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ORIGINAL ARTICLE

Financial burden of national health insurance for treating patients with transfusion-dependent thalassemia in Taiwan

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The thalassemias are a heterogeneous group of inherited hypochromic anemias of varying severity. The mainstay of supportive treatment is regular blood transfusion accompanied by iron-chelating therapy. Hematopoietic stem cell transplantation (HSCT) provides an alternative option when curative therapy is considered. More than 400 patients in Taiwan have β-thalassemia major or other transfusion-dependent thalassemias, and their treatment costs account for a considerable percentage of the National Health Insurance expenditure. In this report, we estimated the treatment costs of conventional therapy (regular blood transfusion accompanied by iron-chelating agents) and HSCT. The undiscounted medical cost of 20 years of follow-up (20 years from diagnosis) and the undiscounted total lifetime cost were NT$ 4 739 888 (NT$ means New Taiwan Dollars)/US$ 149 288 and NT$ 11 529 990/US$ 363 149, respectively, for patients undergoing conventional therapy, and NT$ 2 639 982/US$ 83 149 and NT$ 3 511 172/US$ 110 588, respectively, for those undergoing successful HSCT. Comparisons of treatment costs and other parameters between these two modalities can add to the information base on which policy is made by health authorities or clinicians.

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Introduction

Thalassemia has a very wide clinical range of severity from transfusion dependency beginning in infancy to a mild condition requiring little if any medical intervention. Thalassemia major is the severe form of the disease, presenting with transfusion-dependent anemia, generally in the first year of life. The mainstay of supportive treatment is regular blood transfusion accompanied by iron-chelating therapy. In recent years, oral iron chelators have been widely used to improve compliance with treatment and overall quality of life for patients with transfusion-dependent thalassemia. Aside from monotherapy with an iron-chelating agent, there are several strategies of chelation, such as combination therapy and organ-targeted chelation. Hematopoietic stem cell transplantation (HSCT) provides an alternative option when curative therapy is considered. Newer therapies include inducers of fetal hemoglobin and antioxidants, but their therapeutic role in β-thalassemia major is not yet clear.[1]

Treatment of thalassemia major is complex, requiring a multidisciplinary approach. In the developed world, life expectancy is 25–55 years, depending on compliance with medical treatment. In the developing world, the vast majority of affected children die before the age of 20 years because of the unavailability of most forms of effective treatment.[2,3] The lifetime cost of treating a patient with thalassemia major is estimated to be £80 000 (>US$ 110 000) in the United Kingdom[4,5] and US$ 284 154 in Israel.[6]

Recent data from the Taiwan Thalassemia Association indicate that more than 400 patients have β-thalassemia major or other transfusion-dependent thalassemias in Taiwan, and their treatment costs account for a considerable percentage of the Taiwan's National Health Insurance expenditure. The pediatric HSCT program started in Taiwan in 1984, when an allogeneic bone marrow transplantation was performed in a patient with β-thalassemia major.[7] Median survival now exceeds 50 years in well-chelated patients with regular blood transfusions,[8,9] leading to debate about the role of allogeneic HSCT in the

management of thalassemia major in well-resourced countries. However, some reports have indicated that, despite the availability of good medical treatment, approximately 50% of affected patients die before the age of 35 years.[3] Here, we estimate the treatment costs of these two therapeutic modalities: conventional therapy (regular blood transfusion accompanied by iron-chelating agents) and successful HSCT. Comparisons of treatment costs and other parameters between these two modalities can add to the information base on which policy is made by health authorities or clinicians.

Patients and methods

Patients

From the databases of two teaching hospitals in Northern Taiwan (National Taiwan University Hospital and Tao-Yuan General Hospital), a total of 111 patients with transfusion-dependent thalassemia were identified between September 1964 and March 2004. Among them, only 66 patients born after 1984 were enrolled in this study.

*The group 1 cohort (*n = *40).* Of the 66 transfusion-dependent thalassemia patients born after 1984, 40 (17 boys and 23 girls) receiving regular blood transfusions every 2–4 weeks were assigned to group 1. The median age at diagnosis was 6 months (range, 2 months to 2 years). Iron-chelating therapy started for all of them when the serum ferritin level reached 500 ng/ml. However, one boy died of congestive heart failure at the age of 15 years, 13.5 years after initial diagnosis (Table 1).

*The group 2 cohort (*n = *26).* Twenty-six out of the 66 transfusion-dependent thalassemia patients born after 1984 received stem cell transplantation when a compatible donor was available. There were 12 boys and 14 girls. The median age at the time of HSCT was 5 years 9 months (range, 10 months to 12 years 7 months). Three of the 26 patients died, and of the remaining 23 patients, 15 are alive and free of thalassemia and eight have transfusion-dependent anemia. These 15 patients showed evidence of engraftment on Y-probing using fluorescence *in situ* hybridization (FISH) in gender-mismatched patients, and DNA profiling using polymerase chain reaction (PCR) to amplify variable number tandem repeat (VNTR) sequences in other cases. These 15 patients with successful stem cell transplants were assigned to group 3 (Table 1).

*The group 3 cohort (*n = *15).* They were successfully grafted and alive as mentioned above. There were four boys and 11 girls. Their median age at the time of HSCT was 4 years 11 months (range, 10 months to 8 years 8 months).

Baseline analysis

The treatment costs of transfusion-dependent thalassemia patients born now were estimated on the basis of a number of considerations. First, our estimates of lifelong survival for the index population (group 1 and group 2) had to be based on the data of subjects followed for less than 20 years. We used a Monte Carlo approach[10] to extrapolate survival beyond the end of the follow-up period. The main idea of this approach is that we can borrow information from a reference population, of which the survival function

Table 1 Comparisons of clinical characteristics and the treatment outcome between conventional therapy and hematopoietic stem cell transplantation (HSCT)

Patients undergoing regular blood transfusions (group 1, n = 40)	
Age of diagnosis	
Median	6 months (range: 2 months ~ 2 years)
Mean ± s.d.	8.5 months ± 5.8 months
Sex	
Male:female	17:23
Frequency of blood transfusion	2–4 weeks
Mortality	1/40 (2.5%)
Morbidity	39/39 (100%)
Disease-free survival	0/39 (0%)
Patients undergoing stem cell transplants (group 2, n = 26)	
Age of diagnosis	
Median	7 months (range: 2 months ~ 4 years 5 months)
Mean ± s.d.	1 year 2 months ± 1 year 3 months
Age at the time of stem cell transplant	
Median	5 years 9 months (range: 10 months ~ 12 years 7 months)
Mean ± s.d.	5 years 8 months ± 3 years 3 months
Sex	
Male:female	12:14
The origin of stem cells	
HLA-compatible sibling donor	23
HLA-matched unrelated donor	2
Umbilical cord blood	1
Mortality	3/26 (11.5%)
Morbidity	8/23 (34.8%)
Disease-free survival	15/23 (65.2%)
Patients with successful stem cell transplants (group 3, n = 15)	
Age of diagnosis	
Median	7 months (range: 2 months ~ 4 years 5 months)
Mean ± s.d.	1 year ± 1 year 1 month
Age at the time of stem cell transplant	
Median	4 years 11 months (range: 10 months ~ 8 years 8 months)
Mean ± s.d.	4 years 10 months ± 2 years 10 months
Sex	
Male:female	4:11
The origin of stem cells	
HLA-compatible sibling donor	15
HLA-matched unrelated donor	0
Umbilical cord blood	0

Table 2 Cost factors assessed for patients receiving regular blood transfusions

Cost factors	*Description (including the frequency of intervention)*	*Average annual cost per category (NTD[a]/USD[b]) (%)*
Registration fees	For outpatients; every 2–4 weeks	2086/66 (0.9)
Blood products	Washed red blood cells (used at National Taiwan University Hospital) and leukocyte-poor red blood cells (used at Tao-Yuan General Hospital); every 2–4 weeks	28 165/888 (11.7)
Cross-matching tests	Every 2–4 weeks	6259/197 (2.6)
Iron-chelating agents	Mainly desferrioxamine subcutaneously; daily	187 767/5923 (77.9)
Medical appliances for home infusion of iron-chelating agents	Infusion pump, syringes and winged-needles; daily	2629/83 (1.1)
Laboratory and diagnostic tests	Hematology; every 2–4 weeks Biochemistry; three-monthly Ferritin levels were monitored biannually (before year 2004) or trimonthly (after year 2004)	6769/214 (2.7)
Follow-up ultrasonography (cardiac and abdominal)	Annually	3168/100 (1.2)
Non-routine interventions	Diabetes treatment, gonadal function tests and treatment, growth evaluation and treatment, cardiac disease treatment, splenectomy for hypersplenism, osteoporosis treatment, psychotherapy, etc.	4215/133 (1.9)
Total amount		241 058/7604 (100)

[a]NTD = New Taiwan Dollar(s).
[b]USD = US Dollar(s).

is easily obtained from some available life table data such as a table of vital statistics. The accurate extrapolation is obtained mainly because of the property that logit transform of the ratio between survival functions for the index and the reference populations approximates a straight line, except for the two tail ends. A program package MC-QAS built in a free software R, which is available from the website http://www.stat.sinica.edu.tw/jshwang/qas.htm, can be easily used to obtain the lifelong survival estimates.

The frequencies of routine health service interventions were based on current protocols (derived and modified from the literature) for diagnosis, routine follow-up and management of complications. The medical costs of evaluation and treatment for nonroutine episodes of morbidity were also taken into account (Table 2). To collect the information on the relevant parameters, we were granted use of the data from the nationwide health insurance claims database and hospital database management system. The medical costs of every transfusion-dependent thalassemia patient were divided into three categories: outpatient care, emergency care, and inpatient care costs. The average annual medical costs per patient were calculated.

For a given survival curve, the lifetime treatment cost was estimated by the mathematical formula 1:

$$\mathrm{TC} = \int_0^\infty S(t) \cdot C(t)\,\mathrm{d}t$$

where $S(t)$ is the estimated survival function and $C(t)$ is the average medical cost function for the index population. The yearly cost function was assumed to be

$$C(t) = \mathrm{DC}\left(\frac{1}{1+r}\right)^{I_t}$$

where DC is the dollar value of the average annual medical costs, r is an annual discount rate, I_t is number of full years from onset to time t. The integration of the lifetime treatment cost TC was obtained approximately by the trapezoid method.

To assess the lifetime medical costs of group 3, three stages of treatment were considered: pretransplant, transplant, and post transplant stages. Medical costs of the pretransplant stage were calculated and aggregated up to the median transplant age of 4 years 11 months. During the median period of 2 months for transplantation admission (range, 1–6 months), the medical costs were described by the relevant parameters detailed in Table 3. The post transplant treatment costs were mainly from outpatient follow-up and interventions associated with previous or transplant-related complications. Therefore, the lifetime medical costs of group 3 were obtained by calculating and aggregating using formula 1 from the pretransplant, transplant, through the post transplant stage.

Costs up to the age of 50 years were included and subject to a discount rate of 0, 3, and 5%.

Results

*The group 1 cohort (*n = *40)*

Mortality. One boy died of congestive heart failure at the age of 15 years, 13.5 years after the initial diagnosis, giving an overall mortality rate of 2.5%. The morbidity and disease-free survival rate was 100 and 0%, respectively (Table 1).

*The group 2 cohort (*n = *26)*

Engraftment after hematopoietic stem cell transplantation. Twenty-six patients with transfusion-dependent thalassemia received allogeneic HSCTs (HLA-identical

sibling donors for 24 patients, HLA-matched unrelated donor for one patient, and umbilical cord blood of origin for one patient). Engraftment was documented in 15 patients either by FISH or DNA profiling using PCR to amplify VNTR sequences.

Nonrejection mortality. There were three deaths, giving an overall mortality rate of 11.5%. The causes of death were grade IV acute graft-versus-host disease (GVHD) followed by chronic GVHD and multiorgan failure ($n=1$), and septic shock with multiorgan failure ($n=2$).

Rejection. Graft rejection was observed in eight of the 26 transplants; in all patients, this was followed by autologous reconstitution. The median time of rejection was 35.5 days (range, 31 days to 1 year 8 months). Patients were subsequently transfusion-dependent.

Actuarial overall survival and disease-free survival. Actuarial 5-year survival for the 26 patients is 88.5% with a disease-free survival of 65.2%. Three of the 26 patients died, and of the remaining 23 patients, 15 are alive and free of thalassemia and eight have transfusion-dependent anemia (Table 1).

Estimation of treatment costs. The mean life expectancy ($\pm$s.d.) of groups 1 and 2 was estimated to be 48.8 ± 1.6 and 41.9 ± 4.6 years, respectively, whereas that of the reference population was 49.1 years$\pm$0.2 months. The average annual medical cost of regular blood transfusion was NT$ 241 058 (NT$ means New Taiwan Dollars)/US$ 7604 (Table 2). For patients receiving HSCT successfully, the average medical cost of transplantation was NT$ 1 061 584/US$ 33 488 (Table 3) and the average annual medical cost for post transplant care was NT$ 37 773/US$ 1190.

The undiscounted medical cost of 20 years of follow-up (20 years from initial diagnosis) for groups 1 and 3 was NT$ 4 739 888/US$149 288 and NT$ 2 639 982/US$ 83 149, respectively. The undiscounted total lifetime cost for groups 1 and 3 was NT$ 11 529 990/US$363 149 and NT$ 3 511 172/US$110 588, respectively. The discounted lifetime medical costs for group 1 were NT$ 6 179 076/US$ 194 617 (3% discount rate) and NT$ 4 499 031/US$ 141 702 (5% discount rate), while for group 3, they were NT$ 2 651 663/US$ 83 517 (3% discount rate) and NT$ 2 334 472/US$ 73 527 (5% discount rate) (Table 4).

Table 3 Cost factors associated with patients receiving hematopoietic stem cell transplantation during transplantation admission (including pretransplantation evaluation)

Cost factors	*Average cost per category (NTD[a]/USD[b]) (%)*
Pretransplantation evaluation	72 090/2274 (6.8)
Room cost	371 735/11 727 (35)
Conditioning regimen	17 554/554 (1.7)
Lab and diagnostic tests	61 053/1926 (5.8)
Transfusions	
Red blood cells	17 739/560 (1.7)
Platelets	70 736/2231 (6.7)
Antimicrobial agents	
Antibacterials	68 858/2172 (6.5)
Other anti-infectious agents	164 686/5195 (15.5)
Post-transplant G-CSF[c]	51 626/1629 (4.9)
Harvesting	12 211/385 (1.2)
GVHD prophylaxis	36 469/1150 (3.4)
Other drugs	67 586/2132 (6.4)
Medical appliances	49 241/1553 (4.4)
Total amount	1 061 584/33 488 (100)

[a]NTD = New Taiwan Dollar(s).
[b]USD = US Dollar(s).
[c]G-CSF = granulocyte colony stimulating factor.

Discussion

The mainstay of supportive treatment for patients with thalassemia major is regular blood transfusion accompanied by iron-chelating therapy. Nevertheless, this poses many complications attributable to iron overload. Excess iron is toxic to the heart, liver, and endocrine system. In β-thalassemia major, 70% of deaths are the result of cardiac failure or arrhythmia. Chelation with desferrioxamine can improve quality of life and life expectancy of these patients,

Table 4 Comparison of financial burden of the National Health Insurance (NHI) between thalassemia patients undergoing conventional therapy and successful hematopoietic stem cell transplantation (HSCT), stratified by different discount rates

Annual discount rate	*Conventional therapy*			*Successful HSCT*		
	0%	*3%*	*5%*	*0%*	*3%*	*5%*
20 years F/U[a]						
NTD[b]	4 739 888	3 643 618	3 117 440	2 639 982	2 326 898	2 157 200
USD[c]	149 288	114 760	98 187	83 149	73 288	67 943
50 years F/U[a]						
NTD[b]	11 529 990	6 179 076	4 499 031	3 511 172	2 651 663	2 334 472
USD[c]	363 149	194 617	141 702	110 588	83 517	73 527

[a]F/U = follow-up.
[b]NTD = New Taiwan Dollar(s).
[c]USD = US Dollar(s).

provided that a lifelong iron chelation program is consistently followed. Only half of the patients meet this criterion, because iron chelation is burdensome, painful, and time-consuming.[4] Besides, desferrioxamine itself can be toxic when given in excessive doses. It can affect sensorineural function (vision, hearing) and the skeletal system (short stature). Recent data from the UK Thalassemia Registry showed a steady decline in survival from the second decade, with fewer than 50% of patients remaining alive during their 30s.[3] The principal reason appeared to be poor compliance with the chelation regimens. Data from Torino showed that where compliance with chelation therapy is good and consistent, 90% of patients survive into their 30s, but where compliance is poor, fewer than 10% will survive into their 40s.[11]

HSCT remains the only curative treatment for thalassemia major. HSCT offers the prospect of an improved quality of life and freedom from transfusion and lifelong chelation. For patients whose compliance with chelation therapy is erratic and who therefore have a low chance of reaching their 50s, HSCT offers a much greater chance of long-term survival. However, it is limited by donor availability because only 30–40% of all patients can find a fully matched donor. The use of mismatched related or matched unrelated donors is associated with a higher risk for graft rejection and GVHD, and these donors have therefore seldom been used in the treatment of thalassemia,[12,13] although successful outcomes can sometimes be achieved.[13–15] Matched, related, cord blood stem cell collections offer a convenient alternative to marrow donations, but the risk of graft rejection in the setting of the hemoglobinopathies may be unacceptably high.[16–18] The disadvantages of HSCT are significant transplant-related mortality and high risk of infertility, growth disturbances, and endocrine complications. Chronic GVHD is one of the other worrying hazards. Pre-existing iron overload also requires treatment either by regular phlebotomy or chelation therapy.[19]

From an economic perspective, thalassemia major is currently an expensive condition to treat. Although the estimated survival rates show a large proportion of patients surviving into their 50s, it appears that any survival assumptions made and medical costs incurred beyond that age would be uncertain to justify 50 years as a cutoff point for the inclusion of treatment costs for thalassemia major. The discount rates (as 0, 3, and 5%) we adopted here were based on the mean annual change of consumer price indices for medicine and medical care during 1993–2002, which was 1.97% (standard deviation = 0.95%, ranges from 0.93 to 3.75%). Discounting the annual costs minimizes the impact of excluding costs incurred past 50 years. Owing to the chronic nature of thalassemia, the results were sensitive to changes in the discount rate, as observed in Figure 1.

The estimates presented in this report were minimum values, as only major health service interventions have been included. For patients with transfusion-dependent thalassemia, some non-health care parameters should be taken into account for economic evaluation, such as child care, transportation, and lost earnings. However, these non-health care parameters were not included in this report because of the complexities and uncertainties inherent in them.

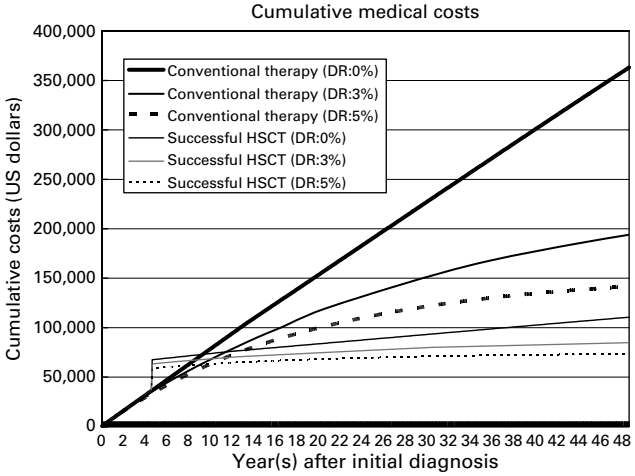

Figure 1 Cumulative medical costs for transfusion-dependent thalassemia by different discount rates (DR: 0, 3, and 5%). DR = discount rate.

In recent years, oral iron chelators have been widely used to improve compliance with treatment and overall quality of life for patients with transfusion-dependent thalassemia. Currently, two iron-chelating agents are licensed for the treatment of iron overload: desferrioxamine (subcutaneously) and deferiprone (orally). A third compound, ICL670, is currently in the late stages of a comprehensive clinical development programme.[20] Aside from monotherapy with either iron-chelating agent, there are several strategies of chelation, such as combination therapy and organ-targeted chelation. Mourad *et al.* reported that giving deferiprone (DFP) every day and desferrioxamine (DFO) 2 days a week produced iron excretion comparable to that achieved with DFO administered 5 days a week.[21] Although the use of oral chelators was not the key point of this article, we believed that medical costs from different regimens of chelation will become an important issue in the future.

In conclusion, HSCT is one of the curative therapies currently in use nowadays for patients with thalassemia major. From our point of view, it provides a better quality of life and is more cost-effective than conventional treatment. However, the actuarial survival curves following HSCT demonstrated decreased overall survival of transplanted patients. We therefore suggest that HSCT should be performed when a fully HLA-matched donor is available. These benefits should be balanced against the small risks of early death and the possibility of chronic GVHD and other transplant-related complications. The risks and disadvantages of HSCT should be discussed with patients and families before HSCT is chosen. Comparisons of treatment costs and other parameters between these two modalities can add to the information base on which policy is made by health authorities or clinicians.

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