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Interferon treatment of chronic hepatitis C in patients cured of pediatric malignancies

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ABSTRACT

Background and Objectives. **Chronic hepatitis C was a frequent complication in patients treated for malignancy until the introduction of anti-HCV screening tests for blood donors. The association between chronic hepatitis C and progression to cirrhosis and hepatocellular carcinoma has been reported in about 20% and 5% of patients, respectively, within 20-30 years of infection. In adult patients, interferon has proved to be effective in decreasing the abnormal values of transaminases and the level of HCV viremia. Our purpose was to assess efficacy of and tolerance to interferon in a group of young patients who had acquired HCV infection during a period of chemotherapy.**

Design and Methods. **Interferon-α (IFN) was administered to 26 adolescents and young adults (13 males, age range 17-36 years; median age 24) with chronic hepatitis C, including 4 with hepatitis B virus co-infection, who had been treated for leukemia or solid tumor 5 to 19 years before joining this trial. Patients were treated with natural IFN alpha at a dose of 4 MU/m^2 thrice weekly for 12 months and followed up for another 6 months thereafter.**

Results. **Nine patients stopped treatment during the first 6 months because of side effects (2 cases) or lack of response. At the end of the trial, 8 (31%) cases had responded, with alanine amino-transferase normalization and clearance of hepatitis C virus (HCV) RNA. A sustained response was only documented in 15% of cases, however, irrespective of any hepatitis B virus co-infection. The 2 patients with HCV genotype 2 were both responders, whereas only 8% of those with genotype 1 responded.**

Interpretation and Conclusions. **These data show that the efficacy of IFN in this series of young patients is similar to that reported for otherwise healthy adults with hepatitis C. Patients with genotype 2 are strong candidates for IFN treatment while other therapeutic strategies should be designed for patients with HCV genotype 1.**
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Key words: chronic hepatitis C, hepatitis C virus genotype, interferon, cancer, pediatric malignancy

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Before the use of hepatitis C virus antibody (anti-HCV) tests for screening blood donors, chronic HCV infection was a frequent finding in pediatric patients cured of cancer.[1] In a series of 658 cases observed at our Pediatric Hematology Oncology Unit in Padua (Italy), the prevalence of anti-HCV was 17.8%.[2] Of the 117 anti-HCV positive patients, 92 (78%) had abnormal alanine aminotransferase (ALT) levels during follow-up, suggesting chronic hepatitis, and 81 (69%) were persistently HCV RNA positive. Although chronic liver disease did not progress to liver failure, spontaneous and sustained ALT normalization associated with persistent HCV-RNA negativity was only found in 11% of cases over a median follow-up period of 14 years. Moving from these observations, progression of liver disease later in life cannot be ruled out in such patients.[3]

Reports in the literature suggest that interferon (IFN) can induce sustained ALT normalization and loss of HCV RNA in a proportion of adult patients with chronic hepatitis C, thus preventing evolution to cirrhosis.[4-8] To date, the use of IFN in children and young adults cured of malignancy has been limited and small-sized trials have yielded controversial results.[9,10] We report here on the results of an uncontrolled open-label study of IFN treatment in 26 adolescents and young adults who had had a malignancy during childhood.

Design and Methods

Design of the study

The study was designed as an uncontrolled open-label prospective trial including patients with abnormal ALT who were HCV-RNA positive. As of 1995, 117 patients with chronic hepatitis C, who were long-term survivors after treatment for pediatric malignancies, were being followed-up at the Pediatric Hemato-Oncology Division of Padua Hospital. Treatment was proposed to all patients seen at the outpatient clinic over a 6-month period (June to December 1995) who fulfilled the inclusion criteria.

Patients

During the enrollment period, IFN was offered to 35 HCV-RNA positive patients with abnormal ALT levels. Five patients refused liver biopsy or treatment and 30 agreed to undergo pre-treatment evaluation. The following enrollment criteria were adopted:
a. patients of any age, who had been off anti-neo-

plastic therapy for at least 5 years;
b. ALT levels at least 1.5 times above normal in the preceding 6 months;
c. HCV-RNA positive at the time of enrollment;
d. liver histology compatible with chronic hepatitis.

The following exclusion criteria were established:
a. concomitant cirrhosis;
b. hepatitis D and HIV co-infection (co-infection with hepatitis B virus alone was acceptable);
c. serological markers of auto-immunity: antibodies to liver-kidney microsomal antigen at any titer; antinuclear and antimitochondrial antibodies at titers greater than 1:40;
d. biochemical features compatible with Wilson's disease, α_1-antitrypsin deficiency and hemochromatosis;
e. diabetes and neurologic diseases or abnormal thyroid function.

Treatment schedule

Eligible patients received 6 million units of natural leukocyte interferon-α (Cilferon-A®, Janssen-Cilag, Pomezia, Italy) thrice weekly for 6 months. Response was evaluated and partial and complete responders were treated for a further 6 months, while treatment was withdrawn from non-responders. Treatment was also withdrawn from any patient who developed an ALT flare greater than 5 times the baseline value. Patients were then followed up for 6 months after suspending IFN.

Patients received paracetamol (10-15 mg/kg or 500 mg three times a day) and chlorpheniramine (2-8 mg/day) for the first 1-2 weeks of treatment. These symptom-limiting drugs were progressively reduced if mild or no side effects were observed.

During treatment, patients were seen twice during the first month, then monthly for physical examination and biochemical and virological investigations. A monthly check-up was also scheduled during follow-up.

Evaluation of response

The response was evaluated at the end of the treatment period and at the end of the follow-up. Partial response was defined as a reduction in ALT levels without HCV RNA clearance. Complete response included both ALT normalization and HCV RNA clearance. Sustained response was defined as the persistence of complete response 6 months after stopping the treatment.

Informed consent was obtained from patients and guardians before enrollment. The study was approved by the Pediatric Department's ethical committee.

Methods

Hepatitis B surface antigen (HBsAg), hepatitis Be antigen (HBeAg) and anti-hepatitis delta virus antibodies were searched for using commercial assays (Abbott Laboratories, North Chicago, IL, USA). Hepatitis B virus (HBV) DNA was investigated using commercial hybridization techniques (Digene Hybrid Capture System, Beltsville, MD, USA). Antibodies to human immunodeficiency virus were assayed using a commercial enzyme immunoassay (Wellcozyme, Murex Biotech, UK). Anti-HCV were detected by an enzyme immunoassay (ELISA II and RIBA; Ortho Diagnostic Systems, Raritan, NJ, USA). HCV RNA was assessed by polymerase chain reaction (PCR), as reported elsewhere.[2] HCV RNA genotypes were investigated in serum by a modification of the method by Cha *et al.*, as reported in detail elsewhere,[11] and classified according to criteria from Simmonds *et al.*[12]

Percutaneous liver biopsies, obtained within 6 months before starting treatment, were evaluated by the same experienced pathologist (MG). Histologic activity index (HAI) and fibrosis were assessed according to Scheuer.[13] Statistical analysis was performed with the SAS for Windows package (SAS Institute Inc., Cary, NC, USA). Fisher's exact test and the chi-squared test were used to analyze dichotomous variables; Student's t-test and the Wilcoxon test were used for continuous variables.

Results

Twenty-six patients met the inclusion criteria while having none of the exclusion ones. The epidemiological, clinical and virological features of their disease at the beginning of IFN treatment are shown in Table 1. Most patients had been infected by transfusion and genotype 1b was largely prevalent.

Seventeen patients were infected by HCV alone and 4 were co-infected with HCV and HBV, including 3 who were HBeAg and HBV DNA positive.

Serum albumin, prothrombin time and bilirubinemia were within the normal ranges in all cases.

Response to treatment

Three patients, all HBsAg negative, abandoned treatment between the 2nd and 3rd months: one because of thrombocytopenia associated with anti-platelet antibodies, one because of dysmenorrhea and hypothyroidism associated with anti-thyroid antibodies (this patient had previously been treated with 24 Gy cranial irradiation for leukemia), and the other because of an increase in ALT level beyond 5 times the baseline value.

Six further patients, infected with HCV alone, abandoned the treatment after 6 months due to a lack of response. Of the 17 patients who completed the

Table 1. Features of the 26 patients at the beginning of IFN treatment.

Sex (M/F)	13/13
Age (years)	median 24; range: 17-36
Previous disease	Leukemia/lymphoma 16 Solid tumors 10
Concomitant HBV infection (yes/no)	4/26
Blood transfusions (yes/no)	21/26 (81%)
Duration of liver disease (years)	median 12.5; range 4.3-19.4
ALT (n.v. < 55 IU/L)	median 83; range 59-355
HCV genotype (no.)	1b = 14 1a = 10 2 = 2
Histologic Activity Index	4 (range 2-6)

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treatment, only 8 responded; 4 of these relapsed during follow-up, as indicated by the reappearance of HCV-RNA in the serum and a rise in ALT levels. Thus only 15% of patients (intention to treat) were sustained responders, including 3/22 (14%) HBsAg negative and 1/4 (25%) co-infected with HBV. The effects of therapy are summarized in Table 2.

Side effects

Apart from the above-mentioned events which prompted withdrawal from treatment, IFN was generally well tolerated: mild fever appeared in 11/26 (42%) cases during the first 2 weeks of treatment and symptom-limiting drugs were quickly withdrawn within 2-4 weeks. Asthenia developed in 15 (58%); headache in 7 (27%), transient alopecia in 5 (19%) and transient neutropenia < 1.5 and > 0.7 neutrophils $\times 10^9$/L in 10 (38%). All these side effects were compatible with normal daily activity.

One patient developed auto-immune thrombocytopenia (Plt = 25×10^9/L) that regressed on withdrawal of IFN. Conversely, the patient with autoimmune hypothyroidism continued to have impaired thyroid function after cessation of treatment and replacement therapy was instituted.

Predictors of response

By univariate analysis, no risk factor was significantly associated with end-of-treatment response. Genotype 2 was significantly associated with sustained response in both univariate and multivariate analyses (Table 3).

Discussion

Patients with a previous pediatric malignancy represent a particular subgroup of chronic HCV carriers infected mainly, but not exclusively, by blood or blood products during a phase of impaired immunocompetence induced by chemotherapy.[1,2,14] The results of this study confirm that IFN can induce sustained ALT normalization and clearance of viremia in such patients. The proportion of sustained responders is, however, limited in keeping with the well-established rates (15-25%) reported for otherwise healthy adults and recently also for children.[4-8] Our data thus seem less encouraging than those previously reported by Komatsu *et al.*[10] in 13 children with acute leukemia, 54% of whom were complete responders at the end of treatment and 38% at the end of follow-up. This difference is unrelated to any HBV co-infection in a subgroup of our patients: in fact, the prevalence of sustained ALT normalization and disappearance of HCV RNA was similar in patients with and without HBV co-infection. The better results obtained by Komatsu might be explained, to some degree, by the different timing of the IFN treatment in the two studies. The chronic hepatitis C in the patients reported by Komatsu *et al.* was of shorter duration than that in our cases so that IFN treatment may have contributed to normalize ALT values that would have returned to normal anyway, even without IFN treatment. We observed a normalization of ALT values in 12/117 (12%) patients with chronic HCV after a median follow-up of 4.6 years.[9] In otherwise healthy patients with hepatitis C, a shorter duration of disease, lack of cirrhosis, genotypes 2 and 3 and a low viral charge are good predictors of response to treatment.[3] In our series, duration of illness was relatively homogeneous and none of the patients had cirrhosis, and the viral charge could not be measured in baseline sera,[15] so only genotype 2 was found to be significantly associated with response to treatment.

In sustained responders, ALT normalization and clearance of viremia was always obtained during the first 6 months of treatment, so treatment withdrawal is justified in patients without complete response by this time.

IFN was generally well tolerated and severe adverse events were only observed in two cases - a prevalence similar to that reported in otherwise healthy adults.[15]

In conclusion, the results of this study show that IFN treatment is effective in a minority of adolescents and young adults with hepatitis C acquired during treatment for malignancy. Patients with genotype 2 (we had no cases of genotype 3) certainly deserve a six-month course of IFN, whereas other therapeutic strategies should be adopted for patients with HCV genotype 1. Recently, therapeutic trials combining ribavirin with IFN have yielded promising results both

Table 2. Response to interferon treatment in the 26 patients.

	6 months	*12 months*	*18 months*
ALT normal HCV RNA-	9 (35%)	8 (31%)	4 (15%)
ALT normal HCV RNA+	8 (30%)	4 (15%)	3 (12%)
ALT abnormal HCV RNA+	9 (35%)*	14 (54%)	19 (73%)

**Three patients stopped treatment after 3 months and 6 after 6 months; all patients were included in the follow-up evaluation.*

Table 3. Analysis of factors associated with sustained response to IFN in the 26 patients.

	Responders (4)	*p*	*Non-responders (22)*
Sex (M/F)	2/2	1.0	11/11
Diagnosis of malignancy (AL/lymphoma vs solid tumor)	2/2	0.86	10/12
Mean duration of chronic hepatitis (years)	14.1	0.5	12.4
Mean age at onset of hepatitis (years)	8.6	0.4	10.5
Mean ALT value pre-IFN	125	0.17	100
Histologic Activity Index (mean value)	3.7	0.57	4.2
Genotype 2 vs. 1	2	0.003	22

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in *naive* patients and in patients who have relapsed after a transient response to IFN.[16-18] Moreover, the development of new agents, such as inhibitors of viral protease helicase or RNA-dependent polymerase with specific anti-HCV activity may open new prospectives for definitive eradication of HCV infection.[3]

Contributions and Acknowledgments

All authors contributed to the conception and design of this study. SC, MGP, FR and AB were the principal investigators and were directly involved in patient follow-up. SC designed the study and obtained its ethical approval. MG performed the histologic examinations and RC the virological tests (HCV-RNA and HCV genotype). SC, FB, and LZ wrote the paper. LM performed the statistical analyses. All authors contributed to the analysis of data, gave their critical contribution to the manuscript and approved its final version. Authors has been listed on the basis of their contribution to the research.

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

Manuscript processing

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Potential implications for clinical practice

- Chronic C hepatitis acquired during treatment for pediatric malignancy can be cured by interferon.
- Response rate to interferon treatment is satisfactory only for patients with genotype 2.
- Treatment lasting more than 6 months is not associated with better response to treatment.
- Patients with genotype 1 need a new type of treatment.
- HBV co-infection did not affect the response rate negatively.

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