304 POSTER

Biologic activities of trail in soft tissue sarcoma cell lines: induction of apoptosis and interaction with cytotoxic agents

S. Tomek[1], T. Brodowicz[1], W. Koestler[1], I. Pribill[1], A. Peffer[1], A. Budinsky[1], M. Krainer[1], C.C. Zielinski[1,2]. [1] *Vienna University Hospital, Dep. of Internal Medicine I, Div. of Oncology, Vienna, Austria;* [2] *Ludwig Boltzmann Institute for Clinical Experimental Oncology, Vienna, Austria*

The Tumor Necrosis Factor (TNF)-related apoptosis-inducing ligand (TRAIL or Apo2L) constitutes a member of the TNF cytokine family. In contrast to TNF, TRAIL induces apoptosis in a variety of cancer cell lines without affecting normal cells. TRAIL interacts with the pro-apoptotic death receptors TRAIL-R1, p53-regulated TRAIL-R2 as well as with the decoy receptors TRAIL-R3 and TRAIL-R4.

In the present study, we analyzed 5 human STS cell lines (HTB-82 [rhabdomyosarcoma], HTB-91 [fibrosarcoma], HTB-92 [liposarcoma], HTB-93 [synovial sarcoma] and HTB-94 [chondrosarcoma]) for expression levels of TRAIL-R1, -R2, -R3, and -R4 and of apoptosis- modulating proteins FLICE - like inhibitory protein (FLIP), osteoprotegerin (OPG) and bcl-2 as well as for TRAIL-, doxorubicin- and paclitaxel- induced apoptosis.

TRAIL induced significant apoptosis (>90%) in HTB-92 and HTB-93 STS cells, whereas no effect was observed in HTB-82, HTB-91 and HTB-94 STS cells.

Expression levels of TRAIL-R1 mRNA were high in TRAIL-sensitive HTB-92 and HTB-93 STS cell lines, as compared to low or undetectable levels in TRAIL-resistant HTB-91 and HTB-94 STS cell lines. However, TRAIL-R1 mRNA as well as TRAIL-R1 protein expression was detected in TRAIL-resistant HTB-82 cells. TRAIL-R2, -R3, -R4 mRNA expression did not correlate with TRAIL sensitivity. Based upon these data, it can be concluded that the sole pattern of TRAIL-receptor expression did not predict for TRAIL-sensitivity or -resistance. Furthermore, no correlation of the presence of FLIP, OPG or bcl-2 with resistance to TRAIL was seen in the present model.

Doxorubicin weakly induced apoptosis (<40%) within the panel of tested STS cell lines. However, co-incubation of TRAIL-resistant HTB-82, HTB-91 and HTB-94 STS cells with doxorubicin plus TRAIL was able to overcome apoptotic resistance to either agent alone. In TRAIL-sensitive cell lines the combination of TRAIL with doxorubicin or paclitaxel achieved an additive effect. TRAIL-induced apoptosis occurred independently from wild-type p53, as assessed by sequence analysis.

Based upon the present data, the clinical application of TRAIL/Apo2L in combination with the mentioned cytotoxic agents in patients with soft tissue sarcoma might be considered.

305 POSTER

Docetaxel as rescue medication in anthracycline- and ifosfamide-resistant locally advanced or metastatic soft tissue sarcoma: results of a phase II trial

W.J. Koestler[1], T. Brodowicz[1], Y. Attems[1], S. Tomek[1], M. Hejna[1], W.C.C. Fiebiger[1], G. Amann[2], C. Wiltschke[1], M. Krainer[1], C.C. Zielinski[3]. [1] *Clinical Division of Oncology, Dept. Internal Medicine I, University Hospital, Vienna, Austria;* [2] *Clinical Institute for Clinical Pathology, University Hospital, Vienna, Austria;* [3] *Chair for Oncology, Department of Internal Medicine I, University Hospital, Vienna, Austria*

Background: Metastatic soft tissue sarcoma not amenable for curative surgery has a dismal prognosis. Aggressive treatment with anthracyclines and ifosfamide represents the current therapeutic mainstay in these patients, most of whom succumb to relapses. Thus, the efficacy of subsequent therapeutic approaches has to be weighed against toxicity caused by palliative treatment.

Patients and Methods: Patients with locally advanced or metastatic soft tissue sarcoma refractory to treatment with anthracyclines and ifosfamide were enrolled into the present phase II study. Patients were assigned to receive docetaxel at 100 mg/m2 every three weeks. In case of severe toxicity or inadequate bone marrow reserve, patients were switched to a weekly schedule of docetaxel (40mg/m2).

Results: A total of 106 cycles (80% at the scheduled 100mg/m2 dose level) were administered in 27 patients. Partial response was observed in 4 (15%) patients and 4 (15%) patients experienced disease stabilization. After a median observation period of 21.0 (range: 4 to 44.4) months median progression free survival and overall survival were 2.4 (range: 0.9-23.9) and 7.7 (range: 1.0-44.3) months, respectively, with 10 (37%) patients still being alive at the time of analysis. In patients with PR or SD median OAS was 21.1 (range: 4.7-44.3, 95% CI 8.7-35.6) months vs. 6.5 (range: 1.0-30.9, 95% CI 4.4-11.6) months in patients with PD (p<0,02). Upon renewed progression, three patients initially responsive to treatment with docetaxel were successfully reinduced by treatment with docetaxel. The safety profile of docetaxel was tolerable and the administration mostly manageable on an outpatient basis.

Conclusions: Our results suggest that docetaxel represents an efficacious and tolerable treatment in a minority of patients refractory to standard treatment. There is a need for better identification of patients most likely to benefit from salvage treatment with docetaxel.

306 POSTER

Adult rhabdomyosarcoma: Outcome and prognostic factors

D. Little[1], M. Ballo[1], G. Zagars[1], A. El-Naggar[2], A. Garden[1], S. Patel[3], R. Benjamin[3], P. Pisters[4]. [1] *UT MD Anderson Cancer Center, Radiation Oncology, Houston, USA;* [2] *UT MD Anderson Cancer Center, Pathology, Houston, USA;* [3] *UT MD Anderson Cancer Center, Sarcoma Medical Oncology, Houston, USA;* [4] *UT MD Anderson Cancer Center, Surgical Oncology, Houston, USA*

Purpose: To determine outcome and prognostic factors for adult patients with rhabdomyosarcoma.

Methods and Materials: From 1960 to 1998, 82 adult patients with non-metastatic rhabdomyosarcoma were treated with surgical resection and radiation or radiation alone, with or without adjuvant chemotherapy. All patients were 17 years of age or older and the diagnosis was confirmed by pathologic review. Histological sub-type was as follows: embryonal, 28 patients; alveolar, 19; and pleomorphic, 35. Radiation was delivered preoperatively (median, 50 Gy) to 10 patients, postoperatively (median, 60 Gy) to 34 patients and alone (median, 60Gy) to 38 patients. Chemotherapy was given to 61 patients: induction in 28 patients and adjuvant in 33 patients.

Results: At a median follow-up of 10.5 years, 47 patients (57%) developed disease relapse. The 10-year actuarial overall and disease-free survival rates were 40% and 40%, respectively. The 10-year actuarial local, nodal and distant control rates were 75%, 82%, and 52%, respectively. Univariate analysis revealed that tumor size >5cm predicted for decreased actuarial 10-year metastasis-free (32% vs.73%, p=0.0002), disease-free (26% vs. 56%, p=0.003) and overall survival (35% vs. 47%, p=0.07) rates. The significance of tumor size remained on multivariate analysis. Univariate analysis revealed an inferior actuarial 10-year local control rate in those patients treated with radiotherapy alone after biopsy (68% vs. 79%, p=0.09) and those with head and neck primary sites (63% vs. 89%, p=0.02). On multivariate analysis head and neck primary site remained the most important predictor of decreased local control. Amongst the sub-group of patients treated with radiotherapy alone there was an improved local control rate if there was a response (complete or partial) to neo-adjuvant chemotherapy (p=0.007) and if radiation doses were >60Gy (p=0.09). No factor, including presence or absence of nodal disease or treatment of nodal disease correlated with subsequent nodal recurrence. The actuarial 10-year radiation-related complication rate was 19%, and appeared to be more common at doses >60Gy (p=0.08).

Conclusion: Rhabdomyosarcoma in adults is an aggressive disease with high distant metastasis rates, particularly for tumor size >5cm. Local control appears superior in those patients undergoing surgical resection and radiation. For those patients with unresectable primary disease radiation doses >60Gy are required.

307 POSTER

Factors predicting survival of patients with retroperitoneal soft-tissue sarcoma; does surgical experience influence survival?

T. van Dalen, H. Hoekstra, F. van Coevorden, A. van Geel, A. Hennipman. *Dutch Soft Tissue Sarcoma Group, Utrecht, The Netherlands*

Purpose: Surgery is the principle modality of therapy in the management of retroperitoneal soft-tissue sarcomas (RSTS). Individual experience is usually limited and may be of prognostic importance. Among other possible prognostic factors the influence of surgical experience on outcome was studied in a population based study in the Netherlands.

Methods: With help of the Dutch Network and National Database for Pathology (PALGA), data were collected on 143 patients in the Netherlands in whom a RSTS was diagnosed between 1-1-1989 and 1-1-1994. Median age was 60 (range 18-88) years, there were 79 females (55%). Follow-up was done until 1999. The prognostic importance of tumour-and treatment related factors was evaluated.

Results: After a median follow-up of 84 months, 5-year survival for all patients was 39%. Univariately, complete resection (p<0.001), age < 60

yr. (p<0.001), low malignancy grade (p=0.02), lipomatous histomorphology (p=0.003), non-invasive growth (p<0.001), and the absence of distant metastasis (p=0.005) were associated with favourable outcome. Malignancy grade, and the extent of surgical treatment remained independent prognosticators in a multivariate context. The level of experience was associated with a higher rate of radical resections (p=0.009), but did not affect outcome.

Conclusion: Survival of patients with RSTS was determined independently by the extent of surgery, and malignancy grade. The level of experience, although influencing the result of surgery, did not affect long term outcome.

308 POSTER

Long term results of expanding prostheses for limb salvage surgery of children

G. Delepine[1], F. Delepine[2], S. Alkallaf[1], B. Markowska[1], N. Delepine[1]. *[1]Oncologic Ped. Sce Hop. Avicenne, 125 rue stalingrad, 93009 Bobigny; [2]5 passage du bon Pasteur, 76000 Rouen, France*

Introduction: Conservative surgery for young children with bone sarcoma of lower limb remains a challenge. In 1985 we proposed an expandable prosthesis and present here our long-term results.

Patients: 44 patients (20 males and 24 females aged 4–28 years) with tumors of the limbs were treated by our team between 1984 and 1999. Histology was mostly osteosarcoma (32) and Ewing's sarcoma (9). Locations were distal femur in 30, upper tibia in 5, total femur in 5 and proximal femur in 4.30 were first hand patients (28 with localized disease and 2 already metastatic) en bloc resection. The 14 other patients were referred to us after induction therapy, with progressive disease, metastase (3) or local recurrence (1).

Method: In 14 patients the expanding prosthesis was inserted immediately after the resection, in 8 during the following year and for the 22 other patients later on to treat a length discrepancy. 107 sequences of lengthening have been performed in 40 patients. All patients were followed up by their surgeon and their chemotherapist every 3 months during 2 years, then every 6 months for 2 other years and yearly thereafter.

Results: 6 patients died from illness. All other are disease free survivors with a median follow up of 91 months (maximal 192 - minimal 6). Half (22) of the patients are adults. The average lengthening is 4.07 centimeters (minimal 0.5 - maximal 12). Half of the patients had to be reoperated for complications. Deep infection occurred in 10 patients (22%) resulting in amputation for 3 of them. According to EMSOS criteria the functional result is excellent in 14, good in 15, fair in 10 and poor in 5.

Conclusion: Long term results of lengthening prostheses confirm that this procedure is an excellent alternative to amputation and permit to keep a functional limb in nearly 90% of patients. The most severe complication is deep infection underlining the interest of last generations of grower with minimally invasive lengthening.

309 POSTER

Intraperitoneal chemotherapy (IPC) after complete resection of peritoneal sarcomatosis (PS): Results of a monocentric randomized study

A. Cavalcanti, S. Bonvalot, D. Elias, P. Terrier, D. Vanel, C. Lepechoux, A. Le Cesne. *Department of Surgery, Institut Gustave Roussy, 94805 Villejuif, France*

Purpose: In order to decrease locoregional relapse after complete resection of PS, the role of IPC was prospectively evaluated.

Methods: Patients (pts) with complete resected PS were randomised between adjonction of IPC or not. IPC consisted of Doxorubicin, 0.1 mg/kg and Cisplatine, 15 mg/m^3 every day for 5 consecutive days.

Results: Thirty-eight consecutive pts have been enroled in the study, 19 in each group (IPC–, IPC+) with a M/F sex ratio of 14/24. Median age was 58 (39 to 72) and 48 yrs (31 to 71) in IPC– and IPC+ group respectively. Ratio of retroperitoneal (RPS) and visceral (VS) sarcomas were 9/10 and 6/13 in IPC– and IPC+ group respectively. Histoprognostic grade were similar in both groups. Sugarbaker score of sarcomatosis were 13 (3, 27) and 13.7 (2, 20) in IPC– and IPC+ respectively. Mean number of resected organs in each group (IPC–, IPC+) was 3.1 and 2.7 respectively. There was no toxic deaths and morbidity was similar in both groups (4 pts in each group). Median time of hospitalization was 22 days (range 11 to 39) for IPC– and 24 days (range 15 to 42) for IPC+. The median follow-up is 36 months. The median local relapse-free, metastatic relapse-free survival and overall survival were identical in both groups, 12.5, 18 and 29 months respectively with no difference between RPS and VS.

Conclusion: Addition of IPC did not modify outcome of pts after complete resection of RPS and VS. OS and DFS of this study are similar to those observed in phase II studies combining IPC with hypertermia. An optimal surgery of PS remains the only pronostic factor for survival.

310 POSTER

Efficacy of the neoadjuvant chemotherapy with regional hyperthermia in high-risk soft tissue sarcomas. 1

B. Bokhyan, S. Ivanov, R. Karapetyan, A.S. Tkachov. *N.N. Blokhin Russian Cancer Research Centre., Kashirskoe sh. 24, Moscow 115478, Russian Federation*

Purpose: The efficacy of neoadjuvant thermochemotherapy was investigated.

Methods: We report the results of phase I/II studies of treatment of 22 patients with II and III grade extremities soft tissue sarcoma (STS). All patients had extracompartmental lesions, tumour size > 8 cm (mean 12 cm). Mean tumour volume was 540 cm^3. The preoperative chemotherapy with Cisplatin (DDP) 120 mg/m^2 and Adriamicin (ADR) 90 mg/m^2 (1 day) for 6 weeks (2 cycles) combined with 2 fraction of regional hyperthermia (RHT), (60 min., 43.0° C.) day 1, 3.

Results: Limb - saving surgery was performed in 19 (86.4%) cases consisting of wide compartmental excision of the tumour. Mutilating surgery was performed in 3 cases. Treatment efficacy was assessed by clinical, morphological response and follow - up for systemic and local relapse. The efficacy rate was 50% or more. The mean tumour necrosis (>70% cells) rate in the resected specimens was 81.8%. There was no correlation between the histological response and the observed reduction in tumour volume. Postoperative complications were observed in ten (45.5%) patients; among these, 4 patients developed wound infection that required surgical treatment as a complication of surgery performed in the early stage following the preoperative treatment. After a mean postoperative follow-up of 27 months, distant metastasis occurred in six (27.3%) patients resulting in 5 fatalities. The three-year cumulative survival rate was 64.3%. No local recurrence was observed in any patient during the follow-up, thus confirming our hypothesis that DDP + ADR + RHT treatment has an excellent local efficacy.

Conclusions: The results of this study suggested that DDP + ADR + RHT was an effective local treatment for limb salvage in limb-threatening STS. We think that it would be valuable to conduct, at many facilities, phase III studies on the treatment of soft tissue sarcoma by a combination of surgery and preoperative multidisciplinary treatment using hyperthermia.

311 POSTER

Neoadjuvant chemotherapy in limb soft tissue sarcoma: the significance of C-ERBB-4 expression

O. Merimsky[1], J. Issakov[2], V. Soyfer[1], I. Schwartz[2], Y. Kollender[3], J. Bickels[3], I. Meller[3], M. Inbar[1]. *[1]Tel-Aviv Medical Center, Oncology, Tel-Aviv, Israel; [2]Tel-Aviv Medical Center, Pathology, Tel-Aviv, Israel; [3]Tel-Aviv Medical Center, Orthopedic Oncology, Tel-Aviv, Israel*

Purpose: ErbB-4 is a recently described member of the epidermal growth factor receptor (EGFR) family. Relatively little is known about the expression of erbB-4 in human tumors. In the present study we assessed the possible role of c-erbB-4 expression product as a tissue marker for STS, and its correlation with the response to chemotherapy.

Patients: The histological specimen of 29 patients with STS of a limb who had received preoperative doxorubicin-based chemotherapy were studied. The extent of tumor necrosis was evaluated histologically. Paraffin blocks of preoperative incisional biopsy were available for immune staining (avidin-biotin-peroxidase technique) from 29 patients, and blocks of the surgical specimen after pre-operative chemotherapy were available from 27.

Results: The objective response rate to preoperative chemotherapy was 34%. Wide resection of the tumor was feasible in 12 patients, marginal resection in 14 cases, amputation in 2 patients with disease progression, and no surgery in one case. The tumor necrosis was above 90% in 9 patients, 60-90% in 12, and less than 60% in 7 patients. An increase in C-erbB-4 expression was more common in cases with no response to chemotherapy, while no change of or decrease in C-erbB-4 was more common in responsive tumors (p=0.004). No correlation could be found between the degree of necrosis or the chemotherapeutic regimen and the change in expression of c-erbB-4. The median DFS was longer for patients with a decrease or no change in expression of C-erbB-4 than for patients with increased expression.