Transdermal deferoxamine for treatment of irradiated soft tissue

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Clinical Need

Approximately one-third to one-half of all patients with cancer receive radiation therapy, and greater than 90% of patients experience radiation-induced collateral soft tissue injury including severe, debilitating chronic fibrosis. Current therapeutic approaches for patients with radiation-induced soft tissue fibrosis are limited. A mechanism to improve local perfusion and skin quality would help to address the pathophysiologic limitation preventing rehabilitation in these patients.

Solution

We have developed a transdermal patch delivery system for an FDA-approved medication, deferoxamine, to treat chronic, fibrotic radiation-injured soft tissue. Preclinical studies demonstrated that serial direct injection of this medication into irradiated tissue results in improved blood flow and tissue quality. However, translation for this route of administration is limited by logistical challenges of repeat injections as well as potential for poor patient tolerance. A transdermal patch delivery system is far more attractive to both clinicians and patients. Given the frequency and severity of debilitating radiotherapy side effects and limited available treatment options, our novel approach meets a large clinical need with potential for rapid clinical adoption.

Competitive Advantage

There are no approved topical formulations or transdermal delivery patches for deferoxamine in the EU or US. This transdermal deferoxamine patch would be a new product that could bring significant improvement in the care of post-radiation patients without encountering any therapeutic competition for quite some time.

Target Market

The largest targeted market would likely be represented by breast cancer reconstruction, with current market size estimated to be $526.5M worldwide in 2017. Breast reconstruction typically involves silicone or saline implants, and radiation is associated with increased implant exposure/failure risk and scar formation. A second potential target market would be head and neck cancer reconstruction. There are over 60,000 new cases diagnosed each year in the US, and 27,898 reconstructive procedures were performed in 2017 alone.

Regulatory Pathway

Combination product (Drug–Device) with the PMOA being the drug so the regulatory pathway will be an IND with CDER as the lead agency. Deferoxamine is already FDA approved and in clinical use for other indications. Therefore, the team may ultimately go through a 505(b)(2) application pathway.

Intellectual Property

Deferoxamine is off-patent. Application for improvement of radiation-induced fibrotic tissue represents a new indication. We have filed a patent for transdermal delivery of deferoxamine for wound healing and a patent application on the use of transdermal deferoxamine patch delivery to improve irradiated tissue to facilitate subsequent reconstructive procedures. US12/577,006, US20100092546A1, PCT/US2018/050626, WO2019055490A1

Related Publications

When radiation fibrosis is severe, significant cosmetic and functional consequences may result. With an estimated 60,000 new cases each year, and rising, annual health care expenditure potentially even larger market for our product exists among patients with breast cancer, with over 250,000 newly diagnosed patients annually. Over one in five women with breast cancer receive adjuvant radiation therapy.

**UNMET CLINICAL NEED**

Over half of all patients with cancer receive radiation therapy as part of their treatment, and while this improves overall survival, over 80% of patients experience radiation-induced collateral soft tissue injury. Late effects of radiation therapy may include development of radiation fibrosis, characterized by dermal thickening and loss of vascularity, leading to hypoperfusion and hypoxia. When radiation fibrosis is severe, significant cosmetic and functional consequences may result which can substantially impact quality of life. Furthermore, reconstruction of soft tissue defects following cancer resection are challenging owing to hypovascular changes and poor tissue compliance.

Current therapeutic approaches are limited to physical therapy, pentoxifylline, and vitamin E. However, poor compliance and variable outcomes have been reported with these regimens. Therefore, a commercially available mechanism to improve local perfusion and tissue quality using an FDA-approved medication would help to address the fundamental pathophysiological limitation preventing successful rehabilitation of patients following radiation therapy. Given the frequency and severity of debilitating radiotherapy side effects and with limited available treatment options, a novel treatment strategy would meet this large clinical need with potential for rapid clinical adoption.

**MARKET ANALYSIS**

Cancers of the head and neck account for 3% of all malignancies in the United States. With an estimated 60,000 new cases each year, and rising, annual health care expenditure exceeds $3.6 billion for treatment of head and neck condition. (1) And beyond the head and neck region, a potentially even larger market for our product exists among patients with breast cancer, with over 250,000 newly diagnosed patients annually. Over one in five women with breast cancer receive adjuvant radiation therapy.

**INTELLECTUAL PROPERTY**

- Deferoxamine originally trademarked as Desferal by Novartis in 1962 and is now off-patent.
- Application of deferoxamine for radiation-induced hypovascular tissue represents a new indication for an existing drug.

**IP / Licensing Status:**

- "Topical and transdermal delivery of hif-1 modulators to prevent and treat chronic wounds"  
  - USPTO Patent # 2010/0295456 - filed October 9, 2009
- "Conditioning irradiated tissue for fat graft retention"  
  - Provisional Application Filed September 14, 2017 - #2555,698
- "International Application for Patent Filed September 12, 2018  
  - PCT/US2018/056925
- "Recorded with USPTO October 31, 2018 at Reel 04737, Frame 0095
- "Prophylactic skin treatment for radiation therapy"  
  - Provisional Application filed November 22, 2019

**RESULTS**

Local delivery of deferoxamine to mouse skin has been shown to chelate iron (Fig. 2a) and stabilize HIF-1a (Fig. 2b) (4,5). This results in downstream activation of pro-angiogenic growth factors (Fig. 2c) and restoration of perfusion in irradiated tissue (Fig. 2d). Iron also catalyzes formation of reactive oxygen species (ROS) via the Haber-Weiss and Fenton reactions, which results in oxidative stress and cellular apoptosis. Formation of ROS has been established as an etiopathogenic feature of radiation fibrosis. Transdermal deferoxamine reduces ROS in irradiated mouse skin, as shown by decreased dihydroethidium staining (Fig. 2e).

**REGULATORY PATHWAY**

- Our transdermal deferoxamine patch is purchased through a third-party company and is manufactured in compliance with GMP guidelines.
- Deferoxamine is USP grade and is obtained from supplier listed in the Orange Book.
- Surfactants used for construction of reverse micelles are GRAS and have been tested for impurities and stability.
- Patches sterilized using Eubeam in a validated process.
- 12-month stability testing at 25°C on sterilized patches completed by manufacturer.

**MANUFACTURING**

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**UNMET CLINICAL NEED**

In the current clinical setting, patients are commonly treated with external beam radiation therapy and recent advances in radiation therapy techniques, such as intensity-modulated radiation therapy (IMRT), have been shown to increase local control and cure rates for a variety of malignancies. However, radiation therapy is not without side effects; the development of late radiation toxicity is a major concern, particularly in the context of an already compromised immune system. Radiation fibrosis, a common long-term complication, results in collagen deposition, dermal thickening, and hypervascularity. Radiotherapy side effects and with limited available treatment options, a novel treatment strategy would meet this large clinical need with potential for rapid clinical adoption.

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**METHODS**

- Local delivery of deferoxamine to mouse skin has been shown to chelate iron (Fig. 2a) and stabilize HIF-1a (Fig. 2b) (4,5). This results in downstream activation of pro-angiogenic growth factors (Fig. 2c) and restoration of perfusion in irradiated tissue (Fig. 2d). Iron also catalyzes formation of reactive oxygen species (ROS) via the Haber-Weiss and Fenton reactions, which results in oxidative stress and cellular apoptosis. Formation of ROS has been established as an etiopathogenic feature of radiation fibrosis. Transdermal deferoxamine reduces ROS in irradiated mouse skin, as shown by decreased dihydroethidium staining (Fig. 2e).

**RESULTS**

Chronic, radiation-induced mouse scalps also demonstrated reduced perfusion; however deferoxamine was noted to improve perfusion as seen on laser doppler analysis (Fig. 3a) (4). Histologic analysis of treated irradiated mouse skin also revealed decreased dermal thickness on H&E staining and improvement in collagen deposition on picrosirius red staining (Fig. 3b). A large animal red Duroc pig model was developed to evaluate effects of transdermal deferoxamine on irradiated tissue more similar to human skin. Pigs were treated with 30 Gy radiation delivered to each flank and then were allowed to recover for 6 weeks to develop chronic fibrosis (Fig. 4a). Regions (5x5cm, 3x3cm, and 1x1cm) were treated to patch, a control patch with no deferoxamine, or the transdermal deferoxamine patch (1mg/cm2). Patches were changed daily for four weeks. No adverse reactions were appreciated with either the control or transdermal deferoxamine patch at any treatment size (Fig. 4b). Clinical assessment of irradiated skin demonstrated improvement in pliability over four weeks of treatment using Common Terminology Criteria for Adverse Events (CTCAE) v4.03 grading for radiation injury (Fig. 4c).

**REGULATORY PATHWAY**

- Our strategy integrates deferoxamine into a transdermal patch delivery system and will be viewed as a combination product regulated by the FDA Center for Drug Evaluation and Research.
- A 505(b)(1)(i) pathway to approval of an NDA is planned. Reference to IND 135603 submitted by the Tautona Group for Deferoxamine Intradermal Delivery Patch (DIDP) will be included with the IND submission.
- Objectives of Pre-IND meeting:
  - Confirm proposed indication for treatment of chronic, radiation-induced soft tissue injury
  - Define key study design considerations regarding proposed clinical trial including efficacy endpoint and secondary endpoints for measuring treatment effects
  - Determine whether additional conduct of in vivo toxicology or pharmacology studies in animals is necessary
  - Establish specifications for both the drug substance and the drug product
  - Obtain guidance from the FDA to consider breakthrough, fast track, or other submissions for expedited programs related to rare or unmet medical needs

**TIMELINE & FUTURE DIRECTIONS**

- **Milestone 1 (Q1 2021)** – Formatting and submission of Pre-IND packet to FDA including nonclinical pharmacology, dosing analysis, pharmacokinetics, and toxicology studies. Additional data from IND 135603 to also be included.
- **Milestone 2 (Q2–Q3 2021)** – Completion of additional GLP toxicology/pharmacology studies as necessary. Previous GLP animal studies performed by Care Research LLC.
- **Milestone 3 (Q4 2021)** – Design of Clinical Trial and IRB approval for a randomized, double blinded, placebo-controlled Phase II study of transdermal deferoxamine patch treatment in patients with radiation fibrosis.

**REFERENCES**

(1) https://www.cdc.gov/cancer/factsheet/index.htm
(2) https://www.biorxiv.org/content/10.1101/2020.02.22.949674v2.full.pdf
(3) https://www.biorxiv.org/content/10.1101/2020.02.22.949674v2.full.pdf

**Funding Sources:** NIH NDCR 5 U24 DE026914, NIH NIDCR 5 R01 DE027346