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Management of local recurrences of soft tissue sarcomas in an irradiated field after prior surgery and radiotherapy: the role of TNF-based isolated limb perfusions to achieve limb salvage.

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Background: Recurrent extremity soft tissue sarcoma (STS) in a previously operated and irradiated area can usually only be managed by amputation. TNF-based isolated limb perfusion (ILP) is an established alternative to achieve limb salvage.

Methods: Prospective database of TNF-based ILPs at the Daniel den Hoed Cancer Center in Rotterdam. Out of 326 TNF-based ILPs between 1991-2002, 27 ILPs were done in 24 patients with recurrent STS in a highly irradiated field (50-70 Gy) after prior surgery and radiotherapy. Thirteen patients (54%) had multiple tumors (2->20). All patients were candidates for amputation. This represents a unique experience with a very rare subgroup of patients that present with a desperate clinical problem, for which only amputation can be considered normally.

Results: After 27 ILPs we observed: 6 complete responses (22%), 14 partial responses (52%) and in 7 patients no change (26%). The Mean duration of response was 17.6 months (2 - > 56, at a median follow up of 30+ months. With multiple tumors in 13 patients the local recurrence rate was 38% after ILP, also 38% of the patients developed systemic metastases and died. Limb salvage was achieved in 16 of the 24 patients (67%), but of course not all patients were tumor-free in the extremity at time of death. Regional toxicity was limited and systemic toxicity minimal to moderate, with no toxic deaths.

Conclusion: Amputations in patients with recurrent extremity STS in the irradiated field after prior surgery can be avoided in the majority of patients by TNF-based ILP.

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Assessment of the tolerability, safety and efficacy of increasing doses of peginterferon alfa-2a (40KD) in a randomised study in patients with metastatic malignant melanoma

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Background: Metastatic melanoma, a tumour of the pigment-producing cells in the skin, has a poor prognosis. The median survival of patients with systemic metastases is 6-12 months. Overall response rates to interferon alfa-2a and other agents is 10-15%, suggesting the need for new treatments. The sustained absorption and prolonged half-life of peginterferon (PEG-IFN) alfa-2a (40KD) (PEGASYS) may provide benefits over conventional interferon-alfa in terms of convenience and toxicity.

Materials and methods: This open-label, Phase II trial was conducted in patients with confirmed metastatic malignant melanoma (stage IV AJCC) to evaluate the tolerability, safety and efficacy of 3 doses of subcutaneous PEG-IFN alfa-2a (40KD). Patients were randomised to receive PEG-IFN alfa-2a (40KD), 180 µg (n=48), 360 µg (n=53) or 450 µg (n=50), once weekly for an intended period of 24 weeks or more. The median duration of treatment was 8.1 weeks (range 0.1-72.4 weeks; 20% of patients were treated for >24 weeks).

Results: Patient demographics were similar between groups. More patients required a dose adjustment for safety reasons (adverse events or laboratory abnormalities) in the 360 µg (51%, n=27) and 450 µg groups (41%, n=20) than in the 180 µg group (23%, n=11). Study withdrawal due to an adverse event during treatment was low, but more frequent in the 360 µg group (17%) vs the 180 µg (4%) and 450 µg groups (10%). Tumour response data are shown (table). The most frequently reported adverse events were fatigue, pyrexia, rigors, nausea, anorexia, myalgia, headache

Dose group	Major response (CR+ PR)	Complete response (CR)	Partial response (PR)	Stable disease (SD)	Progressive disease (PD)	Median days alive (95% CI)
180 µg	6.3%	2.1%, n=1	4.2%, n=2	23%, n=11	65%, n=31	203 (153-330)
360 µg	7.6%	1.9%, n=1	5.7%, n=3	19%, n=10	61%, n=32	295 (189-401)
450 µg	12%	6.0%, n=3	6.0%, n=3	20%, n=10	58%, n=29	237 (198-348)

and dizziness. No differences were measured between groups for the time to achieve a major response or disease progression, or the duration of a complete response. The median patient survival is given in the table.

Conclusions: Overall, PEG-IFN alfa-2a (40KD) 180 µg, 360 µg, and 450 µg, appear to demonstrate similar efficacy to interferon. This study shows that the 180 µg dose is better tolerated and seems to have an immunomodulatory effect in patients with metastatic malignant melanoma. The prolonged serum half-life of the pegylated interferon allows a more convenient once-weekly dosing regimen, thereby improving patient quality of life.

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Evaluation of a clinically applicable post-surgical classification system for primary retroperitoneal soft tissue sarcoma

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Purpose: A prognostic tool enabling comparison of outcomes for patients with primary retroperitoneal soft tissue sarcoma (STS) would be useful for designing clinical trials, comparing results from different institutions and evaluating effects of treatment modalities. In the present study a simple post-surgical classification system based on well documented predictors of survival for retroperitoneal sarcoma is evaluated.

Patients and methods: Based on malignancy grade (low versus high), completeness of resection (complete versus incomplete), and distant metastasis (no metastasis versus metastasis), four classes were defined: I, low-grade/complete resection/no metastasis; II, high-grade/complete resection/ no metastasis; III, any-grade/ incomplete resection/ no metastasis; IV, any-grade/any resection/distant metastasis. The prognostic value of this classification system was analyzed in a population based multi-center group (MCG) of patients with primary RSTS (n=124), and in a cohort of patients treated in a single-(tertiary referral) center (SCG; n=107). Median follow-up was more than 5 years in both groups.

Results: Overall 5-year survival rates were 55% in the SCG, and 43% in the MCG (P=0.015). class III (incomplete resection) was more frequent in the MCG than in the SCG (33% vs 16%; P=0.02). In the SCG, stage-specific 5-year survival rates were 89%, 40%, 26%, and 17% for class I to IV respectively(P

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Synergistic antitumor activity of histamine in combination with chemotherapy in the regional treatment of soft tissue sarcomas

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Background: Soft tissue sarcomas are tumors of mesenchymal origin accounting for about 1% of all adult malignant tumors in the USA. Circa 60% of them affect the extremities and are often large at first diagnosis. Isolated limb perfusion (ILP) with TNF+mephalan is now established as an excellent method to achieve limb salvage in the management of irresectable extremity sarcomas with a response rate of 76% and a limb salvage index of 71%. We used the experimental ILP model in rats in order to evaluate the potential effect of histamine. This inflammatory mediator is formed and stored mainly in the granules of mast cells and basophils, but also in cells of the epidermis, gastric mucosa, neurons within CNS and cells in regenerating or rapidly growing tissues. Histamine's classical effect on fine vessels is the formation of edema by an increase in the flow of lymph and its protein content to the extracellular space and also the formation of gaps between endothelial cells increasing transcapillary vesicular transport.

Methods: Twenty BN and 18 Wag/Rij rats had the BN-175 soft tissue sarcoma and the ROS-1 osteosarcoma, respectively, inserted on the right hind limb. After the tumor reached a volume between 12 and 15mm3 they were submitted to one of the following ILPs: SHAM (n=5 and n=4), mephalan (n=5 and n=6), histamine (n=6 and n=4) or histamine + mephalan (n=6 and n=4). In vitro bioassays of histamine with and without mephalan were