Evaluation of the immunotoxin, Proxinium™ in combination with chemotherapy and radiotherapy

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ABSTRACT

Proxinium™ is a recombinant fusion protein consisting of a tumor-targeting antibody fragment fused to a truncated form of Pseudomonas exotoxin A (ETA252-608). Proxinium™ specifically targets the epithelial cell adhesion molecule (EpCAM) that is highly expressed on a wide variety of epithelial carcinomas, including squamous cell carcinoma of the head and neck (SCCHN). Head and neck cancer accounts for approximately 5% of all newly diagnosed invasive malignancies in North America each year and is the 6th most common cancer worldwide. With a five-year survival rate less than 40%, the current prognosis for patients is poor, indicating the lack of effective treatment. Proxinium™ is currently being evaluated in a phase II/III trial as a monotherapy for SCCHN patients. To assess the potential for administration of Proxinium™in conjunction first line standard of care therapy for SCCHN, in vitro cytotoxicity and in vivo pharmacokinetic studies were conducted to evaluate the potential antagonistic, additive, or synergistic interactions with chemo- or radiotherapy. In vitro cytotoxicity was evaluated pre-concurrent, and post-treatment with Proxinium™ in SCCHN cell lines CAL 27 and SCC-15. Cell growth inhibition, in combination with various chemotherapeutic agents (cisplatin, carboplatin, paclitaxel, 5-fluorouracil, docetaxel, bleomycin, and methotrexate) was assessed using an MTS assay. The combination of Proxinium™ with cisplatin, carboplatin, paclitaxel, 5-fluorouracil, and docetaxel resulted in a significant additive cytotoxic effect ($p < 0.05$) as compared to chemotherapeutic agents administered alone. The sequence of drug administration did not influence the outcome. Growth inhibition, in combination with radiotherapy, was assessed using a clonogenic assay. The combination of Proxinium™ with radiotherapy led to a synergistic cytotoxic effect when Proxinium™ was administered after radiotherapy or additive effects when Proxinium™ was administered before or at the same time as radiotherapy. In vivo pharmacokinetic profiles generated from drug administration to Sprague-Dawley rats indicated that the pharmacokinetics of cisplatin, paclitaxel, and 5-fluorouracil was not affected when administered in combination with Proxinium™. In summary, no antagonism was observed in in vitro or in vivo studies with Proxinium™ in combination with either chemo- or radiotherapy. The additive and synergistic cytotoxic effects demonstrated in this study indicate the potential utility of Proxinium™ in conjunction with more conventional treatment modalities for patients with SCCHN.