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Letters

Ferritin Levels in Malignant Effusions: a Useful Marker?

Semra Paydaş, Özoğul Sargin, Süleyman Özbek and Elif Gürbüz

FERRITIN IS a good marker in various tumours [1] and may be a good indicator of disease activity in patients with malignant histiocytosis and virus-associated haemophagocytic syndrome [2]. Ferritin has been suggested as a valuable tumour marker compared with α-fetoprotein (AFP) in follow-up of patients with hepatocellular carcinoma, and can be produced by tumour cells [3–5]. Increased levels of ferritin in cerebrospinal fluid can be a useful guide in cancer patients with central nervous system involvement for diagnosis and follow-up [6]. In addition ferritin levels in malignant pleural and peritoneal fluids can be used in differential diagnosis of the malignant and non-malignant effusions [7].

Our aim was to assess the value of ferritin as a marker in malignant effusions and to compare it with other tumour markers.

Our study group was 43 patients with peritoneal or pleural effusion. In 23 patients the fluid was exudate associated with malignancy (group I). In 8 patients there was tuberculosis (group II), and in 12 patients effusion was transudate associated with chronic liver disease, chronic renal failure, or cardiac failure (group III). Human chorionic gonadotropin (HCG), AFP, carcinoembryonic antigen, and ferritin were measured with radioimmunoassay in serum and effusate. Protein, sugar, density, lactate dehydrogenase and cytology were also assessed. Normal ferritin level was 25–400 ng/ml for males and 10–120 ng/ml for females.

Table 1. Tumour markers (mean, S.D.)

	Group I (n=23)	Group II (n=8)	Group III (n=12)
Serum			
Ferritin (ng/ml)	110 (119)	143 (172)	205 (168)
CEA (ng/ml)	25	3	2.6
HCG (ng/ml)	7.3	0	0.3
AFP (ng/ml)	1.3	0.5	0
Fluid			
Ferritin	336 (331)	298 (295)	341 (303)
CEA	16.8	4.9	2.3
HCG	0.3	0	0
AFP	62.5	2.2	0.9

HCG, CEA, and AFP levels were low in groups II and III (non-malignant) and generally heterogeneous in group I (malignant) with a few high values (Table 1). Although some patients had high ferritin levels in serum or fluid, there was no pattern to distinguish the groups. Serum and fluid ferritin and the ratio between the three groups were not significantly different (t test). 11 patients in group I had a ratio above 5. Corresponding figures in groups II and III were 1 and zero.

We found that HCG, CEA, AFP, and ferritin levels were not useful markers for diagnosis of malignant effusion. These measurements did not even differentiate between transudative and exudative fluids. We also found that ferritin levels in serum and effusate were highly variable in all three groups and unrelated to HCG, CEA, and AFP.

In addition, the ratio between fluid and serum ferritin could not differentiate malignant and non-malignant effusions.

Correspondence to S. Paydaş.
The authors are at the Departments of Oncology and Nuclear Medicine, Çukurova University School of Medicine, 01330 Blacali, Adana, Turkey.

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Cyclophosphamide, Doxorubicin and Vincristine with Amphotericin B in Sonicated Liposomes as Salvage Therapy for Small Cell Lung Cancer

J.P. Sculier, J. Klastersky, P. Libert, P. Ravez, D. Brohee, G. Vandermoten, J. Michel, J. Thiriaux, G. Bureau, J. Schmerber, R. Sergysels and A. Coune for the European Lung Cancer Working Party

IN SMALL cell lung cancer (SCLC) second-line or salvage treatment is needed to prolong survival and to achieve regimens that

Correspondence to J.P. Sculier.
The authors are at the European Lung Cancer Working Party, Institut Jules Bordet, Rue Héger-Bordet 1, B-1000, Bruxelles, Belgium.

are not cross-resistant with the primary therapy. We have used cyclophosphamide/doxorubicin/vincristine (CAVi) as salvage therapy for SCLC in progressing patients [1]. In two phase II studies CAVi was first used alone and then with amphotericin B entrapped in sonicated liposomes.

In the first trial, ten intravenous courses of cyclophosphamide 1 g/m^2, doxorubicin 45 mg/m^2 and vincristine 1.4 mg/m^2 with a maximum dose of 2 mg, all on day 1, were given repeated every 3 to 4 weeks according to haematological recovery. Response was evaluated after three and ten courses. Only the responders after three courses received further CAVi. In those with limited disease, irradiation (45 Gy in 4.5 weeks, five fractions per week) was delivered to the primary lung tumour, the mediastinum and the supraclavicular nodes, after the first three courses. Complete responders received prophylactic cranial irradiation (30 Gy in 2 weeks, five fractions per week) when complete response was obtained and if they had never received cranial irradiation before.

In the second trial, treatment was exactly the same except that amphotericin B 2 mg/kg entrapped in liposomes (ampholiposomes) was infused intravenously (7 ml/min) 24 h before each course. Ampholiposomes [2] consisted of sonicated liposomes made of egg yolk lecithin, cholesterol and stearylamine and incorporated a mean amphotericin B concentration of 454.3 μg/ml.

There were 49 registered patients in the CAVi trial and 12 in the CAVi-ampholiposomes trial. 4 and 1 patients, respectively, were unevaluable because of incomplete data before treatment [4] and treatment refusal [1]. In the CAVi-ampholiposomes trial, there were more patients with limited disease and the interval between the last day of first-line therapy and first day of second-line therapy was longer (Table 1).

6 patients had an objective response in both trials (Table 1). One partial response became complete with further CAVi-ampholiposomes therapy. There was 1 toxic death in the CAVi trial due to infection during leucopenia, and 6 early deaths due to malignant disease. All responses after CAVi-ampholiposomes were observed in patients who still had limited disease when second-line therapy was started. A similar rate of responses was observed in the CAVi study in patients with limited disease (2/15) and in those with disseminated disease (4/30). Longer intervals between the last day of first-line chemotherapy and the first day of second-line therapy were associated, in responders to first-line chemotherapy, with higher rates of response. In the CAVi study, intervals less than 90 days were associated with an overall response rate of 6% (1/17) rates, while those greater than 90 days were associated with a 40% (2/5) rate. In the CAVi-ampholiposomes study, these figures were 0/2 for short intervals and 4/5 (80%) for longer intervals. In patients with a primary failure to first-line chemotherapy, response rates were, respectively, 13% (3/23) and 50% (2/4).

Table 1. *Details of evaluable patients response and toxicity**

	CAVi (n=45)	CAVi-ampholiposomes (n=11)
M/F	42/3	11/–
Mean age (range)	59 (36–74)	57 (40–73)
Limited disease	15	7
< 90 days between 1st and 2nd line treatment	40	6
Partial response	6 (13%)	6 (55%)
Median duration (mo)	6	10
No change	14	1
Progression	18	4
Overall median survival (mo)	6.2	7.5
Leucopenia grade III-IV	30%	45%

*Response evaluated after three courses.

Leucopenia was usually moderate (Table 1) and thrombocytopenia was not a problem. Other significant toxicities were alopecia and nausea-vomiting, but they were not more severe after CAVi-ampholiposomes.

Our first trial [1] showed that CAVi is an ineffective salvage therapy in SCLC, although it is considered as a first-line standard chemotherapy by some North American investigators [3, 4]. Our results confirmed other studies with response rates between 10 and 20% [5–7]. In our series, response to CAVi was not influenced by the type of response to previous chemotherapy and disease extent at the time of second-line therapy. These results demonstrate that CAVi and cisplatin plus etoposide and/or vindesine are non-cross-resistant regimens. The disappointing results obtained in the first trial led us to attempt to overcome resistance to CAVi. Amphotericin B is a polyene antibiotic that causes, at sufficiently high concentrations, an increase in membrane permeability, leading to enhanced uptake of various drugs. The compound potentiates the cytotoxicity of various anticancer agents, including carmustine, cyclophosphamide, vincristine and doxorubicin [8].

Some clinical trials of Fungizone to potentiate chemotherapy have been reported [9]. Although objective responses were obtained in patients who were resistant to chemotherapy, controlled studies demonstrated no survival advantage. All these trials used a preparation in which a dispersing agent, sodium deoxycholate, is used to allow the intravenous use of amphiphilic amphotericin B. This preparation induces many side-effects and its administration does not result in serum amphotericin B concentration above 3 μg/ml. By incorporating amphotericin B in sonicated liposomes, we obtained blood peak levels over 20 μg/ml while trough levels were between 5 and 10 μg/ml. Moreover, tolerance was excellent.

We used our preparation of amphotericin B to try to overcome resistance to CAVi. In 11 evaluable patients, 6 (55%) had an objective response. These results were encouraging. In the CAVi-ampholiposomes trial, patient selection was more favourable with more patients with limited disease and a long interval between the last day of first-line therapy and the first day of second-line therapy. However, despite this, the results were interesting and the preparation merits further investigation. If amphotericin B acts directly on tumour cells, it could also, when given as ampholiposomes, stimulate macrophages and induce a cytotoxic response against resistant SCLC.

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Interferon plus Vinblastine in Renal Carcinoma Patients who had Failed on Interferon Alone

Ofer Merimsky and Samario Chaitchik

TREATMENT OF patients with metastatic renal cell carcinoma (RCC) by an alpha interferon (IFN-α) has yielded a response rate of 5–27%, with median duration of response ranging from 3 to 16 months [1]. Better results were suggested for the combination of IFN-α with vinblastine than for IFN-α alone. The response rate for the combination was 30–40% and the median duration of response ranged from 3 to 18 months [2–6]. We have administered this combination to 9 patients who had not responded or had relapsed while on treatment with IFN alone. The 9 patients were part of a group of 38 patients with RCC, some of whom were treated in our ward by recombinant IFN-α_{2c}. This IFN is a new type (specific activity of $1–2 \times 10^9$ U/mg protein) that is active against RCC, achieving a response rate of 10% and stabilization in 26% [7]. Of the 9 patients, 7 had previous nephrectomy, 5 had previous hormonotherapy, but none had previous chemotherapy.

1 of the patients had had a partial response, 1 stable disease, and 7 had progressed on IFN-α alone. After progression was documented in all the disease sites, the IFN was changed to α_{2a} ('Roferon A', Roche) in 4 patients because of temporary unavailability of commercial α-C. The dose of IFN was gradually escalated to the maximal tolerated dose in each patient, which ranged from 3 to 18 MU given every second day (Table 1). Vinblastine 0.1 mg/kg every 3 weeks was added to the treatment only after reaching the maximal tolerated dose without affecting the disease course.

Table 1. IFN-α plus vinblastine in RCC patients who failed on IFN alone

No.	Karnofsky score (%)	No. of courses	IFN-α Type	IFN-α Dose (mu)
1	80	4	2c	6
2	70	3	2a	9
3	100	6	2c	12
4	70	8	2a	12
5	80	6	2a	18
6	70	5	2c	7
7	100	3	2a	9
8	100	11	2c	16
9	90	2	2c	6

Results were disappointing. Response rate was zero. Stable disease was documented in 1 patient for 7 months in lymph nodes, lungs, and local recurrence, and in a second patient for 2 months in lungs and lymph node metastases. IFN toxicity included a temperature of 37.8°C–40°C and influenza-like symptoms in all the patients, weakness and neurasthenia syndrome in 3 patients, and loss of appetite and loss of weight in 5. Vinblastine side-effects included peripheral neuropathy in 1 patient, grade II leukopenia in 1 patient, grade II anaemia in 1 patient, and vomiting in a fourth patient.

All of our patients had sufficient IFN-α treatment to have had a beneficial effect from this agent alone. Vinblastine had little effect, if any, when added to IFN as second-line therapy in the treatment of metastatic RCC. Thus the role of vinblastine in combination with interferon is doubtful, which also applied in a first-line regimen [8]. The stable disease seen in 2 patients may simply have resulted either from the continuing treatment with IFN and have been a manifestation of delayed response effect, or from the natural course of this disease.

Correspondence to O. Merimsky, Department of Oncology, Ichilov Hospital, 6 Weizman Street, Tel-Aviv 64239, Israel.
The authors are at the Department of Oncology, Tel-Aviv Sourasky Medical Center, Sackler School of Medicine, Tel-Aviv University, Israel.

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