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Malignancies in Patients With β-Thalassemia Major and β-Thalassemia Intermedia: A Multicenter Study in Iran

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Background. Beta thalassemia is one of the most common genetic disorders in the world. The aim of this study was to determine the frequency, characteristics, and pattern of malignancies in patients with beta thalassemia major (BTM) and beta thalassemia intermedia (BTI) in Iran. ***Methods.*** We conducted a multicenter study via a retrospective chart review of patients with BTM and BTI between 2002 and 2007 in four thalassemia centers in Iran. A total of 4,630 records of patients with thalassemia were evaluated. Statistical analyses were done with SPSS software v. 15. *P*-values <0.05 were considered significant. ***Results.*** We detected 11 patients with beta thalassemia who also had malignant disease. Five patients (45.4%) were diagnosed with lymphoma and five with leukemia. The proportion of patients with cancer was higher in those with BTI. Cancer was diagnosed in patients with thalassemia aged 0–39 years, but not in any of the older patients. In patients with thalassemia overall and in patients with BTI, the highest age-specific rate of cancer incidence was seen in children <10 years old, whereas in the BTM group the highest incidence was observed in patients 20–29 years old. There were no statistically significant differences between patients with BTM and BTI and cancer regarding age, sex, splenectomy, hemoglobin, ferritin level, or malignancy type. ***Conclusion.*** The coexistence of malignancy and beta thalassemia is not rare. Any alarming signs and symptoms including worsening anemia, splenomegaly, or lymphadenopathy should be a motive for concern because these symptoms may signal malignant disease. Pediatr Blood Cancer 2009;53:1064–1067. © 2009 Wiley-Liss, Inc.

Key words: beta thalassemia intermedia; beta thalassemia major; Iran; malignancy

INTRODUCTION

Beta thalassemia is caused by impaired production of beta-globin chains and instability in the resulting excess alpha chains [1]. It is one of the most common genetic disorders in the world [2], especially in Mediterranean countries [3]. The number of beta thalassemia patients in Iran is among the highest in the world [4]: more than 20,000 patients with thalassemia major live in Iran and according to the latest epidemiologic data, with the highest prevalence of the disease in the north and south of the country [3].

With better treatment approaches and improvements in chelation therapy, thalassemia patients now live longer than before, so associated diseases such as cancers may be expected to develop more frequently [5,6]. However, the presenting symptoms of malignancies—anemia and splenomegaly—can be overlooked in patients with thalassemia and considered as complications of the underlying disease [7].

Few articles have reported the occurrence of malignancies among patients with thalassemia in different parts of the world. Some researchers have hypothesized that malignancies are more common in patients with thalassemia because of predisposing factors such as iron overload resulting in iron-induced oxidative damage, high levels of oxygen free radical, and high cellular turnover (especially in thalassemia intermedia). In addition, these patients are more prone to infections transmitted via transfusion—such as hepatitis—which increase the risk of cancer. The aim of this study was to compare the frequency, characteristics, and pattern of malignancies in patients with beta thalassemia major (BTM) and beta thalassemia intermedia (BTI) in Iran.

MATERIALS AND METHODS

We conducted a multicenter study via retrospective chart review of patients with BTM and BTI in different parts of Iran during 2002–2007. A total of 4,630 records of patients with thalassemia were evaluated. The patients were followed at four different thalassemia centers including Shiraz (southern Iran), Isfahan (central Iran), Tehran (north central Iran), and Amol (northern Iran). Table I summarizes the populations of patients with BTM and BTI at these centers. As these centers are located in different geographic parts of Iran and each of these centers is the referral center for patients from neighboring provinces, we believe that these centers and patients are reasonably representative of all patients with thalassemia in the rest of Iran.

The diagnosis of BTM was based on clinical history including regular blood transfusions, complete blood count (CBC), and hemoglobin electrophoresis. The diagnosis of BTI was based on clinical history including long intervals between transfusions or no history of blood transfusions, as well as CBC and hemoglobin electrophoresis.

All participating thalassemia centers are equipped with comprehensive laboratories for the required diagnostic tests including biochemical, hormonal, and genetic tests for prenatal diagnosis. All patients are routinely screened for hepatitis and HIV every 6 months by testing for HCV Ab, HIV Ab, and HBS Ag. The patients are routinely followed by hematologists, endocrinologists, cardiologists, and dentists.

The standard of care for our patients involves regular follow-up, blood transfusion every 2–4 weeks, and iron chelation therapy with deferoxamine (Desferal®) in patients with BTM. Patients with BTI have no need for blood transfusion or need only two or three

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TABLE I. Frequency of Patients With Thalassemia Major and Thalassemia Intermedia in Four Thalassemia Centers in Iran

	Patients with thalassemia major	Patients with thalassemia intermedia	Total
Centers	n	n	n
Shiraz	2050	250	2300
Isfahan	660	100	760
Tehran	950	150	1100
Amol	420	50	470
Total	4080	550	4630

transfusions per year. The decision to begin deferoxamine is based on a ferritin level of more than 1,000 ng/ml, and an initial dose of 20–50 mg/kg/day is given during 4–7 nights per week by deferoxamine infusion pump. The dosage is adjusted according to ferritin level. A leukocyte filter and packed cells are used for all blood transfusion.

The diagnosis of malignancy in patients with thalassemia was based on examination by a hematologist or oncologist, clinical investigation, laboratory data, and tissue diagnosis by an expert pathologist. Cancer patients are referred to a specialized oncology center at the same city for the treatment of their malignant disease.

Data were collected from the clinical records with an ad hoc data-recording form. For all patients with thalassemia and malignancy we recorded age, sex, type of thalassemia, serum ferritin, hemoglobin level, tissue diagnosis, malignancy type, HIV and hepatitis status as well as kind of treatment and response to treatment.

The study protocol was approved by the Research Ethics Committee of the Vice Chancellery for Research of Shiraz University of Medical Sciences. Written informed consent was provided by each patient with malignant diseases, or by one of the parents for the children included in the study.

Statistical Methods

We determined age-specific rates of cancer incidence in the study population (Table II). Data were analyzed with the Statistical Package for the Social Sciences (SPSS) v. 15, using the Mann–Whitney test for quantitative data (age, serum Hb, serum ferritin) and Fisher's exact test for qualitative data (sex, splenectomy, type of malignancy). *P*-values <0.05 were considered to indicate significant differences between patients with BTM or BTI who also had malignant disease.

RESULTS

We detected 11 cases of malignancy among 4,630 patients with thalassemia who resided in different parts of Iran between 2002 and 2007. This is a proportion of 0.002375 or about 0.24% of these patients. Mean age of the entire thalassemia patient cohort was 24.5 ± 1.5 years. Mean Hb and ferritin concentrations were 9.5 ± 0.3 g/dl and $1{,}621 \pm 255$ ng/ml, respectively.

Mean age of the patients with cancer was 18.6 ± 9.4 years with the minimum age of 6 years and maximum age of 35 years. Of the 11 cases, 8 (72.7%) were BTM. Five patients (45.4%) were diagnosed as having lymphoma, and five others were found to have leukemia. Only one patient (9%) was diagnosed as having a non-hematological malignancy. Demographic data and clinical characteristics of the patients with malignancy are presented in Table III.

Chemotherapy was started for all patients after diagnosis. Eight patients (72.7%) responded to treatment. Three of them died from postsplenectomy sepsis, diabetes and infection, and bleeding as a consequence of chemotherapy.

The proportion of cancer was calculated as 0.001960 (0.20%) in patients with BTM, and 0.005454 (0.54%) in patients with BTI. In patients with thalassemia overall and in patients with thalassemia intermedia, the largest value for age-specific rate of cancer was seen in the age range of 0–9 years, whereas in patients with thalassemia major the largest value was observed in the 20- to 29-year-old range.

Comparisons of the demographic and laboratory data between patients with thalassemia major and intermedia who also had cancer did not detect any statistically significant differences between the two groups regarding age, sex, splenectomy, hemoglobin, or ferritin level ($P > 0.05$). We found no statistically significant relationship between the type of thalassemia and the type of malignancy ($P > 0.05$).

DISCUSSION

In our study, the occurrence of cancer in patients with thalassemia was limited to age less than 39 years. The values of age-specific rates of cancer incidence in our patients with thalassemia were greater than age-specific rates of cancer incidence

TABLE II. Distribution of Cases of Cancer and Age-Specific Rates of Cancer Incidence in *Patients With Thalassemia* in Four Centers in Iran

	Thalassemia major			Thalassemia intermedia			Total		
Age range	Total number	Cancer cases	Age-specific rates	Total number	Cancer cases	Age-specific rates	Total number	Cancer cases	Age-specific rates
0–9	516	1	*32.29*	44	1	*378*	560	2	*59*
10–19	1,631	2	*20.4*	134	1	*124*	1,765	3	*28*
20–29	1,528	5	*54.5*	143	0	0	1,671	5	*49.8*
30–39	324	0	0	120	1	*138*	444	1	*37.5*
40–49	71	0	0	92	0	0	163	0	0
≥50	10	0	0	17	0	0	27	0	0

Age-specific rates of cancer incidence reported per 100,000 populations.

TABLE III. Demographic and Clinical Characteristics of Patients With Beta Thalassemia Major and Intermedia Who Had Also Cancer

Patient no.	Sex	Age	Hb[a] (g/dl)	Serum ferritin level (ng/ml)	Type of thalassemia	Type of malignancy	Type of treatment of malignancy	HIV/hepatitis status	History of splenectomy
1	Male	10	9.8	3,000	Major	Hodgkin lymphoma (classic type)	Chemotherapy	Negative	Positive
2	Male	6	11.1	1,100	Major	Hodgkin lymphoma (classic type)	Chemotherapy	Negative	Negative
3	Male	20	9.9	2,200	Major	Chronic myeloid leukemia (CML)	Chemotherapy	HCV positive	Negative
4	Male	16	8.3	1,023	Major	Acute lymphoid leukemia (ALL) (pre-B cell type)	Chemotherapy	Negative	Positive
5	Male	23	9	6,200	Major	Non-Hodgkin lymphoma (large cell type)	Chemotherapy	HCV positive	Positive
6	Female	28	7.7	869	Major	Acute lymphoid leukemia (T-cell type)	Chemotherapy	HCV positive	Positive
7	Male	25	9.4	1,400	Major	Non-Hodgkin lymphoma (classic type)	Chemotherapy	HCV positive	Positive
8	Female	24	10	3,500	Major	Hodgkin lymphoma (classic type)	Chemotherapy	Negative	Positive
9	Male	6	7.8	896	Intermedia	Acute myeloid leukemia (M4)	Chemotherapy	Negative	Positive
10	Male	12	11.2	1,100	Intermedia	Acute lymphoid leukemia (T-cell type)	Chemotherapy	Negative	Negative
11	Male	35	9.4	857	Intermedia	Osteosarcoma	Sugery + chemotherapy	Negative	Positive

[a]In patients with beta thalassemia major the pretransfusion value of Hb is reported.

in the general population under 39 years old in southern Iran which reported by Mehrabani et al. [8] are as follows: 8.41, 15.55, 14.37, and 27.27 in 100,000 population for the age ranges of 0–14, 15–24, 25–34, and 35–44, respectively. Benetatos et al. [2] identified 35 cancers in patients with beta-thalassemia in a review of articles published in the last 5 years. Zurlo et al. [9] reported death of eight patients with thalassemia major who developed malignancy. Suggested hypotheses for the possibility of malignancy in patients with thalassemia are iron overload with the mechanism of iron-induced oxidative damage, production of oxygen-free radicals and suppression of the tumoricidal action of macrophages as well as multiple transfusions which causes more exposure to transfusion-transmitted infections [2,10].

It may be worthwhile to point out that the patients with thalassemia and cancer in this study had mainly hematologic malignancies. Compared to our results, Otrok et al. [1] reported five cases of lymphoma occurring with beta thalassemia. Benetatos et al. [2] reported two cases of cancer including non-Hodgkin lymphoma and Hodgkin disease in patients with thalassemia, and in their review they showed that hematologic malignancies are the second most common cancer among patients with beta thalassemia. Panich et al. [11] reported that the coincidence of beta thalassemia and hematological malignancies was about 9.5%.

Tozzi-Cecchetti et al. [12] suggested that Epstein Barr virus (EBV) and chronic antigenic stimulation could be responsible for the development of lymphoma in patients with beta thalassemia. In addition, high cellular turnover of hematopoietic cells in these patients might predispose them to hematological malignancies (lymphoma and leukemia) more than to cancers of other origins. Taken together, it is very important to consider the possibility of hematological malignancies in patients with thalassemia who develop suggestive signs and symptoms including worsening anemia, hepatosplenomegaly, and lymphadenopathy which are common in hematological malignancies [13]. Moreover, leukocytosis in CBC of BTI patients may be always interpreted as high number of nucleated RBC in these patients despite the fact that the patient may have developed a hematologic malignancy.

As expected, we found a higher proportion of cancer in patients with BTI than BTM. This may result from the fact that bone marrow in BTM is suppressed due to regular transfusions, in contrast to the high bone marrow cell turnover in patients with BTI. This in turn can lead to a higher rate of DNA repair faults and mutations and therefore a higher rate of hematologic malignancies.

Hyroxyurea is increasingly used to treat thalassemia [14]; however, there is concern that hydroxyurea may increase the risk of malignancies. None of the patients with BTI in our study received hydroxyurea as a regular treatment, so we have not considered this as a confounding variable in our analysis.

On the other hand, many hypotheses have been proposed to explain the occurrence of malignancy in patients with sickle cell disease, which is similar to suggested mechanisms in thalassemia. These hypotheses include the transmission of infectious agents via transfusions, non-specific immunomodulation, and cellular damage with subsequent malignant transformation resulting from chronic organ damage and inflammation. Other possible factors include bone marrow transplantation and hydroxyurea [15]. Dawkins et al. [16] reported five cases of malignancy in sickle cell patients with a cancer incidence rate of 5/2,864 or 1.74 per 1,000 patient-years. Schultz et al. [15] reported 52 cases of cancer (49 patients) among 16,613 patients with sickle cell disease. The most common cancers

in pediatric patients were leukemia and Wilms tumor, whereas in adults the most common malignancies were solid tumors, especially carcinomas.

The causes of death in our patients with thalassemia who had also cancer appeared to differ from the most common causes reported in other series of patients with thalassemia. The most common cause of mortality in patients with thalassemia overall is cardiomyopathy and heart failure due to poor chelation therapy resulting in iron overload in different body organs, especially in heart [17,18].

In conclusion, this study in an Iranian cohort of patients with BTM and BTI showed that the coexistence of malignancy and beta thalassemia is not rare. Any alarming signs and symptoms including worsening anemia, splenomegaly, or lymphadenopathy should be a motive for concern because these symptoms may signal malignant disease, especially hematological malignancies. These types of cancer seem to occur more frequently than other types in patients with beta thalassemia.

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