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HUMAN LEUKOCYTE INTERFERON ALPHA (HLI-α) FOR TREATMENT OF PLEURAL EFFUSION CAUSED BY NON SMALL CELL LUNG CANCER

A pilot study

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Abstract

Fourteen patients with ipsilateral pleural effusion from non small cell cancer of the lung, 10 of them with generalized metastasis, were treated with local application of HLI-α in addition to other symptomatic treatment. Cytology of pleural fluid at the beginning of treatment yielded cancer cells in all but one. HLI-α, 2×10^6 International Units (I.U.) diluted in 20 ml of distilled water was injected intrapleurally each time. The mean survival of the HLI-α treated patients, measured from the first treatment of the pleural effusion, was 10.8 months. The performance status improved in 9 patients following HLI-α treatment. The pleural effusion eventually ceased accumulating in all patients. To judge from cytology of tapped pleural fluid, the cancer cells disappeared during treatment with HLI-α in 11 patients.

Key words: Lung cancer, non small cell, pleural effusion, interferon.

The survival of patients with pleural effusion from bronchial carcinoma is usually short. Van de Molengraft & Vooijs (1) in a recent series of 41 such patients noted an average survival of 4.6 months with 19% of the patients alive after 6 months. Other authors have reported similar experience (2–4).

A number of therapeutic methods have been tried in patients with malignant pleural effusion. High response rates have been achieved with local application of tetracycline (5, 6), bleomycine (7, 8), nitrogen mustard (9, 10), quinacrine (6, 11), talc (12), colloidal ^{198}Au and ^{32}P (13) or Corynebacterium parvum (14). Pleurectomy (15) and external radiotherapy (16) have sometimes been effective. Most of these studies were made on pleural effusions caused by a variety of primary tumors, often unspecified.

Human leukocyte alpha interferon has been in use for treatment of malignant tumors for about two decades. Especially pronounced effects have been obtained after local application in tumors of the head and neck, uterine cervix, breast and malignant melanoma (17–19).

A study by Holsti et al. (20) suggested enhancement of radiation effects on small cell lung cancer by systemically administered interferon.

Jereb et al. (21) reported on 7 patients with pleural effusion due to breast cancer, treated by HLI-α, where cancer cells largely disappeared from the effusion and fluid production was arrested.

Rosso et al. (22) in a series of 21 patients with non small cell lung cancer with pleural effusion which was treated with locally natural beta interferon, reported a 38% response rate, partial or complete.

Material and Methods

Fourteen patients with ipsilateral pleural effusion from non small cell cancer of the lung, most of them with generalized metastasis (n = 10), were treated with local application of HLI-α in addition to other palliative and symptomatic treatment. They were 46–75 years of age, 8 males and 6 females, all smokers. The aspiration of pleural fluid at the beginning of treatment yielded cancer cells in all but one in whom cancer cells were found at a later aspiration only to disappear again during the course of treatment. All were deemed inoperable but in none was the

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pleural effusion the sole criterion of inoperability. Ten had distant metastasis, in 12 the tumor was locally inoperable and in 7 the pulmonary function tests did not allow surgery.

Six patients received palliative radiation therapy, following HLI-α treatment, three of them to the affected hemithorax. Two patients received simultaneous systemic chemotherapy. Before HLI-α administration, as much of the pleural effusion was removed as was compatible with the patient's comfort and a sample was sent for cytological examination; 2×10^6 I.U. HLI-α was then injected into the pleura, diluted in 20 ml of distilled water. This was repeated with 2–3 days' intervals or when the fluid accumulated and had to be removed.

The possible effect of treatment was evaluated cytologically (cancer cells and inflammatory cells in pleural effusion) and clinically (amount of effusion, performance status and survival). The patients were admitted to the Institute Golnik in 1987 and 1988.

Results

The table summarizes the HLI-α treated patients.

The mean survival of the HLI-α-treated patients, measured from the first treatment of pleural effusion, was 10.8 months. Thirteen patients have died of metastatic disease and one patient with primary inoperable cancer died from unknown cause. The performance status improved in 9 patients following HLI-α treatment. The pleural effusion eventually ceased accumulating in all patients. It diminished in 8 patients, disappeared in 3, was unchanged in 3 and became clear (from hemorrhagic component) in 9 patients. The reference value for the amount of fluid was a roentgenogram of the chest obtained immediately following thoracocenthesis at the first HLI-α instillation. The cancer cells disappeared from the tapped pleural fluid during treatment with HLI-α in 11 patients, decreased in number in 2 and remained unchanged in one patient. Inflammatory cells, mostly monocytes, in the effusion increased in 8 patients during the same time as the cancer cells decreased or disappeared. The mean survival of 14 comparable patients, admitted to the Institute Golnik during the same time period but not treated with HLI-α, was 2.3 months.

Twelve patients experienced mild to moderate pain locally and some malaise within 24 h of application of HLI-α. These effects showed a tendency to diminish with consecutive applications of HLI-α. The pleura showed a tendency to become progressively thicker in most patients thus rendering the tapping increasingly difficult. One patient had a partial pneumothorax following thoracocenthesis. No empyema or increase in the temperature was noted in our patients.

The HLI-α treatment was discontinued in 11 of our patients when no more pleural fluid could be obtained by thoracocenthesis although there was still some effusion, possibly organized or in pockets, visible on roentgenograms in most patients. One patient died of his cancer during the course of treatment, one refused further thoracocenthesis and for one patient there was no more interferon available for treatment.

Table

Patients with pleural effusion from non small cell lung cancer, treated with HLI-α (2.10^6 I.U. at each application)

Pat. No.	Age	Sex	Other metastases	Other treatment	HLI-α treatment					Survival (months)
					Cancer cells		Effusion after	Monohistiocyte count per vision field		
					before	after		before	after	
1	64	M	Generalized	RT prim. tu	−	−	+	0	21	13
2	55	F	Generalized	RT iliac bone	+	−	Less	5	15	9
3	74	F	—	—	+	−	Less	0	20	8
4	46	F	Skeleton	Pleurodesis, RT, ChT	+	+	Same	1	5	11
5	54	F	—	—	+	−	Less	15	10	31
6	60	M	Skeleton	RT thor. wall	+	−	−	0	2	15
7	69	M	—	—	+	+	Less	0	3	6
8	61	M	Mediast.	RT prim. tu.	+	−	Less	0	2	11
9	70	M	—	—	+	−	−	4	24	14
10	69	M	Lungs	RT prim. tu.	+	−	Less	0	5	11
11	66	F	Generalized	Pleurodesis	+	+	Same	2	24	3
12	61	M	Adrenal gl.	RT prim. tu.	+	−	Same	33	9	3
13	75	F	Liver, brain	—	+	−	Less	5	78	2
14	63	M	Generalized	RT bones	+	−	Less	0	15	11

Discussion

In a previous study (21) on HLI-α treatment of pleural effusion due to breast cancer it was noted that the cancer cells in the effusion usually underwent progressive degenerative changes as they decreased in number. No such changes were observed in the present series. Cancer cells, in responders, simply diminished in number before they, in most cases, eventually disappeared completely. They did show a tendency, though, to adhere to each other more and more during the course of treatment and to form clusters. This may reflect a slightly different biological response to HLI-α of lung cancer as opposed to breast cancer. In contrast to Rosso et al. (22) we observed some temporary morbidity in the form of malaise and local pain attributable to HLI-α application.

On the whole, however, the intrapleural treatment with HLI-α was easily tolerated.

The question of suitable dosage of HLI-α is still open. We have used relatively low doses basically repeated as often as there was a need for thoracocenthesis. Thus, the dosage was not gauged strictly according to the effect of treatment and it is conceivable that the same effect could be achieved with even lower doses of HLI-α, more judiciously applied. Much higher doses were used by Rosso et al. (22) for local treatment and by Holsti et al. (20) for systemic treatment and gave similar results. The presumably uneven distribution of interferon within often encapsulated pleural fluid of varying amount probably contributes to the uncertainty about the dosage. Evidently, more experience is needed both in terms of dosage and timing of HLI-α treatment.

In conclusion, HLI-α treatment of pleural effusion due to non small cell lung cancer may clear the effusion from cancer cells and hemorrhagic admixture in a majority of patients and arrest fluid accumulation with minimal side-effects. It seems likely that this can prolong the survival of these patients.

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