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Proof of Principle for Local Delivery of a c-Met Inhibitor

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ABSTRACT

The reported proof of principle study demonstrated the feasibility of local delivery of a c-Met inhibitor (VXc-140) in a subcutaneous xenograft tumor model. VXc-140 was formulated in a wafer delivery system for direct implantation into the tumor. Systemic and local tumor exposure of VXc-140 was analyzed. High tumor exposures coupled with fast release of compound were associated with significant tumor regression and reduction in tumor levels of phosphorylated c-Met. High VXc-140 tumor-to-plasma ratios (~42 at the tumor periphery) were achieved. The tumor response achieved (7/11 partial response) with VXc-140 with the local delivery in the wafer (4 mg over 15 days) was comparable to the regression observed (11/15 partial response) for VXc-140 in the oral delivery (~8 mg total administered once a day for 2 weeks). Notably, the plasma levels in animals implanted with VXc-140 wafers ranged from 2 to 4 μM, which, although higher than trough levels achieved with oral administration, were well below oral Cmax levels (~42 μM) suggesting that toxicities associated with Cmax exposure may be reduced or eliminated by local delivery. The high tumor to plasma exposure of VXc-140 and the efficacy observed with local wafer delivery warrants further exploration into the utility of local delivery.

Introduction

Local drug delivery in the form of an implant for cancer treatment has become a known way of treating different tumor types across their stages and in a variety of operative conditions. An implant can be defined as a controlled release drug delivery depot system, that is, either adjacently placed to the tumor or placed intratumorally.[1] For cancer treatment, implants have been suggested for application to sites of surgical resection as a preventive measure of tumor recurrence and adjuvant therapy or implantation into unresectable tumors to cause tumor shrinkage and thus enabling a possible resection (note, here, the unresectable tumor is the tumor with excessive mass or location endangering vital structures in the body and therefore making safe removal inoperable).[2] There are a few marketed products of implants including treatment for neuroendocrine tumors with Somatuline Depot,[3] glioblastoma with Gliadel wafer (MGI Pharma/Eisai Pharmaceuticals),[4] prostate cancer with Zoladex (Zeneca Pharmaceuticals),[5] and others. There are also multiple preclinical and clinical ongoing studies that use implants for tumor treatment[6,7]: Recnac for melanoma,[8] fluorouracil implants for gastric cancer,[9] and radioactive seed implantation for prostate and various cancers.[10] Even with implant products on the market, there is an evident and a pronounced need for more implant products, specifically in the cancer therapy field, to enable elimination of the remnant malignant cells after surgery and reduce the tumor mass (debulking) for unresectable tumors.

Implants are made from various biodegradable natural and synthetic polymers to avoid extraction of the implant after the drug is released and to minimize the innate immune response to the foreign body. Examples of the polymeric systems used for implant fabrication are numerous, for instance, collagen,[11] chitosan,[12] tri-block polymer (poly[lactide-co-glycolide]-polyethylene glycol-poly[lactide-co-glycolide]) (PLGA-PEG-PLA) used in ReGel,[13,14] polyanhydrate used in Gliadel wafer,[4] and many others.[15-17] The form of the implant also has a wide spectrum of shapes and

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The authors Irina Kadiyala and Diane M. Boucher have the same level of contribution.

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fabrication procedures, such as wafers, rods, films, compressed microspheres, and many others.[1] There are clear therapeutic advantages of the implant delivery system that make it an attractive tool for cancer treatment, such as:

(1) drug concentration is maximized at the tumor site,
(2) drug administration is less frequent, and amount of the drug given is reduced compared to other prevailed administration routes like intraveneous or oral,
(3) release profile can be modulated, and
(4) off-target toxicity could be minimized.

On other hand, potential therapeutic disadvantages include:

(1) decreased systemic exposure for addressing distant metastases,
(2) risk of dose dumping of cytotoxic agents, and
(3) potential need for removal of the implant in event of poor patient tolerance of the treatment and immune response.

Drugs with various target profiles and mechanisms (small molecules and biomolecules) are amenable for implant delivery; however, the dissolution profile of the drug from the implant has to be adjusted to create the desired local pharmacokinetic profile for treating the type and stage of tumor. Ultimately, the form of the drug in the implant and its method of fabrication will be driven by the nature of the compound and the therapeutic indication. At large, the release profile of the drug from implant is dependent on the properties of the drug itself and the choice of the polymer. Since most chemotherapeutic agents have low solubility and often are hydrophobic in nature, an environment with a higher degree of hydrophobicity is more likely to provide the ability to modulate release with a lessened burst effect and physical aggregation of the drug within the polymeric matrix. PLGA polymer is probably one of the most commonly used polymers due to market presence, known physicochemical properties, and good safety profile, as well as ability to tune properties of the polymeric system to attain the desired release for the specific drug.[15-17] To tune the properties of the polymeric depot, initial considerations are given to adjustment of the ratio between hydrophobic lactic acid and hydrophilic glycolic acid and molecular weight of the coblock polymer.[18,19] Other important considerations are size of the implant, specifically its thickness, and method of its fabrication.[20] PLGA polymers were first approved for surgical use in humans by the US Food and Drug Administration and have since been used to formulate a wide range of therapeutic agents.[16,17,21] A few commercially available formulations for cancer treatment that are PLGA based include Lupron Depot for advanced prostate cancer,[22] Somatuline Depot for acromegaly and neuroendocrine tumors,[3] and Trelstar Depot for advanced prostate cancer.[23]

When selecting a drug for the implant system, in addition to importance of its desired safety and efficacy profile, we need to account for drug properties that would affect the drug's diffusion from the implant system, and therefore, its localization in tumor tissue and systemic concentration leading to potential off-target toxicity. Drug properties that have the most profound effect on its dissolution include protein binding, hydrophilicity, and, overall, competing affinity between a drug and a polymer, as well as a drug and environment. Thus, one could expect that a drug with low protein binding, that is, more hydrophilic in nature would have a larger diffusion area than a drug with a high protein binding and therefore potentially a higher affinity to the tumor mass, and therefore a smaller diffusion area from the implantation site (unpublished data). Therefore, drugs with such properties potentially present a better choice for implantation delivery.

This study demonstrates feasibility of using the PLGA wafer delivery system for local administration of drug and describes tumor regression following VXc-140 wafer implantation in tumor-bearing mice. VXc-140 is a selective inhibitor of the c-Met receptor tyrosine kinase. Autophosphorylation of c-Met (pMet), a biomarker of c-Met activation, was locally decreased in response to wafers containing VXc-140. Compound concentrations in plasma and tumors were monitored, and results demonstrate minimal systemic exposure and maximized exposure in the tumor for VXc-140. As expected from the properties of the drug, VXc-140 exposure in the tumor was significantly greater after low-dose local wafer implantation than after high-dose oral administration indicating that local delivery has the potential to reduce the total efficacious dose as well as the risk of systemic toxicities. Although local delivery via implant may not always be sufficient as a stand-alone therapy in the treatment of all types of cancer, local delivery in combination with existing standards of care may offer a potential benefit for improving patient outcome.

Materials and Methods

Properties of VXc-140

VXc-140 is the c-Met inhibitor compound and is the property of Vertex Pharmaceuticals Incorporated. VXc-140 has molecular weight of 361 D, LogD of 2, and pKas of 1.2 and 4.5. Aqueous solubility is approximately 0.15 mg/mL (measured at ambient conditions, 24 h equilibrium time point). VXc-140 is a highly potent and selective inhibitor of c-Met with a Ki of 16 nM and an *in vitro* IC_{50} of 34 nM in SNU-5 cells. In the *in vivo* SNU-5 biomarker assay, VXc-140 significantly inhibited c-Met activity (as measured by autophosphorylation) for up to 24 h following a single oral dose (25 mg/kg) (unpublished data).

Wafer Formulation

The wafer formulation is a solid disk-shaped implant that incorporates the compound into a PLGA copolymer matrix of 50/50 weight/weight ratio of lactic acid and glycolic acid with molecular weight of 5-15 kDa from Lakeshore Biomaterial (Birmingham, AL). The blends for active and placebo wafers were prepared by blending with PLGA and 0.5% magnesium stearate added for lubrication. The blends were directly compressed on SMI Piccola (NJ) tablet press using dye size 0.1575″ (flat surface). The amount of the PLGA polymer was adjusted to mass balance the amount of VXc-140 added at 10%, or 20%, or 40% by weight/weight of a total wafer amount of 100%. Thus, the wafer with 10% drug load (DL) contained 2 mg of VXc-140, the wafer with 20% DL contained 4 mg of VXc-140, and the wafer with 40% DL contained 8 mg of VXc-140. The placebo wafers were used as controls. The placebo was directly compressed with 99.5% PLGA and 0.5% magnesium stearate only. All wafers, active, and placebo were compressed to the same dimensions targeting 1 mm × 4 mm in size with a target weight of 20 mg. The dissolution studies on wafers were conducted in simulated cerebral spinal fluid (SCF) at 37°C in 40 mL of the medium. At set time points, samples were withdrawn, filtered, and analyzed by UV at 315 nm wavelength corresponding to maximum absorbance of VXc-140. At each time point, the medium was replenished to ensure sink conditions. The recipe for SCF was taken from Alzet site.[24]

Pharmacology Model

The *in vivo* antitumor activity of locally delivered VXc-140 was evaluated in the human gastric cancer SNU-5 xenograft model. This