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IFOSFAMIDE(IF) IN PAEDIATRIC SOFT TISSUE SARCOMAS(STS)

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We studied the replacement of cyclophosphamide by IF in the well known VAC regimen. IF was administered 3000 mg/m^2/i.v. day one and two every 4 weeks. Vincristine 1.5 mg/m^2/i.v. push on day one, every 2 weeks. Actinomycin D 900 µg/m^2/i.v. day one and two every 4 weeks. We studied 3 groups of patients treated with this IVA regimen. Group A: 18 patients with an untreated histologically proven rhabdomyosarcoma (RMS). Primary sites were orbita 6, abdomen 4, bladder or prostate 2, extremities 1, head and neck 4 and trunk 1. After at least 3 IVA courses sometimes limited surgery was performed to establish complete remission(CR). So far 14 patients reached this stage of CR and 4 are still in the induction phase. From these 14 CR patients 5 had a recurrence. So far 2 patients died, one of them therapy related. Follow-up is now from 2-26 months. Group B: 5 RMS patients, resistant (1) to VAC or with a recurrence (4) after VAC. The first patient went into CR. From 4 patients with recurrent disease, 2 went into CR and 2 had no response. Two are still in CR, 1 for 1 year and 1 for 3 months. Group C: other STS patients treated with IVA. There were 2 synoviosarcomas, 2 clear cell sarcomas, 1 Ewing sarcoma and 2 malignant mesenchymal tumours. All went into CR after 3 IVA courses with or without additional limited surgery. All of them are still in CR for 3-20 months (mean 12).

Toxicity of IF: vomiting is the far most acute toxicity. Encephalopathy sometimes occurs. Bladder toxicity can be met by hyperhydration and the use of mesna. Bone marrow depression is mild with a nadir at approximately 10 days. Renal toxicity, especially tubular of origin can be found.

Conclusion: IF is a valuable completion of the therapeutic arsenal in paediatrics but still more information is necessary to establish its true value.

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Treatment results in patients with disseminated soft tissue sarcomas with Adriamycin/DTIC and Ifosfamid/Cisplatin

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Remission rates and duration of remissions of 23 patients (15 male, 8 female) with disseminated soft tissue sarcomas will be presented. First line chemotherapy was: Adriamycin 60 mg/m^2 day 1 and DTIC 600 mg/m^2 days 1 and 2. Second line chemotherapy in non-responding or relapsing patients was: Cisplatin 80 mg/m^2 day 1 and Ifosfamid 1.5 g/m^2 days 1-5. Adaequate hydration and uroprophylaxis with Mesna was given. The median age was 44 years (16 to 70 years). The material comprises the following tumorentities: Malignant fibrous histiocytoma 5, rhabdomyosarcoma 4, malignant schwannoma 4, leiomyosarcoma 3, hemangiopericytoma 2, angiosarcoma 2, mesodermal mixed tumor 1, fibrosarcoma 1, anaplastic carcoma 1.

12/23(=52%) patients responded to Adriamycin/DTIC therapy with a complete or partial remission. Remission duration ranged from 1 to 12 months with a median of 5,5 months. 13 patients (7non-responding to Adriamycin/DTIC, 6 relapsing)were subsequently treated with the second line regimen Ifosfamid/Cisplatin. 5/13(=38%) achieved a partial remission with a duration from 3 to 12 months (median 7,4 months). 4/5 of the second line responders had responded to the first line regimen whereas only 1 of the first line non-responders achieved remission with the second line chemotherapy. Side effect were apart from nausea, vomitting and alopecia severe leucopenia in one patient with Adriamycin/DTIC, severe leucopenia and thrombopenia in 4 patients with Ifosfamid/Cisplatin.

Data of this trial suggest: (1) ADM/DTIC in a 2-day schedule regimen seems to be as effective as CYVADIC or ADM / DTIC in a 5-day regimen. (2) Ifosfamid/Cisplatin seems to be an effective second line therapy in soft tissue sarcoma. (3) Non-responders to ADM/DTIC seem to have only a small chance to respond to Ifosfamid/Cisplatin.

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ALTERNATIVES TO CYVADIC-COMBINATION OF SOFT TISSUE SARCOMA

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For more than 10 years the combination of cyclophosphamide, vincristine, adriamycin and dacarbazine is the favoured chemotherapy for soft tissue sarcomas. The remission rate reaches up to 55 % with a cumulative rate of 35 %. There are many trials to improve these therapy results.In a phase II-study we examined a combination of cis-platinum and ifosfamide on 68 pts. with a locally advanced or metastasized soft tissue sarcoma. The most frequent histologic entities were fibrosarcomas (n=23) and leiomyosarcomas (n=17). The treatment regimen was 1,5 g/m^2 ifosfamide and 20 mg/m^2 cis-platinum per day over 5 days. We achieved a CR in 7/68 pts. and a PR in 23 pts., this means a remission rate of 44 %.

Side-effects were severe nausea and vomiting, on the other hand leucopenia and anemia as well as a general malaise, especially with a successive chemotherapy of more than 4 cycles. In consequence of these side-effects, which we essentially attributed to cis-platinum, we substituted cis-platinum by 50 mg/m^2 adriamycin, distributed on 3 days, in 21 further pts. 3 of these 21 pts. achieved a CR and 9 PR. 4 further pts. with progressive disease came to a stable state for 4,6,9 and 11 months. The gastrointestinal side-effects were significantly lower compared with the combination of ifosfamide and cis-platinum, vomiting being completely suppressed. There was only a moderate bone marrow toxicity: only in 3 pts. leucocytes fell below 2000 and only in 5 pts. platelets were below 70000. Despite the small number of pts. the combination of ifosfamide and adriamycin can be proposed as an alternative therapy for soft tissue sarcomas. On account of the lower toxicity and similar therapy results this combination should be proved on further pts.

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RESULTS OF IFOSFAMIDE-CONTAINING CHEMOTHERAPY IN SOFT TISSUE SARCOMAS

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The standard chemotherapy of advanced soft tissue sarcomas (STS) based on the CYVADIC-regimen. Remission rates varied widely (0-60 %). It is evident that ADM ist the most active drug in this regimen. Ifosfamide (Ifo) became a further potential drug in cytostatic treatment of STS. As single agent response rates of 18 % were published. Between 1978 - 1985 we treated 33 pts with advanced STS using an Ifo-containing drug combination. During this period five different variations of Ifo-containing regimens were applied. The various combinations are detailed in Tab. 1.

Results of Ifosfamide-containing chemotherapy in metastatic soft tissue sarcomas

Regimen	prior therapy	Rem.-rate	PR	Ifo-th. NC	PD	Rem.-rate	Rem.-durat.
VP 16-Ifo-VDN (n=15)	CYVADIC (n=8)	5/8	3	0	5	3/8	6 mo.
	Ø chemoth.(n=7)	/	2	1	4	3/7	3 mo.
VP 16-Ifo-DDP (n=5)	CYVADIC (n=3)	0/3	0	1	2	1/3	2 mo.
	Ø chemoth.(n=2)	/	0	2	0	2/2	4 mo.
DDP-Ifo (n=5)	CYVADIC (n=1)	1/1	1	0	0	1/1	4 mo.
	Ø chemoth.(n=4)	/	0	0	4	0/4	/
ADM-Ifo (n=6)	Ø chemoth. (n=6)	/	0	3	3	3/6	3 mo.
High dose Ifo (n=2)	CYVADIC (n=2)	2/2	1	0	1	1/2	4 mo.

We administered a total of 109 cycles with a medium of 3.3 cycles per pat.. In 10 pts the Ifo treatment was given primarily with a remission rate of 8/19 (42 %). 14 pts received this therapy as second line following CYVADIC. Surprisingly we met a similar response rate of 6/14 (43 %). Looking for the details we found that a second remission was confined in all but one cases on those pts who had already responded to CYVADIC.