THE RISK OF HEPATOCELLULAR CARCINOMA IN PATIENTS WITH THALASSEMIA. A REVIEW

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[Summary]

Patients with thalassemia major, intermedia or double eterozygous with sickle cell disease are exposed to a major risk of developing hepatocellular carcinoma (HCC).

Transfusion-transmitted viral infections and long standing iron overload represent principal carcinogenic risk factors.

Every effort should be made to prevent tumor development, whose prognosis is usually dismal, or at least to make an early diagnosis. Screening should be performed regularly by means of ultra-sonography (US) and measurement of serum alpha-fetoprotein (AFP).

Key words: hepatocellular carcinoma, thalassemia syndrome, risk factors, iron overload, surveillance

[RIASUNTO]

I pazienti affetti da talassemia major, intermedia o doppia -pano-talassemia sono esposti a un rischio più elevato di sviluppare epatocarcinoma.

Le infezioni virali trasmesse mediante trasfusioni ematichhe e il sovraccarico epatico di ferro ne rappresentano i principali fattori di rischio. L'epatocarcinoma ha una prognosi molto infausta; i pazienti dovrebbero pertanto essere sottoposti a regolari programmi di sorveglianza mediante dosaggio dell’AFP ed US per consentirne una diagnosi precoce o, laddove possibile, la prevenzione.

Parole chiave: epatocarcinoma, talassemia, fattori di rischio, sovraccarico di ferro, sorveglianza

[Introduction]

Life expectancy in patients with thalassemia syndromes in the last decades has been greatly improved permitting the appearance of new complications.

Mortality from cardiac disease decreased, although it remains the most common cause of death; in contrast an increased incidence of malignancy-related death has been observed.

The first case of Hepatocellular Carcinoma (HCC) in thalassemia was described in 1986 in an Italian patient.

In 2004 a survey of Italian centers revealed 23 cases of HCC, 37% in patients with thalassemia major, 47% with thalassemia intermedia and 16% in patients with sickle-thalassemia.

The median age of diagnosis had been 45 ± 11 yr and the mean ferritin level was 1981 ng/ml (±1592); 90% of patients were HCV positive, while 47% were HBV positive. All the affected patients died as a consequence of the tumor.

HCC occurs predominantly in patients with cirrhosis, but reports have appeared of carcinoma occurring, although far less commonly, in persons with bridging fibrosis without definitive cirrhosis.

[Pathogenetic factors]

Iron overload and carcinogenesis

In thalassemia major transfusion therapy leads to excess iron accumulation in many organs resulting in tissue damage.

In thalassemia intermedia patients do not require frequent transfusions.

However, progressive iron overload still occurs due to increased gastrointestinal (GI) iron absorption.

Studies in thalassemic patients showed that the rate of iron uptake from the GI tract is approximately 3 to 4 times greater than normal.

This increased iron absorption could be related to an inadequate hepcidin production due to persistent ineffective erythropoiesis (IE) which leads to an endless iron need by the erythroid marrow independent of iron store.

Extreme IE and hypoxia are able to override the expected increase in hepcidin due to high liver iron concentration, whereas in conditions of relatively mild anemia (thal intermedia), the level of expression of hepcidin is likely determined by both the relative degree of iron load and the erythropoietic rate.
A recent study published in 2007 demonstrated that IE dictates the pattern of iron distribution: in conditions of extreme IE, there is relatively little peripheral destruction of red cells and iron accumulates more rapidly in the liver than in the spleen, consistent with the interpretation that iron loading results primarily from increased intestinal absorption. This iron hepatic overload could be associated to carcinogenesis.

In untreated patients with genetic hemochromatosis HCC represents the second cause of death after cardiac disease.

The carcinogenic role of iron includes direct and indirect effects. In hepatoma cell lines iron enrichment enhances proliferation.

It has been suggested that the presence of hepatic iron-free foci, which are considered to be dysplastic lesions in hemochromatosis patients, represents rapid growth of early HCC that may outpace the availability of iron stores. The excess iron in adjacent nonneoplastic tissue could be used to maintain tumor growth.

Free or non-transferrin-bound iron may promote carcinogenesis through a number of possible mechanisms most of which are mediated via increased production of reactive oxygen species, inactivation of tumor suppressor genes (e.g. p53 mutation) and lipid peroxidation with impaired DNA repair.

Peroxidative damage to membrane-bound lipids results in altered membrane permeability as well as disruption of metabolic processes via inactivation of lipid-dependent enzymes and increased lysosomal fragility. Reactive oxygen species also accelerate hepatic fibrosis to cirrhosis by activation of stellate cells and by the profibrogenic effects of lipid peroxidation.

Finally iron could lead to immunologic abnormalities that may be associated with decreased immune surveillance for malignancy. The alteration of immunoregulatory balance can induce suppression of complement system and of tumoricidal action of macrophages, impairment of lymphocyte proliferation and modulation of cytokine activities, enabling the increased growth of cancer cells.

These assumptions suggest a protective role of iron chelation therapy against carcinogenesis.

Desferroxamine (DSF) is known to have an antitumor effect on leukemia and neuroblastoma, through its effect on cell cycle control molecules and on NF-kB, its protective effect against the reactivating effects of oxygen radicals and, finally, its depressive effect on protooncogene expression.

Viral hepatitis and HCC

Due to blood transfusion, patients with beta thalassemia are often infected with either HBV or HCV. The hepatotropic viruses include hepatitis B, C and G (HBV, HCV and HGV).

The prevalence of infection of these viruses in multitransfused patients is very different in different parts of the world and it is directly related to the frequency in that population. In 1992, a serologic pattern of previous HBV infection was found in 19% of French and in 34% of Italian patients, but in 56 to 66% of Indian patients.

HCV infection is widely diffused among thalassemia patients who had been transfused before 1989 when the virus was identified and before a systematic screening of blood units was performed.

Recent data from the Cooley Care Cooperative Group have reported the presence of HCV antibodies in 85% of multitransfused Italian patients, while 23% of patients tested positive in 1990 in the United Kingdom, 34% in France and 21% in India.

In the USA, a third of the transfusion-dependent thalassemia patients were found to have antibodies against HCV. Of these, one third were RNA positive. Unfortunately, HCV infection rarely resolves spontaneously, becoming chronic in 70% to 80% of infected individuals.

Most patients remain asymptomatic for a long period, with liver cirrhosis developing after approximately 30 yr. The risk of cirrhosis seems to be directly related to age at infection.

Chronic hepatitis C with cirrhosis (CHC) is recognized as a major risk factor for HCC; patients with either HBV or HCV infection have a 3-5% per year risk of HCC development. Asian studies reported an annual incidence of hepatocarcinoma in CHC patients of 4-10%, European studies of 0.5-5%, and American studies of 0.1-0.3%. Several early reports have shown that the risk of HCC increases with the degree of liver fibrosis.

In the Inhibition of Hepatocarcinogenesis by Interferon Therapy (IHIT) study, published in 1999, the relative risk was 24 times higher in patients with stage F4 fibrosis (cirrhosis) than in those with stage F0 or F1 fibrosis.

The annual incidence varied from 0.5% among patients with stage F0 or F1 to 7.9% among patients with stage F4.

Preventing HCC

Transfusion of safe blood products is of paramount importance in preventing viral infections.

The risk of chronicity of HBV is around 5%.
A DNA-recombinant vaccine, safe and efficacious, is available and should be administered to all patients who have not yet been infected. The residual risk of transfusion-transmitted infections associated with the window-period donations is extremely low in industrialized countries, especially after the introduction of nucleic acid amplification testing (NAT) technology to screen blood donations, but it remains significant where the prevalence of infection in the population is high.

In addition, intensive chelation and good compliance to chelating agents can prevent the accumulation of iron, the second most important factor in liver carcinogenesis.

**Role of therapy of Hepatitis**

The Inhibition of Hepatocarcinogenesis by Interferon Therapy (IHIT) program studied the effect of interferon therapy on the incidence and prevention of HCC compared with an untreated control group. The annual incidence was lower among interferon-treated patients (RR 0.516) than among untreated-patients at the same stage of liver fibrosis.

In particular the difference was not significant among patients with less advanced liver fibrosis (stage F0 or F1), but it was significant among patients with F2 or F3 fibrosis, and it approached significance among patients with stage F4 fibrosis.

Interferon (IFN) has been proven effective in reducing and eliminating HCV from the circulation, in decreasing serum alanine aminotransferase (ALT) levels, and in improving the histological appearance of the liver in patients with CHC.

Several studies, mostly from Japan, suggested that long term treatment with IFN-based regimens slowed progression of fibrosis and reduced the occurrence of HCC in persons with chronic hepatitis C-virus infection. Recently many investigators have compared treatment with IFN alone or in combination with ribavirin.

IFN-a-2b or pegylated IFN (Peg-IFN) N plus ribavirin seem to be more effective for eradicating HCV than IFN monotherapy.

However, it has not been yet evaluated whether the combination therapy could reduce the development of HCC. Moreover, combination therapy appears able to induce a sustained virologic response (SVR) in a significant proportion of patients with IFN monotherapy-resistant chronic hepatitis C suggesting that a viral relapse after IFN therapy is efficiently suppressed by combination with ribavirin.

Interferon has also been used in the treatment of chronic hepatitis B for decades. A recent study showed that this therapy prevents or delays the development of liver cirrhosis and HCC in patients with chronic hepatitis B.

**Other causes**

Other viruses responsible for transfusion-transmitted infections are EBV, human herpes virus-8 (HHV-8), cytomegalovirus (CMV) and human T-cell Lymphotropic virus-1 (HTLV-1).

HHV-8, HIV, EBV are known to be implicated in B-cell lymphomagenesis, while HTLV-1 has been found to play a role in the pathogenesis of adult T-cell lymphoma/leukemia.

An association between hematological malignancies and hemoglobinopathies could be explained by a long standing hemopoietic stress.

Expression of onco genes has been observed during stimulated erythropoiesis in animal models.

Finally multiple blood transfusions in patients with thalassemia induce a modulation of host immune system. Transfusion-related immomodulation (TRIM) could be associated with cancer recurrence.

**Therapy**

Potentially curative therapies are available for early HCC. Surgical resection could be considered if tumor is <5 cm in diameter, with an accessible location and in presence of an adequate residual liver function. Radiofrequency thermal ablation (RF) and percutaneous ethanol injection (PEI) have been employed in the treatment of small hepatocellular carcinoma (HCC) as curative treatments.

A recent study demonstrated that RF ablation seems superior to PEI in the treatment of small HCC with respect to overall survival and tumor response. Moreover, RF shows a significantly smaller risk of local recurrence. Locoregional therapies are useful as bridging therapy for patients awaiting liver transplantation and as palliative therapies in patient with unresectable HCC. Liver transplantation may be considered as last option for patients with HCC.

**Surveillance**

The frequency of HCV infection in patients with thalassemia and the fact that they are almost uniformly iron overloaded, expose this population to a high risk of HCC.
Given the fact that the mortality due to HCC is very high, it is important to institute adequate surveillance. The two main methods to detect early HCC are ultrasonography (US) and the measurement of alpha-fetoprotein (AFP). US screening should be performed regularly in thalassemia syndromes particularly when there is either HCV or HBV infection or significant iron overload because it can allow early detection and treatment of HCC.

The sensitivity of US is operator dependent, but it has been reported to be >60%, while specificity is >90% and positive predictive value is 70%. Although elevated serum AFP level in patients with CHC has been shown to be a significant independent predictor of the development of HCC, AFP levels are sometimes elevated in patients with chronic hepatitis and cirrhosis who have no evidence of HCC.

AFP sensitivity and specificity depend on the cut-off level used. When a cut-off level of 20 ng/ml is used, specificity has been reported to be 99% while sensitivity has been reported to be 94% in HBV-carrier patients and 60% in cirrhotic patients. Associated with serum AFP level at baseline, further independent predictive factors are hepatic inflammation and serum albumin level. Persistent active inflammation in the liver, that is one of the most important factors influencing serum AFP level, results in hepatocarcinogenesis.

Hepatic inflammation could also be expressed by serum ALT levels; patients with serum ALT levels less than two times the upper limit of normal are at reduced risk for HCC.

In a recent study based on univariate analysis, older age, lower BMI, lower WBC and platelet count; lower albumin level, higher level of alkaline phosphatase, AST, ALT, AFP, DCP and the presence of esophageal varices were significantly associated with HCC.

Conclusion

Patients with thalassemia major, intermedia or double etozygous with sickle cell disease, are at risk of developing HCC, a tumor whose prognosis is usually dismal, unless the diagnosis is made very early. Every effort should be made to prevent its development or at least to make an early diagnosis.

Screening should be performed regularly once or twice a year by means of US and measurement of serum AFP. Older patients with chronic hepatitis who have not had a sustained virologic response to IFN therapy should be followed with special attention.

References


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