SURVIVAL IN MEDICALLY TREATED PATIENTS WITH HOMOZYGOUS β-THALASSEMIA

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Abstract *Background.* The prognosis of patients with homozygous β-thalassemia (thalassemia major) has been improved by transfusion and iron-chelation therapy. We analyzed outcome and prognostic factors among patients receiving transfusions and chelation therapy who had reached the age at which iron-induced cardiac disease, the most common cause of death, usually occurs.

Methods. Using the duration of life without the need for either inotropic or antiarrhythmic drugs as a measure of survival without cardiac disease, we studied 97 patients born before 1976 who were treated with regular transfusions and chelation therapy. We used Cox proportional-hazards analysis to assess the effect of prognostic factors and life-table analysis to estimate freedom from cardiac disease over time.

Results. Of the 97 patients, 59 (61 percent) had no cardiac disease; 36 (37 percent) had cardiac disease, and 18 of them had died. Univariate analysis demonstrated that factors affecting cardiac disease–free survival were age at the start of chelation therapy ($P<0.001$), the natural log of the serum ferritin concentration before chelation therapy began ($P = 0.01$), the mean ferritin concentration ($P<0.001$), and the proportion of ferritin measurements exceeding 2500 ng per milliliter ($P<0.001$). With stepwise Cox modeling, only the proportion of ferritin measurements exceeding 2500 ng per milliliter affected cardiac disease–free survival ($P<0.001$). Patients in whom less than 33 percent of the serum ferritin values exceeded 2500 ng per milliliter had estimated rates of survival without cardiac disease of 100 percent after 10 years of chelation therapy and 91 percent after 15 years.

Conclusions. The prognosis for survival without cardiac disease is excellent for patients with thalassemia major who receive regular transfusions and whose serum ferritin concentrations remain below 2500 ng per milliliter with chelation therapy. (N Engl J Med 1994;331:574-8.)

THE prognosis of patients with transfusion-dependent homozygous β-thalassemia (thalassemia major) has been improved by regular transfusion and iron-chelation therapy.[1] Before the introduction of therapy with deferoxamine, an iron-chelating agent, in the late 1970s,[2] iron overload from transfusions was a frequent cause of morbidity and mortality in these patients. Death was often due to cardiac failure, which typically began before the patient reached 20 years of age.[3] Previous studies have suggested that deferoxamine therapy, begun early in life, prolongs survival without cardiac disease,[4-9] but follow-up was too short for unequivocal conclusions. The need for definitive information about the long-term prognosis of patients with thalassemia major has increased since allogeneic bone marrow transplantation emerged as an alternative treatment.[10-12]

In this report, we present the results of transfusion and chelation therapy in 97 patients with thalassemia major who were followed at three North American centers. The mean age of the group at the close of the study was 23 years, an age at which cardiac disease would be expected in most patients treated only with transfusions.[3] The results demonstrate a markedly improved prognosis for survival without cardiac disease in patients with thalassemia major who begin chelation therapy before iron loading is severe and who comply with this treatment regimen.

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METHODS

Study Design

We examined survival without cardiac disease, which was defined as survival without the need for cardiac inotropic or antiarrhythmic medication, in all 97 patients with thalassemia major born between 1954 and 1975 and treated at three centers: the Hospital for Sick Children in Toronto, Children's Hospital in Boston, and the Children's Hospital of Philadelphia. Pericarditis was not considered an outcome measure; no patient in the study had this complication. The ethnic background of the patients was as follows: 53 of Italian origin, 30 of Greek origin, 5 of Chinese origin, 4 of Indian origin, 3 of Saudi Arabian origin, and 1 each of Lebanese and Turkish origin. Mutations in the β-globin gene had previously been characterized in only half the patients. Beginning in 1970, most patients received approximately 15 ml of packed red cells per kilogram of body weight at each transfusion to maintain hemoglobin levels above 9.0 g per deciliter. They underwent splenectomy if the volume of packed red cells exceeded 250 ml per kilogram per year. Beginning in 1989, one patient in Boston received red cells separated according to density to enhance the collection of young erythrocytes (neocytes) with prolonged survival in vivo.[13] Most patients administered deferoxamine (50 to 75 mg per kilogram) to themselves as a nightly 10-to-12-hour subcutaneous infusion, using standard ambulatory pumps. In Philadelphia, most patients received 2 g of deferoxamine each night regardless of weight; some patients also received intermittent intravenous infusions of 4 to 12 g of deferoxamine. Beginning in 1989, 10 patients in Toronto received deferoxamine by continuous intravenous infusion (50 to 80 mg per kilogram per 24 hours).[14] No patient had clinical manifestations of iron-related diabetes mellitus, hypothyroidism, or hypoparathyroidism at the start of deferoxamine therapy. Patients were followed for a median of 12 years of deferoxamine treatment.

At each center, all the patients were interviewed and examined by a staff physician at intervals of one to six months. Serum ferritin concentrations were measured at similar intervals by a standard method.[15] Cardiac evaluation included an annual history and physical examination by a cardiologist and annual chest radiography, electrocardiography, and resting echocardiography. Cardiac dis-

ease was considered to be present if a patient required inotropic drugs (including digoxin) for signs or symptoms of cardiac failure, therapy for substantial arrhythmias, or both.

Statistical Analysis

For survival without cardiac disease, we considered the following prognostic factors: clinical center, sex, age at the start of treatment with deferoxamine, serum ferritin concentration before chelation therapy, mean serum ferritin concentration, proportion of ferritin measurements exceeding certain threshold values, and degree of reduction in the serum ferritin concentration approximately one and two years after therapy began. The mean serum ferritin concentration and the proportion of serum ferritin values exceeding a given threshold were used because the timing of serum ferritin measurements was irregular. A window of 10 to 18 months was used in estimating the degree of reduction in the serum ferritin concentration at approximately one and two years. The mean serum ferritin concentrations and the concentrations before chelation therapy were analyzed on a log scale to reduce the influence of very high values. Cox proportional-hazards analysis was used to investigate the effect of each prognostic factor on survival without cardiac disease. The Cox model with stepwise selection was then used to investigate the joint effect of the prognostic factors. A significance level of 5 percent was used for the entry of terms, and a level of 10 percent was used for the removal of terms. P values are given for both univariate and stepwise analyses. The results of Cox modeling have been summarized with risk ratios for each variable, 95 percent confidence intervals, and associated P values. Proportions of events are reported relative to the number of patients who could be evaluated. Life-table plots were used to assess disease-free survival over time.

BMDP-PC90 software programs were used to calculate life-table estimates of survival without cardiac disease and for Cox modeling (University of California Press, Berkeley). Data manipulation was performed and descriptive statistics were calculated with the use of SAS software (version 6.07.01, SAS Institute, Cary, N.C.).

Results

Of 101 patients initially enrolled in the study, 97 could be evaluated. Two patients began treatment at or after the onset of cardiac disease, and data on serum ferritin concentrations were unavailable for two other patients. Patients were followed for a median of 12 years after beginning chelation therapy. The mean (±SD) age of the patients at the close of the study in June 1991 was 23±5 years.

Table 1 summarizes the patients' clinical characteristics and outcomes. Fifty-nine patients (61 percent) have no evidence of cardiac disease at this writing. Thirty-six (37 percent) had cardiac disease, and 18 of them (50 percent) had died. Two patients died of causes unrelated to cardiac disease; data on them were included as censored observations in the analysis. Patients without cardiac disease began treatment at an earlier age than those with cardiac disease, had lower mean serum ferritin concentrations before beginning deferoxamine therapy, maintained lower mean ferritin concentrations during treatment, and had lower proportions of ferritin measurements that exceeded the threshold value of 2500 ng per milliliter during treatment. This proportion became the most important factor predicting disease-free survival, as discussed below. Transfusion requirements were similar in patients with and without cardiac disease. The differences in cardiac disease–free survival among ethnic groups were attributable to the degree of iron loading.

For the full cohort, the estimated survival without cardiac disease was 80 percent after 5 years of chelation therapy, 65 percent after 10 years, and 55 percent after 15 years (Fig. 1). As shown in Table 2, factors influencing cardiac disease–free survival were age at the start of deferoxamine therapy, serum ferritin concentration before treatment, mean serum ferritin concentration during treatment, and proportion of ferritin measurements that exceeded 2500 ng per milliliter during treatment. With stepwise Cox modeling, only a higher proportion of ferritin measurements exceeding this threshold value was associated with poorer cardiac disease–free survival (risk ratio, 19.1; 95 percent confidence interval, 6.3 to 58.1; $P<0.001$).

Because some patients had more serum ferritin measurements than others, we also evaluated the proportion of measurements exceeding 2500 ng per milliliter, using only the first serum ferritin determination each year. The relation between this variable and cardiac disease–free survival was unchanged.

For patients in whom less than 33 percent of ferritin measurements exceeded 2500 ng per milliliter, the estimated survival without cardiac disease was 100 percent after 10 years of deferoxamine therapy and 91 percent after 15 years (Fig. 2). In contrast, for patients in whom 33 to 67 percent of ferritin measurements exceeded 2500 ng per milliliter, the estimated disease-free survival was 48 percent after 10 and 15 years of

Table 1. Clinical Characteristics and Outcome.*

Characteristic	No. of Patients Who Could Be Evaluated	Clinical Status			
		Disease-free (N = 59)	Alive with cardiac disease (N = 18)	Dead of cardiac disease (N = 18)	Dead of unrelated causes (N = 2)
Female/male (%)	97	51/49	33/67	61/39	100/0
Mean age at start of chelation therapy (yr)	97	10.5±5.6	14.4±5.7	14.8±3.6	9.0±1.4
Serum ferritin level before chelation (ng/ml)	89				
Mean		3416±2225	4829±3772	4556±2167	—
Median		2740	3450	3960	—
Serum ferritin level during chelation (ng/ml)	93				
Mean		2695±2439	5497±3367	4592±1658	4504±4252
Median		1880	5572	4414	—
Proportion of measurements >2500 ng/ml during chelation	93				
Mean		0.32±0.35	0.77±0.34	0.83±0.23	0.53±0.62
Median		0.20	0.99	0.93	—

*Plus–minus values are means ±SD.

therapy. For patients in whom more than 67 percent of ferritin measurements exceeded 2500 ng per milliliter, the estimated disease-free survival was 38 percent after 10 years of therapy and 18 percent after 15 years.

Discussion

During the past 10 years, strong evidence of improved survival without cardiac disease in patients with thalassemia major has accumulated,[4-9] and the prognosis appears particularly good for children with thalassemia born since the current treatment became widely available.[6] Nonetheless, there are still cases of iron-related illness and death, even in patients who apparently complied with deferoxamine therapy.[16]

This study describes the outcome of the long-term treatment of 97 patients with homozygous β-thalassemia. Using the end point of survival without cardiac disease, which we defined as survival without inotropic or antiarrhythmic therapy, we identified factors related to the success or failure of an iron-chelation program. Some of our patients, although they did not need cardiac therapy, may have had early cardiac dysfunction that could have been detected by methods such as radionuclide angiography. The end points in this study may therefore have overestimated disease-free survival. Evaluation of the effect of transfusion and chelation therapy on subclinical cardiac dysfunction must await the development of tests with sufficient sensitivity and specificity to predict accurately the later development of clinical cardiac disease. We could not ethically compare treated and untreated patients during the same period. However, one of the last reports of survival in patients with thalassemia before the era of iron-chelation therapy described the onset of iron-related cardiac failure in 26 of 41 patients (63 percent) at a mean age of 16 years; more than half of the affected patients died of cardiac disease within one year of its onset.[3] Pericarditis was also frequent, although the relation of this complication to iron overload remains uncertain.[3] Our results indicate a markedly improved outlook for patients who receive

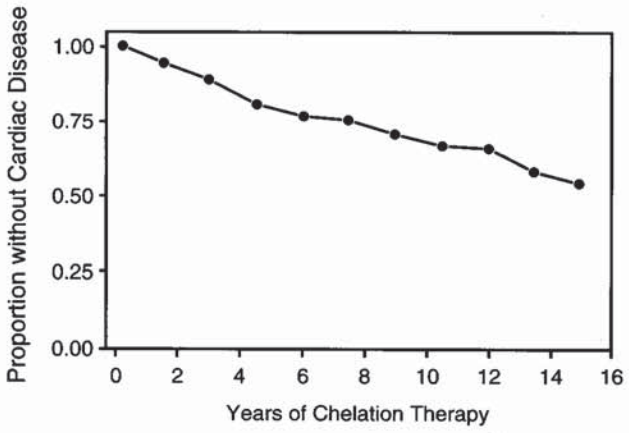

Figure 1. Survival without Cardiac Disease during Chelation Therapy in 97 Patients with Thalassemia Major.

Table 2. Effect of Prognostic Factors on Survival without Cardiac Disease.

Prognostic Factor	No. of Patients	Risk Ratio (95% CI)*	P Value	
			Univariate	Stepwise
Center†	97	1.50 (0.6–4.0)	0.47	0.87
		2.00 (0.6–6.5)	—	0.89
Sex	97	0.80 (0.4–1.6)	0.51	0.56
Age at start of chelation therapy	97	1.10 (1.07–1.2)	<0.001	0.65
Serum ferritin‡				
Natural log of level before chelation	89	2.00 (1.2–3.8)	0.01	0.08
Reduction at 1 yr	89	1.00 (0.8–1.5)	0.68	0.80
Reduction at 2 yr	86	1.40 (1.0–2.0)	0.06	0.51
Natural log of mean concentration	93	3.20 (2.0–5.1)	<0.001	0.46
Proportion of measurements >2500 ng/ml	93	19.10 (6.3–58.1)	<0.001	<0.001

*CI denotes confidence interval.

†Two dummy variables were used for analysis of data from three centers.

‡Serum ferritin concentrations before chelation therapy were not available for eight patients. Patients were excluded if cardiac disease developed before a measurement was obtained.

chelation therapy sufficient to maintain a reduced serum ferritin concentration over a long period. The favorable outcome of patients who began chelation therapy in early childhood emphasizes the benefits of treatment with deferoxamine.

A sustained reduction in iron, as measured by the proportion of serum ferritin measurements that did not exceed 2500 ng per milliliter, emerged as the most important factor in the survival without cardiac disease among the patients with homozygous β-thalassemia we studied. The estimated disease-free survival 15 years after the beginning of chelation therapy was 91 percent among patients in whom fewer than one third of ferritin measurements exceeded 2500 ng per milliliter. Even patients who began chelation therapy later in life but maintained a reduction in their iron stores had a good prognosis. Conversely, failure to prevent the accumulation of excess iron or to remove large stores of tissue iron was associated with a poor prognosis at any age. For example, the probability of survival after 15 years of chelation therapy was less than 20 percent if more than 67 percent of a patient's ferritin measurements exceeded 2500 ng per milliliter.

Although a single measurement of serum ferritin may be an imprecise assessment of total iron stores,[17] serial measurements may be useful in predicting the likelihood of iron-induced cardiac disease. Hepatitis C infection, the most common viral complication of long-term transfusion therapy, may further elevate the serum ferritin concentration, complicating its interpretation. We were unable to analyze the effect of hepatitis C infection on serum ferritin concentrations because assays to detect hepatitis C antibodies were unavailable during most of the period of investigation. A similar effect of hepatitis C would be expected in patients with and without cardiac disease, all of whom began transfusion therapy before donor blood was screened for this infectious agent.

Our study could not determine the influence of var-

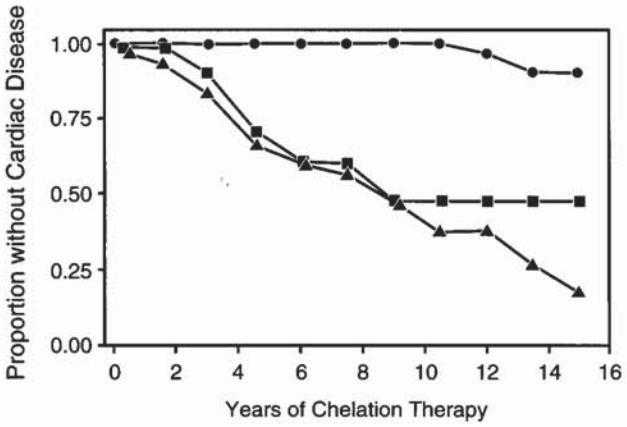

Figure 2. Survival without Cardiac Disease According to the Proportion of Serum Ferritin Measurements Greater Than 2500 ng per Milliliter.

The circles show cardiac disease–free survival among patients in whom less than 33 percent of ferritin measurements exceeded 2500 ng per milliliter; squares show survival among patients in whom 33 to 67 percent of ferritin measurements exceeded 2500 ng per milliliter; and triangles show survival among patients in whom more than 67 percent of ferritin measurements exceeded 2500 ng per milliliter.

ious mutations of the β-globin gene on survival without cardiac disease, because the mutations had been characterized in only half the patients. However, any effect of genotype on disease-free survival would presumably be mediated through transfusion requirements, which did not differ in patients with and those without cardiac disease.

Chelation therapy has improved survival without cardiac disease in patients with thalassemia major, but bone marrow transplantation from an HLA-identical donor has resulted in thalassemia-free survival in many patients. Although we did not compare patients treated with transfusion and chelation therapy with patients who underwent bone marrow transplantation, our results provide valuable information for patients, families, and clinicians faced with a choice between the two forms of treatment. Patients with thalassemia major who begin chelation therapy in early childhood and most of whose serum ferritin measurements are below 2500 ng per milliliter are clinically similar to patients with class I disease as defined by the Pesaro bone marrow–transplantation group.[11,12] Both groups of patients have benefited from good medical care from an early age. The rate of survival without cardiac disease in our study (91 percent after 15 years of chelation therapy) compares favorably with the 3-year disease-free survival of 85 to 93 percent for patients with class I disease treated with bone marrow transplantation.[12] The poor long-term prognosis of patients who have large iron stores because they cannot get or do not comply with deferoxamine therapy may argue for bone marrow transplantation, even in the face of hepatic enlargement or fibrosis, which negatively affect the outcome of transplantation.[11]

Factors other than survival without cardiac disease (for transfusion and chelation therapy) and survival without thalassemia (for bone marrow transplantation) may influence the choice between these treatment options. Cost may be a factor. The estimated cost (in 1990 dollars) of bone marrow transplantation for hemoglobinopathy was $173,250 in 1991.[18] Additional costs can be anticipated during at least the first five years after transplantation.[19] The cost of transfusion and chelation therapy in a patient who weighs 30 kg was about $32,000 per year in 1991, with more than 60 percent of the cost attributable to chelation therapy.[18] The cost of medical therapy would be expected to increase as the patient grew and required more blood and more deferoxamine. The cost of transfusion therapy in some centers is now substantially higher than this estimate and can exceed $30,000 per year in patients who receive two units of packed red cells every three weeks (unpublished data). Although the short-term costs of bone marrow transplantation and transfusion and chelation therapy may be similar, the higher continuing costs of transfusion and chelation may make them the more expensive option.

This study was not designed to establish the optimal serum ferritin concentration required to prevent iron-related cardiac disease or other complications of iron overload. In practice, physicians stress the importance to their patients of reducing body iron to the lowest possible level. It is possible that maintaining the serum ferritin concentration considerably below 2500 ng per milliliter may be optimal on a long-term basis, but physicians must weigh the benefit of treatment against the toxic effects of deferoxamine in patients with reduced iron burdens.[20-23] Measurements of body iron stores, in addition to the serum ferritin concentration, may be useful in determining the duration and intensity of chelation therapy.[24,25]

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