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Experience with ifosfamide combinations (etoposide or DDP) in non-small cell lung cancer

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Summary. In all, 171 patients with histologically verified non-small cell lung carcinoma were treated with ifosfamide 2.0 g/m^2 on days 1–5 in combination with (91 patients) etoposide 120 mg/m^2 on days 1–3 or (71 patients) with cisplatin 75 mg/m^2 on day 1. Therapeutic regimens were repeated after 4 weeks. Supportive treatment with mesna (20% of the ifosfamide doses at 0, 4, and 8 h) was performed. Cisplatin treatment was supported by mannitol-induced diuretic hydration.

The overall response rate of ifosfamide/etoposide was calculated to be 27%, with 1 complete and 24 partial remissions. The median survival time for all patients was 8.5 months, for responders 14 months (P less than 0.05), for patients with no change 9.5 months, and for patients with tumor progression 4 months.

With ifosfamide/cisplatin, there were 4 complete and 21 partial remissions (response rate 35%). The median survival time for all patients was 8.3 months, for responders 11.5 months, and for patients with tumor progression 4 months. Age, sex, and histological tumor type had no significant effect on survival. Patients with better performance stage and limited disease lived significantly longer.

The main side-effects of the cisplatin combination were vomiting, bone marrow depression, and neuropathy. The etoposide combination was tolerated better. Urotoxicity was not significant, as a consequence of treatment with mesna.

The results show that the combination ifosfamide/etoposide or ifosfamide/cisplatin are effective in the treatment of non-small cell lung cancer, being comparable to other combinations of etoposide/cisplatin and vindesine/cisplatin. Because of the better tolerability, the combination ifosfamide/etoposide is superior to cisplatin combinations.

Introduction

In bronchial carcinoma, the treatment decision will depend on the histological type of the tumor, its stage of clinical spread, and the general condition of the patient. For the large heterogeneous group of non-small cell lung cancers, the possibilities of curative surgery must be completely exhausted before radiotherapy or chemotherapy can be started. With few exceptions, these two forms of treatment have so far been indicated only for palliative treatment [1, 3, 22, 26].

The prognosis of a patient with lung cancer is exceptionally unfavorable when specific therapy is no longer possible. This is documented by the mean survival times of 4.3 months in locoregional carcinomas and 2.1 months in generalized carcinomas [18].

In contrast to small cell lung cancers, for which there has been a fundamental change in the concept of therapy in the last decade, the possibilities of therapy in non-small cell lung cancers are still restricted. For this reason, a wait-and-see attitude to chemotherapy is therefore generally regarded as justified outside controlled clinical studies when the patient is free of symptoms. Hitherto it has been considered that the patient would not be deprived of a major chance of therapy if the occurrence of clinical symptoms is waited for before starting treatment. In the symptomatic stage of this tumor, chemotherapy will be decided on when there are no contraindications [28]. According to the experience available so far, on average 20%–45% of patients respond to the combination of the most common cytostatics [10]. Improvement of the results of therapy can be expected from the introduction of new substances and from the combination of chemotherapy with other modalities (operation, radiotherapy). Livingston [21] feels that chemotherapy will be firmly established in the treatment of these tumors when reproducible remission rates of 40%–50% (including 10% complete remission) are attained.

In recent years, the new cytostatics etoposide, ifosfamide, and cisplatinum have been used in addition to adriamycin, mitomycin C, and vindesine, in various combinations for treatment of lung cancers.

Ifosfamide is an oxazaphosphorine derivative which in preclinical studies has shown some advantages over cyclophosphamide and other related alkylating agents. These advantages are manifested especially in the greater accumulation of curative compared with toxic components. In phase II studies, administration of 50–60 mg/kg body weight or 1.2–1.8 g/mg^2 i.v. as a single dose on each of 5 consecutive days has proved to be especially beneficial. Rates of remission between 7% and 31% (on average 27%) [8, 25, 31] were attained in patients who had not been pretreated.

Etoposide, a semisynthetic epipodophyllotoxin derivative [15], has proved to be a very effective cytostatic in the

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treatment of anaplastic small cell lung cancer. Its administration led to average remission rates of 20% (8%–35%) in patients with non-small cell lung cancers that had not been previously treated [2, 7, 13].

In recent years, the inorganic platinum compound *cis*-diaminochloroplatinum has been successfully administered for the treatment of testicular tumors, bladder, ovarian and lung cancers, squamous cell carcinomas of the head and neck region, and sarcomas [24, 29]. The nephrotoxicity of this substance proved to be dose-limiting [16]. This necessitates a special supportive therapy. Its use for monochemotherapy in patients with non-small cell lung cancers that had not been pretreated has so far led to the same average rate of remission, 20%, as that attained with etoposide. However, the variation is appreciable, ranging from 0 to 33% [5, 6, 9, 23, 32]. Extensive experience is already available with combinations of cisplatin and other cytostatics, in non-small cell lung cancers among other malignancies. In some cases, their effect has proved superior to that of the procedures known so far.

Two consecutive phase II studies were performed to check whether ifosfamide in combination with cisplatin or etoposide exerted a marked antineoplastic action superior to that of the chemotherapeutic regimens used thus far in non-small cell lung cancer and whether the toxicity of this combinations were tolerable for the patients. Comparison of the two duplex combinations appeared possible, since the selection criteria of the patients were the same for each study and both were single-center studies.

Materials and methods

Patients. The following inclusion criteria were applied for the two studies: regional or diffuse metastatic spreading of a histologically or cytologically verified non-small cell lung cancer, detection of objectively measurable tumor parameters, estimated life expectancy of at least 8 weeks, age below 70 years, Karnofsky score of at least 60%, and absence of concomitant diseases regarded as contraindications for cytostatic therapy.

Therapy. The patients in the first study ($n = 71$) received an infusion of 2 g/m^2 ifosfamide on each of 5 consecutive days and 75 mg/m^2 cisplatin (also as an infusion, duration 30 min) on the first day. The therapy was repeated on day 29. Because of the possible nephrotoxicity of cisplatin and ifosfamide, the following supportive measures were carried out: hydration with 4 l/m^2 (glucose solution and physiological saline in equal quantities) on days 1–3 and 1.5 l/m^2 on days 4 and 5. The patients received 250 ml 10% mannitol solution the day before the administration of cisplatin and immediately after the cisplatin infusion. A 12-h fluid balance and daily monitoring of the electrolyte balance proved to be necessary. In the case of fluid retention, furosemide was applied. For reduction of the urotoxicity of ifosfamide, the patients received a slow i.v. infusion of mesna at a dose corresponding to 20% of the ifosfamide dose at the time 0 (administration of cytostatic), and then at 4 h and 8 h after ifosfamide infusion. Levomepromazine (15 mg three times a day) was prescribed to prevent emesis.

The patients in the second study ($n = 9$) received ifosfamide at the same dosage, also on 5 consecutive days, and etoposide 120 mg/m^2 on days 1–3 by infusion (duration 30 min). Mesna was administered in the same way as in the first study. The patients received 1.5 l/m^2 parenteral fluid per day. The therapy was repeated on day 29 and performed with dose modification in the case of persistent bone marrow depression.

Table 1. Characteristics of patients

	IFO/DDP	IFO/VP
Sex		
Male	67	73
Female	4	18
Age (years)		
Mean	55	55
Min.	32	30
Max.	70	70
Karnofsky scale (%)		
Mean	80	80
Min.	60	50
Max.	100	100
Extent of disease		
Limited disease	15	10
Extensive disease	56	81
Histological type		
Squamous cell carcinoma	35	34
Adenocarcinoma	25	34
Large cell carcinoma	11	23

At 8 weeks after the beginning of therapy, the result of therapy was evaluated according to international criteria as complete or partial remission, no change, or progression. If no positive effect could be discerned after two therapy cycles the therapy was discontinued. In the case of no change or tumor remission, the treatment was continued with the same schedule up to a maximum of six cycles, depending on the toxicity.

The characteristics of the 162 patients and their tumors are shown in Table 1. With regard to age, sex, performance index, tumor type, and tumor extent, the two patient groups were largely similar. It must be especially emphasized that only 25 patients could be classified as having limited disease. In 137 patients, metastatic tumor spread was far advanced.

Before the beginning of therapy, complete physical examination with clinical laboratory tests, chest X-rays, skeletal scintigram and computer tomogram or sonogram of the liver were carried out in all patients. Follow-up examinations including physical examination, clinical laboratory tests, and chest X-rays were repeated at monthly intervals.

Table 2. Remission rates in two consecutive studies

Regimen	N	CR	PR	NC	PROG	REM. (%)
IFO/DDP	71	4	21	14	32	35
IFO/VP	91	1	24	36	30	27
Total	162	5	45	50	62	31

CR, complete remission; PR, partial remission; NC, no change; PROG, progression; REM, remission rate

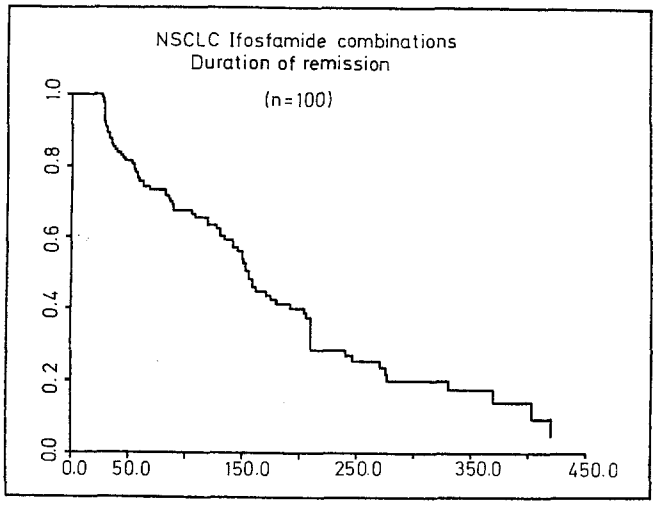

Fig. 1. Duration of remission for 100 patients (CR, $n = 5$; PR, $n = 45$; NC, $n = 50$)

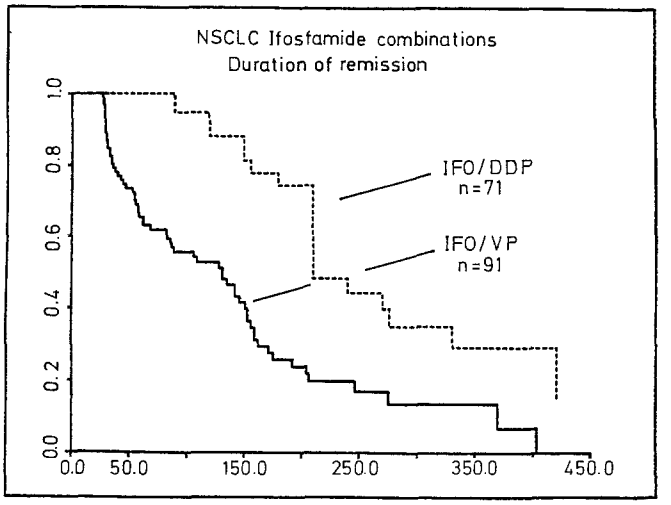

Fig. 3. Influence of therapeutic regimen on remission duration

Results

An objective response manifest in measurable tumor regression was observed in 31% of the 162 patients (Table 2). The combination ifosfamide/DDP led to 4 complete and 21 partial remissions, corresponding to a remission rate of 35%, whereas the combination ifosfamide/etoposide led to 1 complete and 24 partial remissions, corresponding to a remission rate of 27%. Sex, age, performance index, extent and histological type of the tumor, and therapy regimen had no significant influence on the remission rate.

The median duration of complete and partial remission and of "no change" status was 5 months for all 100 patients (Fig. 1). The complete and partial remissions persisted significantly longer than the no change status (Fig. 2): 8 months, as opposed to 5. The remissions attained with ifosfamide/cisplatin were 2 months longer than the remissions induced by ifosfamide and etoposide ($p < 0.01$) (Fig. 3). Sex, age, performance index of the patients, and extent and histological type of the tumor did not significantly influence the duration of the remissions.

The mean survival time for all 162 patients was 8.5 months (Fig. 4), and 68% of the patients survived for 6 months. The 1-year survival rate was 33%, the 2-year survival rate, 11%. In both studies, the responders survived significantly longer than the nonresponders. Patients with complete or partial remission survived for an average of 13 months, patients with no change for 9.5 months, and patients with tumor progression for only 4 months (Fig. 5). There was no significant difference in survival duration of the patients between the two therapy schedules. The patients receiving ifosfamide/cisplatin survived for an average of 9.5 months, and those receiving ifosfamide/etoposide, for 8 months (Fig. 6). The Karnofsky index significantly influenced the survival duration of the patients ($P < 0.01$) (Fig. 7). Age and sex of the patients and extent and histological type of the tumor were without effect on the survival time of the patients.

Side effects

Ifosfamide/cisplatin. Myelosuppression and restricted kidney function proved to be the dose-limiting factors for this treatment. Most patients suffered from general lassitude

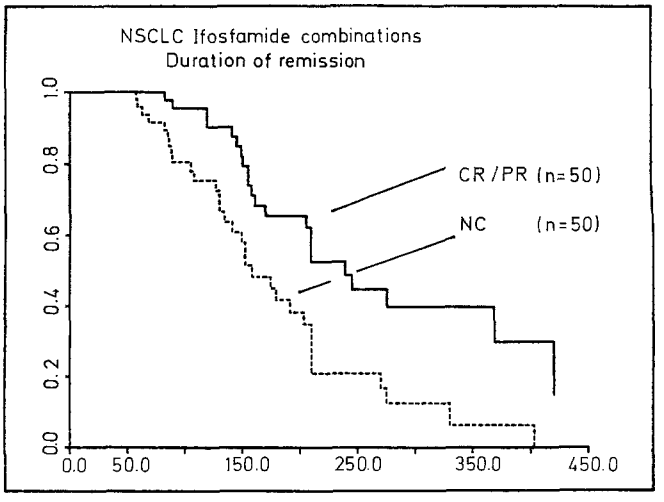

Fig. 2. Duration of complete remission, partial remission and no change

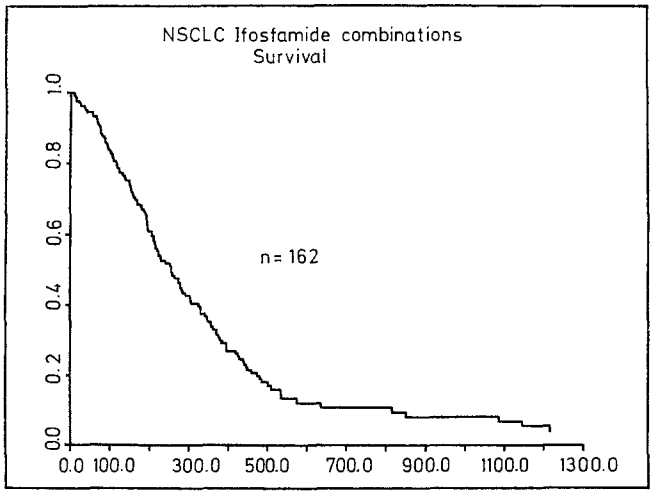

Fig. 4. Median survival time for all 162 patients

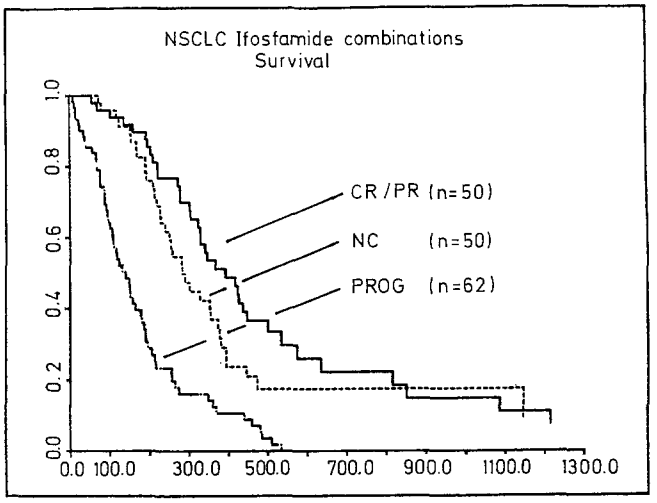

Fig. 5. Influence of remission on survival of patients

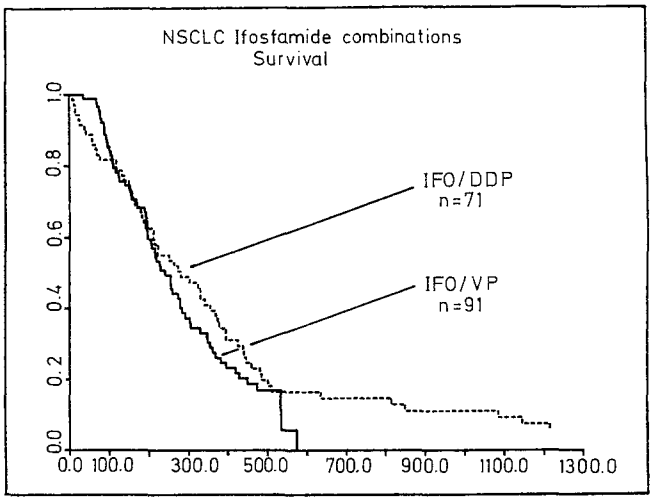

Fig. 6. Influence of treatment regimen on survival of patients

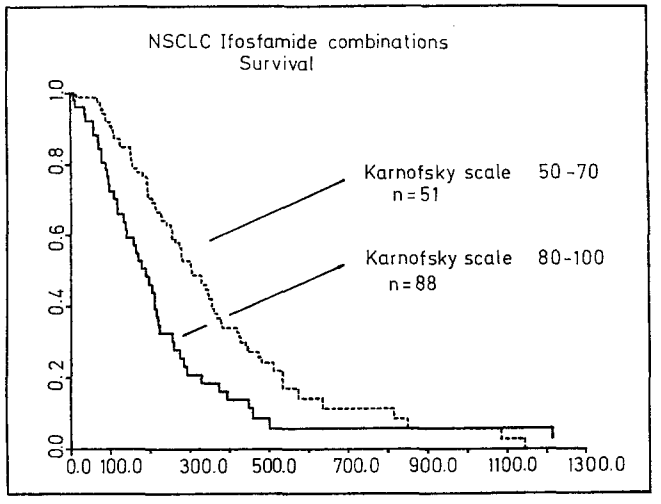

Fig. 7. Influence of performance status on survival of patients

and lack of appetite with nausea and vomiting (Table 3). In all patients who lived for longer than 4 weeks alopecia occurred. Systematic investigations of the creatinine clearance before the therapy cycles did not reveal any appreciable reduction of kidney function in the course of therapy.

Table 3. Side-effects of ifosfamide/cisplatin ($n = 71$) [11]

Side effects		Treatment cycles
Emesis, nausea		179
WHO scale	1	1
	2	33
	3	131
	4	14
Leukopenia		75
Nadir	$3000/mm^3$	16
	$2000/mm^3$	36
	$1000/mm^3$	23
Thrombocytopenia		21
Nadir	$100\,000/mm^3$	12
	$50\,000/mm^3$	9
Neurotoxicity		16
Macrohematuria		4

Macrohematuria, the typical side-effect of oxazaphosphorines, developed in only 4 of the 72 patients. This complication was also reversible after symptomatic therapy. Neurotoxicity was observed in 16 patients. It was manifested in transient states of confusion, moderate ototoxicity, and peripheral neuropathy. Transient states of confusion were explained in 2 patients by excessive hydration and consecutive electrolyte disorders (hyponatremia). In the other patients ifosfamide toxicity must be assumed. The symptoms improved within a few days after treatment with haloperidol.

Ifosfamide/etoposide. During the subsequent study, on the basis of the experience in the first study all side-effects were recorded in accordance with the WHO classification. This allowed an analytic appraisal, which also permits calculation of a cumulative factor (Table 4). Myelosuppression again proved to be the dose-limiting factor. All patients suffered from alopecia. Nausea occurred in almost all patients, but was very much milder than under the treatment with ifosfamide/cisplatin. Nor was such severe general lassitude observed in the patients.

No therapy-related deaths were observed in the two studies.

Discussion

The two consecutive studies with 162 patients yielded remission rates of 27% and 35%. These are the kind of results which can be expected at present in the polychemotherapy of non-small cell lung cancers. A mean survival time of 8.5 months for all patients confirmed that the patients were representative and had not been positively selected. The performance index before the beginning of therapy and the degree of remission attained were once more confirmed as the most important prognostic factors for the survival time of the patients. The latter also significantly influenced the duration of remission. It should be emphasized that the combination ifosfamide/cisplatin led to longer durations of remission than did the combination ifosfamide/etoposide. However, this result was not reflected in the survival time of the patients. The tumor spread could not have a significant effect on the result of therapy, since the proportion of patients in the stage "limited disease" was very low

Table 4. Side-effects of ifosfamide/etoposide

Reaction	WHO scale					Patients of 1–4		Cumulated factor
	0	1	2	3	4	Absolute	%	
Alopecia	0	0	37	54	0	91	100	236
Nausea	4	37	31	19	0	87	96	156
Fever	77	0	12	2	0	14	15	30
Stomatitis	82	7	2	0	0	9	10	11
Neurotoxicity	65	18	3	5	0	26	40	39
Skin changes	86	1	4	0	0	5	5	9
Hematuria	83	8	0	0	0	8	9	8
Diarrhea	87	2	1	1	0	4	4	7
Cardiotoxicity	89	2	0	0	0	2	2	2
Leukopenia	39	3	16	15	18	52	52	152
Thrombopenia	84	3	1	2	1	7	8	15

(25 patients, as against 137 cases in the stage "extensive disease"). The histological type of the tumor did not affect the duration of remission or the survival time of the patients. However, it must be emphasized that the highest remission rate was attained in large cell lung cancers, with as 38%, compared with 33% in squamous cell carcinomas and 24% in adenocarcinomas.

It is a familiar phenomenon that the patients who react to therapy with complete or partial remission survive for significantly longer than the non-responders. This is confirmed by these studies. However, it is not certain whether this is a real effect of therapy and not an effect of the biological characteristics of the tumor, as discussed by Aisner and Hansen [1]. This question could only be answered clearly if a treated group of patients were to be compared with an untreated group in a randomized prospective study. However, such studies are very difficult to carry out.

When the rates of remission obtained with the two duplex combinations are compared with those of other standard combinations in non-small cell lung cancer, no significant difference is discerned (Table 5), nor is there any between the survival time of the patients after the different combinations. In accordance with international experience, the overall survival of the patients treated under study conditions was between 7 and 9 months. The responders survived for an average of 12–15 months, whereas nonresponders can only expect a median survival time of 4 months.

When the result of therapy with regard to rate of remission, duration of remission, and survival time of the patients is about the same with the different therapy schedules, the side-effects attain special significance. The therapy schedule with the fewest and mildest side-effects should be preferred. Of the two ifosfamide combinations, the combination ifosfamide/etoposide is clearly preferable from this aspect; the subjective side-effects and the neurotoxicity were very much lower. In this connection, it must be emphasized that there were far fewer discontinuations of therapy at the patient's request with ifosfamide/etoposide. In a therapy with a purely palliative objective, the toxicity of treatment may not severly impair the patient's quality of life. In this connection, the therapy techniques in which cisplatin is used in single doses of 60 mg/m^2 and more [4, 12, 14, 17, 19, 27, 30] appear to be inferior to a schedule such as ifosfamide/etoposide. Because of its good tolerance and its therapeutic effect, which is comparable to that of other schedules, we regard it as the combination of choice.

Table 5. Polychemotherapy with various drug combinations[a] in comparison with IFO/DDP and IFO/VP

Regimen	N pat.	Remission rate			Total
		Squamous cell carcinoma	Adenocarcinoma	Large cell carcinoma	
MACC	282	20%	33%	34%	29%
CAMP	313	30%	28%	22%	26%
CAP	718	34%	29%	26%	26%
VDS/DDP	329	48%	38%	40%	37%
MiViP	358	62%	33%	45%	45%
VP/DDP	446	38%	24%	24%	30%
IFO/DDP	71	39%	29%	33%	35%
IFO/VP	91	26%	24%	35%	27%

[a] Cumulative analysis of Joss and Brunner [20]

MACC, methotrexate/adriamycin/cyclophosphamide/CCNU; CAMP, cyclophosphamide/adriamycin/methotrexate/procarbazine; CAP, cyclophosphamide/adriamycin/cisplatin; VDS/DDP, vindesine/cisplatin; MiViP, mitomycin C/vinca alkaloid/cisplatin; VP/DDP, etoposide/cisplatin; IFO/DDP, ifosfamide/cisplatin; IFO/VP, ifosfamide/etoposide

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