Treatment Options in Genetic Blood Disorders

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THALESSEMIA-
TO BMT OR NOT TO BMT

- β-Thalassemia major is among the most common hereditary disorders worldwide
- The supportive treatment of β-thalassemia major requires chronic,
- life-long RBC transfusions, which cause progressive iron overload and the potential for impaired endocrine, cardiac and hepatic function.
- The phenotype of thalassemia major is reliably predicted by its genotype.

Burden and Hope in India!

- With 20 million carriers for thalassemia and 10 000 children being born with thalassemia major each year, if one-third of these patients have an HLA-matched sibling donor, there is a potential to cure 3000 children with BMT

SURVIVAL

- Survival with chelation & Blood transfusion
- Western Data – live upto 40-50 yr but still 30-35% die by the age of 30 yr
- In India – Majority die by 25-30 yr
- Cause of Mortality
- Cardiac failure due to Iron overload
- HIV/Hepatitis B/Hepatitis C

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Survival, Mortality, and Complications in Patients With β-Thalassemia Major in Northern Taiwan

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Background. Advances in treatment have improved the prognosis in β-thalassemia major. We present the survival and complications pattern of those patients in northern Taiwan born after 1970. ***Procedure.*** One-hundred and sixty patients with β-thalassemia major born after 1970 were collected. The Kaplan–Meier method and log-rank test were used to estimate and compare survival. Cox regression models were used to examine the associations of bone marrow transplantation (BMT), time of BMT procedure, and time of complications with survival. ***Results.*** Better survival was observed for patients born after 1980 ($P = 0.0121$). Heart disease, BMT-related deaths, and infections were the main causes of death. Among the living patients over age 15, hypogonadotropic hypogonadism, HCV infection, diabetes, heart failure, and arrhythmia were the common complications. No patients under age 15 had complications. ***Conclusions.*** Survival for patients with β-thalassemia major has improved significantly in Taiwan. More time is required to demonstrate whether these modalities added to the treatment of these patients will impact favorably on their outcome. Our success with BMT is improving and we are now in a position to offer this curative alternative. Pediatr Blood Cancer 2007;48:550–554.

Key words: β-Thalassemia major; causes of death; iron-chelation therapy; survival

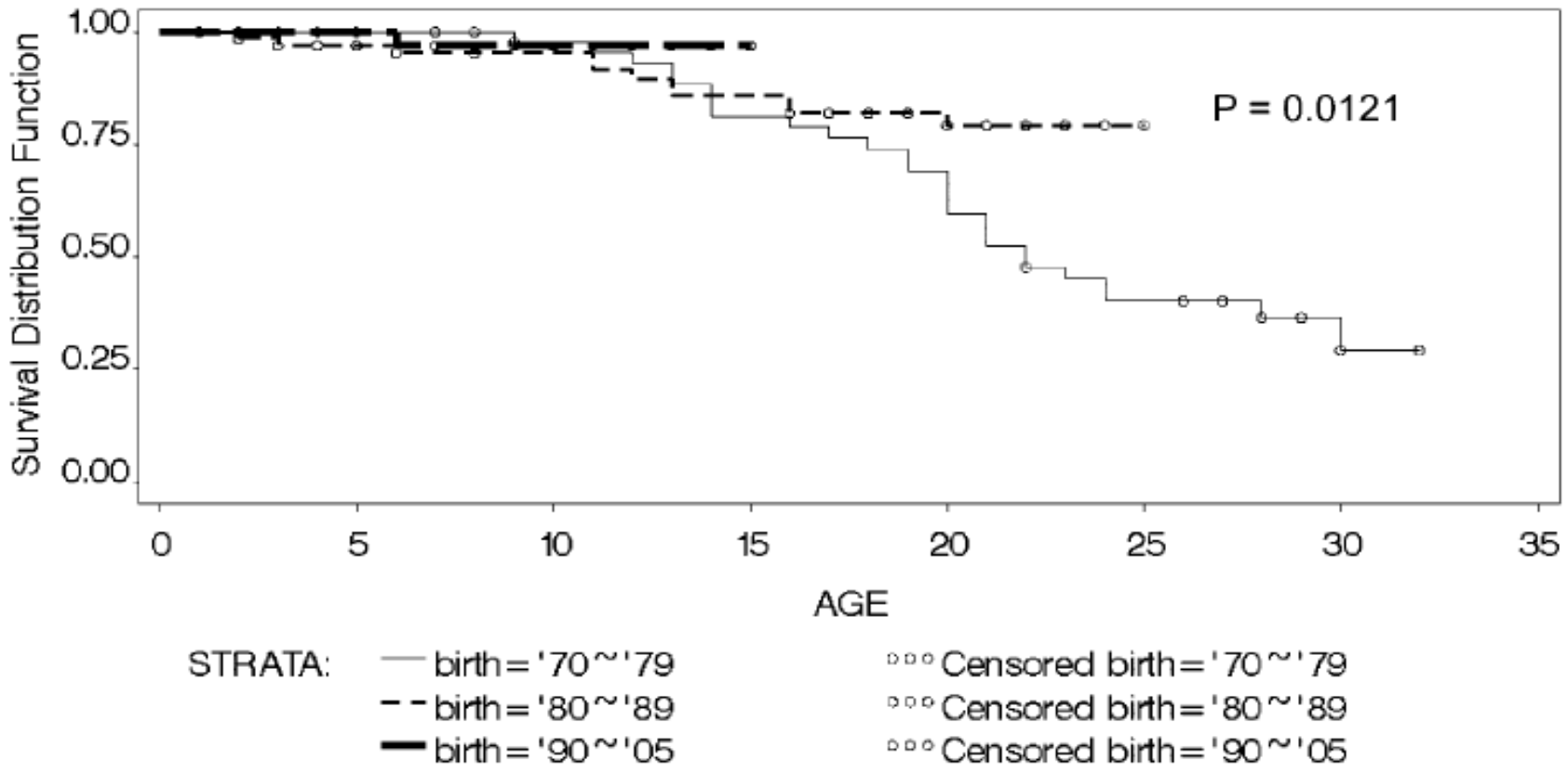

Fig. 1. Kaplan–Meier survival curves by 10-year birth cohort.

TABLE I. The Causes of Death in 39 Patients With β-Thalassemia Major

	1970–1979 (n = 46)	1980–1989 (n = 70)	1990 onwards (n = 44)
Congestive heart failure	17	3	0
Acute myocardial infarction	1	0	0
Sepsis	3	1	0
Arrhythmia	1[a]	0	0
Accident	1	0	0
BMT-related[b]	3 (3/9)	7 (7/24)	1 (1/19)
Unknown	1	0	0
Total	27	11	1

[a]PSVT in a patient complicated by hypoparathyroidism; [b]9 patients born in the 1970s, 24 born in the 1980s, and 19 born after 1990 received BMT, respectively.

TABLE II. The Current Status of Major Complications Found in 85 Patients Who Are Still Alive and Receiving Regular Treatment at Our Hospitals

	1970–1979[a] (n = 14)	1980–1989 (n = 41)	1990 onwards (n = 30)
Heart failure	3	2	0
Arrhythmia	0	2	0
Diabetes mellitus	3	15	0
Hypogonadism[b]	10	24	0
Hypoparathyroidism	0	1	0
Hypothyroidism	0	1	0
Severe infection	6	10	2
Gallstone	6	9	1
HCV infection	9	18	0
HIV infection	0	0	0

Some patients have more than one complication; [a]Age is limited to 32 years of age; [b]Only 57 patients were old enough to be assessed for hypogonadotropic hypogonadism.

TABLE III. Hazard Ratios for Survival Based on Separate Cox Regression Models Using Major Complications as Time-Dependent Covariates (160 Patients, 39 Deaths)

Factor	*P*	Hazard ratio (95% CI)
Heart failure	< 0.0001	9.577 (4.819-19.035)
Arrhythmia	< 0.0001	4.780 (2.297-9.948)
Diabetes mellitus	0.6386	1.216 (0.538-2.746)
Hypoparathyroidism	0.939	1.049 (0.31-3.545)
Hypothyroidism	0.3109	1.662 (0.622-4.437)

QUALITY OF LIFE

- On Blood Transfusions and Chelation is poor

Reasons –

IV cannulation painful

S/C Desferal daily infusions painful

Social stigma/Peer pressure

Assessment of Quality of Life in Thalassemia Major

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Aim: Children with thalassemia major have good survival but little is known about their quality of life. We assessed Health Related Quality of Life in these children.

Method: Quality of life was assessed of 26 children (average age 16 yr±5.5) with thalassemia major on regular blood transfusion, registered with Thalassemia unit at Sir Ganga Ram Hospital by using an 85-item Thalassemia Quality of life questionnaire. This questionnaire was developed by modifying Pediatric Cancer Quality of life scale developed by Varni et al covering five domains - disease and symptoms, physical, psychological, social and cognitive fields. Both desired and present quality of life assessed by patient's response in each domain. Overall Quality of Life given as percentage of desired quality of life score.

Result: Overall quality of life (QOL) was affected (<90%) in 88% of patients and severely affected (<70%) in only 15% of patients. QOL assessed in each domain showed that in disease and symptom domain 96% had QOL<90%, in physical domain 70% had QOL<90%, in psychological domain 81% had QOL<90%, in social domain 81% had QOL <90% and in cognitive domain 65% had QOL<90%

Conclusions: QOL for each child was given as a summary score between 0% (worst QOL) and 100% (best possible QOL). Each child himself acted as a control for his best possible QOL i.e. desired at that point of life according to his understanding and development. This concept can be very useful for serial assessment of QOL of child with Thalassemia major and interventions can be done in various domains to improve QOL

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Cost-Benefit Analysis

- Cost of BMT MSD for Thalassemia in India is US $ 12000 – 20000
- Cost of chelation – Desferal with infusion pump US$ 2000 per year

PESARO RISK CLASSIFICATION

Table 1 Risk factors for BMT in hemoglobinopathies

Risk factors for BMT in thalassemia	
Chelation	Regular vs irregular
Hepatomegaly	Absent vs present
Liver fibrosis	Absent vs present

	Chelation	*Hepatomegaly*	*Fibrosis*
Risk classes for BMT in thalassemia			
Class 1	Regular	No	No
Class 2	Regular/irregular	No/Yes	No/Yes
Class 3	Irregular	Yes	Yes

Abbreviation: BMT = bone marrow transplantation.

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Allogenic Transplant

- Sibling – brother and sister
- Matched Unrelated - from the registry
- Haploidentical - half matched

Table 3 Outcome of allogenic BMT for thalassemia Christian Medical College Hospital, Vellore (5-year Kaplan–Meier estimate of overall survival and EFS)

Class	*Number*	*Survival (%)*	*EFS (%)*	*Rejection (%)*
All patients	218	72.3 ± 3.1	65.3 ± 3.3	14.6
Class I	15	71.8 ± 11.98	71.8 ± 11.98	0
Class II	89	82.6 ± 4.1	78.3 ± 4.4	12.4
Class III	114	64.5 ± 4.6	54.6 ± 4.8	18.4

Our Experience

- 15 pt in 1 years
- All in class 3
- 60 % survival at year

Recommendations

- *Young TM patients with an available HLA identical sibling should be offered HSCT as soon as possible before development of iron overload and iron-related tissue damage.*
- *Transplant-related risk factors should be evaluated according to the Pesaro risk score.*
- *HLA genoidentical CB and BM are equally effective stem cell sources.*
- *PBSCT should be avoided because of the increased risk of cGVHD.*

Results of Matched Unrelated Donor Transplant

Recommendations

- *If a well-matched UD is available, allogeneic HSCT is a suitable option for a child with life-long control of iron overload and absence of iron-related tissue complications.*
- *The UD must be selected using high-resolution molecular typing for both HLA class I and II loci, and according to stringent criteria of compatibility with the recipient.*

Haploidentical for thalassemia

- Haploidentical Hematopoietic Stem Cell Transplantation (Haplo-SCT) with Pre-Transplant Immunosuppression and Post-Transplant Cyclophosphamide (Post-Cy) in Severe Thalassemia: A Novel Approach Transplant for Nonmalignant Diseases

- ALL 15 pts survive thalassemia-free and have sustained full donor chimerism (100%). The thalassemia free survival and overall survival rates are 100%. The median follow up time was 12 months (range 4-22)

Results

- Haplo-SCT for high risk thalassemia pts with our novel approach is safe, and should be considered as a modality to secure thalassemia-free survival with a low risk of graft rejection and treatment-related mortality.
- With this result, Haplo-SCT in thalassemia pts has favorable outcome as related and unrelated HSCT (thalassemia free survival rate > 90%).

Sickle Cell Anemia

Table 1. Major differences between thalassemia major (TM) and sickle cell disease (SCD) on HSCT perspective.

	Thalassemia	Sickle cell disease
Prognostic criteria for disease severity	Homogenous pattern for β thalassemia major	Wide genetic variability; inconsistent development of complications
Currently accepted indication for allogeneic HSCT	Transfusion dependency. For patients with an HLA identical sibling donor or well-matched related or unrelated donor: as soon as possible to avoid transfusion associated complications	Patient with matched sibling donor and complication requiring treatment with hydroxurea or transfusion
Total number of HSCT reported	> 3000 patients transplanted	500-600 patients transplanted
Risk factors for transplant-related complications	Age, organ dysfunction due to iron overload	Age, history of cerebral events
Alternative effective medical therapy	Life-long transfusion with chelation	Hydroxyurea: not curative, but ameliorates some complications. Chronic transfusion and chelation therapy.
Key issue for transplant outcome	Control of iron overload and related tissue damage	Cure from chronic inflammation and prevention of future SCD-related organ damage
Conditioning regimen	Needs to ablate an expanded bone marrow	Reduced intensity regimens seem to induce stable chimerism and full donor erythropoiesis
Possibility for gene therapy	First successful case reported. Phase I clinical trial ready to start	No successful case reported. Phase I clinical trial ready to start

Sickle Cell Anemia

Sickle cell disease (SCD) is associated with substantial morbidity, leading to both reduced quality of life and shortened life expectancy.[58-63] Survival has improved significantly in the last two decades and 94% of children with SCD now survive until the age of 18 years thanks to better surveillance, pneumoccocus vaccination, penicillin prophylaxis and treatment with hydroyurea.[64,65] However, mortality is still significant once patients reach adulthood.[61,66]

NOT all Sickle Cell Anemia pt requires Transpalnt

Table 3. Indication for allogeneic HSCT suggested by Walters *et al.*

Stroke or central nervous system event lasting longer than 24 h, acute chest syndrome with recurrent hospitalizations or previous exchange transfusions
Recurrent vaso-occlusive pain (more than 2 episodes per year over several years) or recurrent priapism
Impaired neuropsychological function with abnormal cerebral MRI scan
Stage I or II sickle lung disease
Sickle nephropathy (moderate or severe proteinuria or a glomerular filtration rate 30 to 50% of the predicted normal value)
Bilateral proliferative retinopathy with major visual impairment in at least one eye
Osteonecrosis of multiple joints
Red-cell alloimmunization during long-term transfusion therapy

- The only curative approach for SCD is HSCT

Recommendations

- *Young patients with symptomatic SCD who have an HLA-matched sibling donor should be transplanted as early as possible, preferably at pre-school age.*
- *Unmanipulated BM or UCB (whenever available) from matched sibling donors are the recommended stem cell source.*

Unrelated Donor in SCD

Recommendations

- *SCT from unrelated BM or CB donors should only be considered in the presence of at least one of the indications suggested by Walters et al.,[71] and should be performed only in the context of controlled trials in experienced centers (Table 3).*

Hemophilia

- Factor Replacment
- Newer factor
- Novoeight® is manufactured without any animal- or human-derived components and is the first recombinant factor VIII to use state-of-the-art double nanofiltration as part of a 5-step purification process.

CONCLUSION

- Allogeneic HCT is curative in selected patients with clinically significant hemoglobinopathies.
- For those with b-thalassemia, results have indicated a thalassemia-free survival and EFS over 70% in patients reported worldwide
- When stratifying patients, initially those with Pesaro Class 1 characteristics < 17 years had a superior thalassemia-free survival; however, recent updates show that outcomes are very similar across all three risk categories after employing risk-based conditioning regimens
- However, not all patients who might benefit are able to pursue this option due to a lack of suitable donors

Conclusion

- With the advent of alternate donor HCT and improving HLA-typing methodology, more appropriate donors may be identified, thus affording more patients the option of cure
- In addition, patient selection is still controversial although there is a trend to treat younger patients in order to decrease the risk of GR and transplant-related morbidity and mortality
- With reduced intensity conditioning regimens which rely on less myeloablation and more immunosuppression, many of the long-term effects, such as growth and endocrine dysfunction observed after myeloablative conditioning regimens, may be ameliorated.
- Furthermore, older patients who would have not been considered for HCT may benefit, although this approach is still under development

Conclusion

- We cant have thalassemic babies
- Need to have robust preventive strategy
- Need to establish transplant centres for thalassemic and sickle cell patients