range of metastatic tumor types was treated. Hepatic PET and CT imaging was obtained prior to and 21 days following therapy and analyzed for tumor response.

Results: Data is available on 15 patients. Regional localization of MTC-DOX to the tumor was achieved in patients with metastatic disease even though many of the lesions were not hypervascular. Dose escalation was completed to a maximum dose of 1 mg DOX, 8 mg MTC /cm^2 of tumor cross sectional area up to a total dose of 60 mg DOX, 500 mg MTC. Adverse events reported to date were predominantly mild to moderate in severity. The most common adverse events (% of reported events) were transient abdominal pain (10%), nausea (10%), malaise (7%), anorexia (7%), and fever (7%). Three patients were not analyzed by PET due to poor uptake of FDG. The treated tumors in six patients demonstrated a significant reduction in FDG activity (between 20-60% of baseline) at 21 days following a single administration of MTC-DOX. Tumor types demonstrating a response by PET imaging following MTC-DOX treatment included adenocarcinoma of unknown origin, breast carcinoma, bladder, cholangiocarcinoma, renal cell, and colon carcinoma. The treated tumors in six patients did not demonstrate any reduction in FDG activity (between 75-116% of baseline).

Conclusion: MTC-DOX can be localized regionally following intra-arterial administration without clinically significant toxicities. MTC-DOX demonstrates possible activity against some hepatic metastases as measured by FDG activity and PET imaging. Further studies are warranted in order to better ascertain the potential therapeutic role of MTC-DOX in patients with metastatic tumors to the liver.

976 POSTER

Stromal contribution to elevated YKL-40 in human cancer

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High serum levels of YKL-40 are found in patients with late stages of colorectal, breast, ovarian, and malignant glioma, and high serum YKL-40 is a prognostic marker of short survival. YKL-40 is a secreted 40 kD extracellular matrix glycoprotein belonging to the mammalian chitinase-like proteins but without chitinase activity. YKL-40 is expressed by chondrocytes, macrophages, and neutrophils as well as several cancer cell lines. The expression pattern of YKL-40 suggests involvement in tissue remodeling. YKL-40 stimulates proliferation of fibroblasts, endothelial cell migration and tube formation.

We have investigated the expression pattern of YKL-40 on mRNA and protein level in 20 human small cell lung cancer (SCLC) and 3 human malignant glioma lines *in vitro* and *in vivo*. None of the SCLC lines had measurable YKL-40 protein expression in cell culture or when grown as solid tumors on nude mice. The three glioma lines had YKL-40 mRNA production but only U87 secreted the protein in measurable amounts both when grown in culture and as solid tumors. Stromal (mouse) YKL-40 mRNA expression was found by RT-PCR in all tumors.

To further investigate the origin of elevated YKL-40 levels in human cancers, human umbilical cord endothelial cells (HUVEC) and primary human fibroblast GM38B were tested for YKL40 expression when grown in culture and after ionizing radiation. Neither HUVECs nor GM38B expressed YKL-40 under these conditions.

Our data on 23 cancer cell lines (SCLC and malignant glioma) suggest that stromal production of YKL40 is responsible for some of the elevated serum YKL-40 levels associated with poor prognosis in several cancer types. However, our data also indicates that neither stromal fibroblasts nor endothelial cells are responsible for the YKL-40 production. Further investigations are needed to determine the possible role of myofibloblasts, macrophages, neutrophils, and other cell types in YKL-40 expression during malignant cancer progression.

977 POSTER

Phase I/II trial evaluating blockade of tumour blood supply and tumour cell proliferation with combined bevacizumab and erlotinib HCl as targeted cancer therapy in patients with recurrent non-small cell lung cancer.

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Introduction: Non-small cell lung cancer (NSCLC) has resisted all therapeutic approaches for decades and its incidence is increasing. Bevacizumab (Avastin") is a recombinant humanised monoclonal antibody against vascular endothelial growth factor (VEGF) that neutralises' VEGF and prevents it from mediating tumour blood vessel growth and maintenance. Erlotinib HCl (Tarceva") is an epidermal growth factor receptor (HER1/EGFR)-tyrosine kinase inhibitor that optimally blocks HER1/EGFR activation and downstream cell signaling pathways, inhibiting tumour growth. Tumours are biologically heterogenous so the rationale for this study exploits this fact by giving these two targeted cancer therapies in combination to patients with recurrent NSCLC.

Materials and methods: Phase I objectives are to establish maximum tolerated dose (MTD) and dose-limiting toxicities (DLTs) for these two agents combined in 18 patients, and to use this information to establish a regimen for subsequent phase II evaluation of efficacy and tolerability at MTD. Pharmacokinetic and pharmacodynamic parameters will be monitored throughout both study phases to look for any interaction. A standard 3+3 design was used with no intrapatient dose escalation allowed. Regimens comprised: dose level 1, bevacizumab 7.5mg/kg iv q3w + erlotinib 100mg/day po; dose level 2, bevacizumab 15mg/kg iv q3w + erlotinib 100mg/day po; and dose level 3, bevacizumab 15mg/kg iv q3w, erlotinib 150mg/day po. DLT is defined as a NCI-CTC grade 3 toxicity or greater, not adequately controlled with appropriate therapy. All patients with advanced or recurrent non-squamous NSCLC who had previously failed at least one chemotherapeutic treatment were eligible for the trial.

Results: To date, 12 patients have been enrolled in phase I of whom three each have been treated at dose levels 1 and 2, respectively, and six at dose level 3. No patients developed DLTs, and of nine evaluable patients, three showed partial responses, including one at dose level 1 and one at dose level 2, and two showed minor response. Preliminary pharmacokinetic analysis revealed no interaction between bevacizumab and erlotinib. Final phase I data will be presented.

Conclusion: Preliminary data from this phase I trial of a combination of two targeted cancer therapies blocking different aspects of cell biology pivotal to tumour growth and development are encouraging. The bevacizumab with erlotinib combination is well tolerated with no unexpected adverse events.

978 POSTER

Microvascular transfers in the elderly in oncology.

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Background: Microsurgery is often considered as a serious surgical procedure, especially in the elderly population. This group is considered to be at a high surgical risk and on the hold receive substandard treatment.In selected cases, a microsurgical free flap is the last chance of a good quality life for those patients.

Material and methods: Thirteen patients over 70 years were operated on from July 1994 to April 2002 (13 patients - 15 flaps - mean age: 74 years; range: 70-87 years - 7 males-6 females). Indications were wide excisions for skin carcinoma or melanoma (N=3), abdominal wall defect after irradiated bladder cancer (N=1), soft tissue sarcoma (N=2),and head and neck cancer (N=7). Musculo/cutaneous (n=9), fascio /cutaneous (n=4) and osteoseptocutaneous (n=2) free flaps were performed under general anesthaesia during the same operative time than cancer resection in 10 cases, to treat a late complication of the medical treatment of the cancer (radiotherapy) in 6 cases or of an early complication in 1 case (flap necrosis). Co-morbidity was studied and evaluated following the ASA criteria.

Results: Complications were: Complete flap necrosis (n=1 (6.5%) - leading to a second successful free flap), skin paddle necrosis in a fibular osteoseptocutaneous flap conservatively treated (n=1). Minor complications were seroma of the donor site (n=2 (13%)). In the other cases, patients recover without any further complications. The mean operative time was 8 hours for the whole procedure (resection and reconstruction) (range: 5h30 - 10h10); the mean blood loss was 950 ml (range: 250 - 3000). Seven patients are still alive without any reccurrence of the cancer except in one case (mean follow-up 57 months), 8 died from a generalization of the cancer except in one case 10 months after microsurgery (range of 1-20 months).

Conclusions: In our limited experience, microsurgery can be the ultimate surgical option in order to resolve difficult problems in a selected group of elderly people with oncological disease. The success rate is about 93.5% without any major complications. In almost all cases, the clinical problem was primarily under treated because the age of the patient was considered as a contra-indication factor for radical surgery. Survival rates with and without recurrence, lead us to conclude that age is not a contra-indication factor and that this surgery can be ethically proposed in a selected number of cases.