EFFICACY OF DEFEROXAMINE IN PREVENTING COMPLICATIONS OF IRON OVERLOAD IN PATIENTS WITH THALASSEMIA MAJOR

GARY M. BRITTENHAM, M.D., PATRICIA M. GRIFFITH, R.N., M.S.N., ARTHUR W. NIENHUIS, M.D., CHRISTINE E. MCLAREN, PH.D., NEAL S. YOUNG, M.D., EBEN E. TUCKER, M.D., CHRISTOPHER J. ALLEN, M.S., DAVID E. FARRELL, PH.D., AND JOHN W. HARRIS, M.D.

Abstract *Background.* To determine whether deferoxamine prevents the complications of transfusional iron overload in thalassemia major, we evaluated 59 patients (30 were female and 29 male; age range, 7 to 31 years) periodically for 4 to 10 years or until death.

Methods. At each follow-up visit, we performed a detailed clinical and laboratory evaluation and measured hepatic iron stores with a noninvasive magnetic device.

Results. The body iron burden as assessed by magnetic measurement of hepatic iron stores was closely correlated ($R = 0.89$, $P<0.001$) with the ratio of cumulative transfusional iron load to cumulative deferoxamine use (expressed in millimoles of iron per kilogram of body weight, in relation to grams of deferoxamine per kilogram, transformed into the natural logarithm). Each increase of one unit in the natural logarithm of the ratio (transfusional iron load to deferoxamine use) was associated with an increased risk of impaired glucose tolerance (relative risk, 19.3; 95 percent confidence interval, 4.8 to 77.4), diabetes mellitus (relative risk, 9.2; 95 percent confidence interval, 1.8 to 47.7), cardiac disease (relative risk, 9.9; 95 percent confidence interval, 1.9 to 51.2), and death (relative risk, 12.6; 95 percent confidence interval, 2.4 to 65.4). All nine deaths during the study occurred among the 23 patients who had begun chelation therapy later and used less deferoxamine in relation to their transfusional iron load ($P<0.001$).

Conclusions. The early use of deferoxamine in an amount proportional to the transfusional iron load reduces the body iron burden and helps protect against diabetes mellitus, cardiac disease, and early death in patients with thalassemia major. (N Engl J Med 1994;331:567-73.)

AN adequate transfusion program for patients with thalassemia major can prevent death from anemia in infancy and permit normal growth and development during childhood. Because the body lacks any effective means for excreting excess iron, transfusion therapy results in a progressive accumulation of iron, which may be augmented by iron absorbed from the diet as a result of the increased ineffective erythropoiesis.[1] Eventually, extensive iron-induced injury develops in the liver, pancreas, heart, and other organs. The severity of iron toxicity seems to be related to the magnitude of the body iron burden.[2,3] Without treatment to remove the excess iron, almost all patients with thalassemia major who regularly undergo transfusions will accumulate toxic amounts of iron by the age of 10 years or earlier and acquire potentially lethal iron burdens by early adolescence.

Deferoxamine mesylate, a naturally occurring trihydroxamic acid produced by *Streptomyces pilosus,* increases urinary iron excretion in patients with thalassemia major[4] and is the only iron-chelating agent approved for clinical use.[5] Therapeutic trials of deferoxamine administered intramuscularly,[3] intravenously,[6] or subcutaneously[7] have shown that regular chelation therapy can decrease hepatic iron,[8] ameliorate cardiac,[9,10] pancreatic,[11] and other organ dysfunction,[12,13] improve growth and sexual maturation,[14,15] and increase survival[16,17] in thalassemia major. Although chelation therapy benefits many patients, others continue to have organ dysfunction and die, sometimes despite intensive treatment with deferoxamine.[18] The reasons for these apparent differences in the response to chelation therapy are unknown.

We report here the results of a 10-year prospective study of patients with thalassemia major in whom we examined the relations among the amount of iron acquired by transfusion before chelation therapy, the total transfusional iron load accumulated, the amount of deferoxamine administered, the body iron burden as assessed by noninvasive measurements of hepatic iron stores, and clinical outcome as determined by periodic evaluations.

From the Departments of Medicine (G.M.B., J.W.H.) and Physics (C.J.A., D.E.F.), Case Western Reserve University, Cleveland; the Department of Mathematics, Moorhead State University, Moorhead, Minn. (C.E.M.); St. Jude Children's Research Hospital, Memphis, Tenn. (A.W.N.); and the Clinical Hematology Branch (P.M.G., N.S.Y.) and Cardiology Branch (E.E.T.), National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Md. Address reprint requests to Dr. Brittenham at MetroHealth Medical Center, 3395 Scranton Rd., Cleveland, OH 44109.

Supported in part by research grants from the Cooley's Anemia Foundation, the Food and Drug Administration (FD-U-000532), and the National Institutes of Health (AM-25105, DK-14370, HL-24198, and HL-42814).

METHODS

Patients

We studied 59 patients with thalassemia major (30 of whom were female and 29 male, ranging in age from 7 to 31 years when last seen) who were evaluated periodically in the Clinical Hematology Branch of the National Heart, Lung, and Blood Institute, National Institutes of Health. The patients were given transfusions of red cells as needed to raise their hemoglobin level from 8 to 9 g per deciliter to 12 to 14 g per deciliter. Each patient began deferoxamine therapy by the age of four or five years or at the time of the initial examination at the National Institutes of Health. The daily dose of deferoxamine prescribed was 1.0 g for patients 4 to 7 years old, 1.5 g for those 8 to 12 years old, and 2.0 g for those over the age of 12. The average prescribed dose was about 42 mg per kilogram of body weight per day (range, 27 to 65), to be taken at least five days each week. The drug was given by subcutaneous infusion overnight for 8 to 12 hours. Assessment of compliance showed that the patients took 20 to 90 percent of the prescribed dose. Two older patients in whom heart disease developed received the drug by continuous intravenous infusion (3 to 4 g per day) during the last three years of the study. This study included only patients for whom there were reliable histories of the number of transfusions received before they began deferoxa-

mine therapy and reliable information on the use of blood products and deferoxamine throughout the study.

Evaluation Procedures

At each follow-up visit, a detailed clinical and laboratory evaluation included an inventory of the number of transfusions and the amount of deferoxamine taken since the last visit. Each unit of blood transfused was considered to contain 4 mmol (225 mg) of iron. Pharmacy records were used to confirm the amounts of deferoxamine dispensed. The diagnosis of cardiac disease was based on symptoms, physical findings, and the results of noninvasive testing, including echocardiography and exercise radionuclide cineangiography in selected patients. Patients over 12 years of age who were not known to have abnormal glucose metabolism were evaluated with an oral glucose-tolerance test.

During the last six years of the study, hepatic iron stores were measured magnetically with a dual-channel superconducting quantum-interference susceptometer (Biomagnetic Technologies, San Diego, Calif.). This instrument and its validation as a method of providing measurements of hepatic iron that are quantitatively equivalent to those obtained by chemical analysis of tissue obtained by liver biopsy have been described elsewhere.[19-22] Serum ferritin was measured with a commercial kit (Ramco Laboratories, Houston).

Statistical Analysis

The Fisher–Irwin exact test was used to compare the proportions of patients in two groups formed with the use of dichotomous variables.[23] Multiple regression models were formed to determine the subgroup of independent variables most predictive of a dependent variable. Differences in the survival of groups were evaluated with the Kaplan–Meier product-limit method and the log-rank test.[24,25] Cox proportional-hazards regression with the likelihood-ratio test and the Wald statistic was used to investigate the effect of several variables on survival.[26,27] The proportional-hazards assumption was examined with use of Schoenfeld residuals.[28] The BMDP and S-Plus statistical computer packages were used for computations. All tests were two-tailed; a P value of 0.01 was considered to indicate statistical significance.

Results

Follow-up of the 59 patients with thalassemia major produced a cumulative total of 440 patient-years of observation. All the patients had been dependent on transfusions since infancy.

Magnetic Measurements of Hepatic Iron Stores

The body iron burden was assessed in 53 patients by noninvasive magnetic measurements of liver iron stores. Six patients died before this method became available. Hepatic iron concentrations ranged from nearly normal to more than 175 μmol of iron per gram of liver tissue (wet weight) (normal, 1 to 9).[19] To evaluate the effectiveness of deferoxamine in reducing the body iron burden, we examined the relation between the value determined by magnetic measurement and the ratio of the total transfusional iron load to the amount of deferoxamine used (expressed in millimoles of iron per kilogram, in relation to grams of deferoxamine per kilogram). As shown in Figure 1, the ratio of transfusional iron load to deferoxamine use, expressed in logarithmic form, correlated closely with the hepatic iron concentration (Pearson's R = 0.89, P<0.001). Multiple regression analysis demonstrated an independent effect of deferoxamine use on hepatic iron stores, both when deferoxamine use was consid-

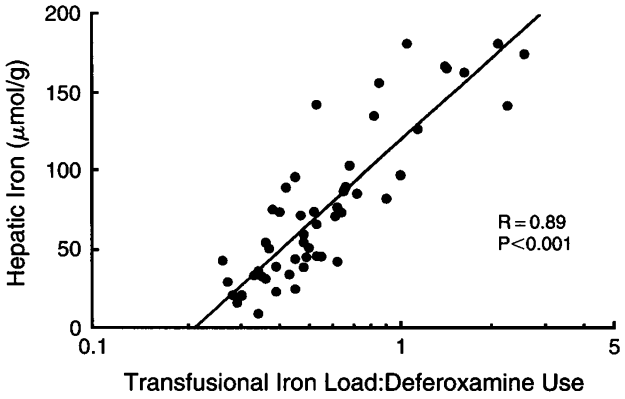

Figure 1. Relation between Hepatic Iron Concentration and the Ratio of the Total Transfusional Iron Load to Cumulative Deferoxamine Use in 53 Patients with Thalassemia Major.

The diagonal line is the simple linear least-squares regression line between the two variables. The ratio, determined in millimoles of iron and grams of deferoxamine, is expressed as a natural logarithm.

interacting with the transfusional iron load (i.e., as part of the ratio) (P<0.001 for each comparison). Regression analysis also revealed that 79 percent of the variation in hepatic iron concentrations could be explained by the variation in total transfusional iron and the ratio of the transfusional iron load to deferoxamine use. This result provided evidence of the accuracy of the data on iron from transfusions and on deferoxamine use.

Serum ferritin concentrations correlated significantly with magnetic measurements of hepatic iron stores in 52 patients (R = 0.72). Overall, the ferritin concentrations qualitatively reflected differences found on direct measurement of hepatic iron stores by magnetic means, but the concentrations of individual patients showed considerable fluctuations that were independent of changes in body iron stores.[21]

Complications of Deferoxamine Therapy

Although most patients reported some local irritation and swelling after subcutaneous infusions of deferoxamine, none of these patients had visual or auditory symptoms of neurotoxicity[29] or of the pulmonary syndrome reported in association with intravenous administration of deferoxamine at doses of 10 g per day or more.[30] No other complications of deferoxamine therapy were observed.

Glucose Metabolism

Glucose tolerance was evaluated in 54 patients who were over 12 years of age: insulin-dependent diabetes mellitus was found in 11 patients (20 percent), and glucose tolerance was impaired in 6 others (11 percent).

Cardiac Disease and Death

On enrollment, 2 of the 59 patients had heart disease that was not the result of uncomplicated iron overload and were excluded from further analysis

patients already had heart disease that was clinically considered due to iron overload: one patient had a history of pericarditis, the second had a history of transient congestive heart failure, and the third had an asymptomatic arrhythmia. Of the 54 patients initially free of heart disease, 12 (22 percent) later had cardiac dysfunction. Of the 57 patients evaluated for cardiac complications, 9 (16 percent) died; 2 of these already had heart disease at entry. Cardiac disease was the cause of death or a major contributor to the cause of death in all the patients who died. Clinical evidence of cardiac dysfunction in the six surviving patients was documented by noninvasive testing. The characteristics of the 15 patients who died or had cardiac disease due to iron overload are shown in Table 1.

Effect of Transfusional Iron Loading and Deferoxamine Use on Clinical Outcome

To assess the independent effect of deferoxamine on the relative risk of death, a proportional-hazards model was constructed in which age, transfusional iron load before the initiation of chelation therapy with deferoxamine, transfusional iron load after the initiation of deferoxamine therapy, and cumulative deferoxamine dose were used as predictor variables. The independent effect of deferoxamine remained significant after adjustment for the other predictors ($P = 0.007$). To assess the effect of deferoxamine when expressed as an interaction (i.e., as a ratio), a second model was constructed in which age, transfusional iron load before deferoxamine, transfusional iron load after deferoxamine, and the natural logarithm of the ratio of the total transfusional iron load to deferoxamine use were used as predictor variables. The effect of deferoxamine remained strong when expressed in terms of its interaction with the total transfusional iron load ($P = 0.007$). In this model, the estimated relative risk of death associated with an increase in the ratio of transfusional iron load to deferoxamine use was 12.6 (95 percent confidence interval, 2.4 to 65.4), implying that an increase of one unit in the natural logarithm of this ratio would increase the risk of death 12.6 times. Similar analyses were performed for the variables of impaired glucose tolerance, diabetes mellitus, and cardiac disease. The estimated relative risk of impaired glucose tolerance associated with an increase in the ratio of the transfusional iron load to deferoxamine use was 19.3 (95 percent confidence interval, 4.8 to 77.4), the relative risk of diabetes mellitus was 9.2 (95 percent confidence interval, 1.8 to 47.7), and the relative risk of cardiac disease was 9.9 (95 percent confidence interval, 1.9 to 51.2).

Clinical outcome was also examined after the patients were classified into four groups according to the pretreatment iron load and the amount of deferoxamine administered. The group of patients with the highest iron load before deferoxamine treatment and the lowest use of deferoxamine in relation to their total transfusional iron load was designated as group 1. The remainder of the patients were designated as group 2, which was subdivided into groups 2A, 2B, and 2C as shown in Table 2. Data on the four groups with respect to the transfusional iron load before chelation therapy and the ratio of the total transfusional iron load to cumulative deferoxamine use are summarized in Table 3; the distribution of the patients among these groups is shown in Figure 2.

To examine further the effects of transfusional iron loading and deferoxamine use on clinical outcome, the 23 patients with the highest transfusional iron load and the lowest deferoxamine use (group 1) were compared with the remaining 36 patients (group 2). The body iron burden of group 2, as assessed by measurement of the mean hepatic iron concentration, was

Table 1. Characteristics of the Patients Who Died or Had Heart Disease.*

Patient No.	Sex/Age (yr)	Pretreatment Transfusional Iron	Ratio of Total Transfusional Iron to DFO	Total Transfusional Iron	Cumulative DFO Use	Hepatic Iron	Plasma Ferritin	Heart Disease on Entry	Status at Last Evaluation
		mmol/kg	*mmol/g*	*mmol/kg*	*g/kg*	*μmol/g*	*ng/ml*		
1	F/24	16	0.8	28.8	35.2	135	8,334	Yes	Died with cardiac disease
2	F/21	14	1.0	37.1	36.0	158	6,777	No	Died with cardiac disease
3	M/18	15	0.8	19.5	23.3	NA	6,400	No	Died with cardiac disease
4	F/20	19	0.6	26.5	42.5	122	1,506	No	Living; abnormal cineangiogram
5	M/23	19	1.6	34.0	21.1	163	3,992	No	Living; ventricular tachycardia
6	M/26	11	1.4	27.6	19.7	167	5,910	Yes	Living; abnormal cineangiogram
7	F/24	30	1.9	43.5	23.4	206	7,669	No	Living; abnormal cineangiogram
8	M/15	22	0.7	35.3	49.3	85	5,766	No	Died with cardiac disease
9	M/25	23	1.3	26.5	19.8	120	4,400	No	Living; abnormal cineangiogram
10	M/15	35	1.7	54.6	32.4	NA	11,800	No	Died with cardiac disease
11	M/21	20	3.1	26.7	8.6	NA	5,780	Yes	Died with cardiac disease
12	F/21	18	1.1	35.1	33.3	182	6,123	No	Living; PVC, abnormal cineangiogram
13	F/24	18	2.1	39.4	18.8	182	9,023	No	Died with cardiac disease
14	F/22	17	0.9	21.5	22.7	NA	1,900	No	Died with cardiac disease
15	F/19	17	1.0	27.9	27.8	97	3,247	No	Died with cardiac disease

less than half that of group 1 (53 vs. 119 μmol of iron per gram of liver, wet weight; P<0.001). In addition, group 2 had a lower prevalence of cardiac disease (P<0.001), impaired glucose tolerance (P<0.001), and insulin-dependent diabetes mellitus (P = 0.01) that developed during the study (Table 3). All of the nine patients who died during the study belonged to group 1 (P<0.001). In this group, the probability of survival to at least the age of 25 years was 32 percent (95 percent confidence interval, 4 to 59 percent) (Fig. 3). When survival in group 1 over the 10 years of the study was compared with that in group 2, survival (adjusted for age) was significantly better in group 2 (L = 10.04, P = 0.0015 by log-rank test).

To examine factors associated with the observed differences in clinical outcome, group 2 was divided according to the transfusional iron load before the initiation of chelation therapy with deferoxamine: patients in group 2A had high pretreatment iron loads and effective chelation therapy, and those in group 2B had low pretreatment iron loads and effective chelation therapy. Group 2C included only two patients, who had low pretreatment iron loads and ineffective chelation and who have been omitted from the comparisons presented below. As shown in Figure 4, the mean ratios of the total transfusional iron load to deferoxamine use and the hepatic iron concentrations of groups 2A and 2B were similar (Table 3). There were no deaths in these groups and no significant differences between them in the prevalence of cardiac disease, impaired glucose tolerance, or diabetes mellitus (Table 3). Thus, differences in the prevalences of clinical complications in groups 1 and 2 could not be attributed to the inclusion in group 2 of patients (group 2B) who had lower transfusional iron loads before beginning deferoxamine therapy than the patients in group 1.

The patients in groups 1 and 2A, who had similar transfusional iron loads before the start of deferoxamine therapy but different ratios of the total transfusional iron load to deferoxamine use (Table 3), did not differ significantly in age, transfusional iron load before deferoxamine, or total transfusional iron load after the start of deferoxamine treatment (Fig. 4). The groups did differ with respect to chelation therapy; on average, the patients in group 2A used more than twice as much deferoxamine as those in group 1 (P<0.001) (Fig. 4). The greater cumulative use of deferoxamine correlated with a substantial decrease in the body iron burden: the mean hepatic iron concentration in the patients in group 2A was less than half that in the patients in group 1 (P<0.001) (Fig. 4). Groups 1 and 2A also differed significantly in clinical outcome: group 2A had a lower prevalence of impaired glucose tolerance (P = 0.009) and cardiac disease (P = 0.001) (Table 3). There were no deaths in group 2A, as compared with nine deaths in group 1 (P = 0.01).

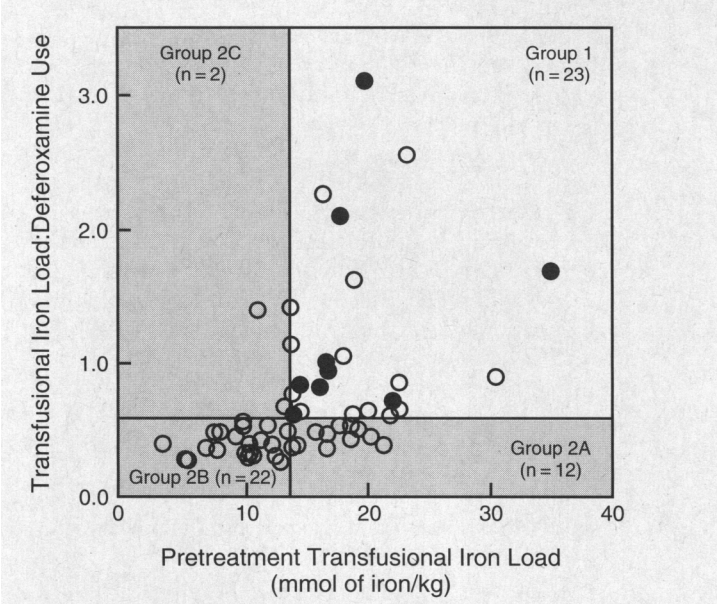

Figure 2. Relation between the Transfusional Iron Load before Deferoxamine Therapy and the Ratio of the Total Transfusional Iron Load to Cumulative Deferoxamine Use in 59 Patients with Thalassemia Major.

The vertical line denotes the geometric mean for the pretreatment iron load (14 mmol of iron per kilogram of body weight), and the horizontal line the geometric mean for the ratio (0.6 mmol of iron per gram of deferoxamine, expressed as a natural logarithm). The solid circles denote the nine patients who died during the study, and the open circles the surviving patients at their most recent evaluation. The means were used to group the patients (groups 1, 2A, 2B, and 2C are defined in the Results section, with details in Tables 2 and 3).

Table 2. Grouping of Patients According to Their Transfusional Iron Load before Chelation Therapy with Deferoxamine and the Effectiveness of Chelation.*

Group	Pretreatment Transfusional Iron	Ratio of Transfusional Iron to DFO	Description
	mmol/kg	*mmol/g*	
1	≥14	≥0.6	High pretreatment iron load, ineffective chelation
2A	≥14	<0.6	High pretreatment iron load, effective chelation
2B	<14	<0.6	Low pretreatment iron load, effective chelation
2C	<14	≥0.6	Low pretreatment iron load, ineffective chelation

*DFO denotes deferoxamine. In the 59 patients studied, the geometric mean of the transfusional iron load at the beginning of chelation therapy was 14 mmol of iron per kilogram (95 percent confidence interval, 12 to 16). The geometric mean of the ratio of the total transfusional iron load to cumulative deferoxamine use was 0.6 mmol of iron per gram of deferoxamine (95 percent confidence interval, 0.5 to 0.7). A pretreatment iron load was considered high if it equaled or exceeded the geometric mean (14 mmol per kilogram); chelation therapy was considered ineffective if the ratio of the transfusional iron load to deferoxamine use equaled or exceeded the geometric mean (0.6 mmol per gram of deferoxamine).

Discussion

We studied 59 patients with thalassemia major treated with regular parenteral infusions of deferoxamine for transfusional iron overload over a 10-year period. When each patient entered the study and periodically thereafter, we performed a clinical evaluation and obtained a

Table 3. Characteristics of Patients and Complications in Groups 1 and 2.

Group	Pretreatment Iron Load	Chelation	No.	Age*	Pretreatment Transfusional Iron†	Ratio of Transfusional Iron to DFO†	Impaired Glucose Tolerance‡	Diabetes Mellitus§	Cardiac Disease¶
				yr	*mmol/kg*	*mmol/g*	*% (no. affected/no. evaluated)*		
1	High	Ineffective	23	19.5 ±1.0	18.6 (11.3–30.6)	1.1 (0.4–2.8)	68 (13/19)	38 (8/21)	60 (12/20)
2			36	15.4 ±0.7	11.5 (4.8–26.9)	0.4 (0.2–0.8)	12 (4/33)	9 (3/33)	0 (0/34)
2A	High	Effective	12	17.3 ±1.1	17.5 (13.4–23.1)	0.4 (0.3–0.6)	17 (2/12)	17 (2/12)	0 (0/11)
2B	Low	Effective	22	13.7 ±0.7	9.0 (4.5–18.1)	0.4 (0.2–0.6)	0 (0/19)	0 (0/19)	0 (0/22)
2C‖	Low	Ineffective	2	27 21	11.1 13.3	1.4 0.7	Yes Yes	No Yes	Yes** No

*Values are means ±SE.

†Values are geometric means with 95 percent confidence intervals in parentheses. DFO denotes deferoxamine.

‡In affected patients an oral glucose-tolerance test showed a serum glucose concentration of less than 140 mg per deciliter (7.8 mmol per liter) at time zero, a concentration of 140 to 200 mg per deciliter (7.8 to 11.1 mmol per liter) after two hours, or a concentration above 200 mg per deciliter during the two hours.

§In affected patients an oral glucose-tolerance test showed a serum glucose concentration above 140 mg per deciliter at time zero or a concentration above 200 mg per deciliter after two hours or during the two hours.

¶In affected patients the resting ejection fraction was less than 45 percent, or the ejection fraction did not increase by at least 5 percent during exercise.

‖For group 2C, individual values are given for the two patients, not group means.

**Heart disease was present at entry.

detailed accounting of the number of transfusions received and the amount of deferoxamine administered. As part of the clinical evaluation during the last six years of the study, body iron burden was assessed with direct, noninvasive, magnetic measurements of hepatic iron stores. Measurement of hepatic iron is the most quantitative means of assessing the body iron burden in patients with thalassemia major.[31]

We found that the concentration of iron in the liver correlated closely ($R = 0.89$, $P<0.001$) with the ratio of the total transfusional iron load to cumulative deferoxamine use, expressed as a natural logarithm (Fig. 1). For a given total transfusional iron load, the principal determinant of body iron burden was the cumulative dose of deferoxamine that had been administered. Multiple regression analysis showed that the independent effect of deferoxamine administration in reducing hepatic iron stores was significant ($P<0.001$).

In evaluating factors influencing clinical outcome, we considered both the ratio of the total transfusional iron load to cumulative deferoxamine use and the extent of transfusional iron loading at the initiation of chelation therapy. The first factor provides a measure of the use of deferoxamine relative to the total transfusional iron, whereas the second provides a measure of the transfusional iron load before the start of deferoxamine therapy. Cox proportional-hazards regression analysis, with adjustments for age and the transfusional iron load before deferoxamine therapy, was used to estimate the increase in the relative risk of complications associated with each increase of one unit in the ratio of the transfusional iron load to deferoxamine use. Before one examines the results, one should put the magnitude of a difference of one unit in the natural logarithm of the ratio in clinical perspective by using regression analysis to estimate the corresponding hepatic iron concentrations and serum ferritin concentrations in the patients studied, also taking into account the considerable fluctuations in serum ferritin concentrations that occur independently of changes in body iron stores.[21] According to these approximations, a patient with a ratio of 2.8 would be expected to have a hepatic iron concentration of about 25 μmol of iron per gram of liver (wet weight) (1400 μg of iron per gram) and a serum ferritin concentration of about 900 ng per milliliter. For comparison, a patient with an increase of one unit in the ratio, to 3.8, would have an estimated hepatic iron concentration of about 100 μmol of iron per gram of liver (5700 μg of

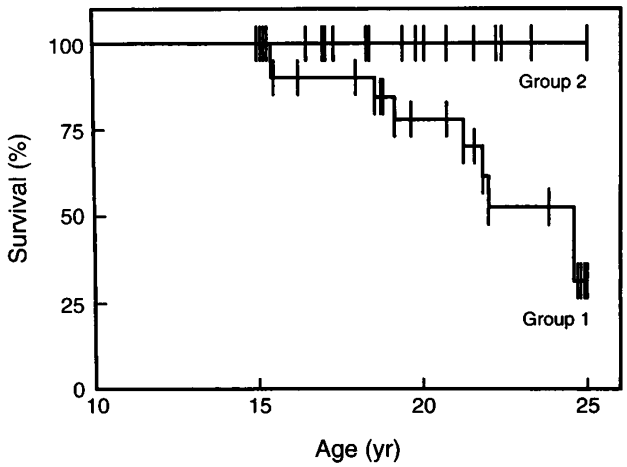

Figure 3. Life-Table Analysis of the Survival of the 38 Patients in Groups 1 and 2 Who Were 15 Years of Age or Older at Their Most Recent Evaluation.

Age-adjusted survival analysis indicated that the cumulative probability of survival to at least the age of 25 years was 32 percent (95 percent confidence interval, 4 to 60 percent) in group 1. A comparison of the survival distributions in the two groups over the 10 years of the study showed that survival was significantly better in group 2 ($L = 10.04$, $P = 0.0015$ by log-rank test).

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