5. Adjuvant interferon treatment in human osteosarcoma

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Introduction

The protocols of Rosen and collaborators have been used for several years in Scandinavia [1], with the exception of our institution, where adjuvant IFN has been utilized for 20 years [2]. The present report is an update of our IFN-treated osteosarcoma series conducted over the period 1971–1984; control patients representing a high-dose chemotherapy group and a nonadjuvant group are also presented.

Patients and methods

During the years 1971 and 1984, 77 osteosarcoma patients were seen at Karolinska Hospital. Nine patients had metastases at presentation, leaving 68 patients for the IFN trial; these 68 patients constitute the IFN-treated group. Two control groups have been elected. One is a nonadjuvant group of 32 patients treated elsewhere in Sweden between 1971 and 1976. The other is a chemotherapy group of 20 patients treated elsewhere in Sweden from 1977 to 1980. The IFN and both control groups comprise all osteosarcoma patients without metastases at presentation in Sweden during the years studied. Hence, these groups together constitute a nonselected series of patients followed for a minimum of 5 years.

IFN treatment

The IFN preparations used in the trial consisted of natural leukocyte IFN processed according to two methods, both yielding semipurified solutions [2]. The IFN was administered (i.m.) daily during the first month after diagnostic open biopsy at a dose of $3 \times 10^6$U and then three times per week for another 17 months.

The side effects of this type of treatment have been described previously in detail [3]; they are typical of those reported for natural IFN alpha therapy. No patients had to stop IFN treatment because of side effects.

Chemotherapy

Chemotherapy was given with either high-dose methotrexate or high-dose Adriamycin according to local protocols.

Clinicopathologic features

Different clinicopathologic features considered to be of prognostic significance were assessed during the course of treatment, as described previously [2]. The surgical margins were not equally distributed among the three groups. There were more radical and wide margins in the two control groups. In fact, an inadequate margin, i.e., a marginal or intralesional, was recorded in as many as 21 of 68 patients in the IFN group, while inadequate margins were recorded in only two patients in the chemotherapy group and in one patient in the nonadjuvant group.

Results

The local recurrence rate was much higher in the IFN group than in the other two groups, i.e., 30% compared to 0% in the chemotherapy group and 4% in the nonadjuvant group. The 5-year metastasis-free survival was 0.38 in the IFN group, 0.50 in the chemotherapy group, and 0.32 in the nonadjuvant group. The overall survival was 49% in the IFN group, 54% in the chemotherapy group, and 35% in the nonadjuvant group (Figure 5-1).

Discussion

The rationale for using IFN in the adjuvant setting of osteosarcoma is multifold. Experimentally, exposure of osteosarcoma cells to IFN alpha has been shown to cause partial reversion of the malignant phenotype, inhibition of proliferation, loss of cell-overlapping capability in confluent cultures, and marked reduction of tumorigenicity [4]. Kirstein and Baglioni [5] reported that human tumor necrosis factor stimulated the proliferation of human osteosarcoma cells and that mitogenic activity could be abolished by IFN. The monocytes probably play a role in host defense against osteosarcoma cells in vivo. The monocyte function of patients with osteosarcoma is normal [6] and can be stimulated by IFN.

Human leukocyte IFN is capable of inhibiting the growth of human osteosarcoma cells in tissue culture [7]. Glasgow and Kern demonstrated an inhibitory effect of IFN on osteosarcoma in rodents in one system, but not in another [8,9]. Transplanted human osteosarcomas growing in nude mice are