High titer of interferon (IFN)-neutralizing antibody in a patient with glioblastoma treated with IFN-α

Case report

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In a patient with glioblastoma treated with interferon (IFN-α) for a long period of time, a high titer of IFN-neutralizing antibody was detected in the serum during and after IFN therapy. Computerized tomography findings and neurological symptoms in this patient were unchanged during IFN therapy. General malaise, fever, anorexia, nausea, and decrease of leukocytes, platelets, erythrocytes, hemoglobin, and hematocrit were recognized transiently as side effects of IFN administration. These side effects were not serious and resolved spontaneously without discontinuation of therapy. The appearance of IFN-neutralizing antibody is clinically important because the antibody probably neutralizes the effect of systemically administered IFN before it reaches the site of action.

KEY WORDS interferon • glioblastoma • interferon-neutralizing antibody

RECENTLY, the clinical results of interferon (IFN) application to various malignant neoplasms have been reported.1-3 The anti-tumor effect of IFN on malignant brain tumors has also been studied.5,6,8 The anti-tumor mechanism is thought to be mediated either directly or indirectly through the host's immune system. We have previously reported that the natural killer activity of IFN in patients with malignant brain tumors was significantly elevated during the course of IFN therapy.6 We report here a patient with glioblastoma who showed a high titer of IFN-neutralizing antibody in the serum during and after a course of IFN therapy.

The IFN used in this study was the recombinant leukocyte IFN (IFN-α Ro22-8181, molecular weight 18,400 to 19,400, specific activity 2 to 4 x 10⁸ IU/mg protein). The IFN was administered intramuscularly, starting at a dose of 10⁶ IU/day and gradually increasing to a maintenance dose of 50 x 10⁶ IU/day for as long as possible. The IFN-neutralizing antibody titer in the serum was assayed before, during, and after the course of IFN therapy.*

Case Report

This 47-year-old woman was well until August, 1980, when she developed motor weakness and sensory disturbance of the right upper limb and memory disturbance. These symptoms gradually progressed, and computerized tomography (CT) scanning revealed a left frontal mass lesion. She was admitted to another hospital and underwent a left frontal craniotomy and subtotal removal of the tumor in September, 1980. Histological diagnosis was glioblastoma multiforme. After surgery, the neurological symptoms improved and she was well until February, 1982, when motor weakness of the right arm and slight dysphasia appeared again. A CT scan showed a recurrence of the tumor and she was referred to our hospital.

A 150-mg injection of ACNU (1-(4-amino-2-methyl primidine-5-yl)-methyl-3-(2-chloroethyl)-3-nitrosourea hydrochloride) was given into the left common carotid artery, followed about 2 months later by a 100-mg injection of ACNU. Because the neurological symptoms were not improved and the tumor size on CT was unchanged after the administration of ACNU, IFN therapy was started 3 months after the last administration of ACNU. Figure 1 shows the dose of IFN administered, the laboratory findings, the clinical symptoms, Karnofsky's performance score, and the IFN-neutral-
izing antibody titer during IFN therapy. Interferon therapy was started at a daily dose of $10^6$ IU, and about 6 weeks after the beginning of IFN therapy the daily dose of IFN was increased to $50 \times 10^6$ IU for about 38 weeks. The total dose of IFN administered was $13,676 \times 10^6$ IU.

The leukocyte count decreased to 3100/cu mm 6 to 8 weeks after the beginning of IFN therapy but returned to normal by the 10th week. The platelet count decreased during the 4th to 8th week but recovered by the 10th week, and thereafter did not decrease markedly. The hematocrit decreased transiently at the 8th and 40th weeks but had recovered by the 44th week. The values of glutamic oxalo-acetic transaminase, glutamic pyruvic transaminase, lactic dehydrogenase, and alkaline phosphatase were within normal limits during IFN therapy. When the IFN dose was increased, fever, general malaise, anorexia, and nausea were noted, but these symptoms gradually improved spontaneously. The neurological findings were unchanged during IFN therapy. Karnofsky's performance score, which was 70% at the beginning of IFN therapy, decreased to 60% during the initial period of IFN therapy because of side effects. A few weeks later, however, performance status spontaneously recovered to 70% and remained at this level thereafter. Interferon-neutralizing immunoglobulin G (IgG) antibody, with a titer as high as 483, was detected in the serum about 6 weeks after the beginning of IFN therapy and the antibody titer gradually increased. The high IFN-neutralizing antibody titer continued during IFN therapy and for at least 3 months after IFN was discontinued. Concomitantly with the increased IFN-neutralizing antibody titer, the concentration of IFN in the serum fell below 6 IU/ml. The prick test had been consistently negative during the period of observation. There was no marked change in the size of the tumor as seen on the serial CT scans before, during, or after the course of IFN therapy (Fig. 2).

Discussion

Interferon has been tried in the therapy of human malignant neoplasms, and the clinical applicability of IFN to patients with malignant brain tumors has also been investigated. We have administered IFN-α

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![Fig. 1](image-url)  
*Fig. 1. Summary of the patient's course during interferon (IFN) therapy for glioblastoma, including the dose of IFN administered, laboratory findings, clinical signs and symptoms, Karnofsky's performance scale (%), and IFN-neutralizing antibody titer during IFN therapy. WBC = white blood cell; PLT = platelet; Ht = hematocrit; GOT = glutamic oxalo-acetic transaminase; GPT = glutamic pyruvic transaminase; LDH = lactic dehydrogenase; AL-P = alkaline phosphatase; WNL = within normal limits; INU = international units.*

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to five patients with malignant gliomas. The patient reported here is the only one in whom a high titer of IFN-neutralizing IgG antibody was detected in the serum. Ingimarsson, et al., reported that they administered IFN to 20 patients with osteosarcoma for 6 to 18 months and IFN-neutralizing antibody was detected in none of these cases. There are only a few cases reported in which IFN-neutralizing antibody was detected during IFN therapy in patients with malignant neoplasms. Vallbracht, et al., reported that human IFN-β-neutralizing IgG antibody was detected during IFN therapy in their patients with nasopharyngeal carcinoma treated with IFN-β. Trown, et al., reported that neutralizing IgG antibody was detected in three patients with cancer treated with human leukocyte IFN. In two of them, a high IFN-neutralizing antibody titer was detected even before IFN therapy.

The mechanism of the appearance of IFN-neutralizing antibody is still unknown. There are several possibilities: 1) the daily IFN dose of $50 \times 10^6$ IU was higher than the dose that most patients could tolerate; 2) the specific activity of $2 \times 4 \times 10^8$ IU/mg protein was not pure enough for a long course of therapy; and 3) the immune system of this particular patient was exceptionally sensitive. In patients with a high titer of IFN-neutralizing antibody, the biological activity of IFN is neutralized immediately if IFN is administered systemically, and no anti-tumor effect can be expected.7 The appearance of IFN-neutralizing antibody raises an important clinical problem in using IFN therapy against malignant neoplasms. Although the anti-tumor effect of IFN is now being extensively investigated, its clinical usefulness is still inconclusive. In view of the fact that IFN-neutralizing antibody was produced in one of our patients, we may conclude that a higher dose of IFN is not necessarily more effective in dealing with malignant tumors.

References


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