

Alternating Recombinant and Natural Alpha-interferon Helps to Prevent Clinical Resistance to Interferon in Cutaneous T-cell Lymphoma Treatment

Sir,

It is well known that prolonged administration of recombinant alpha interferon (r α IFN) in several viral and malignant diseases can be followed by loss of clinical activity of the drug. In the majority of these cases, the occurrence of insensitiveness to r α IFN could depend on the synthesis of biologically active r α IFN-neutralizing endogenous antibodies (1), although some argue that a cause-and-effect relation between these facts has not been proven (2). Recently, others have pointed out that even non-neutralizing IFN antibodies could be relevant in affecting alpha interferon efficacy (3). We started using alternate treatment with different interferons (IFNs) in 1994, when we observed our first case of resistance to r α IFN in connection with the treatment of cutaneous T-cell lymphoma (CTCL). These are our pilot reports.

CASE REPORTS

Case 1

A 44-year-old man with CTCL (Scandinavian MF group stage II) (4) had been treated with r α IFN, 3 MU/day intramuscularly, and etretinate, 50 mg/day orally, according to the protocol described elsewhere for a former series of CTCL patients treated with IFN (4). Clinical resistance ensued 98 days after the beginning of the treatment. His condition deteriorated to stage III in a few days. Thus we decided to treat this patient with natural IFNs, as already done by other researchers in chronic myelogenous leukemia patients (5). In a fortnight the disease regressed to a stationary stage II, which has lasted for more than 3 years up to now.

Cases 2 to 8

Fearing that other cases of resistance to r α IFN could ensue, we prophylactically turned the other patients currently treated with r α IFN or newly enrolled (7 males; 5 stage II, 1 stage III, 1 stage IVa; mean age 57; range 42–74; mean disease duration 0.5 years) to alternating IFNs. Partial remissions (4 cases) or reductions of progressive disease to a stable one (3 cases) were always obtained and maintained (range 9–32 months), except in the stage III case: he became insensitive to IFNs in 1 month and had to be treated with total body electron beam irradiation, which was successful.

DISCUSSION

When we decided to put the first patient of our series on alternating IFNs, we had considered the fact that the development of antibodies to natural IFNs presented with a lower incidence and seemed to induce loss of clinical responsiveness less frequently (6). Moreover, it had already been stated that in many instances therapeutic efficacy could be re-established by resuming treatment with natural alpha-IFN (7). These facts opened up the outlook of administration of various IFN mixtures in rotation to CTCL patients. Our results were quite encouraging; thus we extended the rotation administration of IFNs to all of our CTCL patients currently treated with r α IFN, without expecting the clinical onset of resistance to a given IFN. The "rotation protocol" we now follow consists of alternating 3-month cycles of natural lymphoblastoid

(Wellferon[®], Glaxo-Wellcome), natural leukocyte (Cilferon[®], Janssen-Cilag) and r α IFN (Intron-A[®], Schering-Plough), 3 MU intramuscularly, daily or on alternate days depending on the clinical outcome, evaluated as in our former paper (4). Etretinate, 50 mg/day orally, is routinely coupled. After more than 3 years of experience, we have observed no loss of clinical effectiveness of IFNs in 7 of the 8 patients we have been treating.

Formerly we predicted that alternative use of various kinds of IFNs could prove effective in treating lymphoproliferative diseases of the skin selectively (4). On the ground of our satisfying pilot results we confirm our belief, and we encourage other groups to try such alternating protocols on extended series of CTCL patients in order to lay the groundwork for controlled studies. Incidentally, we must unfortunately recognize that public health service officials are indifferent to, or even mistrustful of empirical therapeutic attempts, which are needed in the specialized management of rare conditions for which codified therapy is unavailable or often ineffective. In Italy the use of natural IFNs is limited by bureaucratic and administrative restrictions, and special authorisations must be obtained.

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