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Correspondence and Short Communications

Comments on published articles, short communications of a preliminary nature, case reports, technical notes and the like are accepted under this heading. The articles should be short and concise and contain a minimum of figures, tables and references.

PHASE II STUDY OF THREE DAYS' FRACTIONATED DOSAGE OF IFOSFAMIDE, EPIRUBICIN AND CISPLATIN IN SMALL CELL LUNG CANCER

At the 6th World Congress on Lung Cancer in 1991 (1) we reported data on small cell lung cancer (SCLC) treated with IEP regimen (ifosfamide 3 g/m^2, epirubicin 60 mg/m^2, cisplatin 60 mg/m^2). In a series of 49 cases we observed a response rate of 87% with 22% complete response (CR). Trying to improve the CR rate we have later on started a new phase II study including the same drugs but fractionated over three days. The main reason for the fractionation is the pharmacodynamics of ifosfamide. Fractionation of ifosfamide over 1–5 days has been reported to increase tolerability and remission rates in several solid tumors (2). Our study, which started in January 1992, has now accrued 19 patients of whom 14 are evaluable concerning initial response.

Material and Methods. All consecutive cases of patients with histologically proven SCLC and Karnofsky ≥ 50 were included in the study. Even patients with radiotherapy for superior vena cava syndrome or brain metastases were included. Before treatment all patients had a complete physical examination. Laboratory work-up included complete blood counts, serum creatinine, albumin, alkaline phosphatase, LDH, radionuclide bone scan and liver ultrasound. Brain scan and bone marrow studies were carried out only when clinically indicated.

Combination chemotherapy was given as follows: ifosfamide 2 gm/m^2 diluted in 500 ml 5% dextrose intravenously (i.v.) as a 4-h infusion on days 1, 2, and 3 with mesna uroprotection (20% of ifosfamide doses at 0, 4 and 8 h after ifosfamide). Epirubicin 20 mg/m^2/day and cisplatin 20 mg/m^2/day i.v. on days 1, 2 and 3. Drug doses for the subsequent courses of therapy should be modified by 25% reduction of epirubicin and ifosfamide dosage if WBC nadir $< 10^9$/l and thrombocytopenia $50 \cdot 10^9$/l. Patients presenting with limited disease received, after complete or partial response to chemotherapy, thoracic radiotherapy (35–60 Gy). Prophylactic cranial irradiation was decided on in each individual case. Tumor response and toxicity were defined according to WHO criteria (3). Response duration and survival were calculated from the data of first treatment.

Results. Nineteen cases were entered into the study, of which 14 were evaluable (Table 1). Of 9 cases with limited disease, 7 achieved partial response (PR) (78%) whereas one case had complete response (CR) (11%). Six cases (5 PR, 1 CR) received thoracic irradiation (55 Gy) after chemotherapy. Survival duration of the responders (CR + PR) was 8+ to 14+ months (Table 2). Of 5 patients with extensive disease, three achieved partial response (60%) and one complete response (20%). Survival duration of the responders (CR + PR) was 5+ to 29+ months.

Toxicity. The most common toxic effects were alopecia, nausea, vomiting and myelosuppression. Neuropathy was seen in one-fourth of all cases. Sixty percent of the patients had grade 3 and 4 leukopenia (with one septic death). Six cases (40%) had anemia of grade 3 and 4. Twenty-eight percent had thrombocytopenia of grade 3 and 4 (Table 3). Due to grade 3 and 4 leukopenia, the dosage of epirubicin and ifosfamide were reduced accordingly.

Table 1

Patient characteristics

Entered (n)	19
Eligible for evaluation (n)	14
Male/Female	8/6
Median age years (range)	60 (38–71)
Median Karnofsky index	70
Limited disease (n)	9*
Extensive disease (n)	5**

* One patient had failed after previous chemotherapy (carboplatin, epirubicin and cyclophosamide).
** One patient had brain metastasis and had received whole brain irradiation prior to the study.

Table 2

Results

	Number (cases)	CR		PR	
		cases	(%)	cases	(%)
Limited disease	9	1	(11)	7	(78)
Extensive disease	5	1	(20)	3	(60)

CR = complete response; PR = partial response

Table 3

Toxicities (%)

	Grade			
	1	2	3	4
Anemia	7.1	28.5	28.5	14.2
Leukopenia	7.1	7.1	28.5	21.4
Thrombocytopenia	–	–	21.4	7.1
Nephrotoxicity	14.2	–	7.1	–
Mucositis	–	7.1	7.1	–

Discussion. The purpose of this study was to increase response rate and survival time of small cell lung cancer by a 3-day fractionated dosage of IEP instead of our initial IEP regimen (1). However, with the dosage modification used we were not able to demonstrate improvement of CR rate or survival time. The toxicity of this regimen seems to be worse than that of the original IEP. Fifty percent had grade 3 and 4 leukopenia (with one septic death), only one case had grade 4 thrombocytopenia. We conclude that the 3-day fractionation regimen did not yield any benefit compared to the original schedule.

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HAIRY-CELL LEUKEMIA AND GLUCOSE-6-PHOSPHATE DEHYDROGENASE

Recently, Egli et al. (1) described an association between glucose-6-phosphate dehydrogenase (G6PD) deficiency and hairy cell leukemia and suggested that a genetic defect for the hairy cell leukemia might also be located on the X chromosome.

Table

Glucose 6-phosphate dehydrogenase in patients with hairy-cell leukemia

		G6PD (IU/g Hb)	
	n	x ± DP	Range
Patients	6	15.6 ± 2.4	12.9 – 20.2
Controls	50	12.0 ± 1.2	11.4 – 19.3

In order to study if this association would be present among other patients with hairy cell leukemia we estimated G6PD in six unrelated hairy cell leukemia patients. The results showed normal values for G6PD in all the patients studied when compared with 50 healthy controls (Table 1). Although these data do not exclude a possible involvement of the X chromosome in hairy cell leukemia, they support the opinion of Beutler et al. (2) that the occurrence of simultaneous G6PD deficiency and hairy cell leukemia in the described patients is probably coincidental rather than secondary to a common defect affecting two genes.

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HYPERBARIC OXYGENATION IN CANCER

A 45-year-old woman was first diagnosed in 1980 as suffering from a soft tissue sarcoma of the left clavicular and base of neck area. During the first three years she underwent three curative resection attempts, radiotherapy and chemotherapy. Since 1985 she underwent repeated local excisions of recurrent sarcoma, always diagnosed histopathologically as spindle cell carcoma. In 1992, when the time span between tumor excision and recurrence shortened significantly compared to what we were used to, another course of radiotherapy to the whole area was administered followed by local injections of interferon. The next excision of a small local recurrence resulted in complete breakdown of the wound which did not heal for 6 months. The patient and her family consulted a hyperbaric institute, which at that time published favorable results with hyperbaric oxygenation therapy for pressure sores, and consented to this mode of therapy in an attempt to heal the indolent open wound at the base of her neck. Hyperbaric oxygenation was claimed to enhance oxygenation of the affected tissues in the wound with an antiseptic effect, to reduce edema, to accelerate collagen production and angiogenesis and thus enhance tissue repair.

Towards the end of the hyperbaric oxygen course of therapy a dramatic change in the behavior of the tumor occurred. For almost 12 years local recurrence was always in the form of well circumscribed small gray nodules in the subcutis and skin which were easy to resect. Following hyperbaric oxygen therapy, the tumor transformed into a fungating and locally invasive process. Particularly impressive was the appearance of a wild looking fungating tumor in the area of the non-healing ulcer at the base of the neck and subsequently the very rapid and invading growth of many similar lesions in this area. Attempts to excise these new tumors revealed diffuse invasion into the subcutis and between muscle fibers. Since then, it became impossible to control this previously 'timid' sarcoma due to its newly acquired invasiveness. Although this report offers only very circumstancial evidence for the possible role of hyperbaric oxygen in the transformation of a slow-growing sarcoma into a florid and aggressive tumor, we would like to call attention to this possibility and to discourage uncontrolled use of hyperbaric oxygen in patients harboring malignant tumors.

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SWEET'S SYNDROME AND HODGKIN'S DISEASE

Sweet's syndrome is an acute neutrophilic dermatosis described by R. D. Sweet in 1964, and characterized by fever, neutrophilia, multiple, red, tender plaques, a dense dermal neutrophilic infiltration, and a dramatic response to corticosteroid therapy (1). Extracutaneous manifestations are rare, and include artliralgia, arthritis, myalgia, conjunctivitis and episcleritis, proteinuria and hematuria, oral ulceration, pulmonary and hepatic neutrophilic infiltrates (2, 3). Eighty percent of the patients have idiopathic Sweet's syndrome, which mostly occurs following an upper respiratory tract infection and is self-limited (4). The remaining 20%

are associated with malignancy, and cannot be distinguished from the idiopathic form, however, extracutaneous manifestations, anemia, platelet count abnormalities, absence of neutrophilia, involvement of the oral mucosa and lower extremities, and a high rate of recurrence bespeak the presence of an associated malignancy (3–6). Sweet's syndrome may occur preceding, concurrently with or succeeding the malignancy, a recurrence sometimes indicating the recurrence of the tumor (4). Hematological malignancies, especially acute myeloid leukemia, constitute the majority of the malignancies associated with Sweet's syndrome, and solid tumors a minor 15% (4–6).

A 40-year-old male patient applied to our clinic with itching, night sweats, fever, generalized lymphadenopathy, and a peculiar rash. The itching and the rash had been present for a year and been treated without success by a dermatologist. The other symptoms had appeared during the last 2 months. The physical examination revealed bilateral cervical and supraclavicular, left axillary and bilateral inguinal lymphadenopathy, tender erythematous plaques mainly located on the head, neck, upper torso and extremities, and conjunctivitis. The erythrocyte sedimentation rate was 140 mm/h, and the leukocyte count $24.0 \cdot 10^9$/l. A thorax CT revealed multiple mediastinal lymphadenopathies. Biopsy of an axillary lymph node and a skin lesion resulted in the diagnosis of Hodgkin's disease and acute neutrophilic dermatosis (Sweet's syndrome). The patient was started on MOPP chemotherapy with additional maintenance steroid. After the first cycle, the lymph nodes were no longer palpable, and there was no sign of an acute skin eruption except for hyperpigmentation on the site of previous lesions. The patient has been followed through 4 uneventful cycles of chemotherapy.

The association of Hodgkin's disease with Sweet's syndrome has been previously reported in two cases (7, 8). Our patient has the cardinal characteristics of Sweet's syndrome, such as skin eruption, fever, conjunctivitis, high sedimentation rate, leukocytosis, histological findings, and dramatic response to corticosteroid treatment. The rare association with Hodgkin's disease, the appearance of skin symptoms 10 months before the manifestations of malignant disease and resistance to previous dermatological treatment constitute the remarkable aspects of the case reported. This resistance to symptomatic treatment, extracutaneous manifestation in the form of conjunctivities, anemia and the long history without any spontaneous regression have been regarded as evidence of underlying malignancy.

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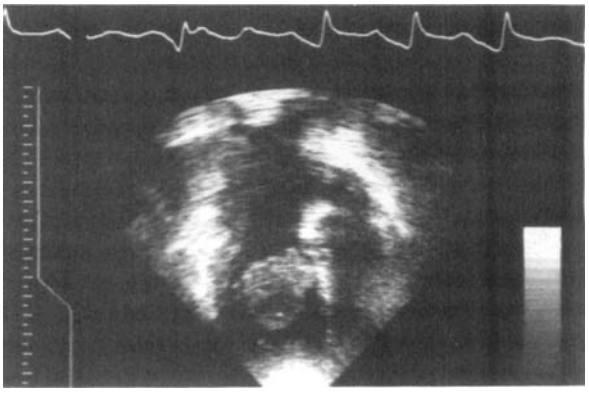
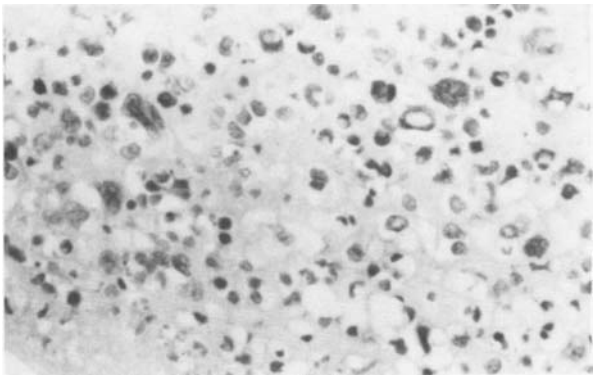
LEFT ATRIAL BALL THROMBUS WITH HISTOLOGIC FEATURES OF EXTRANODAL B-CELL LYMPHOMA—PROLONGED SURVIVAL AFTER SURGERY

Primary cardiac lymphomas themselves are extremely rare with poor prognosis (1, 2). We document a case of primary lymphoma in which the initial presenting feature was heart failure because of large mass in the left atrium, with recovery after surgery.



A)



B)

Fig. 1. A) Echocardiogram (mono- and bidimensional): large mass in the left atrium. B) Malignant lymphoma showing large cells with folded nuclei. H.E. × 400.

Case report. A 33-year-old woman was referred in December 1987 to the Service of Internal Medicine following a surgically excised intracavitary tumor of the left atrium, attached to the mitral valve (Fig. 1A), responsible for the initial clinical picture of heart failure. Microscopic examination revealed a thrombus with involvement by polymorphic, large and multinucleate neoplastic cells, with occasionally prominent nucleoli (Fig. 1B). Immunohistochemical studies showed the immunophenotype CD45 and CD20 and because the study was on paraffin-embedded tissue, surface immunoglobulin was not performed. She had had mitral valve disease for 5 years and a transient ischemic attack. Physical examination revealed no lymphadenopathy or hepatosplenomegaly; it was also otherwise unremarkable. Complete blood counts, urinary analysis and chemistry profile were normal. Computed tomographic (CT) body and cranial scans, radionuclide bone scan, bone marrow, tumor markers (alpha-fetoprotein, carcinoembryonic antigen, beta-human chorionic gonadotropin) and HIV-virus antibody test, were negative. Periodical examinations till June 1993 with CT body scan and tumor markers showed no evidence of recurrent disease.

Discussion. Primary cardiac lymphomatous tumors are large, may involve the pericardium and any chamber, most frequently the right atrium, and lead to death after the onset of symptoms (3). Our case had a large thrombus in the left atrium with involvement by neoplastic cells, and with clinicopathologic features of extranodal B-cell derived lymphomas of large cells, expressing a B-cell restricted antigen (CD20). Unlike most reported primary lymphomas of the heart (1, 4), our patient recovered after surgery. The diagnosis of a primary lymphoma in the heart is beyond any doubt, as no tumor was detected elsewhere. It is also remarkable that the disease was not associated with acquired immune deficiency. The histogenesis of cardiac lymphomas is unclear, though extranodal lymphoma can occur in any organ of the human body (5). Malignant lymphoma may be confused with malignant angioendotheliomatosis (MAE), which is characterized by massive proliferation of mononuclear neoplastic cells within the blood vessels of the skin and central nervous system primarily, but any organ can be involved (6). Some investigators have demonstrated that both conditions express the leukocyte common antigen and have characterized the antigen phenotype of MAE as being an angiotropic large cell lymphoma (7). A search of the literature revealed no previous reports similar to the present one. The clinical presentation of our case was not similar to those of primary cardiac lymphomas (2, 3) nor MAE (6, 7), but histological and immunohistochemical analyses suggested a lymphoid origin.

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