Ifo 23

VP-16 PLUS IFOSFAMIDE PLUS CISPLATIN (VIP) IN REFRACTORY GERM CELL TUMORS

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Forty-eight evaluable male patients with germ cell tumors (GCT) failing to be cured with first line therapy were treated with VP-16 (100 mg/m^2), ifosfamide (1.2 mg/m^2), and cisplatin (20 mg/m^2) all given daily for five consecutive days every three weeks. All patients either achieved an unresectable partial remission as their best response to induction chemotherapy (Group A), relapsed from complete remission $\leq$ 2 months after induction therapy (Group B), or had previously received cisplatin plus VP-16 as previous salvage therapy (Group C). In our experience, these three groups represented patients in whom conventional salvage therapy with cisplatin plus VP-16 alone rarely produced durable complete remissions. Nine (19%) had extragonadal GCT and 37 (77%) had advanced disease. Twenty-three (48%) of the patients had $\geq$ 2 prior treatment regimens. Sixteen of 48 (33%) achieved a complete remission (CR) to VIP alone or following surgical excision of residual disease. Six of 22 (27%), 3 of 7 (43%) and 7/19 (37%) of patients from groups A, B, and C respectively attained a CR. The median survival time of all patients was 7 months (range 0-28+) with 7 patients remaining continuously free of disease (4 patients > 1 year). Myelosuppression was significant with median WBC nadir of 900/mm^2 and platelet nadir of 24,000/mm^2. Fourteen (26%) had granulocytopenic fever and 15% developed renal insufficiency. VIP combination chemotherapy demonstrates activity in this highly unfavorable population of patients with germ cell tumors. These results compare favorably to our previous experience in similar patients treated with cisplatin plus VP-16 alone suggesting an important role for ifosfamide in this disease. Further studies with VIP as initial salvage therapy for patients with GCT are under way.

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Ifo 24

IFOSFAMIDE/MESNA IN COMBINATION CHEMOTHERAPY OF METASTATIC NONSEMINOMATOUS TESTICULAR CANCER AND SEMINOMAS

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Although the prognosis of metastatic nonseminomatous testicular cancer has been dramatically improved during the past decades due to the development of combination chemotherapy, the search for new chemotherapeutic alternatives for salvage therapy has become one of the major challenges.

Since 1977 we have investigated on the cytotoxic efficacy of ifosfamide alone (60mg/kg/day iv, days 1-5, q 21-28 days) or in combination with etoposide (40mg/kg/day ifosfamide iv, days 1-5, 120mg/m^2/day etoposide iv, days 1, 3, and 5, q 21-28 days) in 150 patients with metastatic nonseminomatous testicular cancer resistant against vinblastine, bleomycin, adriamycin, and cisplatinum.

Response rates - including minor responses - were 33% for ifosfamide (CR + PR 19%) and 46% for ifosfamide/etoposide (CR + PR 30%), respectively. The incidence of urinary tract complications, the dose limiting toxic side effect of ifosfamide, could be effectively reduced from 27% to 4% by co-administration of mesna (12mg/kg iv, 0, 4, and 8h after ifosfamide).

Ifosfamide proved to be one of the most potent cytotoxic drugs in the primary treatment of metastatic seminomas, as well. Complete responses could be achieved in 16/17 patients (94%) by ifosfamide, ifosfamide/etoposide or ifosfamide/cisplatinum (40mg/kg/day ifosfamide iv, days 1-5, 20mg/m^2/day cisplatinum iv, days 1-5, q 21-28 days). Presently, all complete responders have no evidence of disease at a medium follow up of 28 months.

In conclusion, ifosfamide/mesna - one of the most active cytotoxic agents in metastatic testicular cancer - may not only be included into effective combination chemotherapy regimens for salvage therapy but also in the first line treatment of this malignant disease.

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Ifo 25

IFOSFAMIDE IN TREATMENT OF LUNG CANCER

P. Drings

Ifosfamide is used as single drug or in combination with other cytostatic agents in the treatment of lung cancer. Different schedules of single agent therapy-24 hours infusion, bolus (5mg/m^2) infusion over 30 minutes or treatment with 1,0 to 2,0 g/m^2 days 1-5 are performed.

Small cell lung cancer (SCLC):

Different study groups reported response rates after ifosfamide alone of 5-34% even in pretreated patients. Ifosfamide was introduced into different combinations. In a randomized study, including 305 patients, alternating chemotherapy with etoposide, ifosfamide, vindesine (VPIV), adriamycin, cisplatinum, vincristine (APO), and cyclophosphamide, methotrexate, CCNU (CMCC) was compared to standard treatment alternating therapy resulted in higher response rate, and a longer median survival time. Regarding toxicity, VPIV was similiar to ACO, whereas APO and CMCC had more side effects.

In a 2nd randomized study 142 patients were treated either with ifosfamide/etoposide (IVP) or with cisplatinum/etoposide (PVP). Both regimes were comparable regarding to reserved in patients with PVP.

Non-small cell lung cancer (NSCLC):

With response rates from 10 to 39% ifosfamide is one of the most active drugs in NSCLC, too. In 2 consecutive phase II studies including 162 patients the cytostatic effect of ifosfamide in combination with cisplatinum or etoposide was investigated. An objectively measurable tumor regression was achieved in 31% of the patients including 5 complete and 45 partial remissions. The median survival time for all 162 patients was calculated with 8.5 months. In both studies responders survived significantly longer than nonresponders (13 versus 5 months). Because of the better tolerability the combination ifosfamide/etoposide is superior to some cisplatinum combination (especially high dose cisplatinum). Therefore we would prefer this combination in the treatment of NSCLC.

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Ifo 26

BIOAVAILABILITY OF IFOSFAMIDE IN PATIENTS WITH BRONCHIAL CARCINOMA.

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The aim of this study was to assess the biovailability of Ifosfamide (I).

Within patient pharmacokinetics of (I) were determined following the administration of 1g and 2g p.o. and i.v. in seven patients with bronchial carcinoma. Serial serum and urine samples were collected during the first 48 hours after administration and concentrations of (I) were assayed by HPLC using a method developed in this laboratory. The AUC ($\mu g.L.h^{-1}$) for both the 1 and 2g doses were the same following p.o. and i.v. administration indicating 100% bioavailability (Table 1). The i.v. serum concentration/time curve exhibited a biphasic decay with a terminal half life of 5.92h (SD 1.15, SEM 0.47) for 1g and 5.29 (SD 0.73, SEM 0.27) for 2g. Drug clearance was similar for both methods of administration. We conclude that up to 2 g of (I) p.o. is an alternative route of administration and makes out patient use a possibility.

Table 1. Bioavailability of Ifosfamide

Dose g.	1		2	
	p.o.	i.v.	p.o.	i.v.
AUC $\mu g.L.h^{-1}$	266.3	294.2	511.8	478.2
SD	12.02	29.82	83.97	34.86
SEM	4.90	12.17	31.73	13.17

AUC = Area under the curve
SD = Standard deviation
SEM = Standard error of the mean.

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