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PHASE II-STUDY OF IFOSFAMIDE(IFS) + ADRIAMYCIN(ADM) IN ADVANCED SOFT TISSUE SARCOMA IN ADULTS - A PRELIMINARY ANALYSIS.

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ADM and, as more recently demonstrated, IFS each as a single agent have documented activity in soft tissue sarcomas (sts). Thus, in order to assess the efficacy and feasibility of the combination of both drugs, so far 120 patients (pts) with previously untreated advanced sts were entered into this ongoing trial. Eligibility criteria included: measurable,progressive disease; age > 15, < 70 years; performance status < 2; WBC > 3,500/µl;thrombocytes > 100,000 /µl. Treatment consisted of ADM 50 mg/m² iv followed by IFS 5 g/m² as a 24h-infusion plus mesna. Treatment courses were to be repeated every 3 weeks.
As of the interim analysis of May 1985, 66 pts (median age : 48 years; 36 ♂, 30 ♀) were evaluable for response. The response rate was 30% (95% CI: 19-41%) including 4 CR and 16 PR. Median time to response induction was 6 (range: 3-14) weeks. Stable and progressive disease were recorded in 53% and 17% of the pts, respectively.
Toxicity: WBC nadirs < 1,000/µl were observed in 12% of the pts during the first 3 treatment courses. Thrombocytopenia < 100,000/µl was recorded in 2 pts after the first cycle and in each 1 pt after the second and third course. Non-hematologic side effects: nausea/vomiting 92%, alopecia 88%, oral toxicity 15%, microhematuria 14%, diarrhea 12%, severe infection 6% and renal toxicity (grade I) 3%.

The preliminary conclusion is that the combination of ADM with IFS is an active chemotherapy for advanced soft tissue sarcoma and - after a further follow-up - will have to be compared with other standard regimens applied in this disease. An update of these results and an analysis of remission duration, time to relapse and survival will be presented.

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PRECLINICAL CHEMOSENSIVITY STUDIES WITH HUMAN SOFT TISSUE SARCOMAS IN NUDE MICE

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During the last two years we obtained 84 specimens of soft tissue sarcomas (STS) from our department of surgery for xenotransplantation. 36 (43%) of these tumours were established in nude mice for an average of 7 passages by serial subcutaneous grafting (range: 3 to 37 pass.). Our interest was to investigate the individual and interindividual chemosensivity of different STS quantitatively. Therefore we have tested the cytotoxic effects of 5 drugs in 4 subtypes of STS. Toxicity studies have been performed previously to determine the lethal dose levels of the cytotoxic drugs. Each substance was given as a single ip.-injection. The growth delays caused by the different drugs were the parameters to judge the effectivity of chemotherapy definitely. Drug doses, corresponding LD-50 values and the growth delays for the tested STS are given in the table:

DRUGS	Ifos	Cy	ADM	E-ADM	DDP
DOSES(mg/kg)	300	300	10	12,5	9
LD-50(mg)	550	530	10	12,5	-
HISTOLOGY	growth delays (days)				
Leiomyo-sa.	40	-	4,5	-	-
MFH	18	-	+	+	-
Spindle-cell-sa.	32	22	11	-	+
Neurofibro-sa.	29	-	+	-	-

Cy=Cyclophosphamide, +=not statist. significant

The results are listed in order of decreasing drug efficacy: Ifos > Cy > ADM. The other drugs were not effective. Our findings are in agreement with the clinical experience concerning these substances. The availability of this animal model for preclinical chemosensivity studies will be discussed.

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STUDIES OF IFOSFAMIDE IN CERVICAL CANCER

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Ifosfamide (IFX) has been demonstrated to have activity in a number of malignancies. It can be given safely, with minimisation of urothelial toxicity, by the concurrent adminstration of sodium-2-mercaptoethane sulphonate (Mesna).
Alkylating agents have been shown to have some activity in cervical cancer. IFX/mesna was therefore evaluated in advanced cervical cancer. 30 patients with biopsy proven advanced or recurrent squamous cell carcinoma of the cervix were treated with 5Gm/M² of IFX with equal doses of mesna. IFX/mesna was given as a 24 hour infusion, and 3.2Gm/M² of mesna were infused over the next 12 hours. The treatment was repeated every three weeks.
Ten out of 30 patients (33%) showed objective response to treatment. All patients with responses and 4 patients with static disease noted subjective improvement of disease related symptoms. The median duration of response was 6.5 months with one complete remission sustained for 12+ months. Median survival for the responders was 11 months (5 months for non-responders, p=0.0008).
50 lesions were assessible for response. 4/22 (18%) lesions in previously irradiated sites showed response compared with 15/28 (54%) responses in non-irradiated sites.
Toxicity was minimal apart from three patients who developed a severe and characteristic encephalopathy within 20 hours of starting treatment. One patient recovered spontaneously, one died of peritonitis and the third patient became comatose and died.
This toxicity led us to try to identify the underlying problem related to this highly active therapy in cervical cancer. In a larger study of 77 patients with a variety of malignancies, 7 (9%) developed signs of encephalopathy. Discriminant analysis identified low serum albumin, high serum creatinine concentration and the presence of pelvic disease as variables which pre-dispose patients to the development of severe encephalopathy. The risk of an individual patient developing encephalopathy can now be predicted accurately using a nomogram. High risk patients can then be monitored closely, or considered for other forms of therapy.
With this information a combination study in cervical cancer has now begun. IFX 5Gm/M² with mesna, bleomycin 15mg., and cis-platinum 50mg/M² are given intravenously with hydration every four weeks. 20 patients have been entered into this trial, of whom 17 are evaluable. 13 (76%) patients have shown a response (2CR, 11PR). Toxicity is manageable and predictable, and with this high response rate a study is now in progress to assess the value of this combination as debulking therapy prior to local radical treatment for patients with locally advanced disease (Stage IIB, III and IV, FIGO classification). This study will form the basis of a trial to test this approach of 'neoadjuvant' therapy in cervical cancer.

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THE TREATMENT OF BRAIN METASTASES WITH A COMBINATION OF IFOSFAMID, BCNU AND RADIOTHERAPY

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105 patients with brain metastases (46 male, 59 female, median age 53 years (18 - 78 years)) had been treated between 01. 01. 1982 and 01. 05. 1985. Primary tumor sites were mostly lung and breast, a few had hypernephromas, testes tumors and others. 28.6 % (30/105) of the patients had a solitary brain metastasis, 71.4 % (75/105) a multiple manifestation of the cerebral metastases. The brain metastases had been found on an average of 24.5 months (0 - 136 months) after first tumor manifestation. 84 from 105 patients had been pretreated.

A daily dose of 1.2 gr/m² ifosfamid was applied for five days. An additional dose of 30 mg/m² BCNU was applied on day 1, 3 and 5. A whole brain radiation therapy of 5 x 1.5 Gy/week (15 Gy/cycle, 45 Gy/ all over) was applied simultaneously during the chemotherapy. Three therapeutic cycles with a four to six week interval had been given. The therapeutic tolerance was excellent.

All patients could be followed up by cranial CAT-scan and evaluated according UICC criteria. 24.8 % (26/105) achieved complete remission (CR), 45.7 % (48/105) partial remission (PR), 6.7 % (7/105) reported a general improvement without fulfilling the criteria for PR. No change (NC) 10.4 % (11/105) and progressive disease (PD) 12.4 % (13/105). Only 22.5 % of the patients died of their brain metastases. The survival rates will be reported.

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