Intratumoral Chemotherapy: from Research to the Clinic for a New Lung Cancer Treatment Paradigm

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Statement of Purpose: Systemic drug toxicity severely limits the effectiveness of conventional chemotherapy. In spite of significant advances in cancer diagnosis, drug development, and multiple drug therapy regimens, the CDC has reported no meaningful decline during the past 20 years for mortality due to colorectal, prostate, or breast cancers. Indeed, there has been a 75% increase in lung cancer mortality with 200,000 deaths now attributed annually to lung cancer.

There is clearly a need for new therapeutic concepts which are more effective, less toxic, and clinically practical. The development and translation to the clinic of a new treatment paradigm that has special value for lung cancer, *intratumoral (IT) chemotherapy,* is presented here. The scope of this work embraces the synthesis of modified drugs, preclinical animal evaluation, and human clinical studies in lung cancer patients.

More specifically, we report our research on (1) a novel steric stabilization synthesis of cancer drug loaded protein nano-mesospheres (drug-MS) of 0.1-1.0 and 1.0-10um particle size, (2) evaluation of various techniques for intratumoral injection of drugs and drug-MS, (3) pre-clinical animal studies of IT chemotherapy in a murine Lewis lung carcinoma and a murine breast cancer model, a mammary adenocarcinoma, and (4) IT clinical studies in non-small cell lung cancer patients, especially patients presenting with endobronchial obstruction and acute breathing distress.

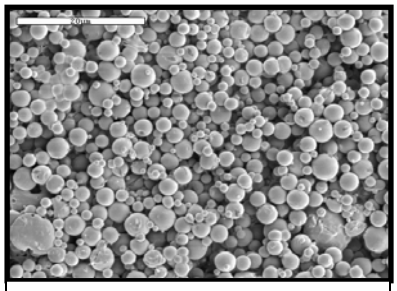
Methods: Drug-loaded MS were prepared by a steric stabilization method we have previously described [1,2]. Preclinical IT chemotherapy studies were conducted comparing conventional systemic i.v. mitoxantrone (MXN) delivery in mice in a metastatic lung cancer model, a murine Lewis lung carcinoma, and a murine 16.C mammary adenocarcinoma. For the breast cancer model, multiple IT injections (5x 0.02ml each) of MXN-BSA-MS dispersions were typically given at doses of 24-48 mg/kg. Animals surviving tumor-free for >60 days (5x survival for untreated controls) were considered "cured".

In human IT clinical studies, patients presenting with NSC lung cancer, often with severe obstruction of the bronchial tract, were treated by multiple IT injections of cisplatin (CPT) or MXN through a needle-equipped bronchoscope. Treatment sessions were weekly for up to 3 weeks as needed and necrotic tumor tissue was removed by dissection and aspiration. .

Results: Biodegradable BSA-MS containing the cancer drugs MXN or CPT were readily prepared with good therapeutic activity and drug loadings up to 15 wt% by our modified steric stabilized dispersion synthesis. Particle size domains were readily controlled by varying the dispersion energy. Drug loading, ease of aqueous dispersion, and drug release by diffusion and biodegradation were designed for IT chemotherapy.

IT injections of MXN-BSA-MS in the murine Lewis lung and mammary adenocarcinoma yielded 80% "cures" at doses of 24-48 mg/kg with no systemic toxicity. Even free drug injections given intratumorally were much more effective than systemic drug delivery, achieving 40-60% prolonged survival with little toxicity [1,2].

Initial clinical studies have been conducted by IT injection of MXN or cisplatin through a needle-equipped bronchoscope in NSC lung cancer patients. Such patients respond poorly to conventional chemotherapy. In most cases there was relief of collapsed lungs and breathing difficulties after 1-2 bronchoscopic IT treatment sessions. In two clinical studies, inoperable patients presenting with NSC lung cancer and bronchial obstruction were treated by IT injection of cisplatin. The bronchial lumen was cleared and breathing distress was relieved in all patients after 3 weeks thereby permitting subsequent radiation treatment or tumor resection with prolonged patient survival [3,4].



Mesospheres for IT Therapy

Conclusions: Preclinical animal studies using murine models of lung and breast cancer demonstrated greatly prolonged survival for IT chemotherapy using cancer drugs such as MXN and CPT with more effective response using drug-loaded albumin microspheres. In clinical studies, the treatment of NSC lung cancer by IT drug delivery via a needle bronchoscope was shown to be a clinically practical patient-friendly procedure which was much safer and more effective than conventional systemic chemotherapy and showed virtually no systemic toxicity.

References:

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