

High-Dose Vitamin C for Cancer Patients with Refractory Non-Hodgkin Lymphoma (NHL)

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Introduction

The Non-Hodgkin's lymphomas remain among the most treatable forms of cancer. In spite of success with present chemotherapy and antibody-based regimens, a large subset of patients will recur after primary and secondary treatment. This study is a Brind Center/KCC initiative to assess whether or not administering IV vitamin C (IV C) to patients with advanced NHL will support previous anecdotal and recent animal model reports of decreased tumor burden. Safety and low toxicity has been established for the dosages to be administered in this study, which will generally range between 75-100 grams per infusion, based upon targeted blood levels of 300-350 mg/dl. **This study has received IRB approval (#07U.21) and FDA approval (IND 77,486).**

Background

Previous trials of oral vitamin C therapy failed to demonstrate therapeutic benefit (1). However, recent pharmacokinetic modelling indicates that intravenous administration of Vitamin C produces a 25-fold or greater plasma concentration than the same dose given orally (2). It has been shown that vitamin C levels achievable in vivo only by intravenous infusion are selectively cytotoxic in vitro to various cancer cell lines but not to normal cells by a mechanism involving formation of hydrogen peroxide (3). This mechanism is dependent on pro-oxidant actions, as a consequence of ascorbate concentrations achieved only by intravenous administration. The most sensitive cancer line was a human non-Hodgkin B cell lymphoma. The mechanism of action of Vitamin C as a prodrug for hydrogen peroxide formation in the extravascular space has recently been confirmed by study collaborator Mark Levine, M.D. (4). This action of IV C is consistent with a growing literature that reactive oxygen species play an important role in the mechanism of action of proven cancer treatments and that impaired oxygen-reduction balance in cancer cells might cause induced reactive oxygen species to selectively kill cancer cells (5,6). A recent report found three well-documented cases of advanced cancers, confirmed by histopathologic review using National Cancer Institute Best Case Series Guidelines, where patients had unexpectedly long survival times after receiving high-dose intravenous vitamin C therapy (7); one of the cases was a non-Hodgkin

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lymphoma. In two animal studies (8,9), mice with Dalton's lymphoma showed vitamin C to potentiate the effect of the cis-platin resulting in prolonged tumour free survival of the mice. Overall, recent in vitro biological evidence, limited human case data, and clinical pharmacokinetic data confer biological plausibility to the notion that IV C could effect cancer cell biology.

Hypothesis

We hypothesize that high-dose IV C's action as a pro-drug for hydrogen peroxide formation in the extravascular space will have anti-tumor effects in aggressive lymphomas. We propose a phase II single agent study of intravenous Vitamin C to measure the activity and toxicity profile of this agent in patients with relapsed aggressive NHL.

Protocol Summary

Eligible candidates will be adults with aggressive or very aggressive NHL (WHO classification diagnosis confirmed by histological tumor examination). Patients must have failed one or more prior NHL chemotherapy or antibody therapy with curative intent, and the disease must not have progressed within 60 days of last therapy. In addition, patients must not be candidates for potentially curative therapy, such as HSCT, or they must have refused these alternative therapies. Full inclusion/exclusion criteria are available. History and physical examination, and laboratory and imaging analyses will be done within 14 days prior to registration. IV C infusions will be given three times a week on a schedule that allows at least 24 hours between each infusion, for a total of ten weeks (30 infusions). If disease progression occurs before or at the ten week assessment, then we discontinue protocol, based on futility. Toxicity and adverse events also will result in immediate discontinuation. If there is lack of disease progression or disease improvement, we will proceed and reassess again at 10 week intervals, for a total of three 10 week intervals. Initial criteria are based upon the criteria from the International Workshop to Standardize Criteria for Non-Hodgkin's Lymphoma (10); response for this study will utilize PET in accordance with revised criteria (11). We select 20 patients as the study size to initially evaluate true response rate to therapy.

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