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Abstract

Childhood leukemia, especially acute lymphocytic leukemia, can now be completely cured by a multimodality approach in one out of every two patients. Since prolonged maintenance therapy with anti-cancer agents for three years is required for complete cure, a significant problem during this course of treatment is death due to secondary infection. Those with childhood leukemia receiving anti-cancer chemotherapy who became secondarily injected with chicken pox can now be treated successfully with interferon in the four cases reported here. Chicken pox was cured even while one of them was in relapse. Therefore, it can be said that a bright prospect, namely interferon, is on the horizon in the treatment of secondary viral diseases associated with acute leukemia.

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SUCCESSFUL TREATMENT WITH INTERFERON OF CHICKEN POX IN CHILDREN WITH ACUTE LEUKEMIA*

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Abstract. Childhood leukemia, especially acute lymphocytic leukemia, can now be completely cured by a multimodality approach in one out of every two patients. Since prolonged maintenance therapy with anti-cancer agents for three years is required for complete cure, a significant problem during this course of treatment is death due to secondary infection. Those with childhood leukemia receiving anticancer chemotherapy who became secondarily injected with chicken pox can now be treated successfully with interferon in the four cases reported here. Chicken pox was cured even while one of them was in relapse. Therefore, it can be said that a bright prospect, namely interferon, is on the horizon in the treatment of secondary viral diseases associated with acute leukemia.

Key words : acute leukemia in children, interferon, opportunistic infection.

Secondary infection by varicella-zoster virus following anticancer chemotherapy for malignancies, organ transplantation, or immunosuppression can be fatal. In the past, many patients who were infected by chickenpox while in remission died during the treatment of acute leukemia (1-3).

In 1957, lsaacs and Lindemann discovered interferon and reported that interferon was effective in the treatment of viral infection (4). In view of the fact that production of interferon was recently begun in Korea, with the possibility of its widespread use in the near future, I would like to report the results of treatment with interferon of four patients with acute leukemia who developed secondary chickenpox infection and have subsequently recovered completely. These patients were seen from December 1982 to May 1983, at the Yonsei Cancer Center.

CASE PRESENTATION

Case 1. A seven-year old boy was admitted due to generalized rashes, vesicles, and high fever. At three years of age, he was diagnosed as having acute lymphocytic leukemia at Yonsei Cancer Center. During the maintenance therapy

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following remission induction, acute lymphocytic leukemia relapsed at the testes. Orchiectomy was performed and chemotherapy was continued for an extended period of time. During this period his brother became ill with chickenpox. Soon after the onset of his brother's illness, the patient showed the same symptoms as his brother and was admitted to the Center. Two days prior to admission this patient developed generalized eruptions on body and a high fever.

On admission, he appeared acutely ill, and the body temperature was 39.5 ℃. Most of his body surface was covered with erythematous maculopapular rashes, vesicles, and pustules. Vesicles severely extended to the oral mucosa and tongue. His laboratory findings showed WBC of 3,400/mm^3, Hct of 28.4 %, and platelets of 64,000/mm^3. SGOT and SGPT were within normal limits. Chest X-ray revealed pneumonia on both lung fields and enlargement of the hilar lymph nodes.

Immediately after admission, antibiotics and one million units of alpha-interferon were administered by intramuscular injection. To prevent hematoma, a 25-gauge needle was used for the injection and the injection site was compressed for more than five min. On the second day of interferon therapy, clinical improvement was appreciated. Continuous injection of interferon for three days prevented the formation of new lesions. Crust formation was noted after five days, and on the seventh day, interferon injection was discontinued when the fever dropped and his condition improved. On the ninth hospital day, the patient showed a normal chest X-ray and was discharged on the eleventh hospital day. With early institution of interferon, this patient shortened his disease course and recovered uneventfully. The bilateral fluffy infiltrates in the chest roentgenogram were assumed to be varicella pneumonitis, but bacterial pneumonia could not be excluded. One month after the discharge, multiple chicken pox scars were evident on the face (Fig. 1).

Case 2. A five-year old boy was admitted due to generalized rashes, vesicles, and high fever. Four months earlier, he had started remission induction therapy (adriamycin + cytosine arabinoside) for acute myelogenous leukemia. Seven days earilier during the maintenance therapy with 6-mercaptopurine and methotrexate, he developed a morbilliform rash on the thigh region. This rash rapidly spread over the entire body. On admission, he was acutely ill-looking and the body temperature was 39.2 ℃. Vesicles and pustules covered his entire body surface (Figs. 2, 3).

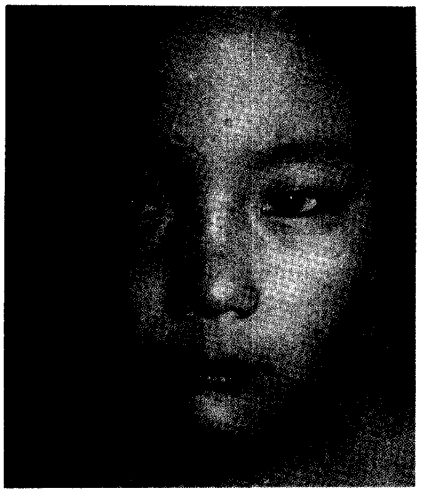
Fig. 1. One month after discharge, chicken pox scars remained on the face, indicating the severity of the illness (Case 1).

Figs. 2, 3. On the 9th day of illness, the patient developed generalized chicken pox (Case 2).

Fig. 4. The recovery stage (Case 2).

Fig. 5. On the 7th day of eruption, this patients developed generalized illness (Case 4).

Fig. 6. On discharge, the patient showed complete healing (Case 4).



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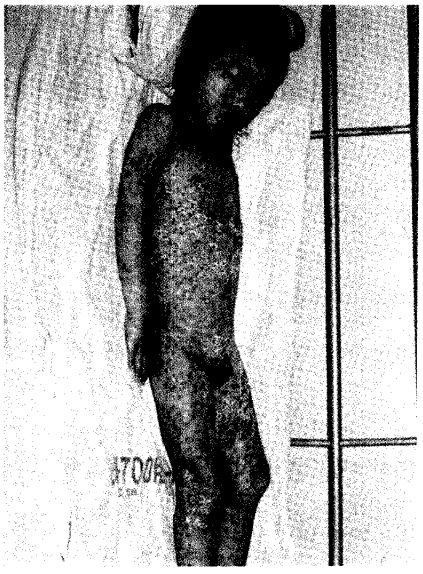

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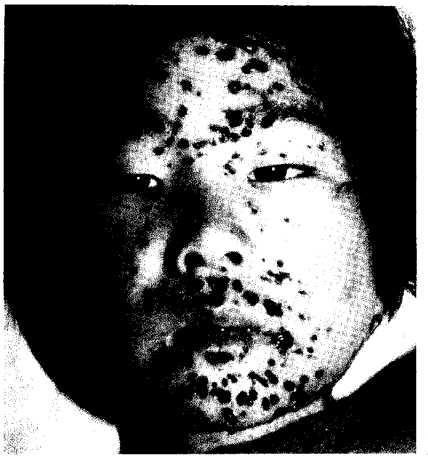

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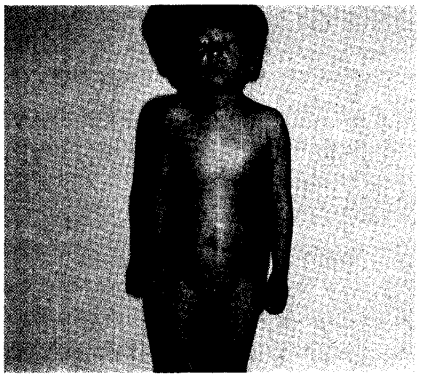

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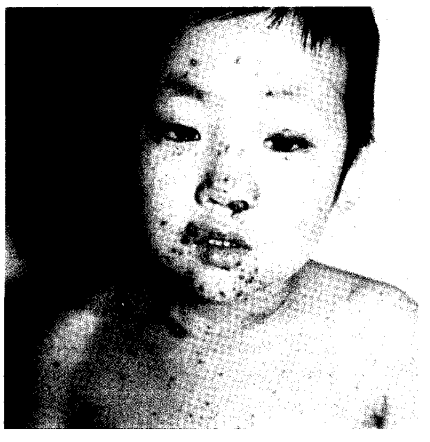

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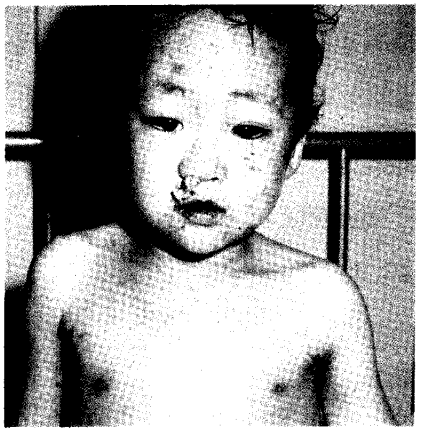

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His laboratory findings were WBC of 2,300/mm³ with 53 % neutrophils, Hct of 27 % and platelets of 130,000/mm³. The liver function test and the serum electrolytes were within normal limits. His chest X-ray revealed interstinal pneumonia. Blood culture was negative.

Immediately after the admission, blood transfusions and antibiotics were administered. In addition, one million units of interferon was also administered simultaneously by intra-muscular injection, and a daily dose was given thereafter. On the third hospital day, the patient showed worsening signs of pruritis, vesicles, and hepatomegaly. In spite of a persisting high fever and poor general condition, his skin lesions improved remarkably with continuous interferon administration. *Staphylococcus aureus* coagulase was detected on pus culture. The fever was still present, but crust began to form on the face on the sixth hospital day. On the 12th hospital day, interferon injection was terminated. The hepatomegaly disappeared on the 15th hospital day, and he was discharged in satisfactory condition (Fig. 4).

Case 3. A ten-year-old boy came to the outpatient clinic for the prevention of chicken pox after contact with his chicken-pox-infected younger brother five days earlier. Prior to his contact with chicken pox, he had been under maintenance chemotherapy for 28 months for acute lymphocytic leukemia.

His general appearance was satisfactory and physical examination did not reveal any positive signs. The laboratory findings showed WBC of 4,200/mm³, Hct of 30 % and platelets of 100,000/mm³.

For the purpose of chicken pox prevention, he received treatment at the outpatient clinic. He was given daily intramuscular injections of one million units of interferon. Ten days after the initial treatment with interferon, he developed a mild itching sensation and red papules. Concurrently, he developed vesicles on the abdominal and thoracic regions. However, two days after their appearance, the skin lesions disappeared and complete recovery was evident.

Case 4. A five-year-old boy developed chicken pox while scheduled to begin chemotherapy again for acute myelogenous leukemia which relapsed during his seventh month of maintenance therapy.

The onset of infection was indicated by the appearance of typical papulovesicular lesions on the face and head, extending to the trunk rapidly 5 days prior to admission. On admission, he appeared to be critically ill. His body temperature was 42℃ and erythematous maculopapular rashes, vesicles, and pustules extended over his entire body (Fig. 5).

The laboratory findings showed WBC of 2,500/mm³ (segmented neutrophils 12 %, eosinophils 1 %, lymphocytes 62 %, blasts 25 %), Hct of 25 %, and platelets of 20,000/mm³. Blood culture was negative.

Immediately after admission, a fresh whole blood transfusion and intravenous antibiotics were administered. On admission, one million units of interferon was also administered intramuscularly and daily thereafter. The hepatosplenomegaly

worsened (liver ; 5 cm, spleen ; 10 cm) and high fever persisted. On the fifth hospital day, the fever dropped and new lesions ceased to develop. On the seventh hospital day, crust formation began and on the eleventh hospital day, the patient showed evidence of complete healing or crust formation. He was discharged from the hospital a few days later, and subsequently was scheduled for induction chemotherapy for acute myelogenous leukemia (Fig. 6).

DISCUSSION

The incidence of infection by varicella-zoster virus increases in patients with cancer involving the hematopoietic organs such as malignant lymphoma or leukemia, after organ transplantation, or during anti-cancer chemotherapy or immunosuppressive chemotherapy (1-4). The increasing survival rates for childhood leukemia and other malignancies suggest that a greater number of children receiving prolonged anti-cancer therapy will risk varicella infection. The severity of infection in such patients appears to be greater than in healthy children. Varicella infection in patients with leukemia manifests lengthened duration and widely disseminated eruptions. The infection is likely to be more severe in children with acute leukemia in relapse. Among the 60 patients receiving anti-cancer therapy when they developed varicella, 19 (32 %) had visceral dissemination (3).

The frequency of severe infections and visceral dissemination increases when radiation and chemotherapy are combined (5). This increase in frequency is due to decreased cell-mediated immunity and decreased production of endogenous interferons (6). Hence infection by varicella-zoster and its dissemination within the skin or organs cannot be prevented (5, 7). Finkel (8) reported that six of 13 cancer patients (46 %), but none of noncancer patients, died of disseminated varicella. At the Yonsei Cancer Center, chicken pox in patients with acute leukemia has been the mortality rate of about 30 %.

Anti-viral agents such as Amantadine (9) and Marboran (10) have been utilized in the past, but their effectiveness has not been up to our expectation. It has been reported that following contact with varicella-zoster virus, infection can be prevented or changed by administration of varicella vaccine (11) or immune serum globulin (ISG) (12, 13). According to schaeffer and Toomey (14), however, infection cannot be prevented even after administration of 0.5-2.2 ml/kg ISG. The use of zoster immune plasma (15-17) and zoster immune globulin from convalescent patients has been reported to improve the recovery course (18, 19).

In order for these agents to be effective they must be administered within three days of exposure and readministered after three weeks (20). Cytosine is known to be an effective anti-viral agent with its anti-metabolite action, but cytosine itself can lead to an immunosuppressive state which can prolong the infection period (20). Adenine arabinoside is also effective in prevention of infection or may decrease dissemination of the virus within the organ, but late complications are a problem (22, 23).

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Interferon is a new advance in anti-viral chemotherapy. It was first reported that the substance interfered with infection by other viruses. Subsequently, there has been extensive research in the nature, character, clinical use, and production of interferon.

There are many reports concerning the use of interferon in cases of infection by varicella-zoster virus, especially, in immunocompromised patients. Merigan *et al.* (24) report that in cancer patients with varicella-zoster infection, administration of a large dose of interferon in the early stage of disease can lead to the inhibition of not only dissemination within the skin, but also within the organs. Furthermore, it reduces the frequency of newly forming vesicles, decreases the frequency of acute pain and post-herpetic neuralgia, and reduces the frequency of complications within the organ.

In addition to the treatment of varicella-zoster viral infection, interferon can also reduce the incidence of infection by cytomegalovirus, Ebstein-Barr virus and herpes simplex virus following kidney transplantation (25). It can also reduce the incidence of chronic active hepatitis by reducing the antigenic markers of hepatitis B virus infection such as hepatitis B core antigen and Dane-particle-associated DNA polymerase (26). It is also effective in prevention and treatment of keratitis due to herpes simplex infection (27). In addition to these usages, interferon is known to be effective in the treatment of many other viral infections. Recently there have been many papers written on the anticancer effect of interferon, which may open up a whole new dimension in its application (28, 29).

Interferon is administered at a dosage of 4.2×10^4 u/kg to 5.1×10^5 u/kg daily by intramuscular injection, and a high serum concentration is maintained for 24-48 h. Pain or erythema at the injection site, fever, nausea or vomiting can occur as side effects. Large doses can cause leukopenia or thrombocytopenia, but these side effects disappear when administration is discontinued (4).

To summarise the above four cases, interferon was administered after generalized chicken pox in two patients (Cases 1 and 2), both of whom were receiving anticancer chemotherapy to maintain their remission of acute leukemia, and in one patient (Case 4) who were in a relapse of acute leukemia. In the remaining patient (Case 3), whose acute leukemia was in remission, interferon was given during the incubation period of chicken pox. In these four patients, all of whom were receiving anticancer treatment or were in an active stage of acute leukemia, the mortality rate was supposed to be high without interferon therapy.

However, as demonstrated by complete recovery from these extremely life-threatening situations, interferon definetely has antiviral action. During prolonged anticancer chemotherapy for leukemia or solid tumor, depression of the body defense mechanism can occur. This depression can cause the patients to be susceptible to a variety of infections. Among them, the clinically significant problem in leukemia patients is chicken pox infection. These patients may develop disseminated chicken pox leading to hepatitis and pneumonia which are often

fatal. The complete cure or prevention of these fatal infections by interferon treatment may be regarded as an advance to control opportunistic infection.

The reality must always be kept in mind that we cannot afford the high cost of drugs such as hyperimmune zoster globulin. We anticipate with great optimism more extensive application of interferon in other viral infections, in addition to chicken pox, on leukemia patients.

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