

Methods: From 1993 until 1996 17 patients (pts.) with primary (N = 11); recurrent (N = 4) or metastatic (N = 2) soft tissue sarcomas were treated with preoperative concurrent radio-chemo-therapy (RCT). Sarcomas were localized in the extremities (N = 10); the trunk (N = 4); head and neck region (N = 2) and in the penis (N = 1). Chemotherapy consisted of ifosfamide 1.5 mg/m² and mesna (d 1–5 and 29–33) as well as adriamycin 50 mg/m² (day 2 and 30). Accelerated-hyperfractionated radiotherapy (RT) was applied in 2 fractions/d of 1.5 Gy up to 56 to 60 Gy (day 1–45; after 30 Gy 1 week RT-break). After 4–8 weeks residual tumour mass was excised according to the guidelines of oncological surgery.

Results: Following neoadjuvant RCT 16/17 patients were treated by surgery. All the 16 pts had a histologically complete resection (R0). In 4/16 pts (25%) there was no vital tumour in the specimen. Limb sparing surgery was possible in 7/10 pts. Myelosuppression was most prominent with leucopenia grade 4 in 6/17 and grade 3 in 4/17 pts; thrombocytopenia in grade 3 in 2/17; grade 4 in 1/17. Skin toxicity was grade 3 in 5/17 and grade 4 in 1/17.

Conclusion: Preoperative RCT is feasible with acceptable toxicity. First results indicate that perhaps more R0 resections may be possible compared to surgery alone.

496

POSTER

Serum levels of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) in patients (pts) with soft tissue sarcoma (STS)

U. Graeven¹, E.G. Achilles², M. Peiper², C. Knabbe³, C. Zornig², W.H. Schmiegell¹. ¹Dept. of Medicine, University Hospital Knappschaftskrankenhaus, Bochum; ²Dept. of General Surgery; ³Dept. of Clinical Chemistry, University Hospital Eppendorf, Hamburg, Germany

Purpose: To determine if elevated circulating levels of VEGF and bFGF can be detected in sera from pts with STS.

Methods: 18 healthy controls and 55 STS pts were enrolled in this study. In STS pts sera were drawn prior to initial resection (IR) n = 31 or prior to wide reexcision (WR) 2–4 weeks after inadequate local excision n = 24. VEGF and bFGF levels were determined by ELISA.

Results: Mean levels pg/ml (range) for VEGF and bFGF in healthy controls were 167 (22–404) and 3 (1–9). In STS pts with IR, VEGF levels were 628 (64–2000) and bFGF levels 16 (1–50). 17 STS pts with evidence of disease after WR showed following serum levels: VEGF 515 (44–2000), bFGF 26 (1–78). For 7 STS pts with no evidence of disease after WR the VEGF and bFGF levels were 350 (94–1150) and 23 (1–58).

Conclusion: Elevated VEGF and bFGF levels can be detected in sera from STS pts. Consecutive monitoring of VEGF and bFGF in the serum of STS pts might be a valuable new marker to monitor the tumor follow up.

497

POSTER

Intraoperative (IORT) and external beam radiotherapy (EBRT) for extremity sarcomas

M.J. Eble¹, Th. Lehnert², M. Schwarzbach², V. Ewerbeck³, Ch. Herfarth², M. Wannenmacher¹. ¹Dept. of Radiotherapy; ²Dept. of Surgery; ³Dept. of Orthopedics, University of Heidelberg, Germany

Purpose: IORT offers maximum sparing of mobile radiosensitive tissues. Organs and tissues of the extremities are less radiosensitive. Nevertheless the minimum effective dose for soft tissue sarcomas should be >66 Gy. Late complications and subsequent limb function are related to dose and irradiated tissue volume.

Patients and Methods: 25 patients (mean age 51.5 years), suffering from a stage IIB–IIIB extremity sarcoma had IORT between 7/91–5/95 (recurrent sarcomas n = 10). 4 pat. revealed microscopically residual disease after surgery. IORT dose was 15.3 Gy (15–20 Gy), using a field size 5–26 cm. Mean EBRT dose was 44 Gy.

Results: After a median follow-up of 28.8 months a 92% local control rate could be achieved. The local control rate was independent of the extent of surgical margins and tumor stage. 2 pat. had a lymph node failure, 5 pat. a distant failure. The actuarial overall and disease-free survival was 77% and 58% at 4 years. Perioperative morbidity occurred in 17% of pat., requiring additional surgical treatment in 11% of pat. In 14% of patients a late adverse effect was observed.

Conclusion: Combined surgical resection and IORT for locally advanced extremity sarcomas can provide excellent local control. In view of the reduced late morbidity with subsequent good limb function, the results are encouraging.

498

POSTER

Retroperitoneal sarcomas – Prognostic value of ploidy and other important factors

K. Herman, A. Gruchala. Centrum Onkologii, Kraków, Poland

Purpose: Grading and type of surgery are very important for prognosis in all types of sarcomas. For the better understanding of outcomes and possibilities of treatment retrospective analysis of different factors, including DNA content, was performed in retroperitoneal sarcomas.

Methods: The study was based on 70 patients treated between 1965 and 1994. Leiomyosarcoma and liposarcoma were most common histologic type of classified sarcomas. Different kinds of resection were performed in 49 patients and 33 of theirs available DNA specimens were analysed.

Results: The actuarial 5-years survival rate in resection group was 53% with the median survival of 57 months (compared with 10 months without resection). Patients with diploid resected tumours had better 5-years survival rate (58%), than with aneuploid (25%) – P < 0.005. Patients with grade I and II sarcomas had a significantly longer survival than with grade III (5-years survival rate 44% compared with 29%). There was no influence of adjuvant therapy, histology, type of surgery, localisation of tumour and S-phase on survival in the univariate analysis. In the multivariate analysis (Cox), only ploidy was independent prognostic variables for survival. Relative risk of death was over 3 times higher for aneuploid than for diploid tumours.

Conclusion: The DNA content analysis is an important prognostic factor, which should be performed in every case of retroperitoneal sarcoma for better follow-up and possibility of adjuvant therapy.

499

POSTER

Ifosfamide (IFO) in continuous infusion (C.I.) for 21 days as second line therapy in advanced sarcomas: A phase I study

A. Comandone, A. Boglione, O. Dal Canton, P. Bergnoli, C. Oliva, C. Buma. Division of Medical Oncology, S. Giovanni Antica Sede Hospital, Torino, Italy

Ifosfamide is an alkylating agent active in advanced soft tissue and bone sarcomas. Generally we distinguish between conventional doses and high doses (from 10 to 15 g/sqm for cycle). High doses, delivered in 4–5 days, of c.i. must be reserved to good P.S. pts and request CSF support. In poor P.S. pts or as a second-line therapy, the same total dose can be administered in longer time in order to avoid heavy toxicities with a comparable relative dose intensity. From this rationale, we planned a 21 days-therapy using a low-daily-dose (1 g/sqm). The solution including Ifo and Mesna (1 g/sqm/day equidose), was administered by portable pump as outpatient therapy. Pump was changed every 3 days and the course should be completed at 21st day. Therapy was discontinued until recovery when neutrophil counts was <1500/mm³ or creatinine >1.5 mg/dl. 6 patients (3 male, 3 female) with advanced soft tissue and bone sarcomas, relapsed after first line CT, entered the study. Mean P.S. was 1 and mean age was 37.5 years (median 35). 15 courses were administered (mean 2.5, median 3). No course was completed in 21 days. Only one was completed in 28 days and 14 in more than 28 days. Definitive D.I. was 63%. The delay was due to grade 3 but rapidly recovering myelotoxicity. No other side effects were seen. Generally toxicity appeared after 15 days of c.i. We recorded 1 CR (pelvis relapse of Ewing sarcoma), 1 PR and 4 PD.

Conclusions: Low doses of Ifo as a c.i. in advanced sarcomas seems to be a promising therapy with a good activity and a mild toxicity. However, 21 days c.i. is too much for pretreated patients; in a new protocol we'll use the same daily dose but only for 15 days infusion.

500

POSTER

Evidence of circulating tumor cells of Ewing's sarcoma is associated with higher incidence of local relapse and metastatic spread

J. García-Foncillas¹, P. Philip², M.S. Huárriz¹, M.J. Martínez¹, M.G. Guzmán¹, A. Brugarolas¹. ¹Molecular Oncology Laboratory, University Hospital of Navarra, Pamplona, Spain; ²Michigan Cancer Foundation, Wayne State University, Detroit MI, USA

Background: Different variables have been studied to predict the probability of recurrence and metastases in patients diagnosed of Ewing's sarcoma. In this study, we have evaluated the presence of tumor cells of Ewing's sarcoma (ES) in peripheral blood samples through a reverse-transcriptase polymerase chain-reaction (RT-PCR).

Material and Methods: Forty-two patients diagnosed of localized Ewing sarcoma have been recruited. RNA was extracted from peripheral blood samples. RT-PCR was performed according to detect the EWS/FLI1 fusion mRNA.

Results: From forty-two patients, 16 were RT-PCR positive for EWS/FLI1. Nine of these 16 patients (56.25%) showed distant metastatic disease with a median follow-up of 20 months (10–33) and 3 relapsed locally (18.75%). From the 24 patients with no evidence of circulating tumor cells, 5 patients developed metastatic disease (20.8%) with similar follow-up and 2 patients showed local recurrence (8.3%).

Conclusions: These data suggest that the detection of circulating tumor cells could define a group of patients with a significant higher rate of local failures and/or metastatic spread.

501

POSTER

Growth pattern and development of metastasis in orthotopically transplanted human osteosarcoma xenografts in nude mice

S. Cmalic¹, L.-Å. Broström¹, L. Boqvist², R. Löfvenberg¹. ¹Department of Orthopedics; ²Department of Pathology, Umeå University Hospital, Umeå, Sweden

Purpose: Experimental tumor models which resemble the clinical situation could be valuable in evaluation new treatment strategies in vivo. The aim of the present study was to establish a new human osteosarcoma spontaneous metastasis model using orthotopic transplantation of histologically intact tumor tissue into the tibia of nude mice.

Methods: Subcutaneously growing human osteosarcoma xenografts from the 32nd serial passage was used in the experiment. Solid tumor pieces were implanted into the proximal tibia in 31 nude mice. The animals were sacrificed and autopsied at 2, 4, 6, and 8 weeks after transplantation. The mice were examined macroscopically and microscopically for local tumor growth and metastases.

Results: Intratibial bone tumors were found in all mice at the site of the implantation. The tumors were radiographically and histologically similar to primary human osteosarcoma. Lung metastases were observed in all mice, local and distant lymph node metastases in 15 (48%), and liver metastases in 6 (19%) mice. The microscopic appearance of the metastases was similar to that observed in the donor patient's tumor, corresponding subcutaneous xenografts and orthotopically transplanted intratibial tumors.

Conclusion: Since local tumor growth were found in all animals and spontaneous metastasis were observed in several mice this model seems suitable for further studies on local tumor growth, formation of metastasis and antitumor therapy.

502

POSTER

Intraoperative radiotherapy (IORT) in soft tissue sarcoma

A. Kretzler¹, R. Stepan¹, E. Biemer², M. Molls¹. ¹Klinik für Strahlentherapie; ²Abteilung für Plastische Chirurgie, Technische Universität Munich, Germany

Purpose: In high risk patients with soft tissue sarcoma, percutaneous radiotherapy after extremity preserving surgery is the standard treatment. Local control can probably be improved by intraoperative radiotherapy. There is no data available concerning the function of thus treated extremities. The aim of this work was the evaluation of patients with soft tissue sarcomas (STS) of the extremities after IORT with respect especially to local control and function of the extremity.

Methods: From 1986–1996, 23 patients (T1: 6x, T2: 17x; recurrences: 11x) were irradiated intraoperatively (12–15 Gy) and postoperatively (40–60 Gy). The course of disease was evaluated retrospectively by interviews of the patients, their relatives and treating physicians as well as evaluation of radiotherapeutical and surgical files. The function of the extremity was analysed by a standardised questionnaire and examination.

Results: Local control was obtained in 18 of 23 patients (78%). Survival rate was 65% (15/23 patients) after a mean observation period of 36 months (1–72). 7 of 20 patients who were initially free of distant metastases, developed distant disease. Of 15 patients alive, 11 patients revealed excellent function of the extremity or had only minor functional deficits.

Conclusion: The addition of intraoperative radiotherapy to routine treatment in high risk patients with STS of the extremity achieved 78% local tumour control during a mean of 36 months observation time. Compared to historical data, this could point towards improved local control. The functional result was excellent with no or minor deficits in 11 of 15 patients alive.

503

POSTER

Morbidity of a combined modality therapy of Intra-arterial doxorubicin, neoadjuvant radiotherapy and surgery for locally advanced high grade soft tissue sarcomas (STS) of the extremities

P. Nijhuis, E. Pras, D. Sleijfer, W. Molenaar, H. Schraffordt Koops, H. Hoekstra. Department of Surgical Oncology, Groningen University Hospital, Netherlands

Intra-arterial doxorubicin, neoadjuvant radiotherapy, and surgery was introduced as limb-saving treatment for "unresectable" high grade STS of the extremities.

Patients and Methods: Between 1982–1986 11 pts, 9 ♂ and 2 ♀, median age 52 (range 24–70) yrs, with "unresectable" grade III STS of the extremities were treated by preoperative i.a. infusion of doxorubicin for 3 consecutive days (daily dose 20 mg/m²). Within 24 hours after infusion preoperative XRT of the compartment (10 × 350 cGy) started. After chemo-radiotherapy the tumor was resected. Non-radical resections received 20–30 Gy XRT (9 pts).

Results: No local recurrences (median fu 110); pulmonary met's in 5 pts (45%). Local skin toxicity due to doxorubicin in 3 pts (27%). Preoperative 35 Gy XRT was well tolerated. Limb-saving treatment in 10 pts (91%); in 1 an exarticulation of the hip had to be performed. Three of the 5 longterm survivors (fu > 10 yrs) developed a severe fibrosis of the affected limb (60%). Two severe longterm complications: a stress fracture of the affected femur (91 months), and a severe radiation-induced motor and sensory neuropathy of the sciatic nerve.

Conclusion: The longterm results show a limb-saving rate of 91%, without increasing the risk of a local recurrence. Especially the longterm morbidity is extremely high (60%). This combination therapy should therefore no longer be advocated.

504

POSTER

Conservative possibilities of treatment in sarcoma of the limbs

Th. Ionescu¹, S. Ionescu Goga², M. Ionescu-Goga³, C. Dragosloveanu¹, N. Mihailescu. ¹Orthopaedic Clinic Foisor Hospital Bucharest; ²Oncological Institute Bucharest, Romania; ³University Paris VII, France

The study underlines the value of neoadjuvant and postoperative chemotherapy in the aim to realize a successful conservative surgery in locally-advanced sarcoma (LAS) of the limbs.

From oct. 1990 to dec. 1996 we treated 165 non metastatic sarcoma of the limbs: 96 osteo and chondrosarcoma (OS) and 69 soft tissue sarcoma (STS). From 165, 97 cases with LAS received after biopsy 3–4 courses of neoadjuvant chemotherapy with CIVADIC. 92% of all cases were submitted to conservative surgery: extensive bone surgery, with bone grafts or articulation prosthesis in OS; wide excision in 48% and marginal surgery in 45% of STS. Postoperative chemotherapy 6–8 courses with cisplatin, farnorubicin in OS (CDDP 100 mg/m², farnorubicin 70 mg/m²) and CIVADIC (cyclophosphamide 500 mg/m², vincristine 1 mg/m², farnorubicin 70 mg/m², DTIC 250 mg/m²/day × 2), alternating with CIVADACT (actinomycin D 500 γ/day × 3) in STS. The tolerance to chemotherapy was good with mild manageable side-effects. In the cases with marginal surgery, compartmental radiotherapy was performed with 50 Gy plus local boost. The median follow-up was 4 years. The disease free survival was 8–24 months.

In conclusion, even in the LAS of the limbs complex treatment chemo-radiotherapy makes possible a conservative surgery with good, long lasting results.

505

POSTER

Neoadjuvant long-term continuous intra-arterial chemotherapy of soft tissue sarcomas

B.Y. Bokhian. Department of General Oncology; Cancer Research Center; Moscow; Russian Federation, Russia

Purpose: The efficacy of preoperative long-term continuous intra-arterial infusions of cisplatin (CDDP)+adriamycin (ADR) was investigated.

Methods: 26 patients (15 M., 11 F, mean age 40 years) with soft tissue sarcomas of the extremities (15 synovial sarcomas, 8 malignant fibrous histiocytomas, 3 nonclassified sarcomas) were included in this study. All patients had extracompartmental lesions, tumor size >8 cm, volume >100 cm³. The schedule of chemotherapy consisted of a 5-day