



Review

Thalassemia and malignancy: An emerging concern?

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ABSTRACT

The thalassemias constitute a variable group of anemias that result from autosomal recessive inherited defects in the production of hemoglobin. The life expectancy of thalassemia patients has been extended over the last decades as a result of key milestones being achieved in optimizing management with transfusion and iron chelation therapy. Such advances have prolonged the survival of thalassemia patients and improved their overall quality of life. However, this increase in life expectancy has led to the manifestation of several morbidities, including multiple types of solid and hematologic malignancies. In this review we report the different types of solid and hematological malignancies that can develop in thalassemia patients, in addition to the possible predisposing factors and mechanisms behind their development.

1. Introduction

The thalassemias constitute a variable cluster of anemias characterized by a deficiency that affects the hemoglobin synthesis in one or more of its globin subunits [1]. Most thalassemia patients are born in resource-poor countries, but recent changes in migration patterns have led to the redistribution of this disease, where cases of thalassemia can now be found in areas such as Europe and North America. Thalassemia exists in several clinical forms which have been widely described. Besides an α/β -globin chain ratio imbalance, the hallmarks of the disease include ineffective erythropoiesis, chronic hemolytic anemia, and iron overload [2].

The thalassemia spectrum is clinically divided into two main categories based on the patient's need of blood transfusion. The category of transfusion dependent thalassemia (TDT) encompasses individuals with β -thalassemia major (β -TM), Bart's Hemoglobin, and severe forms of HbE/ β -thalassemia. These patients commonly present with severe anemia in early childhood, requiring a lifelong therapy of regular transfusions to survive [3]. On the contrary, non-transfusion dependent thalassemia (NTDT) patients usually present with mild to moderate anemia in a later stage of childhood or even in adulthood, requiring only occasional or short-course regular transfusions in certain clinical settings [3]. Patients with β -thalassemia intermedia (β -TI),

Hemoglobin H disease, and mild to moderate forms of HbE/ β -thalassemia belong to this category [4,5].

The establishment of optimal transfusion programs, and the application of aggressive iron chelation therapy (ICT) supported by advancements in magnetic resonance imaging (MRI), have led to an increase in the life expectancy of thalassemia patients. Such advances, however, could not fully eradicate the underlying pathophysiology. As such, with advancing age, several morbidities kept on emerging at a higher incidence [3]. For example, this increase in life span has paved the way for the development and subsequent diagnosis of more cancers, some of which may go undetected. While the increased prevalence of solid cancers has been noted, the occurrence of hematologic malignancies has been proposed to be even higher [6,7]. Moreover, different risk factors put thalassemia patients at greater risk of cancer development compared to the general population. These include iron overload-induced oxidative damage and immunologic aberrancies, immunomodulation caused by transfusions, viral infections, hydroxyurea use, and bone marrow stimulation due to chronic anemia. Therefore, in this review we report the different types of solid and hematological malignancies that can develop in thalassemia patients, in addition to the possible predisposing factors and mechanisms behind their development.

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1.1. Epidemiology of cancer in thalassemia

Studies looking at the relationship between thalassemia and malignancies are still scarce, with most of the epidemiological data coming nationwide multi-centers studies and few case reports [8]. Nationwide registries on mortality and morbidity in thalassemia patients have also reported cases of solid and hematologic malignancies. Borgna-Pignatti et al. in 2004 looked at the survival and complication appearance in a cohort of 720 Italian β -thalassemia major (β -TM) patients born after 1970, from seven different centers. Data from this registry showed that cancer was the fifth most frequent cause of death in this population after heart disease, infections, cirrhosis and thrombosis, with a prevalence of 3.6% [9]. Data from the UK Thalassaemia Register on the morbidity and mortality in 850 TDT patients between 1950 and 2003 showed two deaths (1%) due to hematological malignancies (one leukemia, one medulloblastoma), two deaths (1%) due to a hepatoma, and one death from carcinoma of the breast [10]. A longitudinal study on the overall survival, death type and incidence of a Greek cohort of 647 TDT patient showed that death was related mainly to myocardio-pathies, 76.5%, followed by sepsis, 7.8%, and AIDS, 6.1% [11]. One case of lymphoma was also reported [11]. More recent data on morbidity and mortality from the National Registry of Hemoglobinopathies in Greece (NRHG) reported 47 cases of HCC between the years 2000 and 2015 [12]. Most of these HCC-related deaths were seen in β -TM patients belonging to the 41–50 age groups. In β -TI patients, the majority of HCC-related deaths were observed between 61 and 65 years of age [12]. Eighteen cases of malignancy in this group, other than HCC, were also reported by the NRHG [12].

Furthermore, a retrospective cohort study was conducted in 2009 in four thalassemia centers in Iran involving 4630 patients with β -TM and β -TI between 2002 and 2007. This study by Karimi et al. focused on comparing the frequency, characteristics and pattern of malignancies in these patients, and reported 11 cases of malignancies, 5 of which were lymphomas and 5 were leukemias, indicating that hematologic malignancies are more frequent in thalassemia especially in β -TM patients [6].

Recently, a nationwide, longitudinal, population-based cohort study from Taiwan that was carried out by Chung et al. in 2015 included 2655 patients diagnosed with thalassemia between 1998 and 2010 with a total of 19,960 person-years of follow-up. Cancer was divided into several groups, and included hematological, abdominal, prostatic, uterine, head and neck cancers, among others. The study showed that the incidence rate of cancers in thalassemia patients was 3.96/1000 and 2.6/1000 person-years in the control arm. In conclusion, thalassemia patients had 1.47-fold overall risk of developing cancer compared with that of the comparison cohort after age, sex and comorbidities adjustment. In addition, patients with TDT were at a 9.31-fold risk for developing hematologic malignancies and 9.12-fold risk for developing abdominal cancer when compared to patients with NTDT patients. Women with thalassemia were also found to have 70% higher cancer risk compared to the control cohort [7].

1.2. Solid malignancies

1.2.1. Hepatocellular carcinoma

The two well established risk factors predisposing thalassemia patients who develop hepatocellular carcinoma (HCC) are iron overload and transfusion-transmitted viral infections, mainly Hepatitis C [5]. In TDT patients, iron overload is secondary to regular transfusions, while in NTDT patients, it develops from increased intestinal absorption, and increased release of recycled iron from the reticuloendothelial system (due to the suppression of hepcidin synthesis in the liver) [2]. Iron triggers a malignant transformation through induction of oxidation damage, which results in genotoxicity, or immunological aberrancies, thereby attenuating cancer immune surveillance [13,14]. In addition to iron overload, chronic Hepatitis C and B infection lead to

necroinflammation, either independently or in synergy with iron, although a direct role for Hepatitis B infection is not well defined [15]. Furthermore, Moukhadder et al. reported recently a case of HCC in an NTDT, hepatitis C-negative patient who had significant iron overload, which highlights the role of iron overload as a definite risk factor for HCC [16].

A retrospective study by Borgna-Pignatti et al. reported 22 cases of HCC in the entire population of Italian patients with thalassemia. Ten years later, the same group reported 62 new cases of HCC among 5,855 thalassaemic patients in the period between 2002 and 2012. These studies demonstrated that HCC is a substantial complication in thalassemia [14]. The incidence of HCC in thalassemia patients is increasing. After the introduction of iron-chelating agents in the management of thalassemia complications, better outcomes have greatly prolonged their survival. It should be noted that the role of ICT in the setting of HCC is still not clear. Additional factors such as alcohol consumption or obesity may also increase steatosis and oxidative stress, which in turn will accelerate liver iron uptake and increase the risk of liver fibrosis, cirrhosis, and cancer development in patients with β -thalassemia [17].

Screening thalassemia patients for early detection of HCC and iron overload using liver ultrasound and magnetic resonance imaging (MRI) is crucial to decrease mortality. HCC development can be avoided by preventing or treating the risk factors. Whereas prevention can be achieved, treatment tailored to the individual patient optimally provides the best outcome [14,18]. Treatment modalities shown to be safe and effective include surgical resection, chemoembolization, percutaneous radiofrequency thermoablation, and liver transplantation [5,14]. In addition, the kinase inhibitor Sorafenib was shown to improve prognosis at early stage HCC, although its efficacy is still doubted; 3 Italian thalassemia patients produced unknown outcome to Sorafenib treatment, as reported by Borgna-Pignatti and colleagues [14].

1.2.2. Thyroid carcinoma

The incidence of thyroid cancer (mainly papillary carcinoma) in thalassemia patients seems to be higher than that in the general population. In 2011, Poggi and colleagues were the first to describe 2 cases of thyroid cancer diagnosed in a population of more than 100 β -TM patients [19]. Subsequently, De Sanctis et al. reported 3 cases of papillary carcinoma in thalassaemic patients followed in Italy [20]. Both studies suggested that iron was responsible for the development of the disease in an analogy to liver disease, since all patients suffered from iron overload [8].

Several risk factors contribute to thyroid dysfunction in thalassemia patients. Thyroid dysfunction could result from pharmacological doses of iodide in the form of amiodarone administered to thalassemia patients with cardiac arrhythmias. Amiodarone is an iodide rich drug; it generates 6 mg of iodine a day, much higher than the optimal iodine intake (0.15 to 0.3 mg/day), which induces hyper- or hypothyroidism [20]. A higher prevalence of overt hypothyroidism (22.7%) as compared to controls (4.1%) was observed in thalassemia patients 3 months after starting amiodarone, which was resolved spontaneously after amiodarone withdrawal [21]. A 2013 population-based cohort study showed that amiodarone may be associated with an increased risk of cancer especially in males, with a dose-dependent effect [22]. In addition, an autoimmune-induced thyroid disorder was described during anti-IFN alpha therapy in cases of HCV-infected thalassemia patients, knowing that thyroid autoimmune disorders such as Hashimoto's thyroiditis are frequently associated with papillary thyroid cancer [23].

Regular and intensive combination therapy with deferoxamine (DFO) and deferiprone have shown to improve thyroid function in thalassemia patients with iron overload, although the time needed to reverse hypothyroidism varied according to patient age and iron load status [24]. Treatment by oral replacement therapy with synthetic L-thyroxine is classically used for overt hypothyroidism patients. L-thyroxine is converted to the active form of thyroid hormone; FT3, which has a half-life of 6 days. There is considerable variation in the patient

response to thyroxine, hence; adjustment of the dose is based on clinical observation. It should be noted that over-replacement with T4 may cause arrhythmias and bone loss; therefore, a close monitoring of TSH is recommended in hypothyroid thalassemia patients [25,26].

1.2.3. Renal cell carcinoma

The incidence of renal malignancies, such as renal cell carcinoma (RCC), and its relationship to thalassemia has also been studied. In 2014, Richi et al. was the first to report 3 cases of TDT patients diagnosed with RCC [27]. The average age of diagnosis was about 41 years of age. All 3 patients received different levels of nephrectomy depending on the aggressiveness of the tumor. Conversely, this high rate of RCC was not observed among another population with NTDT of comparable age. This shows evidence of a possible link between TDT and RCC [27].

Possible explanations for the increasing incidence of RCC in β -TM patients would be the increasing age of patients and iron-overloading [27]. Post-mortem studies performed on patients that received regular transfusion showed haemosiderin deposition in visceral and parietal glomerular epithelial cells of both convoluted tubules [28]. This deposition of iron in cells leads to the activation of reactive oxidative species which translates to cellular damage in animal models and humans [29,30]. That adds to the accumulating evidence confirming that iron-loading is a risk factor for cancer [30–32]. Another possible explanation is the activation of hypoxia-inducible factors via systematic or regional hypoxia [33]. Hypoxia has been associated with renal tumorigenesis renal cystic transformation which is constitutively activated in most of clear cell RCC [34,35]. Further studies are needed to investigate the exact pathophysiology that links β -TM and RCC.

1.2.4. Breast cancer

The incidence of breast cancer in β -TM is extremely rare. Only 2 cases were reported in the literature [10,36]. Opposing studies concluded with contradicting theories on the relation of breast cancer and different types of thalassemia. Studies supporting the positive correlation of breast cancer in thalassemia, in addition to other malignancies, hypothesized that the increased incidence compared to general population is due to predisposing factors including iron-induced oxidative stress, superoxide production, high cellular-turnover and increased risk of liver infections (hepatitis) [36]. An additional risk factor which is exclusive to females is hormone replacement therapy (HRT), which is prescribed to treat amenorrhea, infertility and pubertal failure (which are common in thalassaemic female patients). Hormone replacement therapy has been associated with an increased risk of breast cancer [37,38]. Different mammogram patterns among thalassaemic patients have been reported [39]. This might be an additional evidence showing pre-neoplastic symptoms but renders diagnosing thalassaemic patients with breast cancer using mammography a difficult task.

With advancements in ICT, the overall survival of thalassemia patients receiving regular transfusions increased [40,41]. The increased life expectancy of thalassemia patients increases the incidence of malignancies including breast cancer where a rapid increase of incidence is beyond the age of 50 [36,42]. Moreover, 2 studies conducted in China and Taiwan found no correlation between serum iron levels and breast cancer incidence [43,44]. Another study suggested that DFO has a role in breast cancer prevention [38]. However, the ineffectiveness of ICT may be linked with decreased risk of breast cancer. Deposition of iron in the skin might lead to less hormonal transcutaneous adsorption, less hormonal blood level and thus less effective HRT [36].

A summary of the solid malignancies in thalassemia reported in the literature is presented in Table 1.

1.3. Hematologic malignancies

1.3.1. Leukemia and lymphoma

Hematologic malignancies have been commonly diagnosed in

Table 1
Summary of the solid malignancies in thalassemia reported in the literature.

Reference	No. of patients	Thalassemia type	Type of cancer
Zurlo et al. [57]	1	TDT	HCC
Borgna-Pignatti et al. [58]	23	TDT, NTDT, HbS/ β -thal	HCC
Mancuso et al. [59]	1	TDT	HCC
Modell et al. [10]	2	NTDT	HCC
Fragatou et al. [60]	5	TDT	HCC
Restivo- Pantalone et al. [61]	9	TDT, NTDT	HCC
Maakaron et al. [62]	2	NTDT	HCC
Ansari et al. [15]	1	NTDT	HCC
Borgna-Pignatti et al. [14]	62	TDT, NTDT	HCC
Moukhadder et al. [16]	1	NTDT	HCC
Poggi et al. [19]	2	TDT	Thyroid
Govoni et al. [31]	5	TDT	Thyroid
De Sanctis et al. [20]	3	TDT	Thyroid
Ricchi et al. [27]	3	TDT	RCC
Picardo et al. [36]	1	TDT	Breast Cancer
Telfer et al. [63]	4	TDT	Unspecified

TDT: Transfusion-dependent thalassemia; NTDT: Non-transfusion dependent thalassemia; HCC: Hepatocellular carcinoma; RCC: Renal cell carcinoma.

thalassaemia patients as early as 1979, which is when the first two lymphoma cases were described. Based on data collected from several national centers reporting cases of Hodgkin's and non-Hodgkin's lymphomas and leukemias in the thalassemia population, it was found that these malignancies are mainly associated with β -TM and β -TI. This was highly supported by the nationwide study in Taiwan that showed a 5.32-fold higher risk of hematologic malignancies in thalassemia patients when compared to the general population, with a 9.31-fold higher likelihood of occurrence in those patients with TDT [8]. It is extremely difficult to differentiate between the worsening of thalassemia course and the emergence of hematologic cancers in these patients, especially with the absence of screening guidelines for these malignancies. Both leukemia and lymphoma can clinically present with deteriorating anemia, fatigue and splenomegaly, all of which can overlap with the clinical manifestations in thalassemia.

Although the understanding of the relationship between hematologic malignancies and thalassemia is still in the early stages, an increasing number of reports in this field have been released in the last few years [4]. Hodgkin's lymphoma was detected in a 7-year old girl who has history of β -TM with failure to thrive. Symptoms at presentation included fever, paleness, bilateral lymphadenopathy and hepatosplenomegaly. The diagnosis of Hodgkin's stage IV was made by an excision biopsy of one lymph node together with bone marrow biopsy that revealed its involvement [45]. Moreover, a case report from Turkey in 2014 described the case of a 12-year old boy known to have thalassemia since the age of 5 years, presenting with headache, pallor, abdominal distension and lymphadenopathies. The boy was found to have hyperleukocytosis, anemia and thrombocytopenia resulting from his acute lymphoid leukemia (ALL), confirmed by 90% blasts on bone marrow aspiration and positive B-ALL clusters of differentiation on flow cytometry [46]. One year later, Sherief et al. reported the first the case of ALL in a child with β -TM. The child presented with recurrent high grade fever, severe pallor and increased blood transfusion requirements, and his bone marrow aspirate showed 94% blasts with positive flow cytometry markers [47].

Furthermore, four out of 370 thalassemia patients treated in the Milan Thalassemia center in Italy were reported last year to be the first cases of thalassemia to be diagnosed with monoclonal gammopathy of undetermined significance (MGUS) [4]. All of the four patients were β -TI and fell in an age range of 34 to 48 years with three of them being exposed to blood transfusions. None of these patients progressed to

Table 2
Summary of the hematological malignancies in thalassemia reported in the literature.

Reference	No. of patients	Thalassemia type	Type of cancer
Schiliro et al. [64]	1	TDT	Lymphoma
Balestrazzi and Butturini et al. [65]	1	TDT	Lymphoma
Zurlo et al. [57]	2	TDT	Lymphoma, leukemia
Kaloterakis et al. [66]	5	HbS/ β -thal	MM
Elhadj et al. [67]	1	HbH/ α -thal	MM
Moschovi et al. [68]	1	HbS/ β -thal	HL
Jabr et al. 2006 [69]	1	NTDT	HL
Tozzi-Cecchetti et al. [70]	1	TDT	NHL
Chehal et al. [71]	1	NTDT	NHL
Richi et al. [72]	1	TDT	Cardiac NHL
Otrock et al. [73]	1	TDT	NHL
Benetatos et al. [74]	3	TDT, NTDT	NHL, HL
Karimi et al. [6]	11	TDT, NTDT	NHL, HL, CML, nonHem
Alavi et al. [75]	2	NTDT	HL, CML
Voskaridou et al. [76]	1	TDT	CML
Russo et al. [77]	1	TDT	ALL
Ruiz-Arguelles et al. [78]	1	TDT	ALL
Galanello et al. [79]	1	TDT	ALL
Perez-Saldivar et al. [80]	1	TDT	ALL
Palomo-Colli et al. [81]	1	TDT	ALL
Halawi et al. [4]	4	NTDT	MGUS

TDT: Transfusion-dependent thalassemia; NTDT: Non-transfusion dependent thalassemia; NHL: Non-Hodgkin's lymphoma; HL: Hodgkin's lymphoma; MM: Multiple myeloma; CML: Chronic myeloid leukemia; ALL: Acute Lymphoid Leukemia; MGUS: Monoclonal gammopathy of undetermined significance.

multiple myeloma; however, a case of 52-year-old female with HbH treated in the same center, was found to have multiple myeloma upon presenting with lymphadenopathy. The patient was treated with blood transfusions but never received any ICT [4].

1.3.2. Myeloproliferative neoplasms

The combination of myeloproliferative neoplasms and thalassemia is extremely unusual, albeit the few cases (4 cases) of concurrent β -thalassemia and polycythemia vera reported in literature [48]. However, the diagnosis of PV in thalassemia patients remains clinically challenging because of the antagonizing hematological effects and overlapping clinical features [49]. In one of the cases reported by Lopez et al., a patient was treated with ruxolitinib (JAK inhibitor) and an excellent response was achieved, with normalization of peripheral blood counts and disappearance of splenomegaly and other symptoms. Hence, the use of ruxolitinib was approved to be safe and efficient in the control of pathology in PV patient with thalassemia [48].

Table 2 summarizes the hematologic malignancies in thalassemia reported in the literature.

1.4. Possible mechanisms of malignancy in thalassemia

The actual mechanism of cancer development in thalassemia patients remains unclear, but many possible hypotheses may be valid (Fig. 1).

1.4.1. Iron overload and blood transfusion

Iron overload due to blood transfusions, is a risk factor for cancer development in both TDT and NTDT patients. Whereas regular transfusions lead to high level of serum iron, hepcidin suppression by anemia and ineffective erythropoiesis lead in its turn in non-transfusion state to increased iron absorption from the gut which accumulates in the cells causing redoxactivity and toxicity. When cellular iron levels increase beyond the ferritin synthesizing capacity of the cells, cell death and

organ damage were observed due to the generation of reactive oxygen species (ROS) and their consequent mutations [7]. Iron overload, due to chronic transfusions, has also led to an imbalanced immune regulation decreasing the antibody-mediated immune responses and mitogen-stimulated phagocytosis held by monocytes and macrophages, which can increase the risk of different infections. Furthermore, the effects of iron overload include an alteration in T-cell ratios with a decrease in the CD4/CD8 ratios, and modulation of cytokine activity impairing the generation of cytotoxic T cells that are responsible for fighting viruses and malignant cells, all of which may lead to cancer development [13,50].

Most of the data in the literature focuses on the anti-tumor effect of the iron chelating agents and their potential role in inducing the apoptosis of cancer cells. Many studies are also investigating the underlying molecular mechanisms of iron chelation in cancer therapy [51]. Recent data have emerged on the potential role of ICT in promoting cancer. Deferoxamine was found to enhance cancer migration and invasion in vitro in colorectal cancer cell lines via a process consistent with epithelial-mesenchymal transition [52]. The same effect of DFO in enhancing cancer cells metastatic potentials was seen in MDA-MB-231 breast cancer cell line through hypoxia-inducible factor-1 α (HIF-1 α) pathway that includes ROS generation and extracellular signal-regulated kinase (ERK) activation [53]. Moreover, in a study conducted on animal models, DFO promoted the growth of human Kaposi sarcoma xenografts in immunodeficient mice compared to the controls [54].

1.4.2. Viral infections

Blood transfusions carry the risk of oncogenic viruses' transmission that may lead to the development of hematologic malignancies in particular. Besides the Hepatitis C virus which was correlated to HCC, cytomegalovirus and Epstein-Barr virus have been identified in patients with TDT and are known to be associated with either Hodgkin's or non-Hodgkin's lymphoma [5]. The human T-lymphotropic virus type-1 (HTLV-1) may also be found in this patient population with a reported underlying relation in the pathogenesis of adult T-cell leukemia/lymphoma [5].

1.4.3. Bone marrow stimulus

It has been shown that NTDT patients exhibit both ineffective erythropoiesis and hypoxia which increase bone marrow stimulation and may also contribute to the induction of hematologic malignancies as myeloproliferative disorders characterized by JAK2/STAT5 erythropoietin driven erythroid hyperplasia [5]. It is possible that the increased bone marrow stimulation which induces the proliferation of erythroid progenitor cell lines, is also responsible for the expansion multiple additional cell lines, thereby prompting genetic aberrations that are implicated in the development of hematologic malignancies [5]. In fact, both CD341 cells and colony forming units-granulocyte/macrophage (CFU-GM) were elevated in the blood of thalassemia patients compared to non-thalassemic controls, also more in those who underwent splenectomy [55].

1.4.4. Hydroxyurea

Hydroxyurea has been used as a therapeutic modality in thalassemia to decrease transfusion needs. It is known to affect both DNA synthesis and repair, thus leading to mutations and subsequent chromosomal damage. Many concerns regarding the carcinogenic potential of this drug have been raised. However, to date, there is no evidence to suggest that hydroxyurea carries an increased carcinogenic potential in thalassemia patients and further studies are necessary to establish any possible relationship [5].

1.5. Importance of patient screening

Patients with thalassemia seem to be more susceptible than the

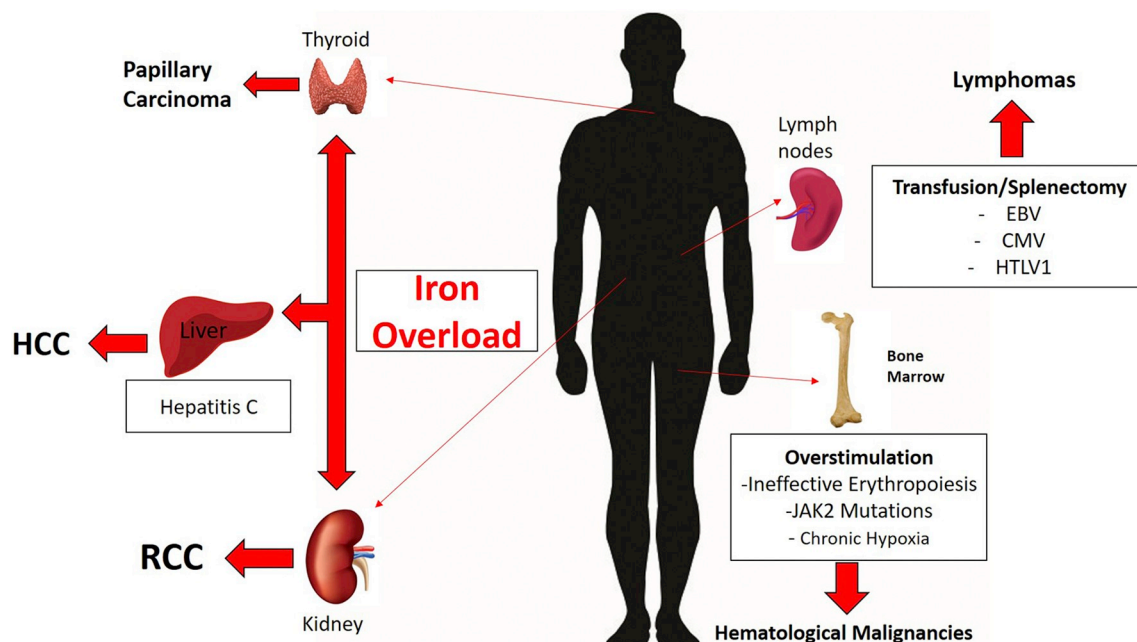


Fig. 1. Possible mechanisms of solid and hematologic malignancies development in thalassemia.

Several mechanisms can be involved in malignancies development such as Iron overload, leading to thyroid, hepatic and renal carcinomas, infections inducing lymphomas beside hepatic carcinomas and bone marrow overstimulation leading to different hematologic malignancies mainly leukemias.

HCC: Hepatocellular carcinoma; RCC: Renal cell carcinoma; EBV: Epstein-Bar Virus; CMV: Cytomegalovirus; HTLV1: Human T-lymphotropic virus 1.

general population to develop malignancies, especially at a younger age. Several factors can contribute to this increase in risk. As such, screening these patients for numerous types of cancer should be implemented. For example, HCC surveillance with ultrasonography should be performed at least once a year for all patients with TDT and biannually in patients with NTDT [8]. Caution should also be taken in the management of hypogonadism using hormonal therapy, as HCC development risk can be increased by androgens and estrogens excess might lead to breast cancer [8]. Novel therapeutic modalities for HCV are now available for those patients with chronic hepatitis that have either not tolerated or responded to previous therapies [8]. Although today the risk of receiving any hepatitis virus through contaminated blood is very low, emerging infectious agents may threaten the transfusion safety, requiring the optimization of new pathogen inactivation methods to alleviate the risk of infection [56]. The role of iron depletion should also be highlighted. Data has shown that iron could lead to the development of cancer and this risk is lowered through iron depletion. Phlebotomy could therefore be the procedure of choice following bone marrow transplantation. However, ICT will always remain the method of choice for TDT and NTDT patients [8].

2. Conclusions and future directions

In conclusion, the thalassemia population appears to be predisposed to a higher risk of developing malignancy. While these solid and hematological malignancies are manifesting and becoming more common due to the increase in lifespan of this population, several potential predisposing risk factors do exist. The actual mechanism behind cancer development in thalassemia patients remains unclear, but many possible hypotheses may be valid. Further studies are therefore needed to aid in determining the optimal methods for early diagnosis and management of malignancies in thalassemia patients. Ultimately, early recognition and management in patients who present with signs and symptoms is key.

Practice points

- Both TDT and NTDT patients have been found to be associated with 1.47-fold higher risk of malignancies, especially hematologic ones.
- Screening for several malignancies in all thalassemia patients should be performed based on the type of cancer and the presence of alarming signs for early diagnosis and treatment.
- Iron chelation therapy remains the main prevention method of malignancy development in TDT and NTDT patients.
- Besides implementing the use of the novel therapeutic agents of HCV, HCC can be avoided by yearly surveillance with ultrasonography performed at least once a year for all patients with TDT and twice a year in patients with NTDT.
- Screening for leukemia and lymphoma should be performed in thalassemia patients when overlapping symptoms as anemia, fatigue and splenomegaly are present.

Research agenda

- As data are still scarce, international multi-center studies are needed for a better understanding of the relationship between thalassemia and malignancies.
- Improvement in understanding on the role of iron overload in the development of solid and hematological malignancies.
- Establishment of a common international registry where all cases of malignancy in thalassemia patients are reported on a yearly basis is necessary.

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None.

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