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INTERFERON COMBINED WITH IRRADIATION IN THE TREATMENT OF OPERABLE HEAD AND NECK CARCINOMA

A pilot study

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Twenty-two patients with operable head and neck cancer were randomized to receive natural leukocyte alpha interferon (IFN) and radiotherapy, or radiotherapy alone (control) before operation. IFN was administered at 6 MU i.m. daily for 4 weeks and thereafter 3 times per week for 2 months. IFN treatment was introduced simultaneously with radiotherapy (2 Gy daily, 5 fractions per week). The preoperative dose was 30–32 Gy. Tumor response and side-effects were registered. The patients underwent radical surgery 3 weeks after the preoperative irradiation, followed by postoperative irradiation with 22–32 Gy. After preoperative treatment there were one complete response and 4 partial responses among 10 patients receiving IFN and 2 partial responses among 12 patients treated with irradiation alone. No difference in survival was demonstrated between the 2 groups. In the histologic examination of the surgical samples malignant cells were found in 6 of the IFN patients and in 8 of the control patients. The IFN patients had considerably more pronounced mucosal radiation reactions than the controls. The accrual of patients to the study was discontinued due to the side-effects.

There are few reports in the literature concerning experimental studies on combined effects of interferon (IFN) and irradiation. Dritschilo et al. (1) reported enhanced killing of mouse Swiss 3T3 cells after concomitant irradiation and administration of mouse IFN. Namba et al. (2) demonstrated significant enhancement of the cell killing effects of ^{60}CO gamma rays when applied in combination with IFN beta in HeLa cell cultures. Chang & Keng (3) found an enhancement of radiation cytotoxocity by various recombinant IFNs with an enhancement ratio of 1.21 to 1.44 in human renal cell carcinoma cell cultures.

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At the Department of Oncology and Radiotherapy of the University Central Hospital in Turku a series of patients with squamous cell carcinoma of the head and neck region was treated with preoperative radiotherapy combined with human IFN alpha. The aim of this study was to find out whether addition of natural IFN might increase the effect of radiotherapy in head and neck cancer and to register the side-effects induced by the combination of these two treatment forms.

Material and Methods

Patients. Twenty-four previously untreated patients with operable squamous cell carcinoma in the head and neck region were randomized by the sealed envelope method to receive radiotherapy and IFN alpha (n = 11) or radiotherapy alone (n = 13, control group) during 3 weeks prior to a radical resection of the tumor. There were two drop-outs, one in the control group as the diagnosis was revised as benign and one in the IFN group due to discontinued treatment after 2 days because of fever and

infection of the tracheostoma. The tumors were evaluated as suitable for combined treatment with radiotherapy and operation and classified as T1–4, N0–3, M0. The mean age of the patients was 59.6 years, 18 were males and 4 females.

Radiotherapy. Radiotherapy was delivered by x-rays from a 6 MeV linear accelerator or cobalt-60 beam with a daily minimum tumor dose of 2 Gy and 5 fractions/week. The total preoperative tumor dose was 30 to 32 Gy in 3 weeks. After an interval of 3 weeks a radical operation was performed. The type of operation was related to the localization of the primary tumor. In lymph node positive disease neck dissection was also performed. Postoperative radiotherapy was given 2 to 3 weeks later with a tumor dose of 22 to 32 Gy. The total dose in the volume of the primary tumor was 52 to 64 Gy (depending on the extension of the operation). At least 50 Gy in the regional lymph nodes was delivered in all patients.

Interferon treatment. Natural human leukocyte IFN alpha was produced and purified as described earlier (4, 5). The schedule was 6 MU daily i.m. for one month starting simultaneously with preoperative radiotherapy. After the first month IFN was delivered 3 times/week for 2 months and then terminated.

Follow-up. Patients were evaluated before treatment, after preoperative radiotherapy, after operation, after postoperative radiotherapy and at 3-month intervals up to 2 years and thereafter twice a year until the disease relapsed or up to 5 years. Clinical examination was made and blood counts, chest x-rays and the immune functions of the patients were studied in addition to the medical history. Responses and side-effects were classified according to the WHO criteria (6).

Results

The minimum follow-up time was 20 months. According to the clinical evaluation there was one complete response (CR) and 4 partial responses (PR) at the time of operation among the 10 IFN-treated patients. After preoperative radiotherapy in the 12 patients not receiving IFN only 2 PR were seen (Table 1). At the histological examination of the surgical specimens in 6 cases of the 10 IFN patients and 8 of the 12 control patients malignant cells were still observed after the preoperative treatment. Due to the small number of patients and various stages of the disease no conclusions can be drawn from the small differences in response rates. After surgery and postoperative irradiation all patients were clinically free from disease.

No significant difference in survival or disease-free survival could be observed, the mean survival being 27.7 months in the IFN group and 26.5 months in the control group. The mean disease-free survival was 25.8 and 21.4 months respectively.

Table 1

Clinical response after preoperative radiotherapy alone (control) or radiotherapy combined with interferon (IFN)

	n	CR	PR	SD
IFN	10	1	4	5
Control	12	—	2	10

CR = complete response
PR = partial response
SD = stable disease

Table 2

Side-effects in patients with head and neck cancer treated with irradiation alone (control) or irradiation combined with interferon (IFN)

	IFN (n = 10)	Control (n = 12)
Acute mucosal reaction*		
grade 1	—	—
grade 2	2	8
grade 3	3	4
grade 4	5	—
Fever	10	—
Weight loss >5 kg	5	5
Leukopenia WHO grade* 2	4	—
Leukopenia WHO grade 3	1	—
Thrombocytopenia	—	—
Severe infections	3	—

*) ref. 6

Of the 10 IFN-treated patients, 5 had severe grade 4 reactions of the oral and pharyngeal mucosa during radiotherapy (Table 2). In 3 cases IFN treatment had to be discontinued after 4 weeks because of 1) the patient's refusal due to a grade 3 mucosal reaction, 2) urticaria and 3) erysipeloid staphylococcus aureus infection in the face and the neck region. In addition 2 patients receiving IFN had serious bacterial infections: one got a staphylococcal sepsis and in one patient with severe alcoholism pneumonia and postoperative wound infection with Pseudomonas developed. No similar problems were seen in the patients receiving radiotherapy alone. Six patients in the IFN group had an extra pause of 1 week during the preoperative radiotherapy because of extensive mucosal reaction in contrast to only one patient in the control group. The side-effects are summarized in Table 2.

Discussion

The accrual of patients with head and neck tumor to this study was stopped due to the high toxicity in the IFN and radiotherapy arm. Thus, the number of patients is low and does not allow any certain conclusions concerning the

efficacy of the treatments. In a study involving 12 patients with small cell lung carcinoma, the response rate was 100% with the combination of irradiation and IFN (7) suggesting an enhanced antitumor effect of irradiation by IFN. In another study, 7 of 9 evaluable patients with non-small cell lung cancer showed partial response after combined treatment with irradiation and interferon (8). In lung cancer only marginal effects with IFN alone have been achieved (9).

In spite of the relatively low daily dose of 6 MU i.m. the combination of radiotherapy and IFN caused more side-effects than radiotherapy alone in the present study suggesting that even early reacting tissues like mucosal membranes show an enhanced radiation reaction during combined radio- and IFN therapy and not only late reacting tissues like the lung (7). The serious acute reactions in our study might have been avoided with another schedule of IFN therapy. In a phase I trial on several types of solid tumors IFN alpha-2b 5 MU given 5 times a week was considered to be an intolerable dose schedule in conjunction with radiotherapy (1.8 Gy daily, 5 fractions/week) and a dosage of 5 MU IFN 3 times a week was recommended (10).

Our results suggest that the therapeutic effect of combined radio- and IFN-therapy on head and neck tumors is increased when compared to radiotherapy alone but this question requires further studies on larger materials. It seems, however, obvious already from the present study that IFN enhances early radiation reactions in the mucosa of the head and neck region. The combined treatment might be tolerated better if IFN is administered only 3 times a week and in somewhat lower doses.

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