Fever Following Administration of Human Interferon- β (HuIFN- β)

by

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INTRODUCTION

In recent years, the clinical value of IFN in the treatment of malignant tumors has been extensively studied. From 1972, Strander et al. with Cantell et al. had started therapeutic evaluation of IFN- α in patients with Osteosarcoma. In 1975, Strander et al. presented a clinical report that attracted world-wide attention in the medical field. A number of problems are still involved in the action mechanisms or clinical application of IFN. Especially in application of IFN- α , - β and - γ , there still remain problems regarding the effects on various types of tumor, the method of administration and the side-effects. As the main side-effect, fever appears most frequently. In our clinic, fever and febrile symptoms following IFN- β administration have been analyzed by the changes in the axillary temperature, pulse rate, blood pressure level and respiratory rate as well as the objective and subjective symptoms. These results are presented and discussed in this paper.

METHODS

1) Subject

The subjects studied were 7 patients with malignant bone and soft tissue tumors, consisting of 4 males and 3 females. The tumor distribution was (1) Osteosarcoma (17-year-old male), (2) Osteosarcoma (10-year-old male), (3) Ewing's sarcoma (9-year-old male), (4) Malignant Lymphoma (38-year-old male), (5) Rhabdomyosarcoma (16-year-old female), (6) Fibrosarcoma (19-year-old female) and (7) Fibrosarcoma (53-year-old female). For measurement of the data, IFN- β was administered after confirming the absence of the effect of previous surgery or antitumor drugs, and also the abnormalities of hepatic, renal, pulmonary and cardiac functions.

2) Drug used and methods of administration

HuIFN- β was used. A solution of 3×10^6 IU in 100 ml of physiological saline was administered by drip infusion for one hour. For intramuscular injection, 6×10^6 IU or 12×10^6 IU were dissolved in 3 ml or 6 ml of physiological saline and injected into the gluteal muscle.

3) Measurement

The axillary temperature, pulse rate, blood pressure and respiratory rate were measured at regular intervals. Simultaneously the subjective and objective symptoms were

Table 1 Febrile symptoms after HuIFN- β administered.

Febrile symptoms	3×10^6 IU iv. (n=7)	6×10^6 IU im. (n=6)	12×10^6 IU im. (n=6)
Chills	7	0	3
Fever up	7	4	4
Febrile feeling	7	5	4
Sweating	3	1	0
Headache	3	1	2
Arthralgia	3	0	2
General malaise	3	0	2

Fig. 1 Changes of axillary temperature, pulse rate and blood pressure after HuIFN- β 3×10^6 IU i.v. drip infusion, n=7.

evaluated. The temperature of the axilla, pulse rate, blood pressure and respiratory rate at the time of intravenous drip infusion of 3×10^6 IU were measured in all the 7 cases. Measurement of these data at the time of intramuscular injection of 6×10^6 or 12×10^6 IU was performed in 6 cases. Anti-pyretics were administered simultaneously with HuIFN- β in 7 cases (Medication before a chill).

RESULTS

1) Intravenous drip infusion of 3×10^6 IU

Chills and shivering occurred in all the cases of this group with elevation of the axillary temperature. Despite no reduction of the blood pressure, the pulse rate increased. And the respiratory rate was not changed. Fever sensation, sweating and headache were common to almost all and some complained of arthralgia. Pyretic symptoms were more frequent in this group than in the intramuscular injection groups (Table 1). The temperature returned spontaneously to 37°C at approximately 7 hours after the administration (Fig. 1). All these symptoms were the transient manifestations of fever and fever induced changes. There was no after-effect on the following day.

2) Intramuscular injection of 6×10^6 IU

Chills did not occur in all the cases. Headache and febrile feeling were noted in 1 and 5 cases respectively (Table 1). There was no change in the respiratory rate. Unlike in

Fig. 2 Changes of axillary temperature, pulse rate and blood pressure after HuIFN- β 6×10^6 IU i.m. injection. $n=6$.

the drip infusion group, pyretic symptoms were mild. The axillary temperature was slightly elevated. The maximum temperature elevation was approximately 1°C from the prepyretic level at 4 hours after the administration (Fig. 2).

3) Intramuscular injection of 12×10^6 IU

Chills occurred in 3 of 6 cases. This chills was mild than in the drip infusion group. In spite of an elevation of the axillary temperature, the maximum elevation stayed at approximately 1.3°C , which was higher than in the intramuscular injection group of 6×10^6 IU (Fig. 3). The side-effects developed more frequently than in the intramuscular injection group of 6×10^6 IU, as shown in the Table 1. Among the 3 groups, fever continued longest in this group and the axillary temperature measured 37°C even at 12 hours after the administration (Fig. 3). Mild elevation of the pulse rate occurred simultaneously with fever. The blood pressure and respiratory rate showed no noteworthy changes.

4) Administration of anti-pyretics

In 7 cases treated with simultaneous administration of 3×10^6 IU by drip infusion and 25~50 mg/body of Indomethacin suppository (Medication before a chill), neither the eleva-

Fig. 3 Changes of axillary temperature, pulse rate and blood pressure after HuIFN- β 12×10^6 IU i. m. injection, $n=6$.

tion of the axillary temperature nor chills were observed. Other pyretic symptoms were also adequately alleviated. Moreover, pyretic symptoms, if any, were very mild. These points will be explained in a following paper.

DISCUSSION

Fever is known to be most frequent side-effect following IFN administration. This paper described the changes in the axillary temperature, pulse rate, blood pressure, respiratory rate, subjective and objective symptoms by the mode of administration, using HuIFN- β . In the intravenous drip infusion group, anti-pyretics were combined to prevent the development of side-effects.

Fever and fever-induced symptoms occurred more severely and frequently in the drip infusion group than the intramuscular injection group. However, chills, shivering and fever were also noted in some of the intramuscular injection group who had received a massive dose (12×10^6 IU). This seems to indicate that fever and other related symptoms depend on the blood concentration of IFN and that headache, arthralgia, general malaise, sweating, febrile feeling as well as the changes in physiological indices such as the pulse rate represent the symptoms associated with fever. Alleviation of all these symptoms by administration of anti-pyretics suggested that Prostaglandins were released at the time of IFN administration.

No remarkable changes in the blood pressure, respiratory rate and pulse rate were noticed in the groups. Moreover, manifestation of a shock symptom was also absent.

Successful alleviation of side-effects was obtained in this study by simultaneous administration of anti-pyretics at the time of intravenous drip infusion of HuIFN- β . Further studies are intended by the authors on the method of combined application.

CONCLUSION

- 1) Fever with concomitant chills occurred in all cases of the drip infusion group of 3×10^6 IU.
- 2) The intramuscular injection groups showed no marked chills.
- 3) The blood pressure and respiratory rate showed transient changes.
- 4) For moderating the side-effects (Febrile symptoms) of HuINF- β , anti-pyretics were combined (Medication before a chill). The side-effects were adequately alleviated.

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人線維芽細胞インターフェロン (HuIFN- β) 投与時の発熱現象

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近年、悪性腫瘍患者等へのインターフェロン投与の報告がなされているが、その副作用についての詳細な報告は少ない。我々は骨軟部悪性腫瘍患者に人線維芽細胞インターフェロン (HuIFN- β) を投与しているが、その副作用の主たるものは発熱であった。今回は7名の骨軟部悪性腫瘍患者に HuIFN- β を投与した時の腋窩温・脈拍数・血圧・呼吸数・自覚症状を経時的に測定・観察したので報告した。結果1) 300万単位点滴静注投与群において全例悪寒戦慄に伴う発熱がみられた。2) 筋注投与群において著しい悪寒戦慄はみられなかった。3) 血圧・呼吸数において大きな変動はみられなかった。4) 発熱症状を軽減するためにNSAID を投与し (Medication before a chill), 充分に発熱症状を軽減する事が出来た。

的に測定・観察したので報告した。結果1) 300万単位点滴静注投与群において全例悪寒戦慄に伴う発熱がみられた。2) 筋注投与群において著しい悪寒戦慄はみられなかった。3) 血圧・呼吸数において大きな変動はみられなかった。4) 発熱症状を軽減するためにNSAID を投与し (Medication before a chill), 充分に発熱症状を軽減する事が出来た。