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Short communication

Intralymphatic infusion of interferon in patients with lymph nodal metastases from melanoma of the lower limbs

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Summary. In five patients with regional lymph nodal metastases from malignant melanoma of the lower limbs, intralymphatic infusion of interferon caused a complete remission in one patient and a partial remission in two others. The remaining two patients, in whom the massive neoplastic infiltration had obstructed the inflow of the drug in the tumoural seat, were unresponsive. Since the efficacy of interferon seems to be dose-dependent, intralymphatic infusion causes the accumulation of massive quantities of the drug in the tumoural seat, thus favouring its antiproliferative action.

Introduction

Interferons seem to be active in some malignancies, and their efficacy seems to vary according to the type of interferon (alpha, beta or gamma), the dose level and route of administration (subcutaneous, intramuscular, intravenous, intracavitary, intralesional) [3]. We used interferon rec alpha 2b by intralymphatic infusion in patients with lymph nodal metastases from melanoma of the lower limbs, with the aim of investigating whether a massive and direct concentration of interferon in the lymph nodes involved by the neoplasm would lead to greater effectiveness of the drug.

Patients and methods

A total of five patients (3 men and 2 women; average age, 35 years) who had undergone previous surgical removal of melanoma lesions of the lower limbs and were subsequently affected by metastases at the inguinal and paraaortic lymph nodes, which had not previously been treated, were submitted to intralymphatic infusion of interferon rec alpha 2b (Intron-A, Schering).

Intralymphatic infusion of interferon was carried out as in diagnostic lymphography. Two catheters were placed on the lymphatics of the feet and connected with two infusion pumps, each containing 10×10^6 IU/m^2 interferon diluted in 10 ml physiological solution, to which 1,000 IU haparin had been added. The 2-h interferon infusion was repeated twice a week for 4 weeks, using the same lymphatic vessel when it remained unobstructed, or a collateral in the case of obstruction. In the responsive cases, treatment was continued subcutaneously at a dose of 3×10^6 IU/m^2 three times weekly.

Results

Among three of the five patients with partial lymph nodal involvement, one achieved a complete remission, with normalization of clinical, lymphographic and computed tomographic scan findings (this situation has persisted under treatment with interferon given by the systemic route for the past 5 months) (Fig. 1), and two showed a partial response. The remaining two patients with extended lymph nodal involvement were unresponsive.

Intralymphatic therapy was well tolerated, with less severe side effects than those correlated to the use of interferon given by the traditional systemic route. At 12–14 h after the infusion of interferon, three patients presented with chills and fever; all five experienced fatigue, myalgia and headache. We found neither remarkable alterations in haematological, hepatic or renal parameters nor neurological toxicity. The total lymphocyte count and the lymphocytic subpopulations did not show any substantial modification.

The pharmacokinetics of interferon by intralymphatic infusion is different from that of other routes used thus far (Fig. 2). The drug flow along the lymphatic vessels is slow and the contact with the lymphatic structures, prolonged, which probably causes the higher therapeutical index. The peak serum concentration was reached as late as 18–20 h. The search for anti-interferon antibodies has thus far been negative.

Discussion

Intralymphatic infusion has been used in the past both for diagnostical purposes and to transport radioactive material and immunogenes to the lymphatic centres in both animals and man [2, 4, 6–8]. Our experience shows that interferon can be given by the intralymphatic route without severe side effects and with the advantage of reaching the regional lymph nodes (the seat of metastases) before any possible inactivation may occur, as more likely happens when interferon is given by the traditional systemic route. The intralymphatic route creates the possibility of concentrating a greater quantity of interferon in the lymph nodes involved by the tumour than that normally achieved by traditional systemic administration, enabling the drug to

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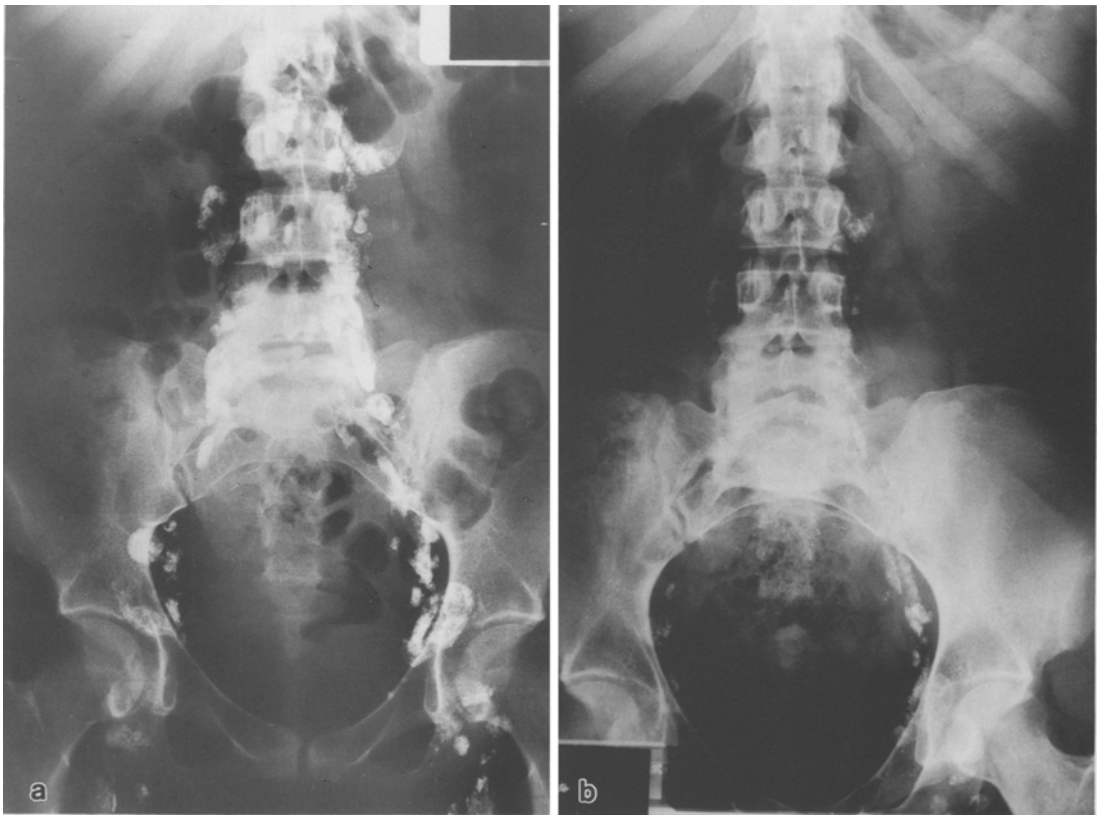

Fig. 1. Lymphographic findings **a** before and **b** after intralymphatic infusion of interferon

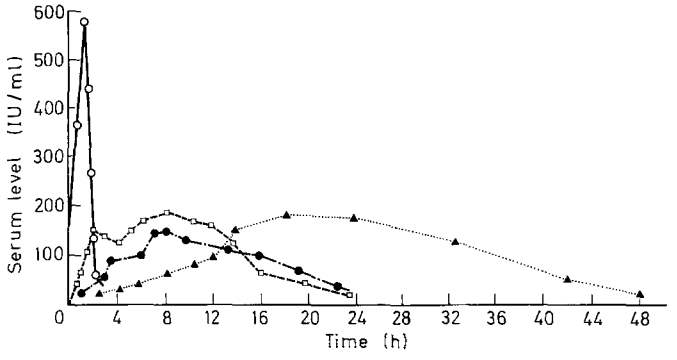

Fig. 2. Pharmacokinetics of interferon a 2b by intralymphatic infusion in two patients with slight lymph nodal tumoural involvement as compared with other standard routes of administration. Serum concentration curves (μg/ml), 10×10^6 IU/m^2 (radioimmunoassay). ○ i.v. infusion; ■ i.m. injection, ● s.c. injection. ▲ intralymphatic infusion

act efficaciously [1, 5]. Similarly, in malignant melanoma, interleukin seems to be more efficacious when given by the intralymphatic route than when given intravenously [5]. If, as has been reported, the effectiveness of interferon is dose-dependent [3], the intralymphatic route, when practicable, seems to be the most reasonable.

Our preliminary data seem to confirm the hypothesis that interferon given intralymphatically is particularly active in the first stages of lymph nodal metastatic involvement, whereas it seems to be ineffective when the tumoural invasion has totally upset the architecture of the lymph node, thus obstructing the inflow of the drug.

More extended case histories and randomized studies are needed to evaluate the efficacy of interferon given intralymphatically, both in the various stages of neoplastic lymph nodal involvement and for the adjuvant treatment of melanomas of the limbs at high risk of metastasis after the surgical phase.

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