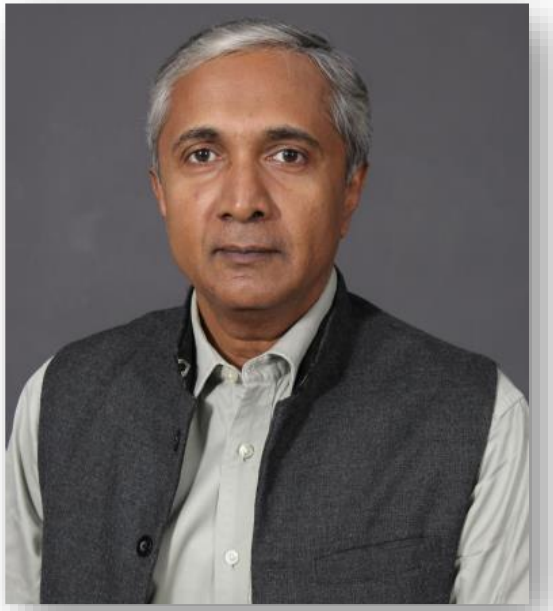
HCT in Thalassemia



Vikram Mathews
Professor of Haematology
Department of Haematology
Christian Medical College
Vellore
INDIA

Overview :

- Risk stratification and limitations
- Experience from India with high risk patients
- Strategies to improve outcomes in high risk patients
- Data with Treosulfan based conditioning
- Role of MUD HCT (matched and mismatched)
- Role of cord blood transplants
- Evolving data with haplo-identical HCT
- Summary

- **Allogeneic stem cell transplantation (SCT) remains the only curative option for patients with β thalassemia major.**

- **The correction of this disorder by an allogeneic stem cell transplant was first described by Thomas et al.**

  (Lancet 1982)

- **Subsequently, a conditioning regimen of busulfan and cyclophosphamide was established for stem cell transplantation in this condition. This myeloablative therapy forms the basis for the currently used conditioning regimens in this condition.**

  (Lancet 1985)

Risk Stratification

Risk Factors:

- Liver size (>2cm)
- Presence of liver fibrosis
- Inadequate iron chelation

Three risk groups:

- Class I: none of the above risk factors
- Class II: one or two of these risk factors
- Class III: all three adverse risk factors

Lucarelli et al. NEJM 1990
Lucarelli et al. Blood 1992

Risk Stratification

- Class I / II patients considered low risk with an excellent long term outcome

- Class III considered high risk
  - Higher incidence of rejection and TRM
  - Novel conditioning regimens being evaluated in this group of patients[1,2]

1. Sodani P, Lucarelli G et al. Blood 2004
2. Bernardo, Locatelli et al. BJH 2008

Risk Stratification

TABLE 1 Outcomes of allogeneic stem cell transplantation (data from Reference 25)

Class of risk	Conditioning regimen*	Survival (%)	Thalassemia-free survival (%)
1	Bu 14, Cy 200	93	90
2	Bu 14, Cy 200	87	84
3	Bu 14, Cy 120–160	79	58
Adults	Bu 14, Cy 120–160	66	62

*Abbreviations: Bu, Busulphan; Cy, Cyclophosphamide. Numbers indicate dosage in mg/kg.

Lucarelli G, Andreani M, Angelucci,E. 2002. The cure of thalassemia by bone marrow transplantation. Blood Rev. 16:81–85

Risk Stratification - Limitations

- Class III a heterogeneous group (in the setting of sub optimal medical therapy prior to transplant)

	Patient I	Patient II
Liver size	3 cms	7cms
Inadequate chelation	+	+
Fibrosis	+	++
Age	3 years	14 years
Spleen size	NP	5 cms

Risk Stratification - Limitations

Biology of Blood and Marrow Transplantation 13:889-894 (2007)

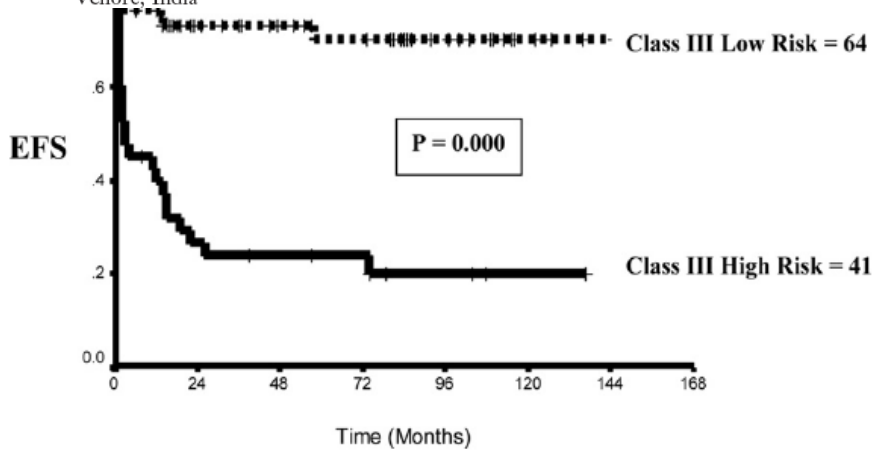
1083-8791/07/1308-0001$32.00/0
doi:10.1016/j.bbmt.2007.05.004

ASBMT
American Society for Blood and Marrow Transplantation

A New Stratification Strategy That Identifies a Subset of Class III Patients with an Adverse Prognosis among Children with β Thalassemia Major Undergoing a Matched Related Allogeneic Stem Cell Transplantation

Vikram Mathews,[1] Biju George,[1] Uday Deotare,[1] Kavitha M. Lakshmi,[1] Auro Viswabandya,[1] Dolly Daniel,[2] Mammen Chandy,[1] Alok Srivastava[1]

[1]Department of Haematology, and [2]Department of Clinical Pathology and Blood Bank, Christian Medical College, Vellore, India



!. Comparison of 5-year EFS of Class III transplants in the high-risk group (n = 41) and rest of transplants in Class III (n = 64).

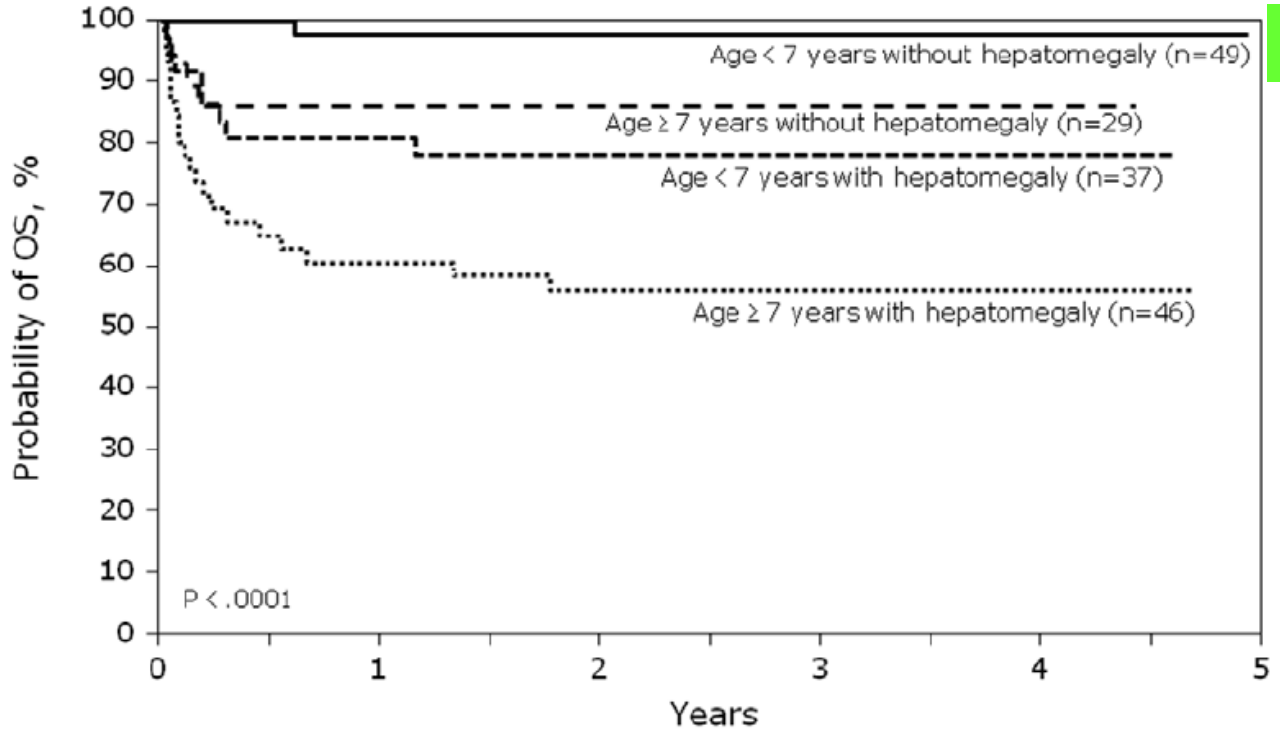
Age	≥ 7years
Liver size	≥5cms
Class III HR	40%

blood

Prepublished online Nov 30, 2010;
doi:10.1182/blood-2010-09-306829

HLA-matched sibling bone marrow transplantation for ²-thalassemia major

Mitchell Sabloff, Mammen Chandy, Zhiwei Wang, Brent R. Logan, Ardeshir Ghavamzadeh, Chi-Kong Li, Syed Mohammad Irfan, Christopher N. Bredeson, Morton J. Cowan, Robert Peter Gale, Gregory A. Hale, John Horan, Suradej Hongeng, Mary Eapen and Mark C. Walters



N = 179

Class III: 142 (49.3%)

>7+he: 132 (45.8%)

REGULAR ARTICLE

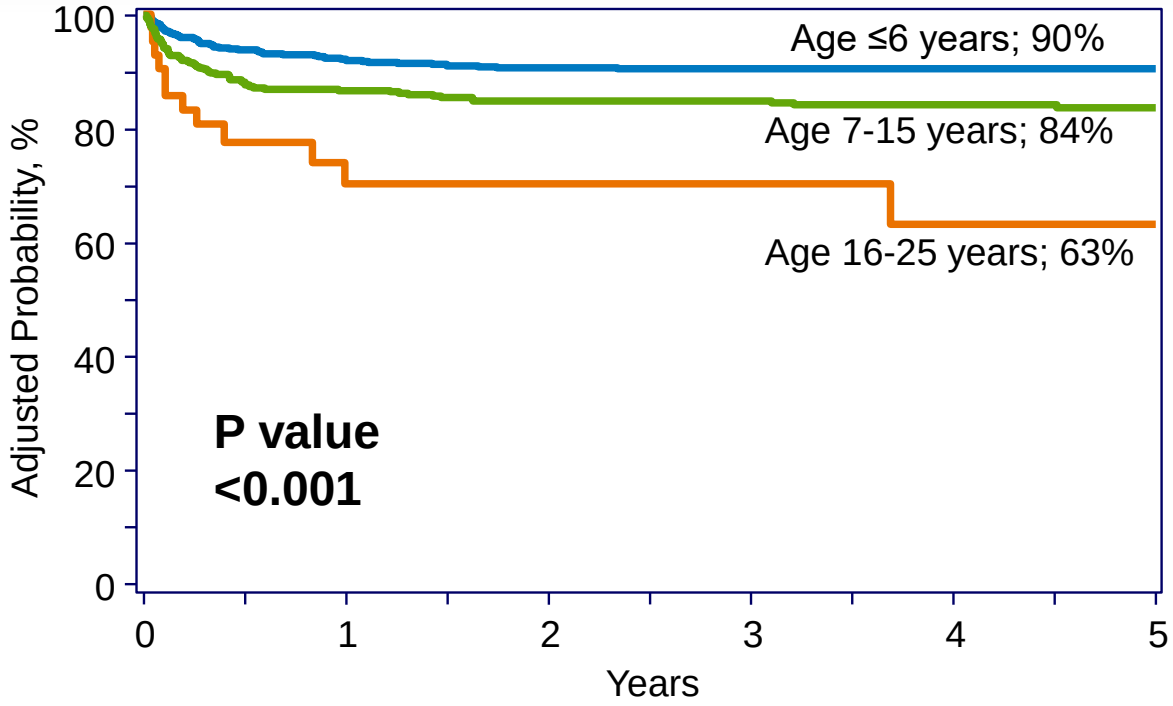
blood advances

Related and unrelated donor transplantation for β-thalassemia major: results of an international survey

Chunfu Li,[1,2,*] Vikram Mathews,[3,*] Soyoung Kim,[4] Biju George,[3] Kyle Hebert,[5] Hua Jiang,[6] Changgang Li,[7] Yiping Zhu,[8] Daniel A. Keesler,[5] Jaap Jan Boelens,[9] Christopher C. Dvorak,[10] Rajni Agarwal,[11] Jeffery J. Auletta,[12] Rakesh K. Goyal,[13] Rabi Hanna,[14] Kimberly Kasow,[15] Shalini Shenoy,[16] Angela R. Smith,[17] Mark C. Walters,[18] and Mary Eapen[5]

Overall Survival

Adjusted for Donor type, Conditioning Regimen, Transplant period



N = 1110

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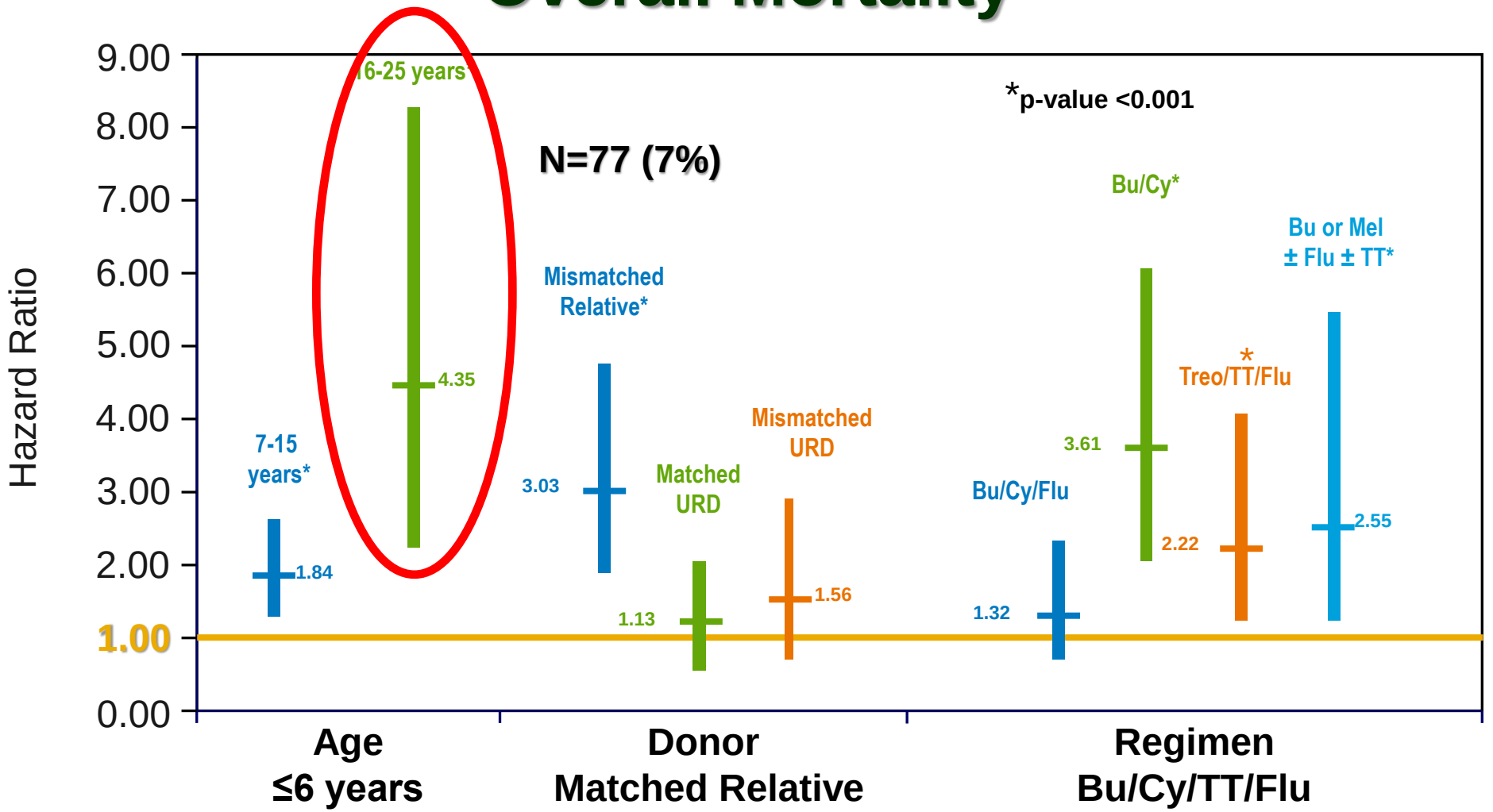
Overall Mortality



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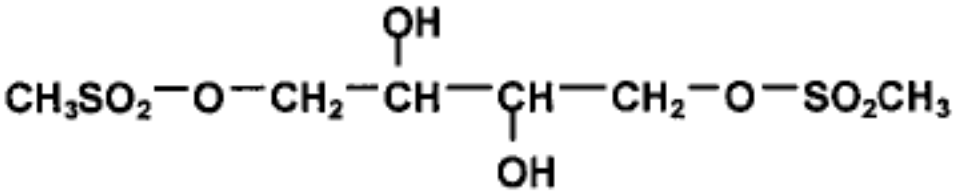
Improving clinical outcomes in Class III and Class IIIHR subsets

- Evaluation of different dose schedules
- Prediction of graft rejection and immune reconstitution
- Increasing the stem cell dose
- Targeted dose monitoring (Bu)
- Reduced intensity conditioning regimens
- Myeloablative reduced toxicity regimens ex: Treosulfan

Treosulfan



Treosulfan

- Unlike busulfan it is water soluble and easy to re-constitute and administer IV
- Pharmacokinetics is linear, good systemic exposure with low intra and inter-individual variability[1,2]
- Toxicity profile favorable. Phase I study even at doses 56 g/m^2/course there was no dose limiting liver, renal, cardiac or CNS toxicity[3]
- No or very low incidence of SOS [3,4,5]
- Multiple reports of use in conditioning regimens for hematolgical malignancies[4,5]

1. Hilger et al. CCP 1998
2. Glowka et al. BMT 2008
3. Scheulin et al. Clin Can Res 2000
4. Beelen et al. BMT 2005
5. Casper et al. JCO 2010

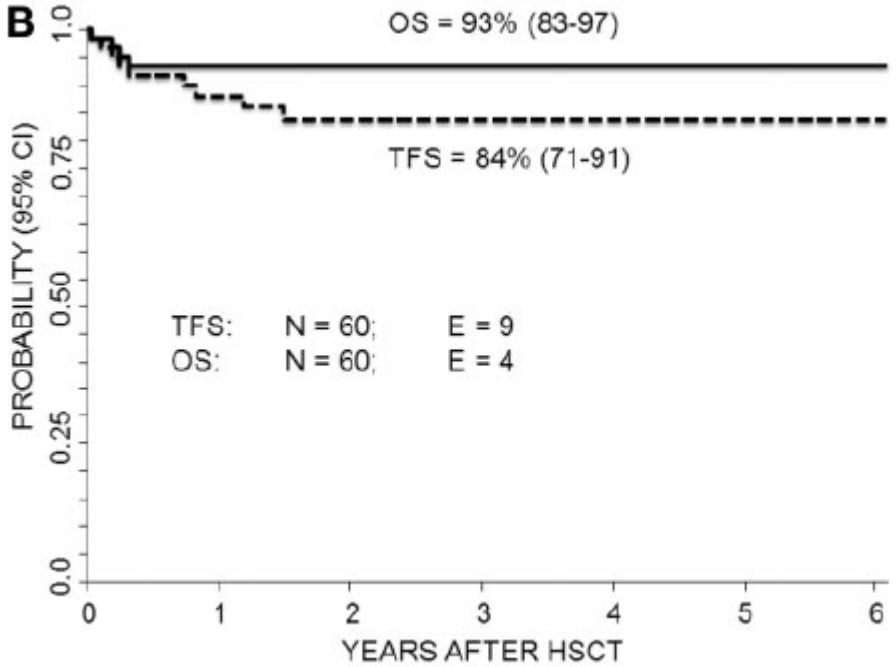
Brief report

Allogeneic hematopoietic stem cell transplantation in thalassemia major: results of a reduced-toxicity conditioning regimen based on the use of treosulfan

Maria Ester Bernardo,[1] Eugenia Piras,[2] Adriana Vacca,[2] Giovanna Giorgiani,[3] Marco Zecca,[3] Alice Bertaina,[1] Daria Pagliara,[1] Benedetta Contoli,[1] Rita Maria Pinto,[1] Giovanni Caocci,[2] Angela Mastronuzzi,[1] Giorgio La Nasa,[2] and Franco Locatelli[1,4]

[1]Department of Pediatric Hematology-Oncology, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Bambino Gesù Children's Hospital, Rome, Italy; [2]Hematology Unit, Department of Internal Medical Sciences, University of Cagliari, Cagliari, Italy; [3]Department of Pediatric Onco-Hematology, IRCCS, Policlinico San Matteo Foundation, Pavia, Italy; and [4]University of Pavia, Pavia, Italy

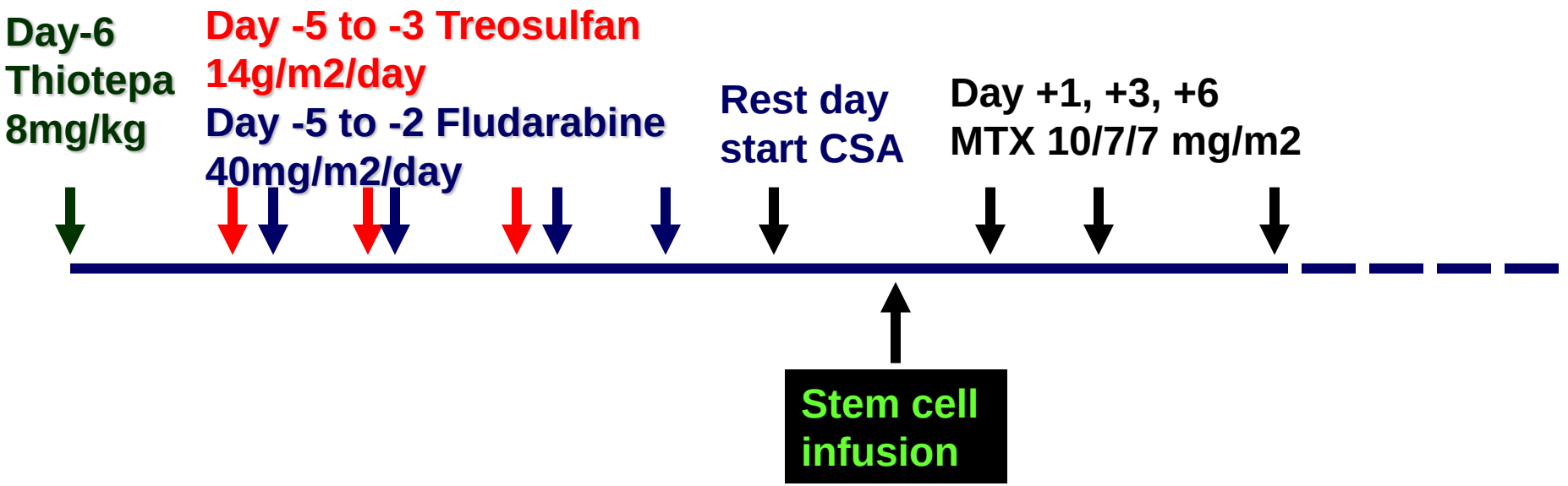
Sixty thalassemia pa
7 years; range, 1-37
neic hematopoietic st
tion (HSCT) after a pre
thiotepa, treosulfan
Before HSCT, 27 child
risk class 1 of the P
17 to class 2, and 4 to
were adults. Twenty



range, 4-72), the 5-year
urvival and thalassemia-
93% and 84%, respec-
e class of risk nor the
luenced outcome. This
preparation proved to
ctive for thalassemia pa-
ogeneic HSCT. (*Blood*.
476)

Treosulfan data CMC Vellore

Conditioning Regimen:



OPEN ACCESS Freely available online

PLOS | ONE

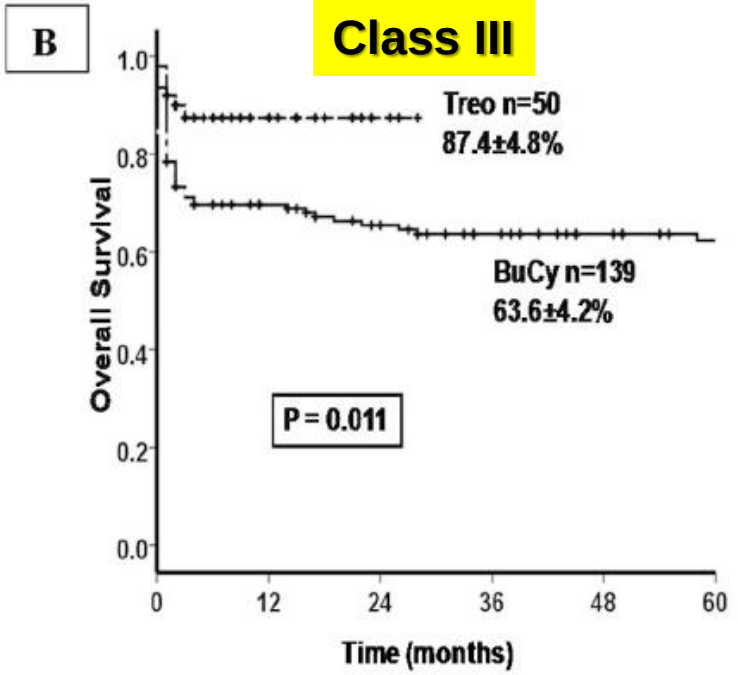
Improved Clinical Outcomes of High Risk β Thalassemia Major Patients Undergoing a HLA Matched Related Allogeneic Stem Cell Transplant with a Treosulfan Based Conditioning Regimen and Peripheral Blood Stem Cell Grafts

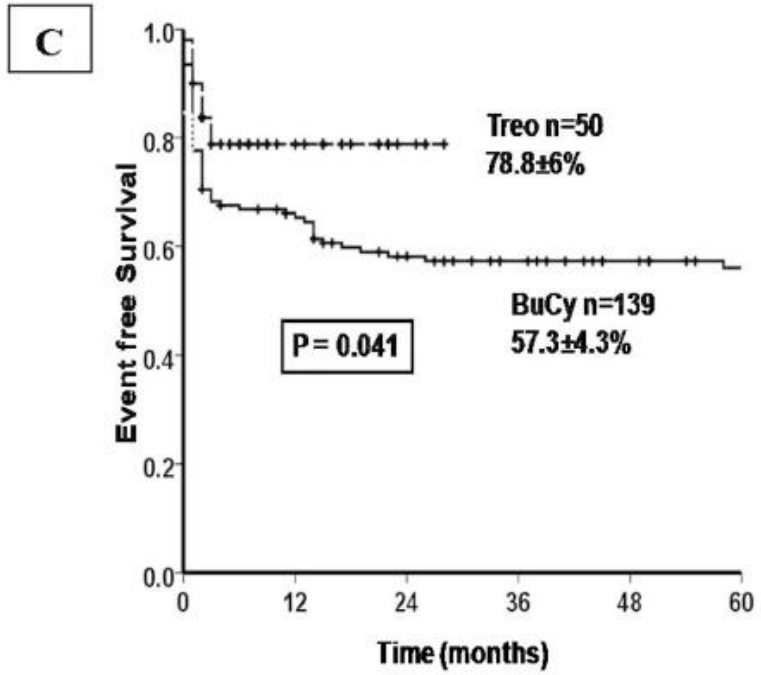
Vikram Mathews*, Biju George, Auro Viswabandya, Aby Abraham, Rayaz Ahmed, Abhijeet Ganapule, Eunice Sindhuvi, Kavitha M. Lakshmi, Alok Srivastava

Department of Haematology, Christian Medical College, Vellore, India

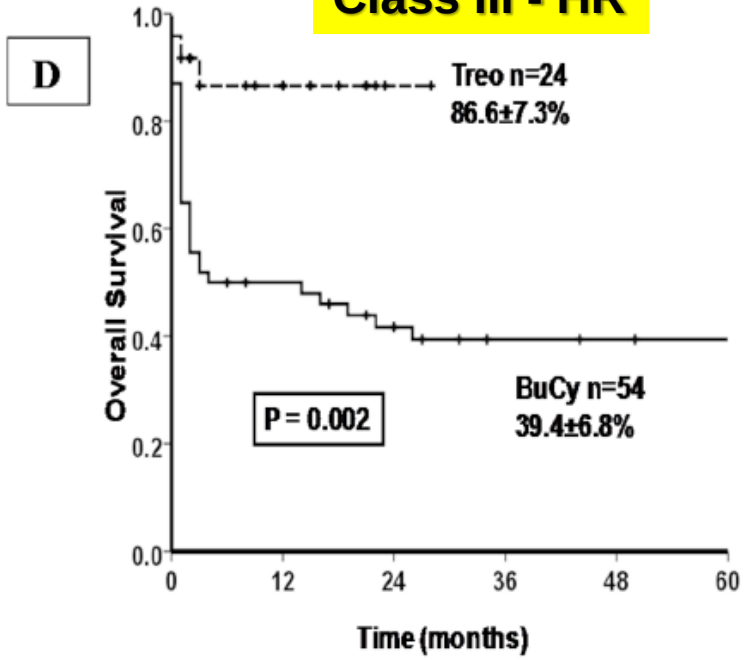
Plos One 2013

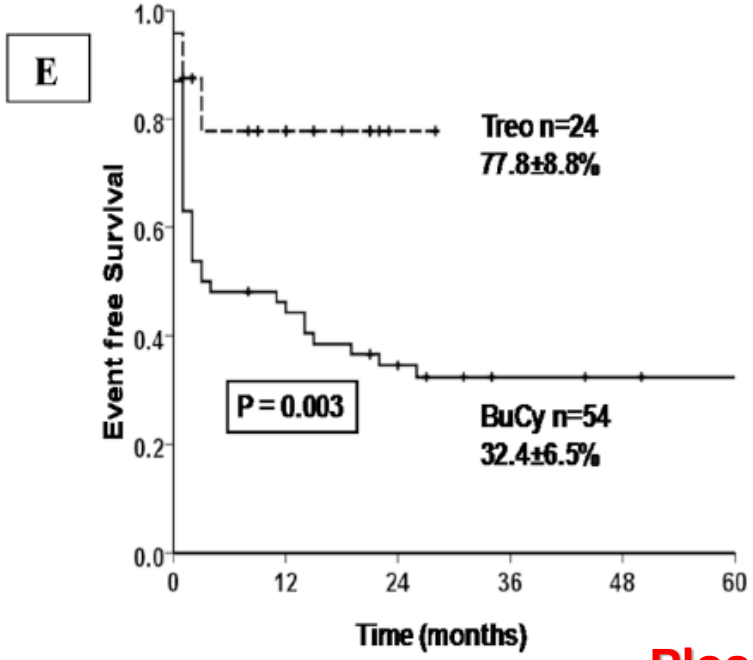
Class III





Class III - HR





Plos One 2013

Biol Blood Marrow Transplant 24 (2018) 103–108

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Second Hematopoietic Stem Cell Transplant for Thalassemia Major: Improved Clinical Outcomes with a Treosulfan-Based Conditioning Regimen

Anu Korula, Nisham PN, Anup Devasia, Kavitha M. Lakshmi, Aby Abraham, Eunice Sindhuvi, Biju George, Alok Srivastava, Vikram Mathews *

Department of Haematology, Christian Medical College and Hospital, Vellore, India

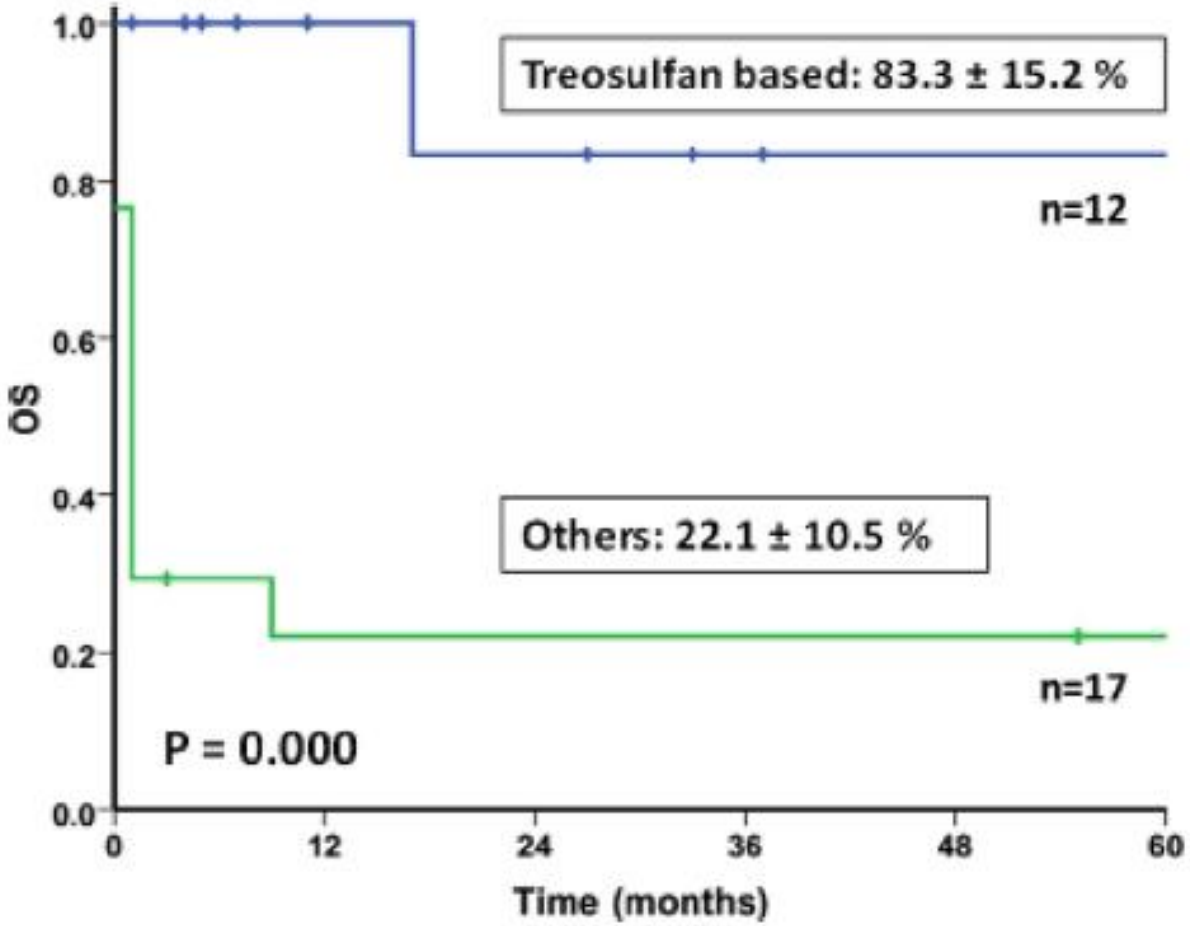
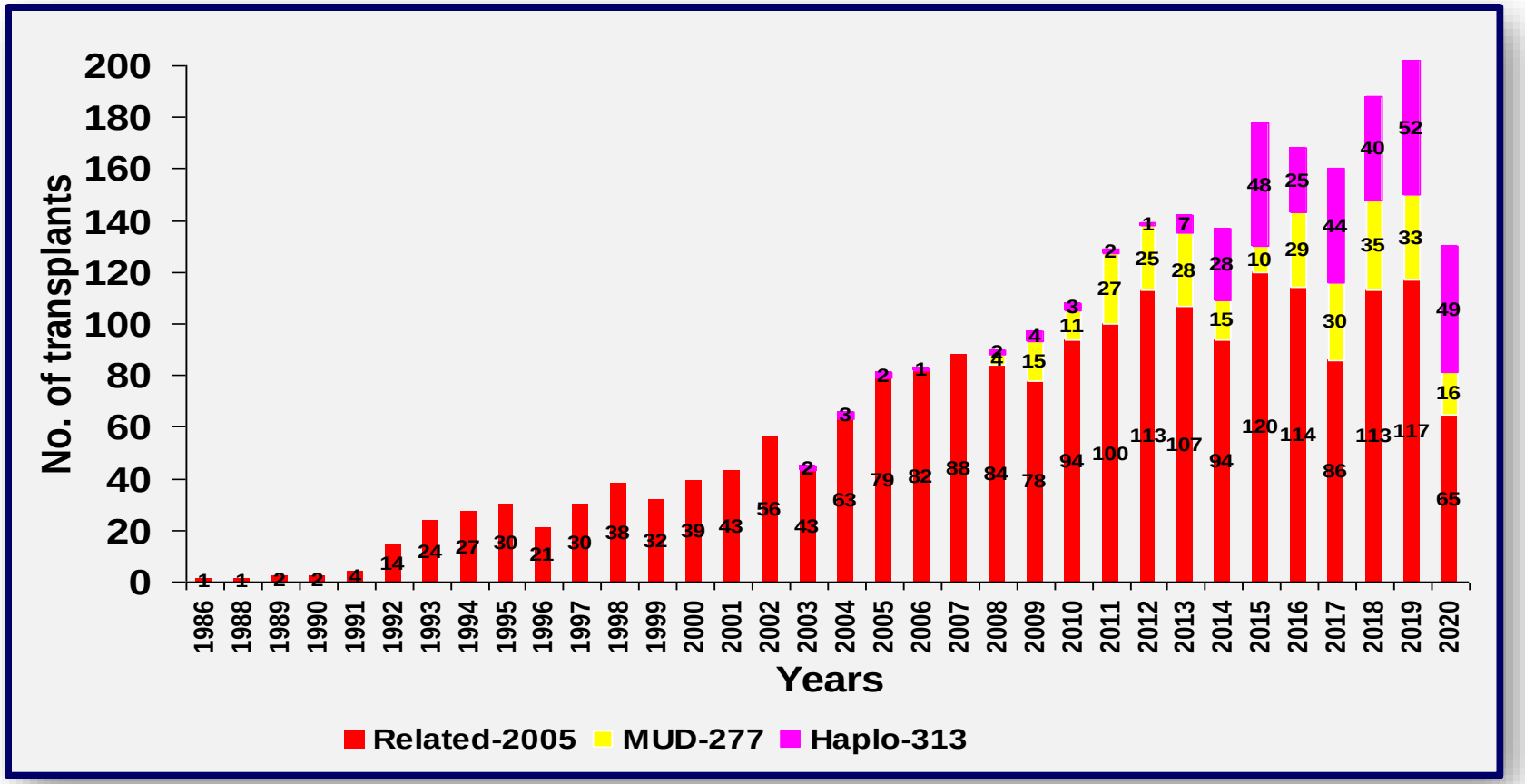
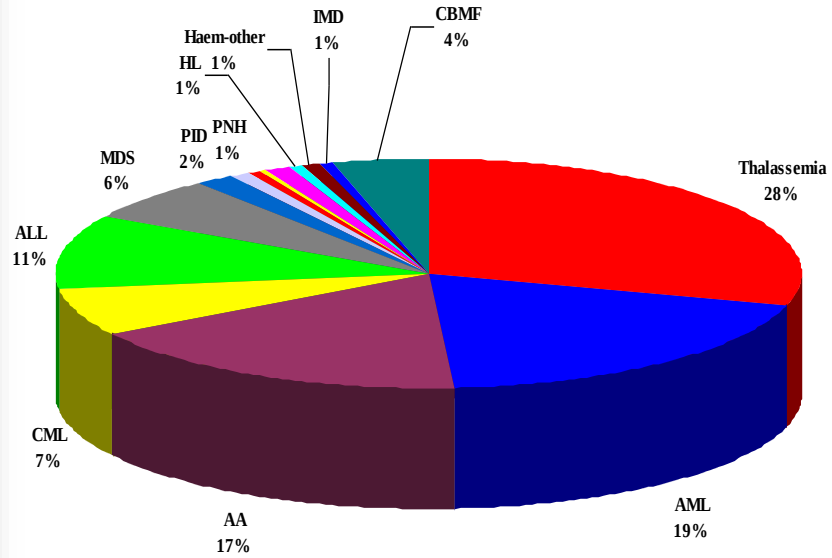


Figure 2. Comparison of OS between patients conditioned with treosulfan-based MAC regimen versus others.

Stem Cell Transplant Program
CMC Vellore



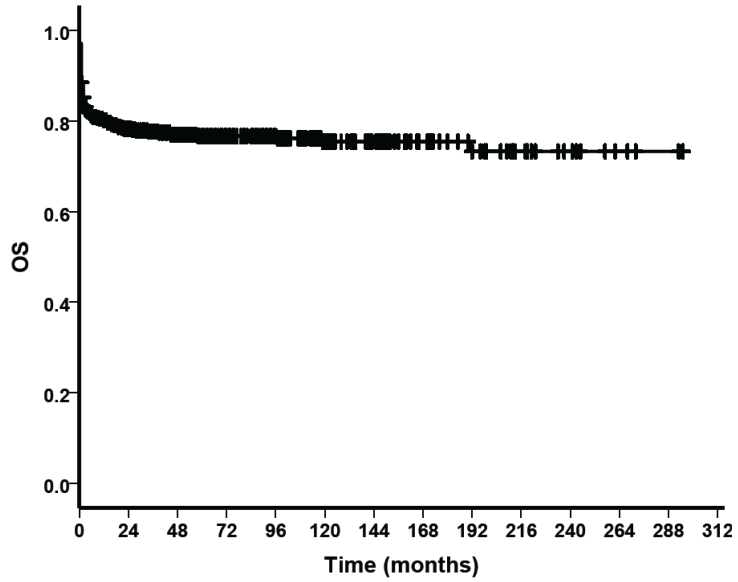


India ~ 100 transplant centers
~ 300+ Thal transplants / year

CMC long term follow up data --

Since 1991 – n= 639

		Frequency	Percent
Valid	1	20	3.1
	2	226	35.4
	3	393	61.5
	Total	639	100.0



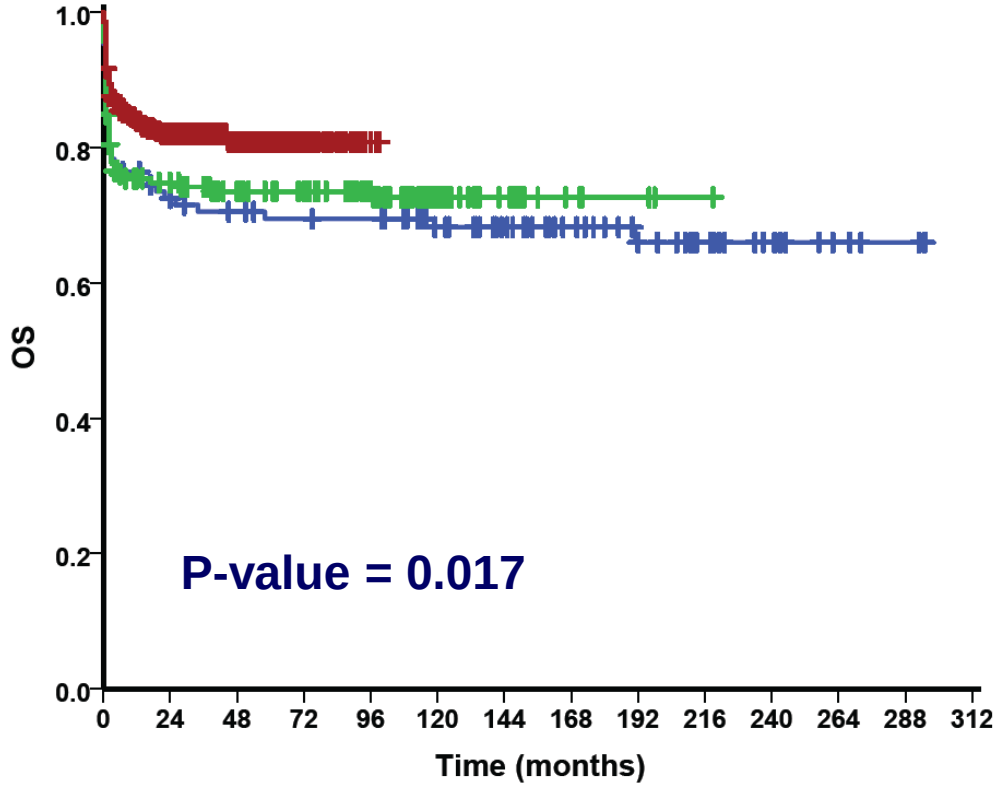
		Frequency	Percent
Valid	<2000	106	16.6
	>=2000-2010	185	29.0
	>=2010	348	54.5
	Total	639	100.0

Mean age

8.0±4.4

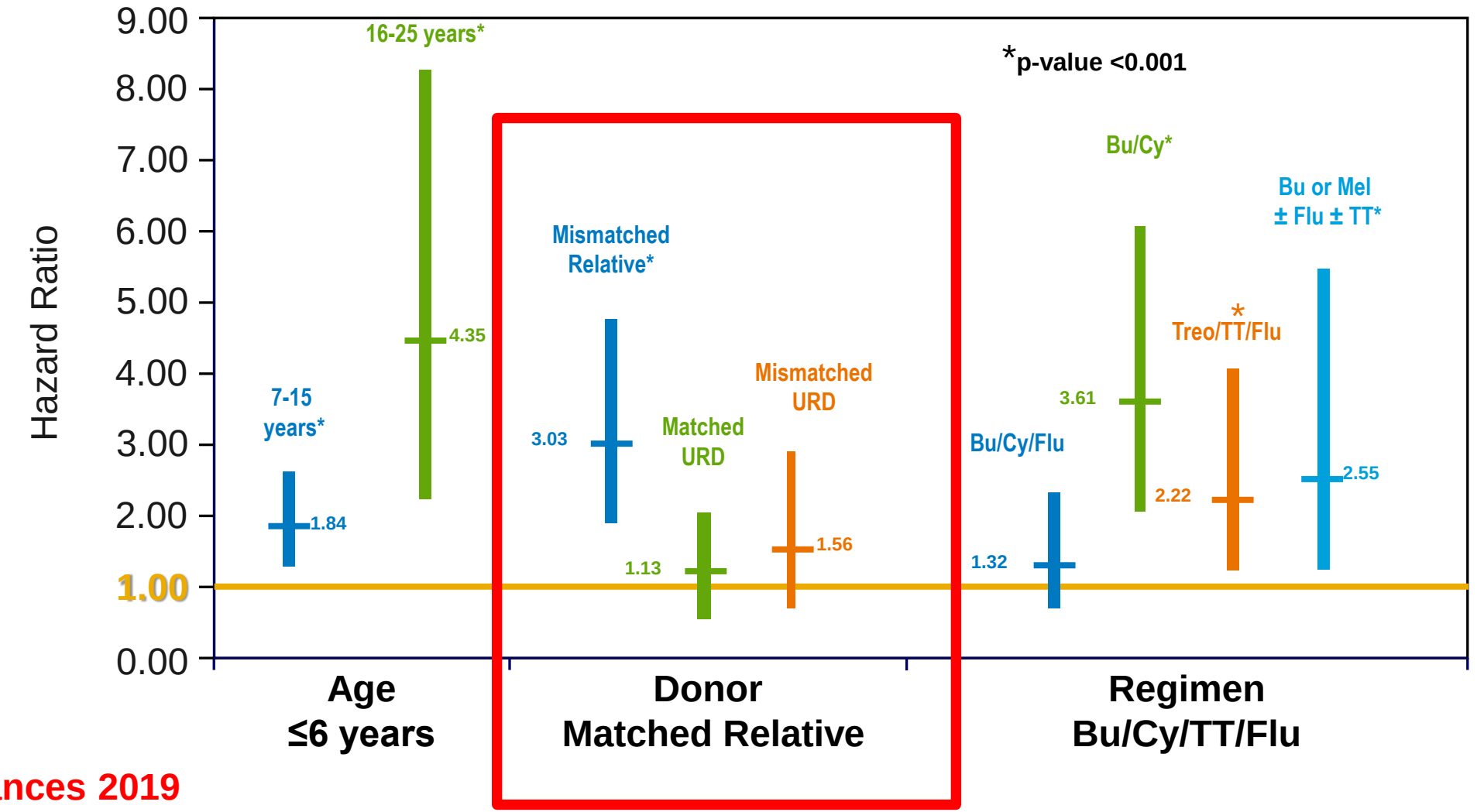
8.4±4.3

8.6±4.9



Matched unrelated donor transplants

Overall Mortality



Blood Advances 2019

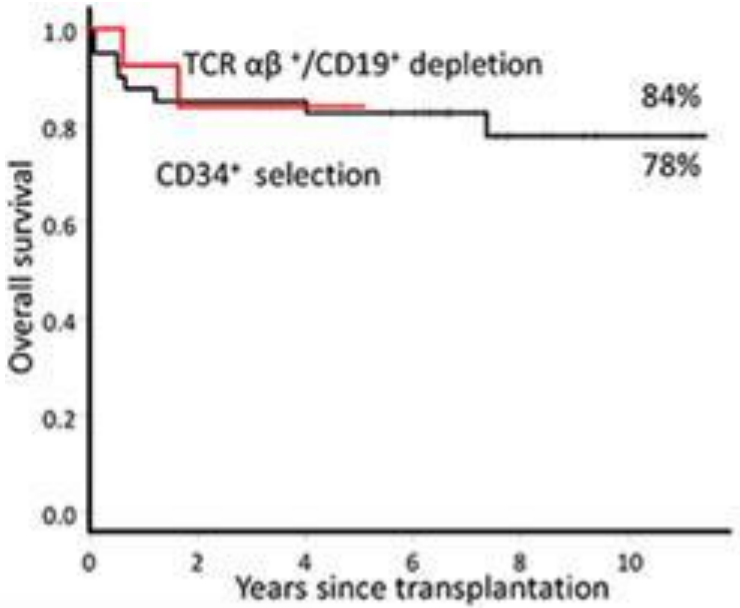
Umbilical Cord Blood Transplants

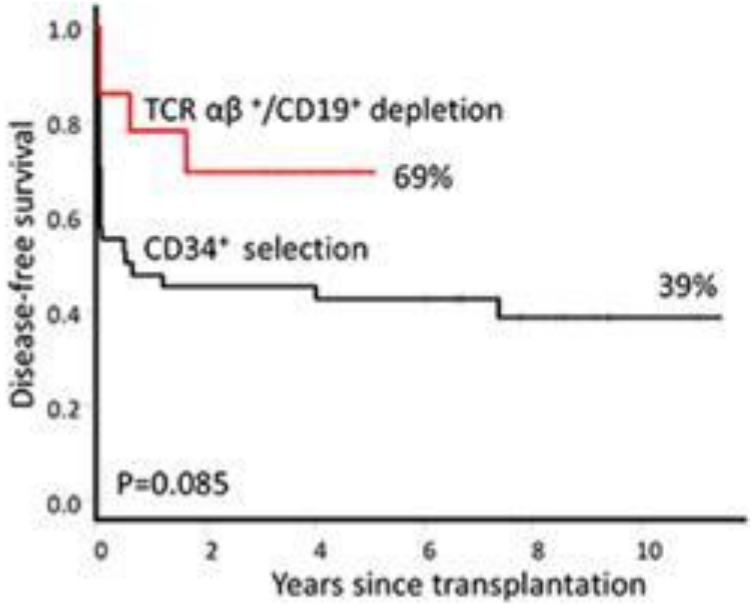
- Related
- Unrelated Matched / Mismatched

Haplo-identical HCT in Thalassemia major

- T cell depleted
- T cell replete - PTcy

T cell depleted data:





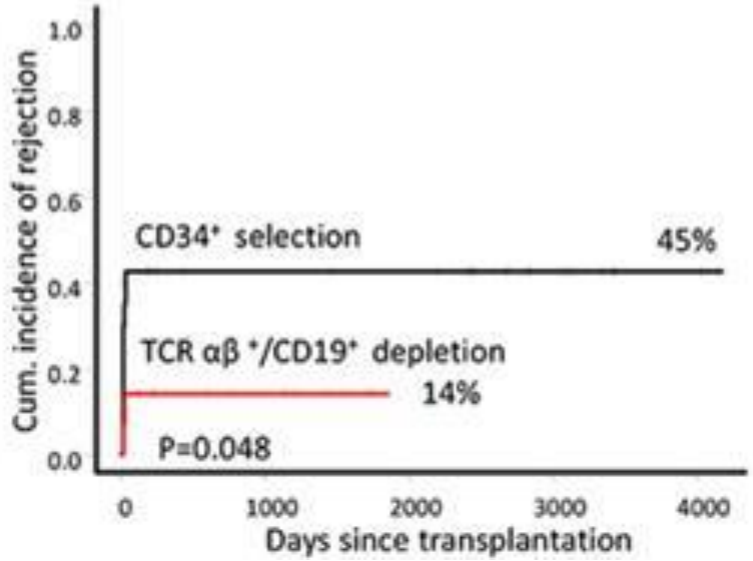
REGULAR ARTICLE

blood advances

Haploidentical HSCT for hemoglobinopathies: improved outcomes with TCRαβ$^+$/CD19$^+$-depleted grafts

Javid Gaziev,[1] Antonella Isgrò,[1] Pietro Sodani,[2] Katia Paciaroni,[1] Gioia De Angelis,[1] Marco Marziali,[1] Michela Ribersani,[1] Cecilia Alfieri,[1] Alessandro Lanti,[3] Tiziana Galluccio,[1] Gaspare Adorno,[3] and Marco Andreani[1]

[1]International Center for Transplantation in Thalassemia and Sickle Cell Anemia, Mediterranean Institute of Hematology, Policlinico Tor Vergata, Rome, Italy; [2]Unità Operativa Complessa Internal Medicine and Hematology, Azienda Ospedaliera Ospedali Riuniti Marche Nord, Ospedale Santo Croce, Fano, Italy; and [3]Servizio di Immunoematologia e Medicina Trasfusionale, Policlinico Tor Vergata Foundation, Rome, Italy



Blood Advances 2017

T cell replete

Concept: Pre-transplant immunosuppression

Bone Marrow Transplantation (2016), 1–6

www.nature.com/bmt

ORIGINAL ARTICLE

Hematopoietic stem cell transplantation for homozygous β-thalassemia and β-thalassemia/hemoglobin E patients from haploidentical donors

U Anurathapan[1], S Hongeng[1], S Pakakasama[1], N Sirachainan[1], D Songdej[1], A Chuansumrit[1], P Charoenkwan[2], A Jetsrisuparb[3], K Sanpakit[4], P Rujkijyanont[5], A Meekaewkunchorn[6], Y Lektrakul[7], P Iamsirirak[8], P Surapolchai[9], W Satayasai[9], S Sirireung[1], R Sruamsiri[10], PA Wahidiyat[11], A Ungkanont[12], S Issaragrisil[13] and BS Andersson[14]

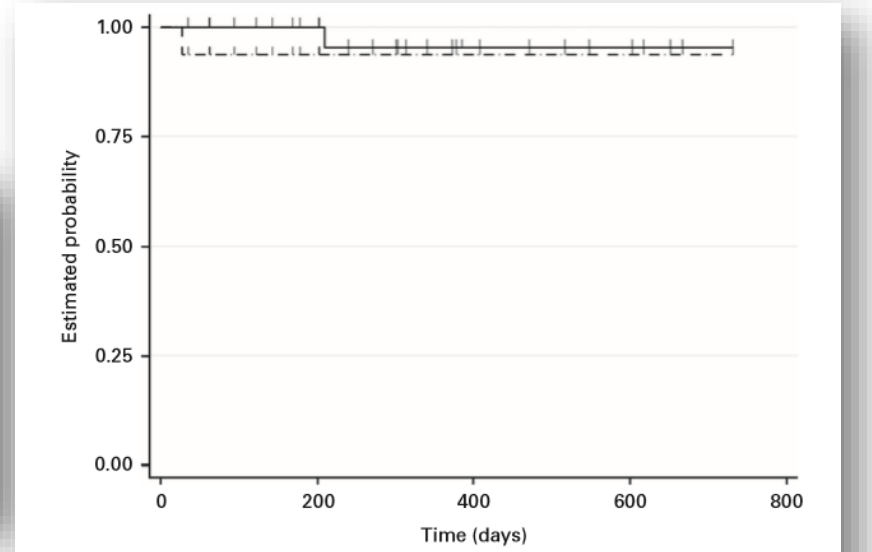
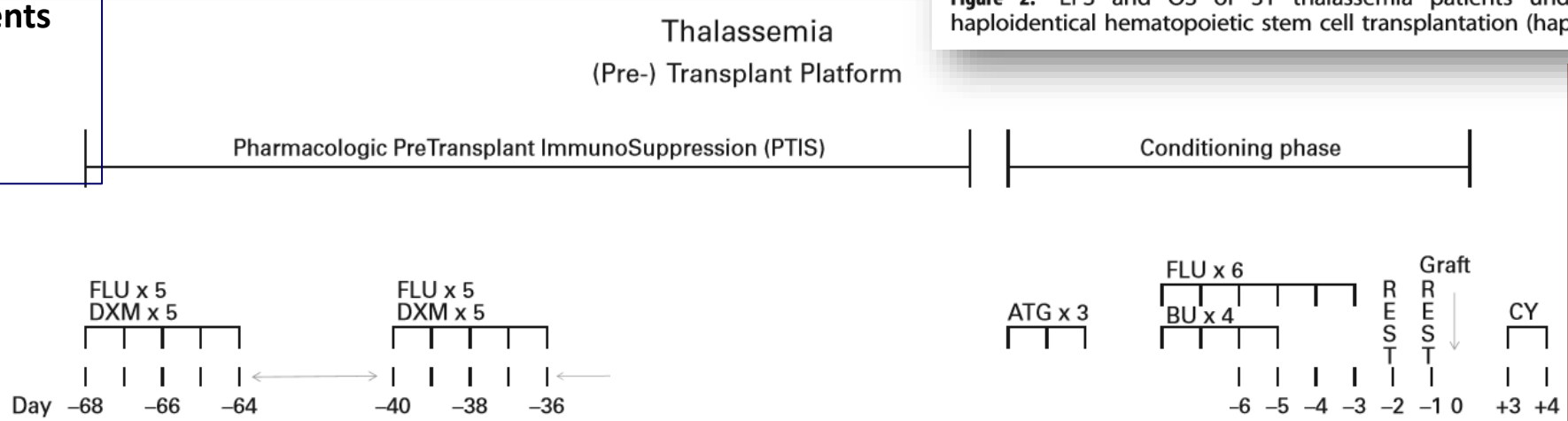


Figure 2. EFS and OS of 31 thalassemia patients undergoing haploidentical hematopoietic stem cell transplantation (haplo-SCT).

Total 31 patients
15 class 3 HR
7 class 1
9 class 2



on day SCT +5 **tacrolimus or sirolimus** was started together with a short course of **mycophenolate mofetil**.

Figure 1. Depiction of the transplant program with first pharmacological PTIS, followed by RTC with ATG, Flu and IV Bu. For the haplo-identical donors, we used post-Cy-based GvHD prophylaxis and delayed-calcineurin inhibitor–/ sirolimus therapy, and short-course mycophenolate mofetil, the latter two starting on day SCT +5. Please see Patients and Methods section for details.

Conclusion:

- Allogeneic stem cell transplant remains the only widely available curative option for patients with Thalassemia major
- Prefer to do it at a younger age with best results reported between 2 and 5 years of age
- Conventional risk stratification for Thal Major has limitations in our population
- The best donor is a matched related sibling
- Mis-matched unrelated donor / cord and haplo-identical transplants should be done with careful assessment of relative risks and benefits preferably in the setting of a clinical trial
- Bone marrow is the preferred options as stem cell source
- Novel conditioning regimens can potentially improve the outcome (RTC) –

  Treo based
- Careful pre-transplant evaluation of the recipient is important
- Family and patient need to be carefully counselled about risks and benefits of transplant

Thank you for your attention