developed metastatic disease. Median intervals between surgery and local or metastatic relapse were respectively 14 and 13 months. Overall actuarial survival and disease-free survival at 2 years are respectively 77 and 47%. Grade, tumor size, tumor depth, bony or neurovascular involvement as well as quality of surgery show significant effects on DFS. Considering prognosis, hyperfractionated radiotherapy did not seem to be superior to standard techniques.

Long term side-effects, although usually mild, occurred in 35% of the patients. Dose of therapy, but not size of treatment fields, positively influenced them.

846 ORAL

NEOADJUVANT SYSTEMIC CHEMOTHERAPY COMBINED WITH REGIONAL HYPERTHERMIA IN ADVANCED OR RECURRENT SOFT TISSUE SARCOMA: RESULTS OF THE RHT-91 STUDY

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From Nov. 1990 to Oct.1994 a total of 97 (72% pretreated) adults with locally-advanced, nonmetastastic soft tissue sarcomas were entered in a protocol (RHT-91) involving regional hyperthermia (RHT) combined with systemic preoperative chemotherapy followed by surgery. Primary tumor grading (84 patients had grade II or III), tumor size (>8 cm) and/or extracompartmental tumor extension (46 patients), or local recurrences (51 patients) were defined as high-risk factors. RHT was produced by an electromagnetic regional heating device (BSD-2000 system). For systemic chemotherapy the 97 patients received etoposide/ifosfamide/doxorubicin (EIA) with RHT being given on day 1 and 4 in repeated cycles (EIA/RHT) every 3 weeks. By the cutoff date for this analysis (Oct. 1994), 70 patients had undergone surgery after receiving EIA chemotherapy combined with RHT; 60 tumors except 10 could be resected without amputation. In 27 patients no further surgical procedure was performed. In 92 evaluable patients, the clinical response rate is 34% (1 CR = complete, 15 PR = partial, 17 MR = minor). 41 patients showed stable disease (NC) and 18 patients showed tumor progression (PD). Pathologic response to preoperative thermochemotherapy was evaluable in 70 patients with 30 responders (=43%) having either >50% histologic necrosis (FHR) within the resected tumors (20 patients) or pathological complete response (pCR) at the time of surgery (10 patients). All patients received—whenever possible—adjuvant chemotherapy and postoperative radiation. At the cutoff date, best response was obtained by the strategy of the RHT-91 study in 40 patients (=41%) showing no evidence of disease (NED) (median observation time = 18 months). An updated report will be given in regard to overall survival for non chemo-pretreated (n = 73) and chemo-pretreated (n = 24) patients. The protocol of a randomized multicenter trial (RHT-95) in patients with primary or recurrent high-risk soft tissue sarcomas will be presented to further test the potential of preoperative thermochemotherapy compared to neoadjuvant chemotherapy alone in regard to local control and survival.

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847 ORAL

CONSERVATIVE LOCAL TREATMENT BY MULTIMODALITY THERAPY IN 361 ADULTS' SOFT TISSUE SARCOMA (STS)

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Methods: From 1975 to 1992, 361 patients (pts) had their initial treatment at Institut Bergonié for non metastatic STS. There were 210 males and 151 females at a mean age of 50 years (16–87 years). 59% of the tumours were localized in the extremities. All pathological slides have been centrally reviewed. Grading according to the FNCLCC system was: G1 (18%), G2 (44%), G3 (38%). The local treatment combined surgery and radiotherapy in 83% of the cases. Surgery was conservative when possible. Marginal surgery was performed in 45% of the cases, wide excision in 48%. Compartmental radiotherapy was performed at a dose of 50 Gy, associated with a local boost (external beam, intraoperative or brachytherapy) when surgery was marginal. Chemotherapy was given in 126 pts (35%), in 60 of whom preoperatively.

Results: Amputation was necessary in only 7 pts (2%). Complete remission was obtained in 97.5%. Severe local complications occurred in 26 patients (7.2%). With a median follow-up of 6 years (1–20 years) local recurrence occurred in 21.4% of the cases, and metastasis in 28.7%. Actuarial 5-year overall and disease free survival are 66% and 59%. The function of the treated members was good in 92% of the pts. In univariate analysis, no difference was seen in local recurrence after marginal vs large excision when radiotherapy was done.

Conclusion: These treatment results compare favourably to those found in the literature. Satisfying functional outcome without amputation can be obtained by a multidisciplinary treatment approach.

848 ORAL

DOCETAXEL (TAXOTERE) AS FIRST LINE THERAPY FOR METASTATIC OR RECURRENT SOFT TISSUE SARCOMA (STS): A PHASE II TRIAL

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The clinical trials group of the National Cancer Institute of Canada is performing a multi-institutional phase II study of docetaxel in patients (pt) with measurable metastatic or recurrent sts with no prior systemic therapy. The starting dose is 100 mg/m^2 q 3 weeks with dose reduction for severe toxicities. Premedication includes 20 mg oral (po) dexamethasone (D) at 12 and 6 hours (hr) before, 50 mg diphenhydramine and 50 mg ranitidine both iv 1/2 hr before a 1 hr infusion docetaxel followed by 8 mg D po every 12 hr for 6 doses.

To date 22 pt have been entered, 1 is ineligible, 6 are too early for evaluation, 13 are evaluable for response and 15 for toxicity. Two partial responses and 6 stable disease have been reported. There have been 2 deaths on study unrelated to drug toxicity. The most common side effects have been: grade III–IV neutropenia (25/32 courses) with a median nadir of 0.4×10^9/l granulocytes; five cases of febrile neutropenia and two with severe infection. There have been five hypersensitivity reactions only one severe. Mild–moderate lethargy (10 pt) and edema (5 pt) have also been seen. The median delivered dose intensity is 33.14 mg/m^2.

Because two responses have been documented the trial will continue until 30 evaluable pt have been entered. At the current rate of accrual it is expected that the final response rates and toxicities will be available by the time of presentation.

849 ORAL

PRELIMINARY REPORT OF A RANDOMIZED PHASE II STUDY COMPARING TWO DIFFERENT IFOSFAMIDE (IF) REGIMENS IN ADVANCED SOFT TISSUE SARCOMA PATIENTS (PTS) FAILING FIRST-LINE ANTHRACYCLINES

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Soft tissue sarcomas (STS) constitute 1% of all malignant tumors. Despite optimal local treatment 50% of pts will relapse. First-line chemotherapy is Ddoxorubicin 75 mg/m^2. The STS group performed a large ph 3 study comparing different anthracyclines. Patients failing at that study were eligible and randomized to receive (a) If 5 g/m^2 over 24 hrs or (b) If 3 g/m^2 in 4 hrs d 1–3 q 3 wks, both with adequate Mesna protection. A total of 86 pts of whom 78 evaluable and 66 off study were entered. Age 50 yrs (22–75), M = F, PS: 27:0, 51:1. Leyomyosa 30/78. *Results:* 34 PD, 1 CR on A, 1 CR and 2 PR on B, RR 3 resp. 8%. No change (NC) resp. 9 and 17 pts. So progression arrest (Resp + NC) 35% with (a) and 53% with (b). *Toxicity:* both gr 3 + 4 leucopenia and thrombocytopenia were more pronounced with B: 33 vs 68% and 3 vs 15% and nadirs of Wbc 3.1 vs 1.35, Pt 203 vs 169.10^9/l. Non hem. tox. did not differ substantially.

Conclusion: Higher IF results in more progression arrest and more manageable toxicity, but the overall response rate is disappointing.

850 ORAL

POST-RADIATION SARCOMAS: PRESENTATION OF A SERIES OF 116 CASES

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Post-radiation sarcomas are a rare and late complication of radiation treatment. The majority of them develops after 10 years.

The prognostic is generally fatal. Histologically, they are malignant histiocyto-fibrosarcomas in the majority of the cases.

In order to determine their risk and prognostic factors, we have decided to study all the post-radiation sarcomas diagnosed from 1975 to December 1994 in nine French anti-cancer centers.

116 cases have been included in this study. When possible, all the cases will be reviewed by the pathologists of the Sarcoma Group of the FNCLCC (Dr J. Simony-Lafontaine, Dr J.M. Coindre) to confirm the diagnosis and the histologic types. Our preliminary results will be presented and all the French anti-cancer centers are invited to participate in this study.

851 ORAL

CHORDOMA—A RARE AND LETHAL DISEASE

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In Denmark only 1–2 chordomas are diagnosed per year. In this national Danish study 37 patients with histological proven chordoma were analyzed. Male:female ratio was 2.7:1. Median age was 59 years (range 1–83). Median duration of symptoms before admission was 12 months (1–84). Dominating symptoms were pain (98%), neurological disturbances (42%) and incontinence (33%). The tumours were located in the sacro-coccygeal region in 68%, spheno-occipital region in 16% and vertebrae in 16% of the patients. Median tumour size was 7 cm (1–30). Treatment was surgical resection in 11, radiation in 10 and a combination of the two in 15 patients. Median radiation dose/fractions were 55 Gy (30–80)/29 (13–50). Symptom relief was obtained in 85% of the patients (67% complete), and the median time to maximum relief was 7 months (5–46). Two patients were lost for follow-up. At the time of analysis 10 patients were alive. Only 4 patients were without symptoms. Distant metastases developed in 23%. The actuarial 5-/10-year rates of overall, progression-free and symptom-free survival were 40%/26%, 31%/21%, and 20%/14%, respectively. Patients with active chordoma may live for a long period but often suffer from pain and other symptoms. The ultimate prognosis of chordomas is very poor.

852 POSTER

ADJUVANT RADIATION THERAPY FOR SOFT TISSUE SARCOMAS OF THE EXTREMITIES

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Between Jan 1990 and Dec 1994, 32 patients with soft tissue sarcomas of the extremities were treated; the mean age was 45 (10–81); 19 were female; 23 had Stage IIIB tumors. Group A consisted of 22 patients who underwent placement of afterloading catheters at the time of resection of their tumor. Patients received a mean dose of 22 Gy (10–30) at a dose rate of 10 Gy/day, with Ir-192. Subsequent external beam radiation therapy (RT) to give total doses of 55–70 Gy was delivered. Group B consisted of 10 patients who received postoperative external beam RT alone to doses of 45–70 Gy. With a mean follow-up of 23 mo (3–60), the overall local control is 78% (86% Group A and 60% Group B). Of the 7 patients who failed locally, 2 were salvaged with amputation and are without evidence of disease; 1 died of uncontrolled local disease and 4 died of distant metastases. Thirty percent of patients developed distant metastases. Adjuvant RT yields excellent local control in patients with large tumors of high grade. There appears to be a trend toward better local control in patients receiving brachytherapy.

853 POSTER

IFOSFAMIDE IN CONTINUOUS INFUSION: THE PHARMACOKINETIC PROFILE IN PATIENTS WITH SOFT TISSUE SARCOMAS

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Ifosfamide, an oxazophosphorin compound, active in mesenchimal tumours has recently been used at high doses (14–18 g/sqm) in order to increase the number of responses. Continuous infusion (C.I.) of Ifosfamide probably decreases toxicity and increases the therapeutic window of the drug. Bone marrow and renal toxicities seem to be modified greatly by C.I.. Aim of our study has been to characterize the pharmacokinetic drug profile during C.I. high dose-fosfamide (HD-IFO). From April to December 1994, 9 patients (pts) with advanced soft tissue sarcomas, 5 pts with osteosarcomas and 1 pts with Ewing's sarcoma with normal liver and renal function, treated with C.I. HD-IFO (14 g/sqm. over 4 days) and Mesna contemporary infusion, entered into the study. 33 chemotherapy courses were administered (range 1–4, mean 2.2). Pts were submitted to blood sampling previous starting of infusion, and 12, 24, 48, 72, 96, 100, 104, 114, and 120 hours after treatment beginning. Plasma samples were stored at 0°C. Chemical analysis was performed using HPLC. Maximum concentration of the drug was observed at 24th hour (C_{24}: 61.5 ± 21.9 μg/mL.) while decreased pseudo-steady rate levels were reached after 70–80 hours (Css: 28.3 ± 11.5 μg/ml). Terminal half life was 3.2 ± 0.4 hours; AUC (following trapezoidal rule) was 3654 ± 1222 mg/l. × hour. Median Clearances (total dose / AUC) was 7.14 ± 3.3 l/h. At the second or following cycles a relevant reduction of T1/2 and AUC (−20% and −25%) due to enzymatic autoinduction was observed. In confront with Ifosfamide administration at the same doses but in 1 hour infusion we observed that C.I. leads to a higher AUC (3650 vs. 1230) to a shorter T1/2 (3.2 h. vs. 5.9 h.) and to a relevant increase of total clearance (7.14 vs. 3.9).

This significant difference in pharmacokinetic profile can explain the different spectrum of activity between the two manners of administration.

854 POSTER

LEIOMYOSARCOMAS (LMS), MALIGNANT MÜLLERIAN MIXED TUMORS (MMT) AND ENDOMETRIAL STROMASARCOMAS (ESS) OF THE UTERUS: DIFFERENCES IN TREATMENT AND PROGNOSIS?

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Objectives: Uterine sarcomas are very rare tumors with a poor prognosis. Present study was undertaken to examine the treatment strategies, the clinical outcome and the aftercare management problems on the background of different prognostic factors.

Material & Method: 75 LMS, 21 MMT, 35 ESS, 1 reticulosarcoma, and 6 no classificable sarcomas (NCS) treated between 1969 to 1994, were evaluated retrospectively. Treatment strategies consisted of surgery, surgery/radiation, surgery/radiation/chemotherapy.

Results: Overall 5-year survival probability was 62%, but it was different in LMS, ESS and MMT. 24% of LMS, 28.6% of MMT, 17.1% of ESS and 28.6% of NCS show No Change or developed local recurrences and/or metastasis. Patients died 6 months after recurrence. *Conclusions:* Adjuvant irradiation seems to be important in the management of uterine sarcomas.

855 POSTER

THE USE OF R-MET HU 6-CSF IN COMBINATION WITH HIGH AND STANDARD DOSES OF IFOSFAMIDE AND DOXORUBICIN IN THE PATIENTS WITH ADVANCED SOFT TISSUE SARCOMA

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Sixty patients with stage III-B and IV soft tissue sarcomas were randomised to receive either Ifosfamide: 5 g/m² × d × 1 and doxorubicin: 60 mg/m² × d × 1 given every 3 weeks or Ifosfamide: 1.8 g/m² × d × 5 and doxorubicin 60 mg/m² × d × 1 given every 4 weeks. The granulocyte colony stimulating factor (r-set Hu 6-CSF: 250 μg/m² × d) was applied with a prophylactic intent in the first group as it was given preemptively in the other group. The response rate was higher in the high dose Ifosfamide receiving group (56% versus 33%, $P = 0.03$). In stage III patients, the CR rate was significantly higher (53% versus, 13.3%, $P = 0.01$) and the duration of response was significantly longer in the high dose Ifosfamide receiving group (20 ± 8.2 months versus, 13.4 ± 7 months, $P = 0.05$). Chemotherapy related myelotoxicity and mucositis were also less frequent in the first group as a result of prophylactic r-met Hu 6-CSF administration ($P = 0.04$, $P = 0.003$).

It was concluded that high dose Ifosfamide and doxorubicin combinations deserve further investigation under the cover of hematopoietic growth factors particularly in patients with stage III soft tissue sarcomas.