Human Leukocyte Interferon in the Treatment of Varicella in Children with Cancer: a Preliminary Controlled Trial

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Eighteen patients who developed varicella while being treated for malignancy received human leukocyte interferon in a randomized double-blind placebo-controlled trial. Complications of varicella occurred in six of nine placebo recipients, but in only two of nine interferon recipients. Interferon was tolerated without significant side effects.

Although primary varicella is a benign disease in the healthy child, its occurrence in the immunosuppressed host may be associated with visceral dissemination and death (1). With the effort that is being made to allow children with malignancy to pursue their normal activities, the risk of exposure to varicella cannot be eliminated. Zoster immune globulin administered shortly after exposure to varicella modifies the course of varicella in immunosuppressed children (2), but an effective antiviral agent is needed for treatment of the established infection. Human leukocyte interferon does modify the course of herpes zoster, caused by the same virus that causes primary varicella, when given to immunosuppressed patients shortly after the onset of the infection (T. C. Merigan, K. H. Rand, R. B. Pollard, P. S. Abdallah, G. W. Jordan, and R. P. Fried, *N. Engl. J. Med.*, in press). To determine the safety and potential efficacy of interferon in treating primary varicella, we evaluated 18 patients treated according to a randomized double-blind protocol over the past 3 years.

MATERIALS AND METHODS

Human leukocyte interferon. Human leukocyte interferon was obtained through the Antiviral Substances Program of the National Institute of Allergy and Infectious Diseases. Five patients received interferon, 4.2×10^4 reference U/kg, given intramuscularly every 12 h until no progression of infection had been observed for 24 h. A further-purified preparation was given to four patients at 2.55×10^5 reference U/kg. The mean duration of therapy was 6.4 days (range = 3 to 11 days). The placebo consisted of the stabilizer for interferon, 0.05% human serum albumin in normal saline, and did not differ in appearance from interferon.

Patients. Thirteen of the 18 patients were being treated at the Children's Hospital at Stanford, Stanford, Calif., and 5 were patients at St. Jude Children's Cancer Research Hospital, Memphis, Tenn. Patients

were eligible for the protocol if they were receiving chemotherapy at the onset of varicella and if treatment could be instituted within 48 h after the appearance of the exanthem. Randomization of all patients was done by the Stanford pharmacy according to a pre-established, randomly generated sequence. Eligible patients were excluded only if consent was not given. Four placebo recipients and five interferon recipients had acute lymphocytic leukemia; other underlying diseases included acute myelogenous leukemia, lymphoma, neuroblastoma, retinoblastoma, Ewing's sarcoma, and Wilm's tumor. In all cases, chemotherapy was withheld during the infection. Three patients (two placebo, one interferon) received a short course of cytosine arabinoside beginning at day 5 or 6 of the interferon-placebo protocol at a time when visceral dissemination had already occurred. Two patients (one placebo, one interferon) received iododeoxyuridine under similar circumstances.

Patient monitoring. Varicella virus was isolated from the lesions of each patient. New lesion formation was monitored daily by lesion count. Serum transaminases (serum glutamic oxalacetic transaminase and serum glutamic pyruvic transaminase) and complete blood counts were measured before treatment and at frequent intervals during infection. A chest X-ray was obtained at admission and was repeated in patients who developed respiratory signs and symptoms. Interferon was measured by the reduction of bovine vesicular stomatitis virus plaques in human foreskin fibroblast monolayers (4). Varicella-zoster complement-fixing antibodies were measured by the method of Schmidt et al. (5).

RESULTS

Patients who received interferon at 4.2×10^4 reference U/kg had serum levels of 21 ± 16 standard error (SE) units at 2 to 4 h after administration, whereas those receiving 2.55×10^5 U/kg had levels of 105 ± 40 SE U/ml. The placebo recipients had serum interferon levels of 5 ± 1.7 SE U/ml. The peak temperatures recorded were $39.1^\circ\text{C} \pm 0.1^\circ\text{C}$ SE for both interferon groups and $38.9^\circ\text{C} \pm 0.2^\circ\text{C}$ SE for the placebo group.

The interferon and the placebo groups were comparable with regard to the duration in days of infection prior to enrollment (placebo: 1.7 ± 0.97 SE; interferon: 1.3 ± 0.5 SE), the number of lesions present at the time of enrollment (Table 1), the leukocyte counts (placebo: 5.21 ± 3.19 SE; interferon: 3.0 ± 1.26 SE), and absolute lymphocyte counts upon initial evaluation (placebo: 467 ± 355 SE; interferon: 516 ± 378 SE). No differences were noted in the incidence of complications in patients with <100 lesions and those with >100 lesions at the time treatment was initiated. A fourfold rise in complement-fixing antibody was detected in seven of eight interferon recipients and seven of seven placebo recipients tested.

There was no significant difference between the interferon and placebo groups in the number of days of new vesicle formation following the initiation of therapy (Table 1).

Table 1 outlines the complications associated with varicella in the two patient groups. The incidence of serious complications in the interferon recipients was 0.33/patient, whereas in the placebo groups it was 1.22/patient ($P = 0.1$). Numbers were too small to distinguish differences between the low- and high-dose interferon groups. The placebo recipient who died 5 days after the onset of infection had meningoencephalitis, severe hepatitis, and coagulopathy. The two patients dying within 3 weeks died at least 2 weeks following the cessation of new vesicle formation. Of these, the placebo recipient had rapid progression of the underlying disease and pneumocystis infection, and the interferon recipient had pulmonary complications of mechanical ventilation and bacterial sepsis. The administration of iododeoxyuridine or cytosine arabinoside did not alter these results, since the drugs were only given after visceral involvement was seen.

Although we have observed bone marrow toxicity in patients treated with high doses of interferon (3), we did not detect greater suppression of granulocytes, platelets, or reticulocytes in the patients with varicella who received interferon than was associated with recent chemotherapy in placebo recipients.

DISCUSSION

Although the number of patients treated is small, the results in this preliminary trial of interferon treatment of varicella in the immunosuppressed host are encouraging. The interferon-treated and placebo groups were comparable in terms of known risk factors. Patients in both groups met the criteria of Feldman et al. for high risk of complications associated with varicella in immunosuppressed patients (1). De-

TABLE 1. Progression of infection and complications associated with varicella in immunosuppressed patients in the interferon-placebo study

Treatment	No. of lesions prior to treatment			No. of days of new lesion formation after initiation of treatment	No. of patients with evidence of visceral disease	Visceral disease				Mortality	
	5-10	11-100	>100			Symptomatic meningoencephalitis	Pneumonia (radiographic evidence)	Severe hepatitis (SGOT ^a $>1,000$)	Hemorrhagic complications	Acute	2-3 weeks after varicella infection
Placebo	0	6	3	5.25 (range, 2-9)	6 ^b	3 ^c	4	2	2	1	1
Interferon	2	3	4	5.66 (range, 2-11)	2 ^b	0	2	1	0	0	1

^a SGOT, Serum glutamic oxalacetic transaminase.

^b $P = 0.152$ by Fisher exact t test (assuming two tailed); $P = 0.07$ if one tailed).

^c A fourth patient had encephalitic symptoms and increased cerebrospinal fluid leukocyte count, but tumor involvement could not be excluded.

spite the fact that four of nine interferon recipients had continued virus replication and new lesion formation for 7 to 11 days after the initiation of treatment, only two developed visceral involvement, whereas six of nine placebo patients showed visceral disease.

No evidence of significant toxicity relating to interferon administration was encountered. Our recent experience in the treatment of herpes zoster with interferon indicates that for optimum in vivo antiviral action, the purified preparation should be given at a higher dose, i.e., 5.1×10^5 U/kg per day (Merigan et al., in press). Interferon at this dose may decrease the number of days of new lesion formation in patients with varicella, since this dose has limited the cutaneous progression of zoster in immunosuppressed patients (Merigan et al., in press). Since, in most cases, visceral disease followed only 4 to 5 days after onset, it is likely that early antiviral therapy will be necessary, as it has been in herpes zoster (6; Merigan et al., in press).

In analyzing the placebo group, it is important to note that, despite their high-risk status, five of the nine patients were able to contain the infection in terms of new lesion formation within 5 days. Although two of these patients developed pulmonary infiltrates, in both cases the infiltrates resolved within 6 days. In an uncontrolled trial, the recovery accomplished by the host's response in these cases might have been attributed to the drug.

We are now conducting a randomized double-blind trial using the higher interferon dosage of

5.1×10^5 U/kg per day. Since interferon may also be expected to inhibit the early phases of virus replication, we are evaluating its effect in the prevention or modification of varicella in a second group of patients identified and treated late in the incubation period who are susceptible to varicella by varicella-zoster fluorescent-antibody testing.

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