Interferon-α and Ribavirin Treatment of Hepatitis C in Children with Malignancy in Remission

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Twenty-eight cases of hepatitis C virus (HCV) infection were identified in children in a pediatric oncology ward during 2 nosocomial outbreaks. HCV infection spontaneously cleared in 6 patients (21%). Eleven patients with persistent HCV viremia who had malignant diseases in remission after treatment were given a 48-week course of combined therapy with interferon-α (5 × 10⁶ U 3 times weekly) and oral ribavirin (15 mg/kg/d). Seven (64%) of the 11 patients had sustained virological responses 6 and 12 months after cessation of therapy. Side effects were common but generally were mild or moderate.

Materials and Methods

Patients. Altogether we evaluated the cases of 28 children aged 2–19 years at the onset of hepatitis C. Antiviral treatment was given only to those 11 children after treatment of their malignant diseases in first remission who had not received immunosuppressive therapy for at least 1 year for whom PCR analysis still revealed HCV RNA. The treatment included subcutaneous administration of 5 × 10⁶ U of IFN-α (Intron A; Schering Plough, Kenilworth, NJ) 3 times a week, plus oral administration of ribavirin capsules (Schering Plough; 15 mg/kg/d) in 2 divided doses. All children were asymptomatic at the start of treatment. The 17 children who were not given combined therapy had recovered spontaneously (6 patients), had previously received IFN monotherapy (2), were still receiving immunosuppressive treatment (4), had no malignant disease (1), or had died of malignant disease (4).

Virological testing. Virological response was determined by PCR analysis as described elsewhere [1]; the assay detects ~100 copies of HCV RNA/mL of serum. Pretreatment serum samples were used in genotyping, as described elsewhere [1], with the addition of primers that detect HCV genotype 4. HCV RNA in pretreatment samples stored at −20°C was quantified by the branched DNA technique (Quantiplex HCV RNA 2.0 Assay, Chiron Corp., Emeryville, CA), which detects 200,000 copies/mL of serum.

Biochemical testing. The following values were determined regularly before, during, and after treatment: full blood cell count, liver enzyme levels, uric acid level, and thyroid hormone levels. Before treatment, all children were tested for total protein levels, serological markers for hepatitis A and B, and autoantibodies to nuclei, smooth muscle, and mitochondria. Liver biopsies were not performed because the parents refused them.

Monitoring of side effects. Monitoring of side effects of treatment was done usually by telephone interviews with the child and/or parents. All side effects were rated on a scale of 0–4, according to recommendations of the World Health Organization [3]: 0, absence of toxicity; 1, mild toxicity; 2, moderate toxicity; 3, severe toxicity; and 4, life-threatening adverse reactions.

Results

Eleven children entered the 48-week course of combined treatment with IFN-α and ribavirin and were followed up for 12 months. Eight of the children had elevated alanine aminotransferase levels before beginning treatment. Six and 12 months after cessation of therapy, 7 (64%) of the 11 children (including the 3 with normal pretreatment alanine aminotransferase levels) had sustained virological and biochemical responses, with undetectable levels of plasma HCV RNA and normal serum alanine aminotransferase (table 1). Five of these
7 patients had infection with HCV genotype 3a, and 2 had infection with HCV genotype 1b. All patients who responded to therapy were HCV RNA-negative at 3 months of treatment. Three children with infection due to HCV genotype 1 were still HCV RNA-positive after 3 months of combined treatment, and treatment for these patients was stopped (table 1). One patient had infection with HCV genotype 4a; this patient had a breakthrough infection at 9 months, and treatment was discontinued.

**Side effects of treatment.** Two children had neutropenia or anemia, and after 11 and 22 weeks their IFN-α dose was reduced from $5 \times 10^6$ to $3 \times 10^6$ U 3 times a week. One child was given a reduced dose of ribavirin because of hemolytic anemia. All treated children had fatigue, but had to stay home from school only on a few occasions. The height growth rate decreased significantly by 1 SD for 4 children and remained decreased for 3 of these children at follow-up. Other side effects were loss of appetite and weight loss (8 children), headache (7), chills and fever (6), hair loss (5), abdominal pain (5), and dry skin and itching (4). No child had depression. All side effects were mild or moderate, with the exception of the temporarily decreased height growth rate.

**Discussion**

To our knowledge, we report the first attempt to treat HCV-infected children with malignant diseases in remission with a 48-week course of combined treatment with IFN-α and ribavirin. We noted a sustained response rate of 64% (7 of 11 children responded). This rate is higher than the rates associated with IFN monotherapy for this patient group [4] but is comparable with the rates associated with IFN monotherapy for children with nonmalignant diseases [5]. Preliminary data on combination therapy for adults that were available when we began using such treatment have been verified in larger studies that included adult patients. In these studies, a 48-week course of combined treatment, as compared with IFN alone, resulted in a significantly higher sustained response rate for adult patients [6, 7]. Combined treatment is currently recommended for all adult patients, and therapy is extended from 24 to 48 weeks for patients with infection due to HCV genotype 1 who have high levels of viremia ($>2 \times 10^6$ copies/mL) [8]. In our study, all patients with infection due to HCV genotype 3a responded to combined treatment, confirming that the response rate may be better in such cases. We found no clear correlation between viral load and outcome, although 2 of 3 patients infected with HCV genotype 1 who did not respond to combined treatment did have high pretreatment HCV RNA levels. Side effects were seen in all children but were generally mild or moderate and reversible.

**References**