LETTERS

Recombinant Interferon-alfa therapy in children with chronic hepatitis B and cured cancer

The incidence of hepatitis B infection is high in children receiving cancer chemotherapy, and the infection tends to be chronic.1,2 Chemotherapeutic agents may reduce antibody titers against hepatitis B virus (HBV) and may cause reappearance of hepatitis B surface antigen (HBsAg) in some patients. In patients with pre-existing HBsAg, such therapy may lead to activation of the infection.3 It is important to stop viral replication in those children in order to prevent chronic hepatitis B infection. It has been shown that interferon (IFN) increases HBV clearance rate.4 Although the data are sparse, IFN is also beneficial for chronic hepatitis B in children with lymphoblastic leukemia or solid tumors.5,6 We evaluated the efficacy of treatment with recombinant IFN-alfa in eight children with cured cancer who had chronic HBV infection.

Eight children (4 boys), aged 6-15 years, with various malignancies were enrolled into this study. They all completed chemotherapy at least two years ago and were free of malignancy at enrollment. Inclusion criteria were positive HBsAg, hepatitis B "e" antigen (HBeAg) and HBV DNA at the completion of chemotherapy and for at least six months more. All were asymptomatic and had normal abdominal ultrasonography. ALT values were high in five patients and fluctuated in three patients, within the 6-month period before treatment. Mild hepatitis was observed on liver biopsy in five patients. Clinical and laboratory features are shown in the Table.

After written informed consent was obtained from the parents/guardians, patients received 5 million units/m² body surface of recombinant IFN-alfa 2b (Intron-A; Schering-Plough, USA) subcutaneously, three times a week for 6 months. They were seen every three months during treatment and during follow up for 6-18 months. At each visit, HBsAg, HBeAg, anti-HBs and anti-HBc were determined by radioimmunoassay kits (Axsym; Abbott, USA) and HBV DNA in serum by molecular hybridization through hybrid capture (Ditogene; Maryland, USA; cut-off 5 pg/mL).

Complete response, defined as clearance of both HBV DNA and HBeAg and seroconversion to anti-HBe, was observed in two patients (case no. 7 at end of therapy, and case 3 at 3 months after discontinuing IFN). During follow up, both patients remained HBV DNA negative and anti-HBe positive. Case 5 had a decrease in HBV DNA levels without clearance of HBeAg. No patient cleared HBeAg during the study period. Initial elevated ALT levels normalized in only the two patients with complete response. All patients tolerated treatment well.

There are conflicting reports on the effect of IFN on HBV infection in children with malignant diseases. In the study by Rokicka-Milewska et al.,7 23 children with chronic hepatitis B and leukemias/lymphomas were treated with IFN-alfa 3 million units/m² body surface for 6 months, after completion of chemotherapy. Complete elimination of HBeAg was not achieved in any of the children, although HBV DNA activity decreased during the treatment. Contingut el at8 obtained a complete response rate of 25% with IFN therapy in 12 children with cancer and chronic hepatitis B infection. The dose and duration of IFN therapy were similar to our study. In our study, 2 of 8 children cleared both HBV DNA and HBeAg and seroconverted to anti-HBe. The discrepancies between these studies may be due to different dosages of IFN or ethnic differences. It is possible that higher IFN dosages are more effective.9 In our group, it is difficult to say whether the type of malignancy was a predictor of response to IFN therapy, but all six non-responders had lymphomas whereas the two responders had neuroblastoma or acute lymphoblastic leukemia.

IFN-alfa treatment may thus be beneficial in children with chronic hepatitis B and cured cancer.

Nurten Koçak, Hasan Özen, Inci Nur Saltık, Ayse Yüksek, Figen Güraşan
Department of Pediatrics, Gastroenterology Unit, Hacettepe University İhsan Doğramaci Children's Hospital, Ankara, Turkey

References


Table: Clinical and laboratory features

<table>
<thead>
<tr>
<th>Case</th>
<th>Age 1 (years)</th>
<th>Age 2 (years)</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Follow up (mo)</th>
<th>ALT (IU/L)</th>
<th>HBV DNA (pg/mL)</th>
<th>Clearance of HBeAg</th>
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<td>&gt;2000</td>
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</table>

Age 1: Age at diagnosis of malignant disease; Age 2: Present age; NHL: Non Hodgkin lymphoma; ALL: Acute lymphoblastic leukemia; BT: Before treatment; AT: After treatment; EP: At end of follow-up period

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Hepatitis B virus: healthy carrier or chronic infection?

Dr Naik's comments on my musings are interesting. I was happy to see him endorse the use of the term hepatitis B 'carrier' for a subgroup of patients. However, his approach is a bit different from mine in some aspects, probably because we practise with different clientele.

Dr Naik feels that "no useful point is served by discussing hazy issues with patients." I feel all issues are hazy for a patient; unfortunately, even doctors understand little of the pathogenesis of many diseases. Dr Naik also wishes that detailed discussions be held only with individuals who demand more information. In my experience, almost everyone, including the illiterate, wants to understand what is happening to him, and why. It's a different matter that the halo and the rush of patients surrounding doctors may intimidate him into silence.

I have been taught that a 'clinical picture' is not just a photograph of a sick man, but of a patient surrounded by his home, his work, his acquaintances and his emotions. Neglecting these factors is as unscientific as neglecting to control conditions which may affect an experiment.

Incidentally, the title of my comment was meant to convey that our knowledge of a virus questions our definitions of health - not that a virus would grill a physician. I stated that a scientist armed with 'molecular vision' may find few persons free of infection, and hence our definitions of health may need re-evaluation.

The case in point is a patient with hepatitis B infection who is clinically, biochemically and histologically normal, and has cleared HBsAg as well as HBeAg, but remains at risk of recrudescence some unknown time in the future due to some HBV DNA (inactive episomal form or replicative form), we do not know) lying dormant in the liver. Is this person healthy, or is he suffering from chronic hepatitis B infection?

A C Anand
Department of Gastroenterology, Command Hospital (WC), Chandimandir 134 107

References

In the article on hepatitis B 'carriers', it seems there is disproportionate emphasis on semantic interpretations, with ultimately the consensus being the same as to what to advise a person detected to be HBsAg positive.

I am surprised that although Dr Tandon confirmed that his HBsAg-positive individuals were negative for HBeAg, IgM anti-HBc and HBV DNA, Dr Naik would like to disregard a normal ALT finding and requests repeated ALT testing. Even assuming that transient ALT elevation may be seen, it cannot be correlated with HBsAg positivity, when HBV DNA is negative (unless it is an HBeAg- and HBV DNA-negative mutant).

Our own experience supports that of Dr Tandon. In screening 174 individuals detected at blood donation to be HBsAg positive, a borderline ALT elevation of 1-1.5 times was seen in only 9% of patients; of 55 tested for HBeAg, all but one were negative. A recent study from Mumbai also showed negative HBV DNA status in all HBeAg-positive individuals with normal ALT.

I agree that symptoms should not be the basis for classifying HBsAg-positive individuals; they should be classified on the basis of normal or raised ALT and whether HBeAg is detected or not. The point is that >90% of individuals who are detected incidentally will fit into a normal ALT / HBeAg-negative classification. Such individuals have excellent long-term prognosis.

In counselling these persons, especially those who...