The total intra-tumoral selenium concentration achieved at 2h post MSC (0.2 mg/mouse × 7) was higher in FaDu tumors than in A253. In normal tissues, total selenium increased post MSC (0.2 mg/mouse × 7) with the highest concentration in the liver then kidney, small intestine, large intestine, and bone marrow.
Conclusions: The data suggest that at least a 14.2 μM concentration of selenium is required after SLM and 5.08 μM concentration for MSC to achieve the optimal therapeutic modulation of anti-tumor activity and protection from irinotecan induced toxicity. The higher concentration of selenium in FaDu tumor (more responsive) than in A253 (less responsive) could be responsible in part for the observed selective increase in antitumor activity of irinotecan, when administered in combination with selenium containing compounds. The levels of selenium after MSC relative to their untreated control in bone marrow and small intestine may be related to its protective effect against irinotecan induced toxicities. The tissue distribution studies with SLM are ongoing.

614 POSTER

Increased tumor extravasation with an elastin-like polypeptide systemic thermal pump

M. Dreher[1], W. Liu[1], C. Michelich[1], M. Dewhirst[2], A. Chilkoti[1]. [1]*Duke University, Biomedical Engineering, Durham, NC, USA;* [2]*Duke University, Radiation Oncology, Durham, NC, USA*

Achieving a therapeutic concentration of chemotherapeutics in solid tumors while minimizing systemic toxicity remains a critical problem in the treatment of cancer. Macromolecular drug carriers are an attractive method for delivery of cancer therapeutics because they passively target tumors through the enhanced permeability and retention effect and have longer plasma half-lives, which result in improved therapeutic efficacy. In our ongoing studies, we use a thermally responsive elastin-like polypeptide (ELP) as a macromolecular drug carrier. ELPs belong to a unique class of biopolymers that undergo an inverse temperature phase transition; they are soluble at temperatures below their transition temperature (T_t) but become insoluble and aggregate at temperatures above their T_t. In this abstract we investigate the feasibility of an ELP systemic thermal pump drug delivery strategy described as follows. First, a heat-sensitive ELP is designed with a T_t of about 40ºC and conjugated to an anticancer drug. Then the tumor is heated with externally focused hyperthermia (T_h = 42ºC) and the ELP is administered intravenously. Upon entering the tumor vasculature, the ELP will undergo its phase transition and form adherent aggregates within the tumor vasculature (T_t<T_h), therefore concentrating the ELP in the tumor vasculature although it is trapped in immobile aggregates. Next, the tumor temperature is reduced to normothermia (T_n=37ºC), which is accompanied by a transient increase in plasma concentration of the ELP as its aggregates dissolve (T_n<T_t). The selective increase in plasma concentration only in the tumor drives more ELP across the tumor blood vessel wall resulting in increased extravascular accumulation. By cycling the tumor temperature between hyperthermic and normothermic temperatures, we may be able to repetitively pump ELP drug carriers into the extravascular space of a tumor. It was our goal to directly assess the performance of the ELP systemic thermal pump in a dorsal fold window chamber model in combination with laser scanning confocal microscopy. In preliminary experiments, we have found that the ELP aggregates form rapidly in hyperthermic tumor vasculature and grow in size during the heat treatment. Upon return to normothermia (one thermal cycle), there is a significant increase in extravascular accumulation of a thermally responsive ELP compared with a thermally insensitive control ($P<0.05$ ANOVA). We observe an increase in plasma concentration of freely mobile ELP as the aggregates dissolve that is most likely the cause of increased in extravascular accumulation. In conclusion, the ELP systemic thermal pump is a viable drug delivery strategy in order to increase extravascular accumulation of macromolecular drug carriers.

615 POSTER

Preliminary results of a phase I/II study of inhaled doxorubicin combined with docetaxel and cisplatin for advanced non-small cell lung cancer

G.A. Otterson[1], M.A. Villalona-Calero[1], A. Grainger[1], W. Hicks[1], J. Murren[2], J. Ellerton[3], C. Mojzisik[4], M. Gerber[5], D. Westaway[5]. [1]*The Ohio State University, Comprehensive Cancer Center, Columbus, OH, USA;* [2]*Yale University, Comprehensive Cancer Center, New Haven, CT, USA;* [3]*Southern Nevada Cancer Institute, Las Vegas, NV, USA;* [4]*Blackburn International, Columbus, OH, USA;* [5]*Zivena, Inc, Columbus, OH, USA*

The addition of molecular-targeted agents to the initial treatment of NSCLC has failed to improve results seen with chemotherapy alone. Targeted delivery of agents to the lung through inhalation has been used in selected situations. Preclinical studies support the use of inhaled therapeutic agents for the treatment of cancer. We have reported the results of a phase I study of inhaled doxorubicin/ Resmycin™ (DOX) in patients with advanced cancers affecting the lungs. 7.5 mg/m^2 was the recommended phase II dose in this study, with minimal systemic toxicity. Dose limiting toxicity was found in the lungs at higher doses. Using the Oncomyst® CDD-2a delivery device we designed a combination trial of DOX, docetaxel (D) and cisplatin (P) administered every three weeks. Patients were required to have acceptable organ function, including PFT entry criteria of ⩾50% predicted FVC, $FEV_{1.0}$ and DLCO, and resting and exercise oxygen saturation of ⩾90% and 85%, respectively. D/P were administered at 75 mg/m^2 with routine premedications and hydration. Since DOX had not been combined with other agents, we performed a 2-level phase I portion starting at 6.0 mg/m^2 of DOX, given prior to D/P, with escalation to 7.5 mg/m^2 if this was safe. To date, we have treated 9 patients (28 cycles at level 1, 9 at level 2). 1 patient experienced febrile neutropenia during cycle 1, and had their D reduced by 25% for subsequent cycles. 1 patient had grade 3 nausea and vomiting after cycle 2 and had 25% reduction of P. One patient (at 6.0 mg/m^2) had possible interstitial infiltrates (on lung CT scan) prior to cycle 2 (unchanged PFTs), but also had worsening of tracheal narrowing that may have led to hypoventilation. This patient was taken off study. An additional 3 patients were treated at this dose level with no further pulmonary problems. To date three patients have been treated at the 7.5 mg/m^2 dose level without pulmonary toxicity during cycle one. Overall, 2 patients had progressive disease and required radiation therapy without undue complications. 2 patients had partial responses, and 4 patients had stable disease for up to 6 cycles of treatment. 1 patient is unevaluable for tumor response. Several patients have had asymptomatic 20% decreases in DLCO 6–8 weeks following their last cycle of treatment with further PFT monitoring. We conclude that it is safe to administer DOX with IV D and P in patients with advanced NSCLC.

616 POSTER

Elimination of liposomes by apheresis-techniques

G. Puetz, J. Eckes, H. Wieland. *University Hospital Freiburg, Clinical Chemistry, Freiburg, Germany*

Background: Using highly toxic drugs like chemotherapeutic agents, therapeutic success is often limited by severe side effects. Most often these side effects occur in other than the target tissue and are caused by a part of the administered dose, that does not reach the target tissue at all. This part of the total dose has no therapeutic value, but must be detoxified and excreted by the patient as well. To lower the side effects of chemotherapy, liposomes can be used as drug-delivery system. Thereby the toxic profile of the encapsulated chemotherapeutic agent is shifted, but detoxification of drugs not reaching the tumor still remains an obstacle. In some respects, liposomes are very similar to low-density-lipoproteins (LDL). LDL can be efficiently eliminated by LDL-apheresis-systems, which are used in therapy for years. If the excess of administered liposomes circulating in the blood could be eliminated by apheresis, side effects of chemotherapy may be lowered or minimised. As a first step towards this goal, the elimination of liposomes by different apheresis-techniques was investigated in vitro.
Methods: The different seperation principles used in LDL-Apheresis were examined to eliminate appropriate liposomes out of a liposomal suspension. The separation principles used were double membrane filtration, precipitation with heparin, adsorption chromatography by the use of either heparin coupled sepharose or polyacrylic acid coupled to polyacrylamide-beads.
Results: Liposomes can be effectively eliminated out of a liposomal suspension by the use of differential filtration, precipitation and adsorption by heparin coupled sepharose. Polyacrylic acid coupled polyacrylamide-beads are not able to adsorb liposomes effectively.
Conclusion: In general, liposomes can be effectively eliminated out of liposomal suspensions by the separation principles used in LDL-apheresis. Among the apheresis-systems used in clinical practice, MDF (membrane differential filtration) and H.E.L.P. (heparin induced precipitation) may be particularly useful, while DALI (adsorption by polyacrylic acid) has to be modified at least.