

β -Thalassemia: the Lebanese experience

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Summary β -Thalassemia is a hereditary anemia that is quite prevalent in Lebanon. Most patients with β -Thalassemia are treated and followed up mostly at a multidisciplinary center, located in the suburban area of Beirut: the Chronic Care Center (CCC), operational since 1994. We will review the experience with β -Thalassemia accumulated through this institution. Four hundred and twenty five patients, aged 2 to 68 years are followed up at the CCC. Sixty four percent have thalassemia major (TM) while 36% have thalassemia intermedia (TI). Lebanese patients with TM receive periodic packed red cell transfusions to maintain a pre-transfusional hemoglobin level of 10 gm/dl at all times and desferrioxamine is the standard iron chelator in use. Since 1994, 12 patients with TM have died from complications of their disease, with heart failure being responsible for the majority of deaths. The incidence of cardiac, endocrinologic, and infectious complications will be reviewed. Finally, both current and prospective preventive measures will be discussed, specifically educational campaigns and premarital screening. The effects of prevention are starting to show as the number of newly diagnosed disease is diminishing.

Keywords β -Thalassemia, genetics, complications, treatment, Lebanon

Introduction

β -Thalassemia is a hereditary anemia characterized by absent to decreased synthesis of β -globin chains resulting in imbalance between α - and β -chains and consequent ineffective erythropoiesis and hemolysis (Schrier, 1997; Olivieri, 1999). The spectrum of clinical manifestations in this disorder is wide, ranging from the asymptomatic state to the lifelong transfusion dependency, with all its accompanying complications.

The two clinical forms of the disease requiring treatment are thalassemia major (TM) and thalassemia intermedia (TI). Patients with TM usually present in the first year of life and subsequently require regular transfusions and iron chelation to survive, whereas those with TI have a late presentation and may be transfusion-independent or require only sporadic transfusions.

β -Thalassemia is particularly prevalent among the Mediterranean populations. Previous reports about the disease coming from Lebanon (Cabannes *et al.*, 1965; Der Kaloustian, Naffah & Loiselet, 1980; Khouri *et al.*, 1986) have shown that the carrier rate is 2–3%, the disease is quite heterogeneous, and the homozygous form is severe and transfusion-dependent. In addition, α -thalassemia was found to be rare (Shahid, 1971) and IVS110 mutation was the commonest mutation seen in 62% of cases (Chehab *et al.*, 1987; Zahed *et al.*, 2000).

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In this study, we will review the experience of the Chronic Care Center (CCC), a multidisciplinary center, located in the suburban area of Beirut, and dedicated to the treatment of chronic diseases, including thalassemia and diabetes mellitus. In this comprehensive center, founded in 1994, patients with thalassemia receive the state of art care and free of charge.

Care at the CCC is multidisciplinary, as patients are treated and closely followed by a team of health professionals consisting of hematologists, endocrinologists, cardiologists, ophthalmologists, dentists, psychologists, social workers, and dietitians. All patients undergo complete assessment by the multidisciplinary team at least twice a year.

A number of patients receive care at the CCC while being also followed up separately by individual hematologists located close to their area of residence. The CCC and individual physicians co-ordinate care by communicating information, such as latest laboratory results, chelation regimen, transfusions schedule. Any relevant clinical information, such as hospitalization and concurrent illnesses are transmitted to the CCC team to be integrated in patients' medical records.

On another level, the CCC prevention program was launched in December 1994, in collaboration with the Ministry of Social Affairs and the Ministry of Public Health. The program consisted of two phases. The first phase focused on information giving, training of health-care professionals, and development of training material. A network has been established in the different regions of Lebanon.

The second phase aimed at disseminating knowledge and awareness among the general public. This phase also entailed a national screening program, as well as conducting research. The CCC trained social workers from the Ministry of Social Affairs to educate laypersons about thalassemia and its impacts on all aspects of life. This was an attempt to increase public awareness, as well as to dispel major misconceptions about the disease.

The great majority of Lebanese β -thalassemia patients receives treatment and is followed up at the CCC, and as such, the CCC's patient population is representative of the global β -thalassemia patient population in Lebanon. During its first few years of operation, a telephonic call was made for hematologists all over the country to refer their patients to the CCC. As a result, only a minority of patients with β -thalassemia are treated in private practice clinics. It is difficult to estimate the number of patients who are not followed up medically at all, but it is believed to be negligible as even the most socially and

economically deprived patients are able to receive treatment at the CCC.

Distribution and demographics

Four hundred and twenty-five patients, aged 2–68 years are followed in the CCC (Table 1). Sixty-seven percentage of patients belong to a young age group (below 20 years of age). Sixty-four percentage have TM while 36% have TI. Fifty-seven percentage are males, and 43% females. A high consanguinity rate (63%) is a distinguishing feature of the disease. Geographically, patients are homogeneously distributed all over Lebanon in contrast to patients with sickle cell disease who are clustered in specific regions of the country. As for religious distribution, the disease is much more prevalent among Muslims (82%) than among Christians and Druze. Demographically, Muslims, Christians, and Druze represent roughly 60%, 35%, and 5% of the population respectively. While the standards of care are the same regardless of religious or cultural background, the only demographic variable that seems to significantly affect patient compliance to treatment is the parental level of education. Moreover, among the parents of patients with β -thalassemia, roughly 70% have not reached high

Table 1. Demographic and clinical characteristics of thalassemia patients in Lebanon

Demographic and clinical characteristics	Percentage of patients
Age range (years)	
0–10	27
1–20	40
21–30	22
31–40	6
41–50	3
>50	2
Gender	
Males	47
Females	63
Religion	
Shia	42
Sunni	39
Maronite	11
Orthodox	4
Catholic	2
Druze	1
Clinical distribution	
TM	64
TI	36
Consanguineous parents	
Yes	63
No	37

TM, thalassemia major; TI, thalassemia intermedia.

school level, and the illiteracy rate is close to 15%. This lack of education is likely to be the most important impediment to the rapid success of prevention strategies. A fact that probably illustrates the impact of lack of education is familial clustering. Nearly one-third of families harboring β -thalassemia mutations carry more than one patient per family.

The disease and its demanding treatment modalities cause significant social impairment among thalassemics, as illustrated by a very high rate of unemployment (close to 70%) among patients above 20 years of age. Similarly, the rate of dropout from school is also considerably high with figures of up to 20% in prehigh school years.

Genotypes

Two hundred different mutations have been reported in β -thalassemia worldwide (Olivieri, 1999). In Lebanon, 18 different mutations have been described (Chehab *et al.*, 1987; Zahed *et al.*, 2000). In a study involving 110 Lebanese parents with β -thalassemia trait, the most common mutations seen were IVSI-110 (G \rightarrow A) mutation comprising 40% of the total, followed by IVSI-1, IVSII-1, IVSI-6 (Zahed *et al.*, 1997). The IVSI-110 is a severe mutation resulting in β^+ thalassemia. The high frequency of IVSI-110 mutation among Lebanese β -thalassemics has long been recognized (Chehab *et al.*, 1987). This contrasts with the Western Mediterranean Arab countries where Codon 39 is the most frequent mutation, found in up to 27% of Tunisian and Algerian thalassemics in comparison with 0.5% in their Lebanese counterparts (Zahed, 2001). Table 2 summarizes the most commonly encountered mutations among the Lebanese β -thalassemia patients population. As for TI, a mild mutation IVSI-6 (T \rightarrow C) was the most frequently observed mutation (occurring in more than 40% of β -thalassemia alleles) encountered in a study involving 73 patients (Table 3). This study has also

Table 2. Five most common mutations among 227 chromosomes of Lebanese β -thalassemics

Mutation	Number of chromosomes (%)
IVSI-110	67 (33.0)
IVSI-6	31 (15.0)
IVSI-1	30 (14.9)
IVSII-1	20 (9.9)
Codon 29	14 (6.9)

IVSI-1 (G \rightarrow A), IVSII-1 (G \rightarrow A).

Data from Zahed *et al.* (2000) with permission.

Table 3. Six most common genotypes among 73 Lebanese patients with thalassemia intermedia

β -Genotype	Number of patients (%)
Mild mutations	
IVSI-6/IVSI-6	23 (31.5)
cd29/cd29	8 (11)
IVSI-6/IVSI-110	7 (9.6)
-88/-88	3 (4.1)
<i>Xmn1</i> -positive	
cd30/cd30	9 (12.3)
IVSII-1/IVSII-1	4 (5.4)

IVSI-6 (T \rightarrow C), cd30 (G \rightarrow C), cd29 (C \rightarrow T), IVSI-110 (G \rightarrow A), -88 (C \rightarrow T).

Data from Qatanani *et al.* (2000) with permission.

shown that the presence of the *Xmn1* polymorphism reduced the clinical severity of the disease in the majority of patients. This polymorphism increases the production of γ -globin and fetal hemoglobin (HbF). In addition, it was shown that the α -thalassemias did not significantly contribute to the clinical severity, as α -deletions are almost always associated with an alleviating molecular defect (a mild β -globin gene mutation, or *Xmn1* polymorphism). Yet in accordance with reviewed literature, our experience does not show tight correlation between genotype and clinical phenotype (Camaschella & Cappellini, 1995; Olivieri, 1999; Qatanani *et al.*, 2000).

Treatment

Transfusion

Lebanese patients with TM receive periodic packed red cell transfusions to maintain a pretransfusional hemoglobin level of 10 g/dl at all times. Blood is screened for common pathogens and administered using a leukocyte-depleted filter and under supervision of a trained hematologist. In exceptional circumstances, blood transfusions are provided by other healthcare facilities, and the event is communicated to the CCC.

Transfused blood is irradiated only if the donor is a close relative in order to minimize the occurrence of graft vs. host disease.

Chelation therapy

The standard of care provided to thalassemia patients in Lebanon is in accordance with the recommendations of the Thalassemia International Federation (TIF). Desferrioxamine is the standard iron chelator used in Lebanon.

The vials are dispensed to patients for self-administration at home via the subcutaneous route. All required equipment, such as tubings and pumps are provided to patients for free. Intravenous desferrioxamine is only used to reverse iron overload-induced cardiomyopathy. The adequacy of chelation regimens is assessed via serum ferritin levels. A steady drop in ferritin levels was observed among 33 patients with TM treated with desferrioxamine (Figure 1). The mean level dropped from 2700 $\mu\text{g/l}$ in the year 1996 to 2000 $\mu\text{g/l}$ in the year 2004. These levels are still far from the desired target of 1500 $\mu\text{g/l}$; however, compliance to desferrioxamine treatment is a major issue of concern. Adherence to chelation regimen is assessed via returned empty vials and specific questioning of the family. In addition, psychological assistance is provided aiming for a better compliance to treatment, in addition to helping patients cope better with the condition in general. It is understandable that both thalassemia and its treatment pose serious psychological stresses on patients. Accordingly, and beginning from early childhood, all patients are routinely seen on a yearly basis by a psychologist for a general assessment, and more often depending on individual needs. While statistics are yet to be conducted, it is estimated that psychotherapy contributes significantly at improving patient well being, and compliance to treatment. Desferrioxamine, a hexadentate iron chelator administered parenterally, has been shown to provide significant improvement in cardiac function (Aldouri *et al.*, 1990; Miskin *et al.*, 2003). The survival and complication-free survival benefits of chelation have been well demonstrated in a large survival study underwent in Italy (Borgna-Pignatti *et al.*, 2004) where TM patients born among recent birth cohorts fared significantly better than patients born earlier. The most likely explanation was the wider implementation of desferriox-

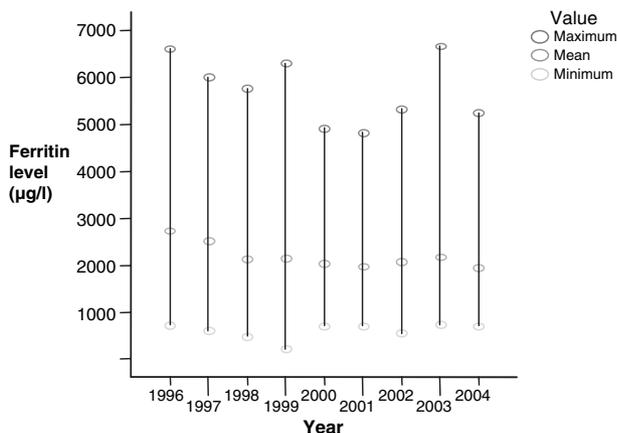


Figure 1. Serum ferritin trend among 33 Lebanese patients with β -thalassemia major followed up from 1996 to 2004.

amine protocols. To date, desferrioxamine is the only European and FDA-approved iron chelator (Cohen *et al.*, 2004) and is still the mainstay of chelation therapy in Lebanon. The desferrioxamine dosing regimen used in Lebanon depends mainly on the serum ferritin level and adequate iron chelation is assessed by means of serial serum ferritin measurements. Even though this test is influenced by many conditions as ascorbate deficiency, fever, acute infection, chronic inflammation, acute and chronic hepatic damage, hemolysis, and ineffective erythropoiesis (Olivieri & Brittenham, 1997), nevertheless, it could be correlated with clinical status above a certain threshold. Olivieri *et al.* (1994) have demonstrated this in a study, where a serum ferritin level of 2500 $\mu\text{g/l}$ and above could be correlated with cardiac disease.

The reference method for measuring iron burden is hepatic iron concentration measurement (HIC) through liver biopsy. Newer noninvasive methods, namely hepatic magnetic resonances are only recently showing promise as becoming the standard method for assessing iron overload (Cohen *et al.*, 2004; Wood *et al.*, 2005). This latter modality may be difficult to implement in Lebanon, where cost remains a primary concern and a major limitation.

Iron chelators other than desferrioxamine

Deferiprone (L1; Cohen *et al.*, 2004), an orally active iron chelator not licensed in Lebanon, is recently being administered in an ongoing clinical trial, to 40 TM patients who are intolerant to desferrioxamine. In a 5-year trial of deferiprone therapy in 12 TM patients (Taher *et al.*, 2004), a significant drop in serum ferritin was demonstrated. However, liver iron concentration was high at the end of the trial, leading to the conclusion that higher doses of L1 should be given, or L1 must be given in combination with desferrioxamine. In this trial, adverse effects were mild, mainly consisting of gastrointestinal upset. Of note was the absence of histologic evidence of liver fibrosis induced by L1. Another 2-year trial using a higher dose of L1 (100 mg/kg/day) was conducted in 12 TM patients (A. Taher, H. Isma'eel, G. Mehio, D. Bignini, A. Kattamis, E. A. Rachmilewitz, M. D. Cappellini, unpublished data). A decrease in mean serum ferritin level was noted, but there was a poor correlation with liver iron concentration of either regimen (Taher *et al.*, 2004, 2005). The side effects encountered were mild, with transient rise in alanine aminotransferase (ALT) in six patients, and a transient decrease in WBC count in two patients. One of those two latter patients was on interferon- α 2a as part of treatment for chronic hepatitis C,

and the neutropenia resolved after discontinuation of this medication. The other patient's WBC count returned to normal and did not necessitate discontinuation of L1. Other trials conducted in Lebanon have also suggested the effectiveness of deferiprone alone and in combination with desferrioxamine. Combination therapy has been shown to be more effective than desferrioxamine alone over a 12-month period (Mourad *et al.*, 2003). In this trial, 11 patients completed 12 months of combined therapy and 14 patients completed 12 months of desferrioxamine alone. Patients receiving combination therapy showed a more pronounced decrease in serum ferritin, and a greater increase in urinary iron excretion compared with patients on desferrioxamine alone. Concomitantly, side effects were similar and mild in both groups, the most notable side effect in the combination group being nausea during the first month. The main limitation of this trial was the difficulty in patient recruitment because of logistic and administrative reasons, thereby affecting the power of the trial. Conversely, in a long-term retrospective study conducted in 1998 among a small number of patients with TM ($n = 19$), L1 has been shown to lack effectiveness as an iron chelator, in addition to worsening liver fibrotic changes in five patients (Olivieri *et al.*, 1998).

Besides clinical trials, L1 is recently administered to patients with intolerance to desferrioxamine because of various reasons (e.g. severe skin reactions).

Deferiserox is a tridentate orally active iron chelator that is still in phase III clinical studies. In 2003, a randomized double-blind clinical trial, involving 24 patients with transfusion-dependent β -thalassemia was conducted to assess the safety and effectiveness of deferiserox at different escalating doses vs. placebo. The length of the study was 12 days (Nisbet-Brown *et al.*, 2003). The drug has shown to be highly selective for iron binding and produced a linear dose-dependent rise in net iron excretion. Except for mild skin rashes and gastrointestinal symptoms, no serious adverse effects related to the drug were recognized. Although run on a very short term, the results of this clinical trial were very promising.

Recently, 67 Lebanese β -thalassemia patients with transfusional iron overload are enrolled in an open-label multicenter trial on efficacy and safety of long-term treatment with deferiserox. The duration of therapy will encompass a year.

Splenectomy

A high percentage (90%) of Lebanese patients with TI have undergone splenectomy. The main indications for splenectomy in TI were a significant enlargement of the

spleen and a decrease in mean hemoglobin level in the absence of other transient factors such as infection. Patients are given heptavalent pneumococcal vaccine prior to the operation, followed by a 5-year penicillin prophylaxis period. The reason for the high prevalence of splenectomy (90% in Lebanon vs. 60% in Italy) is that TI patients in Lebanon were treated similarly to TM patients in whom splenectomy was traditionally recommended. This treatment modality was advocated before the data on hypercoagulable state in TI, and the associated increased incidence of thrombotic events postsplenectomy became known (Cappellini *et al.*, 2000).

Bone marrow transplantation

To date, there have been 17 allogeneic bone marrow transplantations performed in Lebanon and abroad: nine cases were cured of their disease. Five cases had recurrence of their thalassemia and or developed graft vs. host disease. Three cases died from transplant complications.

Mortality

Since the investiture of the CCC in 1994, a total of 12 deaths directly related to β -thalassemia have been reported. All were patients with TM with a mean age of 21 ± 11 years. For comparison, in a study conducted in Italy in 2003 (Borgna-Pignatti *et al.*, 2004) among 720 patients with TM born after 1970, 61 died (8%). Heart failure was the leading cause of mortality in Lebanon with 58% ($n = 7$) of patients succumbing to cardiac decompensation. Similarly, the Italian study reported heart failure to be responsible for 50.8% of the mortality. Infectious complications (mainly pulmonary) were responsible for 33% ($n = 4$) of deaths, compared with 14.8% in Italy. Most of the patients were born in the time period ranging from 1980 to 1991 (67%; $n = 8$). One patient was born in 1957. The period spanning 1980–1989 corresponds to the time-frame of the Lebanese civil war during which medical care and followup was precarious. Data about patients born from 1975 to 1980 is scarce; however, the mortality of β -thalassemia in Lebanon is recently estimated to be close to 4% among patients born after 1975.

Complications

Patients with β -thalassemia suffer from a variety of complications related both to the effects of chronic anemia as well as to those of iron overload. In addition, a

hypercoagulable state peculiar to thalassemia has been recognized (Eldor & Rachmilewitz, 2002). A recently conducted survey was performed in Lebanon to characterize complications between 66 TM and 44 TI patients (Table 4). In addition to patients' interviews and laboratory tests, all underwent trans-thoracic echocardiography, and were screened for hepatitis C virus (HCV) infection by antibody detection. Polymerase chain reaction was used as a confirmatory test in case of a positive screening test result.

Cardiac complications

Cardiac decompensation remains the primary cause of death in thalassemia worldwide (Cohen *et al.*, 2004). Cardiac complications can be divided into pump dysfunction and arrhythmias. Pump dysfunction is characterized by diastolic abnormalities followed by systolic dysfunction leading to death. Diastolic markers of abnormal relaxation patterns and impaired cardiac chamber compliance are not well defined in thalassemia. In a study involving 50 patients with TM, and 38 patients with TI (all with normal systolic function), a prolonged isovolumic relaxation time (IVRT) of the early phase of diastolic filling of the left ventricle was shown to be the earliest sign of diastolic impairment (Gharzuddine *et al.*, 2002). In the recently performed study outlined above involving 66 TM and 44 TI patients, patients with TI had a more prolonged IVRT than TM patients ($P < 0.05$; Isma'eel *et al.*, 2005a).

Table 4. Prevalence of common complications among 44 patients with TI and 66 patients with TM

Complication	TI ($n = 44$; % of patients affected)	TM ($n = 66$; % of patients affected)
Splenectomy	90	95
Cholecystectomy	85	15
Ejection fraction $< 50\%$	3	10
Pulmonary hypertension*	83	10
Thrombotic events	28	0
Extramedullary hematopoiesis	20	0
Leg ulcers	20	0
Hypogonadism†	5	80
Diabetes mellitus	3	12.5
Hypothyroidism	3	15

*Tricuspid regurgitation jet could be detected in 47% of TI and 30% of TM patients. Pulmonary hypertension defined as pulmonary artery systolic pressure (PASP) > 30 mmHg.

†Hypogonadism determined by history of infertility, and/or absence of secondary sexual characteristics on physical examination.

TM, thalassemia major; TI, thalassemia intermedia.

However, variation of diastole with heart rate and hematocrit level (pre- or post-transfusion) continue to be a significant confounding factor. In the same study, systolic failure defined as ejection fraction $< 50\%$ was found in 3% and 10% of TI and TM patients respectively. Similar to results reported by other groups, cardiac chamber sizes were found to be significantly larger in TI than in TM patients ($P < 0.05$; Isma'eel *et al.*, 2005b, unpublished data).

Recently, pulmonary hypertension (PHT) – defined as pulmonary artery systolic pressure (PASP) > 30 mmHg – is the primary cardiac pathology in patients with TI in contrast to a decrease in its prevalence among TM patients. The diagnosis of PHT greatly depends on the presence of a well-enveloped Doppler tricuspid regurgitant jet, which could be detected in 47% and 30% of the Lebanese cohort of TI and TM patients, respectively, described above. PHT has been shown to affect a high percentage of patients with TI (83%) in contrast to only 10% of patients with TM (Isma'eel *et al.*, 2005a, unpublished data) probably pointing to the difference in the pathophysiologic mechanisms operating in both conditions (Cappellini *et al.*, 2000). The high incidence of PHT in TI is likely to be an overestimate because only a subgroup of patients (47% of 44 TI) had a detectable tricuspid regurgitant jet, which could point toward a technical selection bias and the total number of patients studied was small ($n = 44$). Yet the findings are worrisome, and merit a larger scale study in order to better characterize this important complication of TI. It is worth noting here that short of right-sided heart catheterization, echo-Doppler remains the mainstay diagnostic modality of PHT; however, more accurate parameters for diagnosis are needed.

Several iron overload-mediated arrhythmias have been reported in thalassemia as supra- and infra-ventricular tachycardias, prolonged conduction times, and bundle blocks (Borgna-Pignatti *et al.*, 2004). Franzoni *et al.* (2004), from Italy suggested a possible role of signal-averaged electrocardiography to detect myocardial foci of ventricular tachycardias. This group reported ventricular late potentials (VLP) to be present in 31.9% of 19 TM patients. In the Lebanese experience, VLP could be detected in 3% of 66 TM and 4.8% of 44 TI patients, respectively, and none of these patients had ventricular tachycardia detected by 24-h Holter monitoring. Moreover, in a 7-year follow-up study, the incidence of VLP in Lebanese thalasseemics was 3.7% (Isma'eel *et al.*, 2005b). The Lebanese and Italian groups were comparable by age and left ventricular function, which leaves only speculative reasons of variation like possibly a difference in transfusion chelation therapy. Accordingly, we recently

find a limited role for signal-averaged electrocardiography beyond research purposes pending more extensive evaluation.

The role of magnetic resonance imaging (MRI) T2* to detect iron overload in the heart is recently the subject of intense research. The results so far show superiority of this modality over echocardiography and ferritin in detecting iron overload (Voskaridou *et al.*, 2004). This advantage is clear also in asymptomatic patients, and in patients with normal ejection fraction. However, the cost of MRI T2* and availability are serious limiting factors for patients in developing countries. The echocardiography-Doppler maintains its advantage over MRI because of its low cost and easy accessibility. Validation of the MRI available to usage in Lebanon for thalassemia patients is to be undertaken in the near future.

The role of antioxidant therapy in decreasing cardiopathy in thalassemia is a promising approach. L-Carnitine in pilot trials has shown favorable results. El-Beshlawy *et al.* (2004) reported improvement in cardiac function and decreased transfusion needs in TM patients treated with L-carnitine, thought to be due to an antiapoptotic effect of this drug. A possible role for L-carnitine in treating PHT in TI and TM remains to be examined. It is premature to make any recommendations regarding the use of L-carnitine based on the results of the above trials. Nevertheless, the ideal safety profile of this drug, its low cost, and its promising results render a multicenter trial justifiable.

Transfusion-related infections

Patients with transfusion-dependent β -thalassemia are at risk of acquiring viral infections as hepatitis B and C and HIV. Current statistics indicate that 0.3% of Lebanese thalassemic patients are HIV-positive, 0.3% are HbSAg-positive, and 8.5% are HCV-positive by polymerase chain reaction (PCR) analysis.

In a study published in 2002, the most frequent HCV genotype was found to be genotype 4 (37% of all genotypes; Ramia *et al.*, 2002). Genotype 4 is most prevalent in the Middle Eastern regions whereas the most common genotypes in the United States and Western Europe are 1a and 1b (Sharara, Hunt & Hamilton, 1996).

A randomized-clinical trial comparing the effectiveness of pegylated interferon- α 2a with or without ribavirin was conducted in Lebanon the results of which were recently published (Inati *et al.*, 2005). The study spanned 48 months and involved 20 TM patients. Combination therapy resulted in a sustained viral response in a higher percentage of patients (62.5%) than in monotherapy

alone (30%). This study was limited by the small number of patients enrolled and by an increase in transfusion needs in the combination therapy group secondary to ribavirin-induced hemolytic anemia. Despite the aforementioned limitations, an increase in chelation therapy because of increased transfusion needs was not necessary, and a return to pretreatment transfusion needs was noted after cessation of therapy. These results would probably make the benefit of combination therapy outweigh the risks of transient increased iron overload in this subset of patients.

Thrombotic complications

The hypercoagulable state in thalassemia has been recently characterized in a landmark study (Eldor & Rachmilewitz, 2002). Consequently, thrombotic events among patients with β -thalassemia are being increasingly recognized. The possibility of subclinical thrombosis has been suggested by brain MRI results of TI patients (Manfre *et al.*, 1999). In addition, a link between thrombosis, both clinical and subclinical and decreased mental ability in this population of patients may exist.

A case of pulmonary thromboembolism in TI with no other risk factors has been reported in Lebanon (Taher *et al.*, 2002). Thrombotic events are mainly noted in TI (Table 4). Among 44 Lebanese patients with TI, a thrombotic event was seen in 28%. Thrombophilia was not found to be more prevalent in thalassemia patients than in the general Lebanese population. In one survey (A. Taher, H. Isma'eel, G. Mehio, D. Bignmini, A. Kattamis, E. A. Rachmilewitz, M. D. Cappellini, unpublished data), stroke accounted for 9% and 28% of thrombotic events in TI and TM respectively. Moreover, in a recently concluded survey that included 8860 TM and TI in the Mediterranean area and Iran, thrombotic events were more venous than arterial (66% vs. 47%, $P < 0.05$; A. Taher, H. Isma'eel, G. Mehio, D. Bignmini, A. Kattamis, E. A. Rachmilewitz, M. D. Cappellini, unpublished data). Reports have clearly emphasized that splenectomy could be an underlying cause of hypercoagulability in this disease. Before the establishment of the CCC, the majority of Lebanese TI patients were treated as TM, and many of them were splenectomized. Nowadays, splenectomy is offered to few selected cases.

Endocrine complications

The pathophysiologic mechanism that results in endocrine dysfunctions is iron overload with deposition in various glands (Olivieri & Brittenham, 1997), thereby explaining

the higher prevalence of these disorders among patients with TM than in those with TI. Of 66 Lebanese patients with TM, 12.5% are diabetic, 15% have hypothyroidism, and 80% have hypogonadism, manifested by infertility or delayed sexual maturation and bone age. Osteoporosis is a well-documented complication of thalassemia. Bone mineral density (BMD) was measured in 29 Lebanese thalassemic children and 50 healthy controls (Yazigi *et al.*, 2002). Those with thalassemia had a statistically significantly lower height age, bone age, sexual maturation, absolute BMD values, and larger negative Bone Mass Density-Z scores than controls. BMD correlated significantly with the pretransfusion hematocrit, but not with other endocrine or bone metabolism parameter.

The primary treatment of osteoporosis is identification and correction of underlying causes most commonly hypogonadal hypothalamic dysfunction. Failure of this approach entails resorting to the use of bisphosphonates. The diagnosis of osteoporosis depends on the findings of a reduced bone mass density on Dual X-Ray Absorptiometry using Z-scores in children and T-scores in adults. The usually prescribed bisphosphonate is alendronate once daily or once weekly, given with dietary calcium and vitamin D supplements. The relatively high incidence of osteoporosis among thalassemia patients is an incentive to investigate medications with simple dosing regimen. Eighteen thalassemia patients (13 TM and five TI) were enrolled in a phase II clinical trial to demonstrate superiority of addition of zoledronic acid over placebo in comparison with 10 control patients over and above other needed therapy (A. Taher, H. Isma'eel, G. Mehio, D. Bignmini, A. Kattamis, E. A. Rachmilewitz, M. D. Cappellini, unpublished data). The results showed statistically significant increase in BMD over a 12-month period in the zoledronic-treated group in comparison with the placebo group. The limitations of this treatment modality arises from the limited number of participants, variation in the definition of osteoporosis in various age groups and need for longer term follow up to assess clinical response and decreasing fracture rate.

Extramedullary hematopoiesis

Abnormal facies, spinal cord compression, and pleural effusions have been observed in Lebanese TI patients with a prevalence of 20%. Conservative therapy with intensification of transfusions has been reported to reduce extramedullary hematopoiesis (Chehal *et al.*, 2003). Despite transfusions, some patients present a management challenge when imminent irreversible damage is at hand-like cauda equina syndrome. Localized radiotherapy is anecdotally reported to be effective in such conditions.

Leg ulcers

Leg ulcers are more common in older than in younger patients with TI, and overall, are more common than in TM. The skin at the extremities of elderly TI patients can be thin because of reduced tissue oxygenation, and this makes the subcutaneous tissue fragile and increases the risk of lesions from minimal trauma (Gimmon, Wexler & Rachmilewitz, 1982). The prevalence of leg ulcers is 20% and 0% in TI and TM patients respectively. Regular blood transfusions may provide some relief. There are some anecdotal reports about the use of hydroxyurea in combination with erythropoietin for the treatment of leg ulcers in thalassemia (Al-Momen, 1991). Contrary to the reports emerging from Iran (Karimi, Darzi & Yavarian, 2005); hydroxyurea has shown limited success in the Lebanese population. Initiation of blood transfusion/chelation therapy has proven more efficacious with complete resolution in 60% of affected cases and major decrease in size of the ulcers in the remaining patients.

Prevention

In Lebanon, premarital screening for thalassemia is mandatory. The recent screening tests are hemoglobin and red cell mean corpuscular volume (MCV). Hemoglobin electrophoresis is on its way to be implemented as the premarital screening test of choice. Even in the presence of confirmatory results, some couples still decide to conceive children. The Lebanese law has no restrictions on this issue contrary to the other Mediterranean countries such as Cyprus (Hoedemaekers & ten Have, 1998). The practice of prenatal genetic counseling is available in the country. Parents considered 'high-risk' (i.e. patients, carriers, close relatives of patients) are offered prenatal diagnosis through chorionic villous sampling and fetal cells DNA analysis (Table 5 summarizes the results of chorionic villous sampling performed since 2000). In Lebanon, different regulations concerning abortion exist among different religious sects, and this has its impact on decision-making for the couples at risk. Nevertheless, newly diagnosed β -thalassemia is becoming less frequent over the past few years (Figure 2). This can be attributed to increasing awareness, carrier detection, genetic counseling, and prenatal diagnosis.

Conclusion

β -Thalassemia is particularly prevalent in Lebanon, and poses a major public health burden. It is very heterogeneous both phenotypically and genotypically. The disease

Table 5. Number and outcomes of amniocenteses and chorionic villous sampling performed in high-risk pregnancies in Lebanon from January 2000 till July 2005

	Number
Year	
2000	11
2001	9
2002	13
2003	20
2004	9
2005	9
Outcome	
Normal	16
Affected	18
Carriers	37

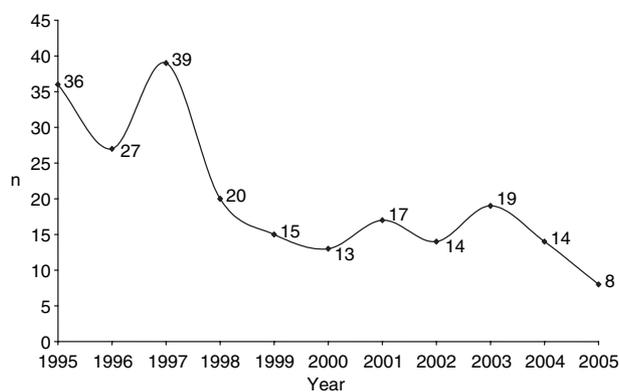


Figure 2. Line diagram showing the number of patients diagnosed with β -thalassemia from January 1995 till July 2005 in Lebanon.

is homogeneously distributed all over the country and is characterized by a very high consanguinity rate. With the foundation of the CCC and the introduction of comprehensive multidisciplinary care coupled with optimal chelation and safe transfusion, the outlook for patients afflicted with this disease has improved and the life expectancy of these patients is expected to increase. As patients are living longer, newer complications are appearing and these warrant careful and thorough attention and proper intervention. While it can be confidently said that the treatment of β -thalassemia has markedly improved in Lebanon, the task of controlling and treating all complications is monumental, and is extremely demanding on all involved parties, most importantly patients. As such, public education and disease prevention are the cornerstone of future strategies.

Fortunately the Lebanese experience with oral chelators seems promising but longer term trials are needed to ascertain the efficacy and safety of these drugs. It is

hoped that in the very near future, an orally available drug will take over desferrioxamine as a standard iron chelator and will improve the compliance and minimize the burdens associated with this highly effective but costly and cumbersome drug (Zahed *et al.*, 2002). The role of hydroxyurea in obviating transfusion requirements in TI patients and its long-term safety and efficacy are worthy issues to address in collaborative trials. Along with its mission to offer expert care, the CCC has, from the very beginning, set the standards for being a center for research in the field of hemoglobin disorders. Over the course of years, it has succeeded in initiating several pioneering trials aiming at abrogating and treating complications.

Finally, as illustrated in Figure 2, the prevention program at the CCC has been successful in educating the Lebanese about thalassemia as reflected by the decreasing number of newly diagnosed disease.

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