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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.

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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.

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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.

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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