1–4), DTIC (200 mg/m^2, days 1–4) and doxorubicin (25 mg/m^2, days 1–2) augmented in time and administered in 14-day-intervals made possible by subcutaneous administration of G-CSF (30 × 10^6 IU/d) on days 5–13. According to the randomization protocol, 28 patients received adjuvant HA-RT only, whereas 31 patients were treated with additional adjuvant ACT. After a mean observation period of 41 ± 19.7 (range: 8.1–84) months, 16 patients (57%) after adjuvant HA-RT vs. 24 patients (77%) after adjuvant HA-RT + ACT were free of disease ($p > 0.05$). Within the HA-RT group, tumor relapses occurred in 12 patients (43%; 6 patients with distant metastases, 2 with local relapse, 4 with both) vs. 7 patients (23%; 5 patients with distant metastases, 1 with local recurrence, 1 with both) from the HA-RT + ACT group. Mean relapse-free survival ($p = 0.1$), time to local failure ($p = 0.09$), time to distant failure ($p = 0.17$) as well as overall survival ($p = 0.4$) did not differ significantly between the two treatment group. However, subgroup analysis of grade 3 soft tissue sarcoma revealed a significant advantage of both relapse-free survival ($p = 0.03$) and time to distant failure ($p = 0.03$) in patients receiving HA-RT + ACT ($n = 25$) as compared to patients treated with HA-RT only ($n = 16$).

Treatment-associated toxicity in patients receiving HA-RT + ACT included alopecia of WHO grade 3 in all cases, leukopenia of WHO grades 1 and 2 in 19 patients (61%), grade 3 in 4 (13%) and grade 4 in 4 patients (13%), thrombocytopenia grades 1 and 2 in 7 patients (23%), grade 3 in 1 patient (3%) and grade 4 in 1 patient (3%). Non-hematologic toxicity consisted of stomatitis WHO grade 3 in 1 patient (3%). In 2 patients (6%), ACT was discontinued after 2 cycles due to impairment of wound healing. Acute local toxicity was mild (2 versus 3 moist desquamations in the HA-RT and HA-RT + ACT groups, respectively). Severe late local toxicity consisted of two infected endoprostheses (one in either group), one fracture of an irradiated thigh (HA-RT + ACT), and one case of severe fistulation with bone necrosis leading to amputation without evidence of local relapse (HA-RT + ACT).

We conclude that the addition of adjuvant ACT to adjuvant HA-RT in patients with surgically adequately removed grade 3 STS significantly improved relapse-free survival as well as time to distant failure. Furthermore, the inclusion of ACT should be considered in the treatment of grade 3 adult STS.

1076 POSTER

Prognostic factors in completely resected liposarcomas (LPS)

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Purpose: The aim of this study was to identify prognostic factors regarding recurrence and survival after complete resection of LPS.

Patients and Methods: All consecutive LPS (reviewed diagnosis), treated with curative intent at the G.U.H. from 1977–1997, were analyzed.

Results: 66 pts (35, 31; median age: 53 (range 11–80) years) were reviewed. 49 primary LPS, 17 recurrent LPS. Histology: myxoid n = 31, well-differentiated n = 22, dedifferentiated n = 7, pleomorphic n = 3, nos n = 3. Grade I: n = 48, grade II: n = 10, grade III: n = 6, nos: n = 2. During a median follow-up of 58 (range: 5–210) months, 20 pts developed a local recurrence (30%), and 11 pts distant metastases (17%). At analysis, histologic subtype and anatomic site were the only independent prognostic factors regarding local recurrence, tumor grade regarding distant metastases, and histologic subtype and tumor grade regarding disease-free and overall survival. Retroperitoneal localization, dedifferentiation and grade II–III were negative prognostic factors. Size, primary/recurrent LPS, and type of resection were not independent prognostic factors.

Conclusion: LPS have a relatively mild biologic behavior, with exception of dedifferentiated LPS and grade II–III tumors. Independent prognostic factors regarding recurrence, metastasis and survival are anatomic site, histologic subtype, and grade.

1077 POSTER

OSAD93: A multicentric pilot study of high dose ifosfamide (HDI) and CDDP in adult patients (PTS) with non metastatic osteosarcoma

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Purpose: Based on previous results in adults (Proc. ASCO 1993, abst. 1646), a multicentric pilot study of neoadjuvant chemotherapy with HDI and CDDP was initiated in pts > 16 years (ys) with osteosarcoma, in 1993.

Methods: 4 preoperative courses (crs) of SHOC (Ifosfamide: 3 g/m^2 d1 to d3 CDDP: 100 mg/m^2 d4) were given, followed by local treatment. Post operative chemotherapy was: *1)* 3 crs of SHOC in pts with ≤10% viable tumor cells, *2)* 3 crs of HOCA (Adriblastin: 60 mg/m^2, d1 to d2; Ifosfamide: 3 g/m^2 d1 to d2, CDDP: 100 mg/m^2 d3) in pts with >10% of viable tumor cells.

Results: 59 pts were included: 14 females/45 males; median age: 28 (range: 16–64). Tumor sites were: femur (25), tibia (10), humerus (6), flat bones (15), others (3). The toxicity of pre-operative SHOC was evaluated in 213 crs. Grade 3 and 4 neutropenia, and febrile neutropenia occurred after 19%, 40% and 10% of crs respectively; growth factors were administered in 20% of crs; grade 3 and 4 thrombopenia in 11% and 5% of crs respectively; grade 3 and 4 anaemia in 9% and 4% of crs respectively; grade 3–4 vomiting occurred after 21% of crs; grade 3 infections occurred after 5% of crs; 2/3 of patients underwent grade 3 alopecia after the 4th course; hospitalisation for toxicity occurred after 20% of crs. 53 pts underwent surgery after pre-operative SHOC (45 conservative; 8 radical). The pts who had progressed before surgery were considered as poor responders. Therefore, the histological response was: 16 (29%) good responders (Huvos 3–4), 40 (71%) bad responders (Huvos 1–2). With a 33 months median follow-up, overall and progression-free survival at 4 ys are 56% and 43% respectively.

1078 POSTER

Neoadjuvant radiochemotherapy (RCT) in soft tissue sarcoma

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Purpose: To evaluate response, long-term control, functional outcome and toxicity following neoadjuvant RCT in advanced and recurrent soft tissue sacoma.

Methods: Between 1992 and 1998, a total of 23 patients in whom primary curative limb sparing surgery seemed impossible entered the study. Sixteen patients (pts) had primary and 7 pts recurrent sarcoma. The stages (UICC 1997) were: rIA (2), rIIA (5), IIA (4), IIB (2), III (7), IV (3). RCT consisted of an accelerated split-course radiation (1.5–1.6 Gy twice daily, median total dose 60 Gy, range 60–64 Gy, break of 1 week after 30 Gy) with concomitant chemotherapy using adriamycin (50 mg/m^2/d on days 2 and 30) and ifosfamide (1.5 mg/m^2/d on days 1–5, 29–33). Median follow-up was 26 months (range 2–92 months).

Results: 22 pts underwent surgery with a curative (R0) resection being achieved in 20/22 (91%) pts and gross residual (R2) tumor or unclear tumor margins (RX) in 1 pt, respectively. Effective tumor-downstagigng was documented in 4/22 (18%) pts (ypT0: 3 pts, ypT1: 1 pt). Long-term local tumor control after R0/X resection remained 100%. Delayed wound healing was only noted in 1/22 (5%) patient. Four pts developed distant metastases. Overall-, NED- and distant-metastases-free survival rates were 83%, 64% and 68%, respectively, at 3 years. Grade 3/4 neutropenia (WHO) was seen after 21/46 (46%) cycles of chemotherapy with one pt dying of sepicemia. The functional results were good to excellent in 18/22 (82%) pts.

Conclusion: Accelerated split-course radiation with 60–64 Gy and concomitant chemotherapy using adriamycin/ifosfamide is a safe and effective treatment for soft tissue sarcoma. This regimen may be considered in all cases with recurrent and advanced disease not amenable to primary curative or limb sparing surgery.

1079 POSTER

Surgical management of gastrointestinal stromal tumors (GIST)

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Purpose: Clarify the surgical treatment of GIST.

Methods: 56 patients were identified from a single institution database. Local (L) or metastatic (M) first recurrence (R) were studied according to the type of surgery: wedge resection (WR) or organ resection (OR). When stomach or rectum were resected, total (T) and partial (P) resection were compared (total/partial gastrectomy; anterior resection/rectum abdomino perineal resection)

Results: Median age was 55 years. Location: stomach (Stom) 25, duodenum (Duod) 6, small intestine (Small int.) 19, rectum (Rect) 6. 7 patients

had palliative resection because of synchronous metastasis (hepatic or peritoneal). Nodal involvement 2/56 (4%). Medium time of recurrence was 26 months. One nod recurrence was detected. Median follow-up 42 months.

	Stom. (n)	LR	MR	Rect. (n)	LR	MR	Duod. (n)	LR	MR	Small int. (n)	LR	MR	Total (n)	LR	MR
Wedge	(5)	4	0	(2)	2	0	(3)	3	0	(0)	0	0	(10)	9	0
P	(6)	0	4	(3)	1	1	X	X	X	(19)	0	15	(9)	1	5
OR T	(7)	0	4	(1)	0	0	(3)	0	1	X	X	X	(8)	0	4

Conclusion: Wedge resection should not be performed because of high rate of local recurrence and organ resection is prefered.

Each time it is possible, partial organ resection is a functionnal alternative because patients are mainly exposed to metastatic recurrence whenever partial or total organ resection is performed.

Lymph node dissection is not systematic.

1080 POSTER

Ecteinascidin (ET-743) in heavily pretreated refractory sarcomas: Preliminary evidence of activity

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ET-743 is a tetrahydro-isoquinolone of marine origin, currently in late phase I, early phase II development, with neutropenia (N) and thrombocytopenia (T) as limiting toxicities. Fatigue and reversible transaminitis (Tm) were also noticed. Antitumoral activity has been detected during the 24 hours continuous infusion (CI)-every 3 weeks schedule phase I (ASCO 1999, abst 690), which has completed accrual. We report here our current overall experience in treatment-refractory advanced sarcoma patients (pts).

Pts charact: Eleven pts (9 soft tissue sarcomas (STS) and 2 osteosarcomas (OS)) received ET-743, 10 at the recommended dose (1500 $\mu g/m^2$), one at the maximum tolerated dose (1800 $\mu g/m^2$). 9 of them were treated in the phase I trial, while 2 received ET-743 on a compassionate use basis. Sex: 6 men/5 women, median age: 37 years (16–71), median number of previous chemotherapy regimens: 2 (1–4) (all pts pretreated with anthracyclines and alkylators); median PS: 1 (0–2), median number of metastatic sites 2 (1–3).

Results: Toxicity is evaluable for the 38 given cycles. Grade 3–4 toxicities are acute reversible Tm peaking at day 3–5 (52%), N (39.5%) and T (10.5%). Febrile N occurred in 2 cycles (5%). All 11 pts are evaluable for antitumor activity. Two PR (1 ongoing), 2 MR (2 ongoing) and 3 SD (lasting >4 months) were observed. Among the 2 osteosarcomas there was 1 PR and 1 MR. ET-743 is a promising new agent for heavily pretreated refractory OS and STS. Based on this experience, a phase II program is ongoing, assessing the 1500 $\mu g/m^2$/24-hours CI schedule in such pts.

1081 POSTER

Toxicity profile of a high-dose (HD) chemotherapy regimen with peripheral blood stem cell rescue (PBSCR) for adults with soft tissue sarcoma (STS)

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Purpose: Prognosis of patients (pts) with metastatic STS is poor with conventional therapy. HD therapy combined with PBSCR may improve prognosis. We report on toxicity of a intensified chemotherapy regimen in pts with metastatic STS that responded to standard dose chemotherapy.

Patients and Methods: Thirty pts with metastatic grade II or III STS received 4 to 6 cycles of DI standard dose chemotherapy (doxorubicin 75 mg/m"; ifosfamide 6 g/m" with G-CSF day 7–14). After assessment of tumor response to DI therapy, responding pts received HD-ICE chemotherapy (ifosfamide 12 g/m", carboplatin 1200 mg/m" and etoposide 1200 mg/m") followed by PBSCR. Toxicity was monitored according to Common Toxicity Criteria.

Results: Of 30 pts on study, 17 responded to 4 cycles of DI chemotherapy (2 CR, 15 PR) and received 2 further cycles of DI chemotherapy. Up to now, 16 pts received HD-ICE with PBSCT. Pts received median 6.6 × 10^6/kg CD34+ cells (range, 2.8–14 × 10^6/kg). Median no. of days with leukocytes <1 G/l was 9 (7–12), median no. of days with platelets <20 G/l was 5 (3–18). Non-hematological toxicity con-sisted mainly in nausea and vomiting (grade 2/3, 9/7 pts) and mucositis (grade 2/3, 3/4 pts). Other grade 3/4 toxicities included hepatotoxicity (4/2 pts), or enteritis (1/0 pts). No grade 3 or 4 nephrotoxitiy or CNS toxicity was observed. All observed tox-icities were fully reversible. Median no. of day of discharge after HD-ICE + PBSCR was 13 (10–23). At last follow-up, 15/16 pts were alive with 3/16 being in CR.

Conclusion: HD-ICE chemotherapy with PBSCR in pts with metastatic STS is feasible. Toxicity of this protocol is mild. Assessment of efficacy requires further accrual and follow-up.

1082 POSTER

Activity of gemcitabine (G) in sarcoma after failure of doxorubicin-based chemotherapy

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Introduction: G has a documented activity and clinical benefit response in relatively chemo- resistant malignancies. G was found to be active on xenograft of soft tissue sarcoma growing in nude mice. Recently we reported a case where G treatment achieved long-term stabilization of an osteosarcoma resistant to doxorubicin based chemotherapy.

Patients: G was given to 14 patients with recurrent sarcoma of bone or soft tissue that was resistant to any previous therapy and beyond any further surgery or radiotherapy. Of the 14 patients, only one was asymptomatic. All underwent systemic workup and signed an informed consent.

Protocol: Weekly G 1000 mg/m^2 for 7 consecutive weeks followed by one week rest, followed by 3-weekly every month until lack of effect.

Results: Three objective responses were observed: one partial response in lung metastases of leiomyosarcoma of the uterus, one minimal response in case of osteosarcoma of the pubis, and one minimal response in case of angiosarcoma of the face. Clinical benefit responses were observed in 80% of the symptomatic patients, manifested by reduction in narcotic consumption, improvement of performance status and well being. Toxic events included myelotoxicity, rash, and limb edema, but none were serious nor required hospitalization.

Conclusions: G was found to be effective in achieving some responses and stabilization of sarcomas refractory to standard-chemotherapy.

1083 POSTER

Phase II study with prolonged infusion gemcitabine in pretreated advanced soft tissue sarcomas of the adult

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Purpose: The objectives of this phase II trial of gemcitabine were to estimate the reponse rate and to define the toxicities of gemcitabine administered as a prolonged infusion in pretreated patients (pts) with advanced soft tissue sarcomas.

Methods: Pts were eligible if they had locally advanced and/or metastatic, progressive, pretreated soft tissue sarcomas. Only one of the pts had a response to previous chemotherapy/-ies which consisted of at least one anthracycline and/or ifosfamide based regimen. Gemcitabine was administered at a low dose of 200 mg/m^2 as a 360-minute infusion once a week for 3 consecutive weeks followed by a week of rest. Eighteen pts (aged 20–70 years; median 58) with a median Karnofsky score of 80 (40–100) were enrolled, and 17 are fully assessable, to date.

Results: A total of 183 gemcitabine (range 3–24; median 9) applications were given to these 17 pts. Two pts (11.7%) who had only pulmonary matastases had a partial remission (PR) lasting 5 and 5+ months, respectively. One further patient also had a PR of lung metastases and other stable metastatic sites. Six pts had stable disease for 3–6 months. Toxicities were moderate and fully reversible, and included leucopenia grade 3 (n = 4)/grade 4 (n = 1), thrombocytopenia grade 2 (n = 2)/grade 4 (n = 1), anemia grade 2 (n = 3), liver toxicity grade 2 (n = 2)/grade 3 (n = 3), nausea/vomiting grade 2 (n = 3), and edema grade 2 (n = 2)/grade 3 (n = 3).

Conclusion: Prolonged infusion of low dose gemcitabine has some activity in heavily pretreated pts with advanced soft tissue sarcomas and is well tolerated.