Prevention of Chemotherapy-Induced Toxicities (Chemotherapy Treatment) Overview and Development Summary

Trial and Development Summary

- **Target:** Chemotherapy-Induced Toxicity for Chemotherapy Treatment
- **Development Status:** Phase 2 randomized clinical trial to start Q2 2017.
- **Phase 2 Trial Design:** Two simultaneous randomized, phase 2 clinical trials – 80 patients total.
- **Population:**
  - Study 1: 40 Cisplatin treated patients. Study 2: 40 Doxorubicin treated patients.
- **Dosage Form:** Liquid Tempol / IV.
- **Sample Size:** 40 patients in each study.
- **Randomization:** 2:1 Tempol vs. placebo.
- **Efficacy Measures:**
  - Cisplatin: Creatinine clearance (baseline vs. end of treatment) and audiometry (baseline vs. end of treatment).
  - Doxorubicin: Reduction in LVEF >= 10% and cardiac troponin 1 levels.

Market Facts & General Information

- 180,000 patients receive cisplatin and doxorubicin annually (IMS -2012).
- **Cisplatin**
  - Nephrotoxicity evident in ~33% of patients after single 50mg/m² dose.
  - Ototoxicity evident in ~30% of patients after single 50mg/m² dose.
- **Doxorubicin**
  - Acute cardiotoxicity in ~15% of patients within 2-3 days of treatment.
  - Chronic cardiotoxicity in ~1.5% of patients 30+ days (up to several years) after treatment.

Toxicities can be life-threatening and often require cessation of treatment.
No FDA approved agents for prevention or amelioration of these effects.
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Chemotherapy Effects on TNF-alpha Cytokine Expression

Tumor Necrosis Factor Alpha (TNF-alpha) Cytokine
- TNF-alpha plays a central role in the side effects of chemotherapy and radiation therapy causing oxidative stress and inflammation.
- Chemotherapy and radiation therapy increases levels of TNF-alpha.

Chemotherapy and radiation therapy induced inflammation creates a host of adverse effects in patients, including:
- Pain
- Tissue damage and death
- Cell damage and death
- Fibrosis
- Fatigue

Oxidative stress causes severe toxic damage throughout the body, including:
- Key cellular components, including DNA, protein, and lipid;
- The heart and cardiomyocytes;
- The brain and neurons;
- Chemotherapeutic insult is particularly problematic for cardiomyocytes and neurons because the damage is generally irreversible. As a result, heart and brain function becomes permanently impaired.

These other cytokines further up-regulate expression of TNF-alpha causing more inflammation and oxidative stress.
- NF-kB
- Interleukin-6 (IL-6);
- Interleukin-1 (IL-1);
- Inducible nitric oxide synthase [iNOS];
- And other genes implicated in oxidative stress.