observed at conservation of tumor stroma. In the 3 series the number of mitosis was 1.4% and apoptosis was 3.6%. It was marked a plural toxic damage of cells and signs of destruction of stroma. In the 4 series mitosis decreased to 0.2% and apoptosis was 2.8%. It was marked the necrosis of cells and destruction of tumor stroma. Results of the 5 series were most interesting. Mitosis was 0, i.e. process of cell fissions practically stopped. Apoptosis was 8.1% against the expressed destructive changes of stroma and almost total cell destruction.
Conclusion: The results received in the 5 series of the experiment open quite new prospects in breast cancer treatment.

1080 POSTER

Functional characterization of TRAP1 pathway in multidrug resistance in human colorectal carcinoma

M. Landriscina[1], F. Maddalena[1], E. Costantino[1], A. Piscazzi[1], A. Fersini[2], G. Laudiero[3], M.R. Amoroso[3], F. Esposito[3]. *[1]University of Foggia, Department of Medical Sciences, Foggia, Italy; [2]University of Foggia, Department of Surgical Sciences, Foggia, Italy; [3]University of Naples Federico II, Department of Biochemistry and Medical Biotechnology, Naples, Italy*

Background: TRAP1 has been recently characterized by our group as a mitochondrial chaperone up-regulated in human colorectal carcinoma (CRC) and involved in favoring a phenotype resistant to apoptosis and chemotherapeutic agents in tumor cells. Interestingly, these findings correlate with the observation that TRAP1 is a component of a mitochondrial pathway, which antagonizes the proapoptotic activity of cyclophilin D and is responsible for maintenance of mitochondria integrity, favoring cell survival.
Materials and Methods: To further characterize TRAP1 function in multidrug resistance of human CRC and to identify novel targets involved in TRAP1 antipoptotic pathway, GST-pulldown experiments and mass spectrometry analysis were performed that allowed us to identifify several TRAP1 ligands. Among others we selected sorcin, a Ca^{2+}-binding protein involved in the development of MDR phenotype in leukemia cells.
Results: Co-immunoprecipitation analyses confirmed TRAP1/sorcin interaction in CRC cells and preliminary experiments suggest a concomitant enrichment of TRAP1 and sorcin, which was known to be a cytosolic protein, in the mitochondrial fraction of CRC cells resistant to 5-fluoruracil, irinotecan and oxaliplatin and in human CRC specimens. Indeed, TRAP1 and sorcin are up-regulated in 60−70% of human CRCs where a significant correlation between the two proteins has been observed (Pearson Correlation test $r = 0.60$; $p = 0.001$). All these findings are in agreement with the observation that HT-29 CRC cells transfected with TRAP1 exhibit a phenotype resistant to 5-fluorouracil-, oxaliplatin- and irinotecan-induced apoptosis and that the inhibition of TRAP1 activity by the TRAP1 ATPase antagonist, shepherdin, or the transfection of a dominant negative TRAP1 mutant increase the sensitivity to apoptosis induced by chemotherapeutic agents in wild type HT-29 CRC cells or in CRC cells resistant to single antiblastic drugs.
Conclusions: It is likely that sorcin and TRAP1 cooperate in a pro-survival pathway responsible for resistance to chemotherapy and that such a pathway may represent a novel molecular target to overcome drug resistance in human CRCs.

1081 POSTER

The effect of sorafenib on Indium-111 labeled bevacizumab uptake in patients with clear cell renal cell carcinoma (ccRCC)

I.M.E. Desar[1], A.B. Stillebroer[2], E. Oosterwijk[2], W.P.J. Leenders[3], C.M.L. van Herpen[1], W.T.A. van der Graaf[1], O.C. Boerman[4], W.J.G. Oyen[4], P.F.A. Mulders[2]. *[1]Radboud University Medical Centre Nijmegen, Medical Oncology, Nijmegen, The Netherlands; [2]Radboud University Medical Centre Nijmegen, Urology, Nijmegen, The Netherlands; [3]Radboud University Medical Centre Nijmegen, Pathology, Nijmegen, The Netherlands; [4]Radboud University Medical Centre Nijmegen, Nuclear Medicine, Nijmegen, The Netherlands*

Background: Patients (pts) with ccRCC are treated with the anti-angiogenic drug sorafenib (sor), a Raf kinase/VEGFR2 inhibitor. In this study we explored the effect of sor on VEGF expression in ccRCC as determined by scintigraphic imaging with In-111- radiolabeled bevacizumab, a humanized anti-VEGF antibody.
Materials and Methods: Pts radiologically suspected of ccRCC scheduled to undergo tumor nephrectomy were included. Adequate bone marrow, renal and hepatic function were required. Exclusion criteria were: prior use of bevacizumab or drugs targeting VEGF or VEGFR, other prior anticancer therapy, pregnancy and lactation. One hour and 5−7 days after iv administration of 100 MBq In-111-bevacizumab, a whole-body scan was performed. In-111-bevacizumab targeting to the tumors was scored qualitatively and semi-quantitatively. After four weeks of treatment with sor 400 mg bid, a second In-111-bevacizumab imaging procedure was performed. Pts underwent nephrectomy 2−3 days thereafter. In a 1-cm slice of the surgical specimen, the distribution of In-111-bevacizumab radioactivity was determined and correlated with tumor viability, VEGF expression and vessel density by immunohistochemical analysis. VEGF-A levels were also determined in tumor extracts by ELISA. As a control, in 5 untreated radiological suspected ccRCC pts a pre-operative In-111-bevacizumab scan was performed.
Results: In 5 control pts with ccRCC, In-111-bevacizumab scintigraphy depicted ccRCC, and antibody accumulation corresponded with intra-tumoral VEGF levels. Neo-adjuvant treatment with sor was well tolerated, although 3 out of 11 pts needed a dose reduction (200 mg bid) because of CTC grade 3 skin toxicity. In 10/11 pts, qualitatively preferential tumor accumulation was observed in the images that were acquired before initiation of sor therapy. One pt with urothelial cancer was negative and replaced. After sor treatment a reduction in In-111-bevacizumab was observed in 8/9 pts with histologically proven ccRCC (mean decrease 58%, range 6%-98%). In contrast, In-111-bevacizumab targeting was stable in 1 ccRCC, 1 urothelial cancer and 1 oncocytoma. Decreased targeting correlated with VEGF expression in vital tumor parts. Necrotic areas in the tumors were not targeted with In-111-bevacizumab despite high VEGF levels, due to low perfusion.
Conclusions: In-111-bevacizumab scintigraphy is able to depict VEGF in ccRCC in-vivo and to monitor the effect of anti-angiogenic therapy on tumor VEGF expression.

1082 POSTER

Extraordinary responses to chemotherapy in metastatic gastric and cervical cancer: gene expression profiling and pharmacogenetics

C. Lo Nigro[1], M. Riba[1], L. Lattanzio[1], A. Comino[2], M. Merlano[3]. *[1]Ospedale S. Croce e Carle, Lab Oncologia Translazionale-SC Oncologia, Cuneo, Italy; [2]Ospedale S. Croce e Carle, Anatomia Patologica, Cuneo, Italy; [3]Ospedale S. Croce e Carle, SC Oncologia, Cuneo, Italy*

Background: Current palliative chemotherapy (CT) regimens achieve clinical benefits in less than 50% of patients treated for metastatic gastric and cervical cancers, and long term survivals are anecdotical.
Different susceptibility to the toxic effects of a given CT treatment has been demonstrated in clinically homogeneous groups of patients. Genetic polymorphisms and different expression of genes involved in drug metabolism, resistance and DNA repair can explain those differences.
We present a case-control comparison for genetic and expression profiling of *long survivors* towards *normal responders* to CT in metastatic gastric and cervical cancer. Four cases of long survivors (2 gastric and 2 cervical) and 9 of normal responders (4 gastric and 5 cervical) have been investigated.
Meterial and Methods: *Expression profiling* using a custom array of real time quantitative RT-PCR assays has been performed on an ad-hoc set of 95 genes chosen from database and literature for being of pharmacogenomic interest. RNA has been extracted from paraffin embedded tumour tissue slices.
Genetic polymorphisms analysis has been done using pyrosequencing for the determination of genetic markers in *MTHFR, DPYD, TYMS, GSTP1, ERCC1, XRCC1, ABCB1, CYP3A4*1B, CYP3A5*3* genes. Restriction enzyme analysis has been used for 5′UTR polymorphism in *TYMS* gene.
Results: *Expression analysis* revealed a consistent up-regulation of genes involved in drug catabolism: *CYP1A1, CYP2C8, CYP3A4* and down-regulation of *ABCC2* in long term survivors compared to controls in gastric tumours. The study of uterine cervix showed up-regulation of *GSTP1, PTEN AND TYMS* and down-regulation of *MMP1*, in long survivors towards normal responders. The pattern of differentially expressed genes showed interesting features of tissue-specificity.
Genetic Screening revealed polymorphisms combinations already described for being associated with prolonged survival to CT. The absence of the *GSTP1* allele, associated with diminished enzymatic activity, and the *ABCB1* polymorphism associated with increased toxicity have been observed in cervical cancer long survivors. Moreover in the group of long survivors, the “3R” allele of the gene *TYMS* presents a frequency superior than the one reported in the Caucasian population.
Conclusions: The present study shed light on a set of genes, which could play a role in driving response to CT and, therefore, could be suggested as markers to guide the choice of CTfor cancer treatment.