Ifo 39

RESULTS OF A NEW COMBINATION CHEMOTHERAPY (ETOPOSID-IFOSPHAMIDE-MITOXANTRONE) IN ADVANCED NHL
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During the last 18 months we treated 45 patients with a new combination: Ifosphamid 1g, VP-16 100mg, Mitoxantrone 4 mg/m², Prednisone 100 mg. These cytostatic agents were given day 1-3, Prednisone was tapered gradually. Bleomycin 15 U was given i.m. on day 15. Cycles were repeated every 3 weeks. 30 patients (LB 3, IB 9, CB 6, CC 4, Cb-CC 7, Lennert's Lymphoma 1) received this combination as salvage therapy. Two third of these patients had never achieved a stable CR with various forms of pre-treatment including anthracycline containing regimens. All had advanced stage of disease. Objective response was seen in 15 patients (5 CR, 10 PR). In addition 7 patients had minor responses lasting up to 8 months. Because of these results in pretreated patients we introduced VIM-schedule in 15 untreated patients (LB 1, IB 3, CB 5, Cb-CC 3, IC 1, pleomorphic T-cell lymphoma 2). All but 2 patients had advanced disease. Objective response was seen in 8 of 10 evaluable patients. 2 patients (pleomorphic T-cell lymphoma) did not respond, in 3 patients is too early to evaluate. Duration of response was rather short. Subjective tolerance was excellent. Dose limiting toxicity was granulocyte depression.

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Epi 01

EPIRUBICIN IN METASTASIZED BREAST-CANCER
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Patients with systemic metastasized breast-cancer are incurable. Remissions with longer survival can be induced by chemotherapy in 50 to 80 % of the cases with 10 to 20 % complete remission, although the recurrence is unavoidable. Therefore the strategy of therapy in breast-cancer must include two aspects. First prolongation of overall survival by multiple remissions with regimens that are not crossresistant and secondly conserve the quality of life by minimization of therapy conditioned side-effects.

EPIRUBICIN, the new anthracycline derivative and analogue of DOXORUBICIN (probably the most active chemotherapeutic agent against breast cancer) exhibits the same high activity but lower side-effects compared with the parent compound.

Complete and partial remissions in 33 % of 313 breast-cancer patients could be achieved with EPIRUBICIN. In three other studies the efficacy and side-effects of EPIRUBICIN were compared with the established drug DOXORUBICIN. The remission rate was nearly the same but side-effects such as nausea, vomiting, stomatitis, bone marrow toxicity and congestive heart failure were lower. In a randomized multicentre study, 520 patients were treated with EPIRUBICIN or DOXORUBICIN in combination with CYCLOPHOSPHAMIDE and FLUOROURACIL. The remission rates were 52 vs. 54 % respectively, but the toxicity of the EPIRUBICIN combination group was significantly lower.

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Epi 02

THE FRENCH FAC VS. FEC STUDY IN ADVANCED BREAST-CANCER
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in behalf of the FRENCH EPIRUBICIN STUDY GROUP

On the basis of the results obtained in the Epirubicin Phase II trial conducted by the EORTC Clinical Screening Group (1 CR, 8 PR out of 28 patients and 6 PR in 11 untreated patients with no major cardiotoxicity) the French Epirubicin Study Group has decided to run a Phase III trial comparing Epirubicin (Epi) to Doxorubicin (DX) in a FAC combination for advanced breast cancer in March 1982. According to the preclinical and Phase II studies the 2 anthracyclines were compared on an equimolar dosage of 50 mg/m² combined with 5 FU and Cytosar both at 500 mg/m². The three drugs were administered on day 1 and cycles were repeated at a 3 weeks interval. The maximal cumulative dose was 550 mg/m² for DX and 700 mg/m² for Epi. Aims of this prospective randomized study was: to compare the efficacy of the two combinations chemotherapy, FEC vs FAC and also the qualitative and the quantitative aspects (in particular cardiotoxicity) associated with these treatments. Therapeutics responses evaluated according the WHO criteria are listed in table I.

	FAC	FEC
Complete Response (CR)	12	13
Partial Response (PR)	49	44
No Change	38	41
Progression	19	22
Response rate (CR + PR)	52 (± 9) %	48 (± 9) %

Table I: Response rate by treatment arm.

Conclusions of this phase 3 trial are:

- There is no difference concerning response rate, time to maximal response, duration of response between Epi and DX in this combination
- FEC is significantly less toxic than FAC regarding myelotoxicity, alopecia and gastro-intestinal toxicity.
- There are 3 congestive heart failures in the Doxorubicin regimen, none in the Epirubicin regimen despite the higher cumulative dose. On the basis of the above results it appears reasonable:
- to replace Doxorubicin by Epirubicin at equimolar doses in the chemotherapy regimen under study,

Epi 03

EPICO in the Treatment of Small Cell Lung Cancer

- Interim Analysis -

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Patients: 59 patients with untreated histologically proven small cell lung cancer were entered into a phase II study. All patients had measurable tumor. The patients underwent a classical staging procedure before entering the study, including chest X-ray, bronchoscopy, tomograms of liver and brain, bone scan, bone marrow biopsy, and blood chemistry. The courses of 50 patients are evaluable.

Table 1: Characteristics of the patients:	performance status	
total number	50-70%	8
mean age (range)	80-100%	42
males / females	limited disease	30
	extensive disease	20

Treatment: The therapeutic regimen consisted of epirubicine 70mg/m² on day 1, cyclophosphamide 1000mg/m² on day 1, and vincristine 2mg on day 1. The treatment was repeated after three weeks, according to hematologic recovery. Evaluation of response was made after 3 and 6 cycles, according to criteria established from EORTC and NCI.

Results: As a whole, the response rate of these preliminary results was 62%, with 16% CR (8/50) and 46 PR (23/50). Table 2 shows the distribution of response according to possible prognostic factors.

Table 2:	CR	PR	NC	Progr.	Total
males	5	18	4	14	41
females	3	5	1	-	9
limited disease	7	15	2	6	30
extensive disease	1	8	3	8	20
total	8	23	5	14	50

Until September 30th 37 patients are alive. The mean survival time of all patients was 378 days, the 6 months survival rate 84%, and the 12 months survival rate 56%. Performance status and extent of disease had a significant prognostic influence on the duration of remission and survival of patients. The result of treatment also influenced significantly the survival time.

Table 3: Survival of patients

	N	mean survival time (days)	p-value
CR + PR	31	425	
NC	5	310	0,026!
Progr.	14	230	

Main side effects were alopecia and gastrointestinal disturbances. Bone marrow depression and neurotoxicity were acceptable. Cardiotoxicity was not observed.

Conclusion: These preliminary results demonstrate the activity of EPICO in the treatment of small cell lung cancer comparable to the combination of doxorubicine, cyclophosphamide and vincristine.