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Natural IFN-α for non-small-cell lung cancer with pleural carcinosis

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The survival of patients with pleural effusion from bronchial carcinoma is short. Ten patients with ipsilateral pleural effusion from non-small cell cancer of the lung, localized to the thoracic cavity, were treated with intrapleural application of IFN-α and radiation therapy. All had malignant pleural effusion confirmed by cytology. Radiation therapy was given to the hemithorax with boost to the area of local tumor and mediastinal lymph node metastases. The dose to the hemithorax was 20-25 Gy, whereas the total dose to the tumor bed and mediastinum was 45 Gy. IFN-α 2 × 10^6 IU diluted in 20 ml of distilled water was injected intrapleurally once weekly. The treatment, as a rule, is suitable for palliation only. The effect of IFN-α was evaluated according to the cellular morphology of the pleural fluid and the patients' survival. The median survival of IFN-α treated patients was 17 months. The median survival of the matched control pts treated only for palliation with pleurodesis or radiation therapy was 7 months. The patients in the experimental group had a slightly better chance of prolonged survival. A randomized clinical trial seems to be indicated.

Key words: carcinoma, non-small cell lung-drug therapy; interferon-alpha

Introduction

Non small cell lung cancer (NSCLC) represents 75 % of lung cancer, the most common cancer in males. The diagnosis is late in the great majority of cases (70-75 %) and the overall survival of NSCLC patients is poor. The 5-year survival of operable (Stage I and Stage II) patients treated by surgery is 30-40 %. The survival of patients with Stage III is less than 5 % whereas the survival of those with malignant pleural effusion and those with Stage IV is practically nil.[1, 2] Neither chemotherapy nor radiation have contributed much to the survival of these patients. Surgery has been attempted for cure in patients with stage III,[3-8] but was not succesfull, especially not in those with pleural effusion. To palliate symptoms and prolong the survival was the aim of several trials; recently, there have been reports with encouraging results of treatment with intrapleural applica-

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tions of chemotherapy and biologic response modifiers.[9-12]

IFN-α has proved to be locally effective in several solid malignant tumors,[13] and systemically effective in several haematological malignancies.[14, 15] As a single therapeutic agent for adenocarcinoma and other solid tumors it has shown only modest results.[16] Enhancement of chemo- and radiation therapy with IFN-α has been shown in vivo[17-20] and in vitro studies.[21] Also, some enhancing effect of IFN-α on chemotherapy and radiation has been established.[22]

Earlier, we have reported on 14 patients with NSCLC and pleural effusion treated with intrapleural application of IFN-α; it was found that IFN-α could clear effusion from cancer cells and haemorrhagic admixture with minimal side effects. The treatment also prolonged the survival of patients.[23]

In the presented series, 10 patients with NSCLC and pleural effusion, without distant metastases (Stage IIIb), were treated by radiation and intrapleural applications of IFN-α, with the aim of permanent local control and prolonged survival.

Materials and methods

Experimental group

Ten patients admitted to the Institute of Oncology between december 1988 through november 1991, were treated for pulmonary cancer and pleural carcinosis. They had malignant cells in the pleural effusion proved by cytology; the primary tumor was confirmed to be adenocarcinoma by bronchoscopy and biopsy in all cases. The extent of the disease was further defined on plain chest radiograms, by CT of the chest and the brain, abdominal echogram, 99mTc bone scan in addition to the conventional biochemical and haematological laboratory tests. Their clinical data are presented in Table 1. The disease was confined to the chest in all patients, those with metastases outside of the chest were not included.

All the patients had radiation therapy 20–24 Gy to the whole hemithorax with a boost to the primary tumor and mediastinal metastases to a total dose of 40-45 Gy (Table 1). IFN-α was given by intrapleural application weekly as long as pleural effusion was present. After that it was given intramuscularly, twice weekly. In one patient (No. 4) it was only given i.m. because of a high risk for bleeding.

2×10^6 units of natural IFN-α were diluted in distilled water and after thoracocenthesis, with removal of as much fluid as possible, injected into the pleural cavity.

Control group

During the same period the great majority of patients with lung cancer and pleural carcinosis were treated for paliation by other methods both, at the Institute of Oncology as well as at the Institute for Lung Diseases, Golnik, the choice being made by the referring physician. Among these, 10 were chosen who matched the patients in the experimental group in terms of age, sex, and extent of disease. There were, however, 3 patients with squamous cell carcinoma in the control group. None of the patients had radical surgery performed previously, two had pleurodesis with Achromycin, 3 received palliative radiation and 5 analgetics only. The mean age of this group of patients was 56 years as compared with the mean age of 54 in the experimental group.

The level of IFN-α was measured in the pleural fluid and in the blood serum before and after IFN-α treatment in 2 patients, one from the experimental group and one from the control group.

In our experiments we used WISH (epithelial cells; European Collection for Animal Cell Cultures, ECACC, England) and MDBKK (bovine kidney, epithelial; American Tissue Type Collection, ATCC). As cell- virus combination using MDBK + VSV is not suitable for the detection of IFN-α, recently we have neglected MDBK cells, esspecially after we have got enough monoclonal antibodies to identify the type of IFN-αin samples of unknown IFN constitution.[24]

Table 1. Clinical data of patients in the experimental group.

Pat. No.	Age	Sex	Site (lobe)	Other metastases	Chemotherapy	RT dose/volume		IFN-α treatment dose effect			Spread	Survival (mos)
								10^6 IU	effusion	complications		
1	60	M	RLL	mediastinum	–	R thorax tumor bed	2100 1500 3600	8 × i.p.	–	fibrosis	brain, L lung, liver, peritoneum	18 DOD
2	26	M	LLL	–	5-Fu, Cis-P VP 16 } 5×	L thorax tumor bed	1500 3000 4500	5 × i.p.	–	fever lymphadenopathy	brain	25 DOD
3	51	F	LLL	–	–	L thorax tumor bed	2000 1750 3750	3 × i.p. 12 × i.m.	–	–	brain	9 DOD
4	50	F	LLL	subclavian ven. thrombosis	–	L thorax tumor bed	1500 2800 4300	8 × i.m. 1 × i.p.	residual	coagulopathy	–	1 tumor on autopsy not proven
5+	38	M	RLL	–	–	R thorax	4000	15 × i.m.	–	fever	L lung, R thoracic wall	46 AWD
6	56	M	RLL	bil. lymph-angiocarcinosis	–	R thorax tumor bed	1500 2000 3500	9 × i.p.	residual	–	lymphangio-carcinosis	5 DOD
7	72	F	LLL	–	–	L thorax tumor bed	1500 2000 3500	9 × i.p.	residual	–	lymphangio-carcinosis	18 DOD
8	72	F	LLL	mediastinum	–	L thorax tumor bed	1650 1800 3450	9 × i.p.	residual	–	–	8 DOD
9	52	M	LUL	mediastinum	Thiotepa i. p. 1×	L thorax	3000	13 × i.m.	residual	fever	liver, peritoneum	23 DOD
10	66	F	RUL	mediastinum	–	R thorax tumor bed	2500 2000 4500	2 × i.p. 11 × i. m.	–	–	L lung	30 DOD

DOD = dead of disease
AWD = alive with disease
+ = pleuropneumectomy

R = right
L = left

U = upper
L = lower

i. p. = intrapleural
i. m. = intramuscular

All patients in the experimental group have been regularly followed by clinical examination, laboratory and blood tests, chest X-ray and CT of the brain. The follow up of the patients in the control group was by the referring physician, who has treated them symptomatically. Therefore, only the date of death is reported for these patients and no details about the

The survival was calculated by the Kaplan-Meier method from the date of diagnosis until death or the date of the last follow up.[25]

The difference in the survival of the two groups was calculated with the log-rank test.

Results

At the end of the study in July 1993, 3 patients were still alive one patient from the experimental group more than 4 years, and 2 from the control group 17 and 15 months respectively (both had squamous cell carcinoma), all with residual disease. The survival is shown in Figure 1. The median survival of the patients in the experimental group was 17 months as compared to 7 months in control patients.

Malignant cells have disappeared from the pleural fluid after treatment with IFN-α in all patients, in the majority the fluid was still present.

Cytology was possible in 9 out of 10 patients, in 2 of them without the influence of radiation therapy. In all patients it showed essentially the same findings as in a previous[26] study of IFN-α in pleural effusions from breast cancer, i.e.:

a) increase in the number of transported lymphocytes and histiocytes in the sediment of the exudate,

b) marked decrease in the number of malignant cells, and

c) marked degenerative changes in the remaining malignant cells.

The levels of IFN-α in the pleural fluid and serum are presented in Figure 2 for patient No. 1 of the experimental group, and in Figure 3 for a patient in the control group. Only a minimal rise was observed in the serum in either of the two patients.

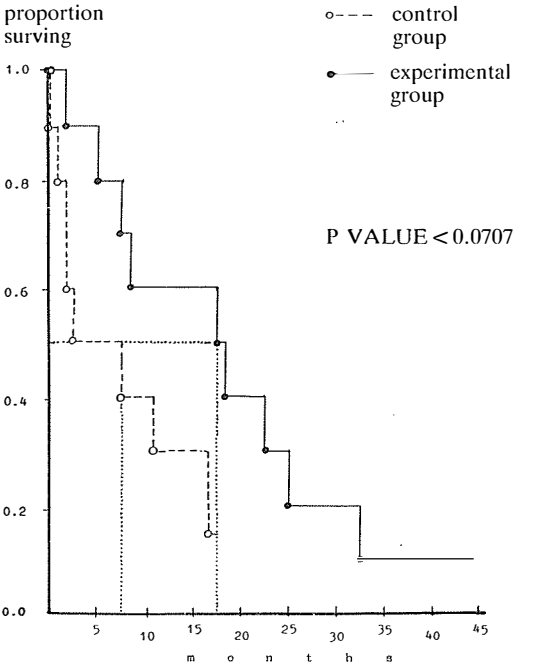

Figure 1. Survival of patients with non-small-cell lung cancer and pleural carcinosis.

Discussion

In a previous study of patients with pulmonary cancer and pleural effusion it was observed that IFN-α treatment may clear the effusion of cancer cells and haemorrhagic admixture and arrest fluid accumulation with minimal side effects.[23]

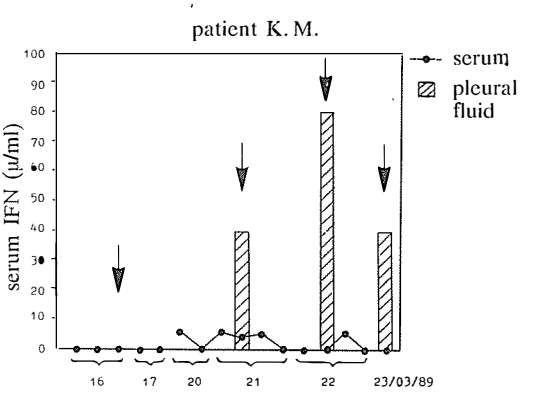

Figure 2. Pharmacokinetics of serum IFN during therapy. Bars represent IFN in pleural fluid. IFN application is indicated by arrows. Curve(s) are daily serum IFN levels.

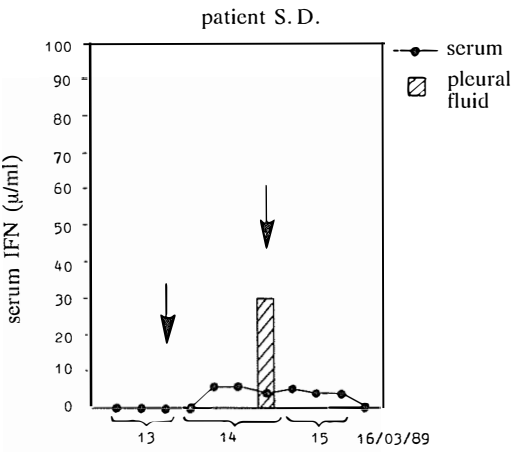

Figure 3. Pharmacokinetics of serum IFN during therapy. Bars represent IFN in pleural fluid. IFN application is indicated by arrows. Curve(s) are daily serum IFN levels.

Improvement in the survival was also noted. Even in this series of patients treated with radiation therapy and IFN-α, the treatment was tolerated well; an increased temperature and local pain within the 24 hours after application and reactive lymphadenopathy (Pat.No. 2) were the only complications. Coagulopathy (Pat. No. 4) was more likely a complication of the treatment for thrombosis than of IFN-α application.

The level of IFN-α in 2 patients under investigation showed only a minimal rise of the serum levels, an observation different from the one in a recent series of patients with pleural effusion due to breast cancer treated in a similar way.[24] As this observation is based only on 2 patients, a larger group studied, though not included in this series, will be part of a separate report.

There are still many uncertainties regarding the treatment of lung cancer with IFN-α, the dosage and the timing of treatment being the most obvious. While in our series a tendency to better survival is shown for the patients treated with IFN-α, the difference in survival is not statistically significant (possibly due to the small series), and on the other hand, it could be due to radiation therapy alone. Radiation therapy has not been shown to affect the survival of patients with inoperable lung cancer. It has, however, not been tried in patients with pleural carcinosis.[27] Because of a trend towards improved survival in patients treated with IFN-α and the good tolerance for combined treatment with radiation and IFN-α we have started a randomized trial.

The patients with lung cancer and pleural carcinosis will be treated either with radiation alone or radiation and IFN-α. We will also continue to study the serum levels after intrapleural applications of IFN-α.

Acknowledgement

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