Efficacy of Interferon in Treating Chronic Hepatitis C in Children With a History of Acute Leukemia

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Interferon (IFN) is effective in treating adults as well as children with chronic hepatitis C. We investigated the efficacy of IFN therapy in 13 children with underlying acute leukemia who had chronic hepatitis C (age range, 5 to 17 years; mean age, 9.9 years). Natural IFN-α was administered at a dose of 0.1 mega unit (MU)/kg (maximum dose, 6.0 MU) daily for 2 weeks and then three times per week for an additional 22 weeks (total dose, 8 MU/kg). IFN treatment was initiated at least 2 years after the completion of treatment for acute leukemia. A complete response was obtained in 5 children (38%). The serum level of anti-hepatitis C virus core antibody was closely related to the response to IFN. IFN therapy was well tolerated by all but 1 of the children, who developed mild transient heart failure 4 months after the initiation of therapy. IFN therapy for children with chronic hepatitis C who had underlying acute leukemia was beneficial. However, further trials are required to confirm the safety and improve the dosage schedule of IFN therapy.

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THE PROGNOSIS of children with acute leukemia in Japan has improved over the past 15 years due to the availability of intensive regimens for hematotransfusion and combination chemotherapy. Blood transfusion is the main route of transmission of hepatitis C virus (HCV). Children with hematologic disorders or malignancies receive frequent transfusions of blood and its constituents and are thus at risk for HCV infection; thus, chronic hepatitis C is a major complication in these children. Because chronic hepatitis C may progress to liver cirrhosis or hepatocellular carcinoma (HCC), adults patients are treated aggressively with interferon (IFN). Although IFN appears to be safe and effective for treating children with chronic hepatitis B, there are only limited data on its benefits in children with chronic hepatitis C, especially in children with hematologic malignancies. We evaluated the efficacy of IFN therapy in children with chronic hepatitis C who had a history of acute leukemia.

PATIENTS AND METHODS

We evaluated the efficacy of IFN therapy in 13 children with chronic hepatitis C whose underlying disease was acute leukemia (Table 1). Informed consent was obtained from the children’s parents. All of the children had a history of multiple blood transfusions and had received intensive chemotherapy regimens that included immunosuppressive agents. All subjects were positive for anti-HCV antibody and negative for the hepatitis B surface antigen, the anti-HBs antibody. The histologic diagnosis was determined by using standard criteria and the Knodell histological activity index. Biopsy specimens were examined by an independent pathologist not connected with this study.

The chi² test was used for continuous variables and the Fisher’s exact test was used for dichotomous variables. A P value of .05 or less was considered to represent statistical significance.

RESULTS

Response in 13 children treated with IFN. At the completion of IFN therapy, serum ALT values were normal in 8 children (62%) and serum HCV RNA had disappeared in 10 children (77%) (Fig 1). Serum ALT values became normal within 6 months of cessation of therapy and remained normal for at least 6 months thereafter in 6 children (46%). Serum HCV RNA disappeared within 6 months after the cessation of therapy and remained negative for at least 6 months thereafter in 5 children (38%). Therefore, a complete response was obtained in 5 children (38%), a partial response...
in 1 child (8%), and no response in the remaining 7 children (54%) at 12 months after the cessation of therapy.

Anti-HCV core antibody response. Anti-HCV core antibody was detected in 10 children (complete response in 4, partial response in 1, and no response in 5) before IFN therapy. Twelve months after the cessation of therapy, the anti-HCV core antibody level was less than 50% of the pretreatment value in 3 of 4 children who had a complete response (Fig 2). In children with a partial response or no response, the anti-HCV core antibody level was not less than 50% of the level of the pretreatment value 6 months after the cessation of therapy, even though the values declined to less than 50% of the levels of the pretreatment values at the completion of therapy.

Factors that predicted the response. Pretreatment HCV RNA titers, the HCV genotype, gender, duration of HCV infection, age at IFN therapy, liver histology, and ALT values before therapy were not significantly related to the response to IFN.

Complications. IFN was well tolerated by all but 1 child (no. 11; Fig 1), who developed mild transient heart failure 4 months after the initiation of IFN therapy. He had underlying acute lymphoblastic leukemia and he had previously undergone several courses of intensive chemotherapy including doxorubicin. We discontinued IFN treatment at 4 months. An influenza-like syndrome, which disappeared within 10 days in most children, was observed in all 13 children, and slight, transient hair loss that resolved completely after cessation of therapy occurred in 2 children. There was a small decrease in the leukocyte count and the thrombocyte count after the initiation of IFN therapy in all children, but no dosage reduction was required. No adverse effect on the underlying acute leukemia were observed during the follow-up period.

DISCUSSION

In previous studies, serum ALT values became normal in up to 50% of adults with chronic hepatitis C treated with IFN. However, 50% to 90% of those patients experienced relapses after the cessation of therapy. In an attempt to achieve a sustained remission of chronic hepatitis C, we have adopted a longer-term, higher-dose regimen of IFN therapy. In our previous study, the complete response rate of chronic hepatitis C treated with IFN was superior to that previously observed in adults. * Ruiz-Moreno et al1 also observed normalization of ALT values in 11 of 12 (91%)

### Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Gender (M/F)</th>
<th>Age (mean ± SD)</th>
<th>Duration of HCV infection (mean ± SD)</th>
<th>Underlying disorder</th>
<th>Histology</th>
<th>HA1 score (mean ± SD)</th>
<th>HCV RNA titer</th>
<th>HCV genotype</th>
<th>IL*</th>
<th>Other genotype</th>
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<tbody>
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<td>12/1</td>
<td>5-17 yr (9.9 ± 3.5)</td>
<td>2-10 yr (5.2 ± 2.2)</td>
<td>Acute lymphoblastic leukemia</td>
<td>Chronic persistent hepatitis</td>
<td>3-17 (6.5 ± 3.7)</td>
<td>10^3-10^6 copies/mL</td>
<td>II</td>
<td>12</td>
<td>1</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Acute myelogenous leukemia</td>
<td>Chronic aggressive hepatitis 2A</td>
<td>8</td>
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<td>Chronic aggressive hepatitis 2B</td>
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</tbody>
</table>

* Including superinfection with another genotype.

Fig 1. Serum HCV RNA and ALT profiles of 13 children treated with IFN-α. (O) HCV RNA (+) and ALT ≥30 IU/L; (△) HCV RNA (+) and ALT <30 IU/L; (□) HCV RNA (-) and ALT <30 IU/L; (△) HCV RNA (+) and ALT ≥30 IU/L; ALL: acute lymphoblastic leukemia; AML: acute myelogenous leukemia; a, therapy discontinued at 4 months.
children with chronic hepatitis C treated with IFN who were studied at 15 months after the initiation of IFN therapy, and IFN treatment in children with chronic hepatitis C was more effective. These data suggest that the immune system differs slightly between children and adults or that a short duration of HCV infection does not induce a high rate of HCV mutation.

In the present study, 5 of 13 (38%) children with underlying acute leukemia showed a complete response to IFN therapy, which indicated that the administration of IFN for chronic hepatitis C in these children was almost as effective as in adults, but not as effective as in children with nonmalignant diseases. IFN therapy was initiated at least 2 years after completion of chemotherapy, because children with hematologic malignancies may be severely immunocompromised, especially if they have recently undergone a chemotherapy regimen including cytotoxic agents.

We previously reported that the histologic activity of transfusion-associated chronic hepatitis C was more aggressive in children with malignant diseases than in those without such diseases. We hypothesized that immunosuppression due to the intensive chemotherapy accelerated the replication of HCV in these patients. Arico et al have suggested that real HCV infection may be present, even in the absence of a detectable humoral immune response to the virus, several years after the cessation of chemotherapy in children who were treated for acute lymphoblastic leukemia. These observations suggest that differences in the immune conditions in these children may be closely associated with the inferior response to IFN in children with hematologic malignancies.

Serum HCV RNA disappeared in 10 of the 13 (76.9%) children at the completion of therapy, indicating that IFN therapy effectively suppressed the replication of HCV in the liver. It is therefore possible that an improved protocol would increase the efficacy of IFN therapy in children with acute leukemia.

Recent studies have identified the serum HCV RNA titers and the HCV genotype as predictors of the response to IFN therapy in adults, especially in Japanese patients. However, we found no predictors of a complete response to IFN therapy. Larger trials are needed to investigate the possible predictors of response.

Anti-HCV core antibody was detected in 10 children. Levels were decreased to less than 50% of the pretreatment values at the cessation of IFN therapy and remained less than 50% 18 months after IFN therapy in 3 of 4 children who showed a complete response. The remaining child in the complete response group was HCV-RNA positive 18
months after the cessation of therapy (no. 6; Fig 1). These results suggest that anti-HCV core antibody levels reflect HCV replication and that a sustained anti-HCV core antibody level less than 50% of the pretreatment value is an indication of therapeutic efficacy.

One child developed mild transient heart failure during IFN therapy. He had been treated with doxorubicin at a total dose of 477.2 mg/m² for acute lymphoblastic leukemia. Therefore, it was not clear if this heart failure was due to the late cardiac effects of doxorubicin or to those of IFN. Children who have received doxorubicin-containing chemotherapy should be considered to be at risk for heart failure and should be monitored carefully during and after IFN therapy.

IFN therapy in children with chronic hepatitis C who had underlying acute leukemia was relatively safe and was as effective as in adult patients. A revised protocol might improve the efficacy of IFN therapy. Because the present study was not controlled and included only a limited number of children, larger trials are needed to confirm the efficacy of IFN therapy in this group of children.

REFERENCES

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