Ifo 07

PHARMACOLOGICAL AND TOXICOLOGICAL EFFECTS OF IFOSFAMIDE (HOLOXAN) COMBINED WITH MESNA (URO-MITEXAN) IN DIFFERENT MURINE TUMOR MODELS
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In spite of the comprehensive investigations of Goldin (1982) and Brock (1983) there still exist doubts if the uroprotectant Mesna influences the antineoplastic activity of Ifosfamide. In preliminary experiments we noticed no change in effectivity of Ifosfamide in P 388 - bearing mice when Mesna was administered up to a dosage of nearly 100% of the alkylant. Further investigations with the Lewis lung carcinoma (i.v. and footpad inoculation) and a newly developed mesothelioma in NMRI-mice are scheduled. As therapeutic parameters lifetime of the animals and tumor growth are registered; for estimation of toxicity leukocyte counts and blood urea nitrogen are determined. Maximum leukopenia was observed between day 2 and 4 after a single Ifosfamide injection of 300 to 600 mg/kg. Simultaneous administration of 50 to 100% Mesna slightly increased this reduction. In a day 1-4 schedule Mesna did not influence the minimum leukocyte counts caused by Ifosfamide. A dose of 400 or 600 mg/kg Ifosfamide led 1 day later to a 2- or 6-fold elevation of blood urea nitrogen; recovery to normal levels was noticed on day 3 or 4, respectively. No increase in BUN was observed, when Ifosfamide was given over 4 days, even up to lethal doses. In the P 388 leukemia a single high dose of Ifosfamide had a better effect on the survival time of the animals than an administration on days 1 to 4.

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Ifo 08

TREATMENT OF RECURRENT SARCOMAS AND PEDIATRIC SOLID TUMORS WITH IFOSFAMIDE (IF)
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We have evaluated the activity of IF in 78 previously treated patients with recurrent or progressive sarcomas or pediatric tumors. Previous chemotherapy included cyclophosphamide in combination with other drugs. Patients received 1800 mg/m² IF daily for 5 days, either as a continuous infusion or as a daily one hour infusion. Mesna was given concurrently to 43 of the patients, in 27 from the initiation of IF and in 16 because of hematuria with IF alone. Among 75 evaluable patients partial responses were seen in 9 of 20 patients with Ewing's sarcoma (45%), 3 of 17 patients with osteogenic sarcoma (18%), 2 of 9 patients with rhabdomyosarcoma (22%), 1 of 7 patients with synovial cell sarcoma (14%), 1 of 3 patients with undifferentiated sarcomas and none of 9 patients with various differentiated sarcomas. Two of 10 patients with other solid tumors had partial responses. Six patients had stable disease for greater than 6 months, giving an overall response rate of 32%. IF was well tolerated, but hematuria occurred in 66% of patients who had received prior pelvic irradiation, regardless of the administration of mesna. However, only 13% of previously irradiated patients treated with IF/mesna had gross hematuria as opposed to 40% of those who received IF alone. The overall incidence of gross hematuria was 22% in patients treated with IF alone and 4% in those treated with IF/mesna from the outset. IF is an active agent in sarcomas refractory to previous chemotherapy, even when this included substantial amounts of cyclophosphamide. Comparative studies of cyclophosphamide and ifosfamide are warranted. IF should be considered for introduction into Phase III protocols for the treatment of selected bone and soft tissue sarcomas.

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Ifo 09

TREATMENT OF ADVANCED SOFT TISSUE SARCOMAS WITH IFOSFAMIDE (IFF) AND ADRIAMYCIN (ADM)
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Conventional polychemotherapy of metastatic soft tissue sarcoma (CYVADIC) is disappointing, poor response rate with a high degree of toxicity are found. In this preliminary study we report on the use of a combination of those substances which had produced the best response rate when given as monotherapy. Treatment schedule: 2,5 g/m² IFF day 1,2,3 as a continuous i.v. infusion, ADM 65 mg/m² i.v. day 1. For uroprotection Mesna was applied. Results: Up to now 14 patients (8 male, 6 female) have been treated. Median age was 45 years (28-59). The histological diagnoses were leiomyosarcoma (4), haemangiosarcoma (3), fibrosarcoma (2), neurofibrosarcoma (2), malignant hamartoma (1), liposarcoma (1), ependymoblastoma (1). Four patients had already received radiotherapy, one patient had had chemotherapy. Complete remission was achieved in one patient, partial remission in five. The responding group received an average of 5 cycles with a preliminary overall response rate of 43%. Minor response was seen in 1 patient, no change in 4 patients. In these patients, however, progression of disease was delayed for three months following cessation of chemotherapy. Two patients showed progress under therapy. One patient showed a mixed response with remission of lung metastasis and progression of the primary tumor. Two patients died, one from sepsis while in partial remission, one from progressive disease six months after failure to respond chemotherapy. Toxicity was moderate. Severe myelosuppression occurred in only one case. The nausea and vomiting which occurred was not marked and could be controlled effectively by dexamethason. Conclusions: Conventional chemotherapy of soft tissue sarcoma (CYVADIC) is hampered by severe toxicity. Using IFF and ADM we achieved similar response rates with fewer toxic side effects. Our results are yet preliminary, long term followup will be required for full evaluation.

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Ifo 10

EFFECTIVENESS OF IFOSFAMIDE (IFO) ALONE AND IN COMBINATION WITH CISPLATINUM (DDP) IN PATIENTS WITH RECURRENT EWING'S SARCOMA
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The effectiveness of IFO and IFO in combination with DDP was evaluated in 23 patients (pts.) with recurrent Ewing's sarcoma. All pts. had previously received vincristine, actinomycin D, cyclophosphamide and adriamycin.

8 pts. (Group I) received IFO alone 2 g/m²/day, days 1-5, as 120 hrs. continuous infusion along with forced diuresis and mesna uroprotection for 7 days. 3/8 pts. had progressive disease, there were 3 partial responses (PR)/>50 % regression of evaluable tumor mass) and 2 complete responses (CR). The duration of response was 3 to 12 months, median 6 months.

15 pts. (Group II) received the combination of IFO (doses and mode of administration as above) and DDP 20 mg/m²/day, days 1-5 every 3 to 4 weeks. 6/15 pts. had progressive disease, there were 7 PR and 2 CR. The duration of response was 3 to 32 months, median 6 months.

The toxicity included marked bone marrow depression, one septic death during neutropenia and two episodes of transient neurologic disorders during IFO infusion. IFO is active in recurrent Ewing's sarcoma and is well tolerated as continuous infusion over 5 days when administered with mesna uroprotection and forced diuresis over 7 days. The response rate was not increased when IFO was combined with DDP, however, longer remissions were seen in pts. who had received the combination of both drugs.