Hepatocellular carcinoma in thalassemia: A critical review

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Abstract
Due to blood transfusions, thalassemics are often infected with either hepatitis C virus (HCV) or hepatitis B virus and often have hemochromatosis. Hepatocellular carcinoma (HCC) has emerged in thalassemics only recently as a result of the improvement in thalassemia outcomes. In fact, a prospective study estimated an HCC incidence in β-thalassemia of about 2%. Although data are scanty, HCC screening in thalassemics with risk factors for HCC should be carried out. HCV treatments have some efficacy in HCV infected thalassemics despite partial contraindication to ribavirin and iron overload. However, there are no data on how HCV treatment translates into HCC prevention. Preliminary data suggest that HCC treatment in thalassemics should generally have the same outcomes as in non-thalassemics. Although coexistence of severe comorbidities makes liver transplantation challenging, this therapeutic possibility should not be precluded for well selected HCC β-thalassemia patients. In fact, 2 transfusion dependent adult HCC β-thalassemia patients have recently undergone successful liver transplantation with a good outcome. In conclusion, HCC seems to be a developing issue in thalassemia and HCC screening should be carried out. HCC treatment, including liver transplantation, can be performed in selected patients. A multidisciplinary effort is needed for management.

Key words: Thalassemia; Hepatocellular carcinoma; Hemochromatosis; Screening; Complication; Liver transplantation

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INTRODUCTION
Thalassemias are rare inherited hemoglobin disorders resulting in chronic hemolytic anemia, endemic particularly in the Mediterranean Area and South-East Asia[1]. Depending on severity, two clinical forms are distinguished: thalassemia major (TM), characterized by severe anemia starting during the first year of life, requiring lifelong transfusion therapy for survival, and thalassemia intermedia (TI), characterized by later onset and generally milder anemia, permitting survival without regular transfusion therapy[2].

Due to blood transfusions, many patients with β-thalassemia are infected with either hepatitis C virus (HCV) or hepatitis B virus (HBV), particularly those who were born before the 1990s[3]. Moreover, most of the patients have hemochromatosis, which is the main cause of morbidity and mortality. In the past, HCC was not a known complication of thalassemia probably because many patients did not survive long enough to develop the condition and also because there was insufficient attention to the issue. In fact, many patients died at a young age, mainly due to heart failure. Recently, the outcome of thalassemia has improved and chronic organ damage, in
particular end-stage liver disease, has become a frequent complication. Better outcome is related to the improved treatment of iron overload with iron chelating drugs in the management of thalassemia complications, particularly heart disease, and in the prevention of infectious diseases secondary to blood transfusion.

Hepatocellular carcinoma (HCC) is a complication of cirrhosis and it affects prognosis. Occasionally, HCC can develop on a cirrhosis-free liver if other risk factors are present. Nowadays, a range of well-established treatments exist that can improve survival of HCC patients. In this paper, the knowledge of HCC in thalassemia will be updated. This review deals with patients with both TM and TI and excludes other thalassemia syndromes, such as Sickle cell/beta thalassemia that are clinically similar to Sickle Cell Disease and quite different from TM and TI.

EPIDEMIOLOGY OF THALASSEMIA-ASSOCIATED HCC

Awareness of HCC as a clinical complication of thalassemia has developed in the last few years. In the past, many patients did not survive long enough to develop HCC. In fact, many patients died at a young age, mainly due to heart failure. Recently, the outcome of thalassemia has improved and chronic organ damage, in particular end-stage liver disease and HCC, has appeared as a frequent complication. In fact, a recent multicenter retrospective study on patients with different thalassemia syndromes, identified 22 cases of HCC in Italian patients, 19 of whom were affected by either TM or TT. Furthermore, a prospective study was conducted on HCC incidence in 108 thalassemia patients (38 with TM and 70 with TI; median age 36.8 yr) screened with liver ultrasound imaging. Seventy-two (31 TM, 41 TI) with one or more risk factors for HCC (iron overload in 72, HCV infection in 46, HBV infection in two, liver cirrhosis in 10) and 33 (4 TM, 29 TI) without risk factors were included in the study; three were excluded (1 with a previous diagnosis of HCC on Child-Pugh class C cirrhosis, and two patients who were under 18 years old). All patients with iron overload were treated with at least one iron chelating drug. Once a liver focal lesion was found at ultrasound, HCC diagnosis was confirmed following current guidelines. Overall, two of the 72 with at least one HCC risk factor were found to have a newly developed HCC, with an estimated HCC incidence in thalassemia of about 2%/y.

Moreover, other new cases have been recently discovered, suggesting that HCC is becoming one of the leading clinical problem in thalassemia (unpublished data). Finally, if the future trend confirms an increase in the number of HCC in thalassemia, it would be reasonable to recommend HCC screening of all thalassemia patients with some risk factor since this could allow early treatment, leading to improved outcomes.

HCC PREVENTION IN THALASSEMIA PATIENTS

Currently, there are no effective tools for preventing HCC in thalassemia. Since hepatic disease is multifactorial in thalassemia, the theoretical possibility of preventing HCC is based on the possibility of preventing or curing HCC risk factors, namely hemochromatosis and chronic viral hepatitis, mainly due to HCV.

Hemochromatosis is a known risk factor for HCC. Treatment of iron overload with iron chelating drugs is certainly the leading reason why thalassemia outcomes have recently improved dramatically. Since subcutaneous or intravenous deferoxamine was first shown to be an effective chelating agent, new oral drugs have been developed which have proven as effective as deferoxamine with better compliance. Moreover, as recent evidence suggests, the use of multiple chelating drugs taken either concomitantly or sequentially seems likely to be the future route for iron overload treatment in thalassemia.

However, while thalassemia outcomes have been improving in recent years mainly because of iron chelation, HCC has emerged as a new complication, suggesting perhaps that current chelating regimens alone are not effective enough to prevent HCC.

Treatment of HCV-related chronic hepatitis in thalassemia using different kinds of interferon with or without ribavirin has had variable results in a number of small trials. Overall, most of the studies reported some efficacy. However, in addition to the rather small number of patients treated, there remain concerns about the safety of ribavirin. In fact, ribavirin increases not only the number of responders but also increases the need for blood transfusion.

Based on the information currently available, there is no evidence suggesting that HCV treatment can translate into HCC prevention in thalassemia. However, it is plausible that prevention of HCV infection due to blood transfusion will, in future, result in a reduction of HCC in thalassemia.

Potential treatments of thalassemia-associated HCC

Since survival of patients with thalassemia has dramatically improved in recent years, thalassemia should not be considered a contraindication per se to HCC treatments that are effective in non-thalassemia patients.

To date, there is little published evidence concerning the treatment of HCC in thalassemia. However, both percutaneous radio frequency thermalisation and ethanol injection, surgical resection and chemoembolization (unpublished data) have been shown effective and safe for the treatment of HCC in selected patients with thalassemia. Recent determinations of the therapeutic efficacy of sorafenib showed some significant improvement in prognosis for earlier stage HCC. It is, as yet, unknown whether sorafenib will be beneficial for the HCC associated with thalassemia.

A special mention should be made of the possibility of
liver transplantation in thalassemia patients. In fact, choice of the best treatment for HCC in thalassemia remains controversial. In particular, the possibility of treating HCC or end-stage liver disease with liver transplantation has long been rejected because of organ shortage and because thalassemia is considered a contraindication. Only one combined heart and liver transplantation has been reported and the outcome is currently not known\(^3\). The recent demonstration of improvements in thalassemia outcomes should prompt a reconsideration of this issue\(^4\). It is no longer reasonable that thalassemia should be considered a contraindication to liver transplantation, provided there is not any significant co-morbidity, namely heart disease and severe pulmonary hypertension\(^5\). In fact, encouraging results in this regard have been achieved in recent studies from the author’s team, which showed successful liver transplantation in 2 transfusion dependent thalassemia patients at 2 different Liver Transplantation Units. Post-transplantation outcome has been satisfactory in both cases after 6 mo and 2 years follow-up evaluations, respectively. Of course, a multidisciplinary effort is needed for management.

CONCLUSION

Thalassemia is a rare disease in which the appearance of HCC as a complication is mainly the result of recently improved outcomes in developed countries. Preliminary data suggest an incidence of HCC in thalassemia of about 2%. However, since thalassemia is endemic in many under-developed countries where patients are probably not screened for HCC, it is possible that present knowledge of this issue represents only the tip of an iceberg.

Periodic liver ultrasound HCC screening should probably be considered for thalassemia patients with risk factors for HCC.

Prevention of HCV infection through blood transfusion is nowadays the only known evidence-based means to prevent HCC in thalassemia.

HCC treatment in thalassemia patients should be the same as for non thalassemic HCC patients. Although coexistence of severe comorbidities makes the role of liver transplantation challenging, this therapeutic possibility should not be precluded for well selected HCC thalassemia patients. Of course, a multidisciplinary effort is needed for management of transplantation patients.

Many of the considerations reported in this review are extrapolated from scanty data that surely lack comprehensive evidence and they are mainly the personal opinion of the author. Multicenter international studies should be performed to strengthen these data.

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