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Antiangiogenetic therapy with pioglitazone, rofecoxib and metronomic trofosfamide in advanced malignant vascular tumors

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Purpose: Systemic therapy options for advanced angiosarcomas are limited and the prognosis is infaust. The idea of angiostatic therapy following the paradigm of metronomic dosed chemotherapeutics combined with pro-apoptotic biomodulators has not yet been considered in these patients. Therefore, in a phase-II-study, the efficacy of metronomically scheduled low dose trofosfamide in combination with the PPARγagonist pioglitazone and the selective COX-2 inhibitor rofecoxib was evaluated in advanced vascular malignancies.

Experimental Design: Six patients with advanced and pretreated, but progressive malignant vascular tumors (5 angiosarcomas and 1 haemangioendothelioma) received a combination of pioglitazone (45 mg/d p.o.) plus rofecoxib (25 mg/d p.o.) and after 14 days additionally trofosfamide (3 x 50 mg/d p.o.). The therapy was administered continuously until progression was observed. If necessary, doses were modified according to side effects.

Results: Two patients responded with complete and one with partial remission, three achieved stable disease. Median progression free time was 7.7 month (2-15 month). Side effects were generally mild (WHO grade 1-2). Hospitalisation was not necessary.

Conclusions: This new triple combination of low-dose metronomic trofosfamide, pioglitazone and rofecoxib might represent a feasible new alternative in the palliative treatment of advanced malignant vascular tumors.

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Preliminary results of a phase I study of rhumab VEGF (bevacizumab) with concurrent radiotherapy (XRT) and capecitabine (CAP) in locally advanced pancreatic cancer

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Background: Bevacizumab is a humanized monoclonal antibody that prevents the binding of VEGF to its receptors. Preclinical studies show that antiangiogenic therapy can increase tumor perfusion (reduce hypoxia), radiosensitivity, and chemosensitivity. Results from phase I/II studies of bevacizumab in combination with radio- and chemotherapy show promising activity against many different tumor types, including pancreatic cancer. This phase I trial was designed to study the safety of bevacizumab plus chemo-radiation in locally advanced pancreatic cancer. Planned correlative studies included functional CT to evaluate blood flow.

Methods: The study was designed to accrue thirty patients with locally advanced, unresectable pancreatic cancer based on CT criteria. Bevacizumab (5 mg/kg IV) was administered to all patients 2 weeks prior to the start of XRT (50.4 Gy treating the primary and gross adenopathy), then every 2 weeks thereafter (2.5 mg/kg IV). CAP was administered concurrently with radiotherapy (650 mg/m^2, then 825 mg/m^2 PO BID, days 1452). Patients with stable or responding disease were offered maintenance bevacizumab (5 mg/kg IV q 2 wks) until progression. Functional CT was performed on days 0, 14, and at the time of restaging (5 weeks after XRT).

Results: To date, nine patients have been treated. There has been no significant hematologic or gastrointestinal toxicity, thrombosis, proteinuria, or hypertension. One patient had a tumor-related duodenal ulcer that bled two weeks after discontinuing therapy. It subsequently healed after the tumor responded to therapy. One of three evaluable patients completing therapy had a partial response and two had stable disease. One patient with stable disease had a Ca 19-9 level of 1000 that dropped to 177 (nadir not reached). Results from perfusion imaging indicated increased blood flow after the initial dose of bevacizumab.

Conclusion: Treatment with this novel combination of bevacizumab and chemoradiation is well tolerated and has activity in pancreatic cancer patients. We plan to escalate the dose of bevacizumab at 2.5 mg/kg increments to10 mg/kg. The data produced will be used as the foundation a randomized RTOG study. Updated data will be presented at the meeting.

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Antitumor activity of trastuzumab (Herceptin®) in human gastric cancer models

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Background: Trastuzumab (Herceptin®) is widely used as a standard therapy for patients with HER2 overexpressing metastatic breast cancer. Since HER2 overexpression has also been reported in gastric cancer, we explored the antitumor activity of trastuzumab in human gastric cancer xenograft models.

Results: Among 9 human gastric cancer xenograft models examined, NCI-N87 and 4-1ST models showed HER2 overexpression. Both lines were HER2 positive in immunohistochemistry (HercepTest®) and showed gene amplification in fluorescence in situ hybridization (PathVysion™) (8.4 and 5.3 signal ratio, respectively). When trastuzumab was administered i.p. twice a week, at an initial dose of 20 mg/kg and maintenance doses of 10 mg/kg, to mice bearing these HER2 positive xenografts, significant antitumor activity was observed. Tumor growth inhibition in NCI-N87 and 4-1ST was 73% and 61%, respectively. In contrast, trastuzumab administered to mice bearing HER2 negative-gastric cancer xenograft, GXF97, did not show any significant antitumor activity. Activity of trastuzumab in combination with standard agents used for gastric cancer chemotherapy was also examined. Trastuzumab administered in combination with either paclitaxel, docetaxel, 5'-DFUR or capecitabine in the NCI-N87 model, or in combination with CDDP or CPT-11 in the 4-1ST model showed potent antitumor activity which was significantly greater than that of either single agent in each case.

Conclusions: Trastuzumab showed significant antitumor activity in HER2 positive-human gastric cancer xenograft models, both as a single agent and in combination with standard agents used for chemotherapy of gastric cancer. These preclinical findings support clinical evaluation of the antitumor activity of trastuzumab in patients with HER2 positive-gastric cancer.

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Induction of apoptosis in herpes simplex virus thymidine kinase/aciclovir transfected experimental breast cancer models.

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Background: The induction of apoptosis of tumor cells by suicide-gene system HSV-TK/ACV was studied in MCF-7 and T47D human breast cancer cells. The mechanism of TK/ACV apoptosis induction considered to be mediated by caspase cascade activation following formation of DISC-complex, TRAIL receptor activation and mitochondrial activation.

Material and methods: Cultures MCF-7 and T47D were transfected with pIRES2-EGFP-TK and control pIRES2-EGFP and pEGFP-N1 vectors. The expression of thymidine kinase in subcloned cultures was shown by RT-PCR 24h after transfection. Then cells were treated with acyclovir and different inductors of apoptosis: TNF-alpha and TRAIL (TNF-related apoptosis induced ligand). DNA fragmentation out of and under the death receptors blockage by anti-APO-1, anti-TNF-alpha antibodies was measured by flow cytometry analysis of propidium iodide-stained cell nuclei. Annexin-V staining was used as a more relevant method for apoptosis detection. Caspase inhibitor zVAD-fmk was used in order to modify the effect of apoptosis inductors, caspase-8, caspase -9 expression was detected by immunoblot assay.

Results: The induction of apoptosis by ACV was evident in pEGFP-TK cells compare to control cultures. Aciclovir induced apoptosis in subcloned pEGFP-TK MCF-7 and T47D cultures in dose-dependent mode; TNF-alpha and TRAIL increased HSV-TK/ACV-induced apoptosis. The blockage of CD95, TNF receptors did not decrease TK/ACV-induced apoptosis effectively. Caspase inhibitor zVAD-fmk can greatly decrease apoptosis induction in pEGFP-TK cells as was demonstrated in both PI, Annexin-V flow cytometry analysis and immunoblot of caspase-8, -9 expression.

Conclusions: The mechanism of HSV-TK/ACV apoptosis induction involves different interchanging ways of receptors activation and caspase signaling. Contrariwise to non-specific caspase inhibition the blockage of one or more of death receptors did not cause the blockage of apoptosis in pEGFP-TK MCF-7 and T47D human breast cancer cells. The sensitization of HSV-TK/ACV cells for CD95, TNFR1,and TRAIL-receptor-induced apop-