 84 96 108 120 132 144 156 168 180 192
MESI
G 1-2 (n= 23)
G 3-4 (n= 5)
NO G (n= 36)


OS (p<0.0001))
NO (n= 31)
LIMITED (n= 15)
EST (n= 4)
NV (n= 14)
Probability of failure
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
0 12 24 36 48 60 72 84 96 108 120 132 144 156 168 180 192
MESI


OS (p=0,0018))
LAL 1° RC (n= 30)
LAL 2° RC (n= 27)
REF (n= 7)
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
0 12 24 36 48 60 72 84 96 108 120 132 144 156 168 180 192
MESI

CONCLUSIONI

- Studi Retrospettivi
- Difficile comparazione tra TBI e Bu iv
- TBI pazienti più giovani
- Farmacocinetica del Busulfano
- Necessario studi prospettici
- Rischio incidenza secondi tumori con TBI