

Simulation-Based Design of Phase I Clinical Trial of Intravenous Vitamin C Treatment

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Abstract

Adjunct therapy with intravenous vitamin C has the potential to enhance effectiveness of current treatments in cancer and other chronic conditions, while decreasing toxicity. Using estimates of toxicity at high vitamin C doses from available literature, we herein describe the use of mathematical simulations in 12 patients by applying the Continual Reassessment Method (CRM) to determine the optimal number of subjects per dose level to be enrolled in a clinical study of Puerto Rican cancer patients receiving high vitamin C intravenous doses. Two sources of a priori data (i.e., data by Hoffer and by Riordan) are used to perform the corresponding simulations. All except two of the episodes were either level 1 or 2 of toxicity. As expected, overall toxicity probabilities are higher from data by Riordan. No significant differences in terms of expected number of patients per dose level were observed after using either of the two sources of data. Based on results of the CRM approach, three subjects ($n=3$) per dose level is a large enough sample size to achieve the scientific goals of future trials. We concluded that the CRM method used in this clinical trial simulation minimizes some ethical and scientific dilemmas in sample size calculations that usually arise with standard designs.

Keywords: Vitamin C, High doses, Clinical trial, Toxicity, Continual reassessment method (CRM) simulations.

Introduction

Recently published research on vitamin C and cancer has increased the interest in the use of intravenous vitamin C as an alternative therapy for the integrative management of cancer and other conditions. The dynamic flow model proposed by Hickey refutes the current low-dose recommendations for dietary intakes and links the Linus Pauling's mega-dose suggestions with other reported effects of massive doses of ascorbate for the treatment of disease [1]. Standard cancer therapy, especially chemotherapy, is highly toxic. There is increasing evidence that intravenous vitamin C has the potential to become an adjunct therapy that improves the efficacy of current treatments while decreasing its toxicity.

Although, a couple of controlled clinical studies conducted at The Mayo Clinic did not support a significant benefit for terminal cancer patients after oral 10 grams of once-a-day oral Vitamin C, other (basic, animal and clinical) trials have demonstrated that ascorbate is safe, may indeed be effective killing malignant cells, decreasing tumor size, improving quality of life and increasing survival when administered intravenously [2-26].

Upon last October 2006, Cancer Treatment Centers of America (CTCA) initiated a US Food and Drug Administration-approved phase 1 study of intravenous vitamin C for patients with solid tumors who have exhausted all other available treatments [15]. In this CTCA study, the first cohort of three patients was treated with 30g/m² of vitamin C infusions on four consecutive days per week for a period of four weeks. High doses of vitamin C are used to

achieve blood ascorbate levels equal or greater than 20 mM that have previously been reported to be cytotoxic to tumor cells grown in hollow fibers and experimental models [7,11,27].

We are planning to conduct a Quality of Life (QoL) clinical study in Puerto Rican cancer patients receiving high Vitamin C intravenous doses in an intermittent scheme. The first step in this effort will be to characterize the disposition pattern of this compound given intravenously at high dose in humans, but without the influence of disease states (i. e., healthy volunteers). The central hypothesis of this study is that high intravenous doses of Vitamin C are safe and results in the desired minimum ascorbate concentration (20 mM) in human subjects. In a second stage, we expect to perform population pharmacokinetic studies in order to design target concentration-driven dosing algorithm for Vitamin C in Puerto Rican cancer patients. The latter is aimed at achieving the target plasma ascorbate concentrations in further clinical trials for dose optimization. The results of this study will further help us maximize the expected therapeutic benefits upon intravenous administration. That is, such information will be used to test the hypothesis that combining the right dose of Vitamin C with conventional chemotherapy will improve the clinical outcomes and QoL criteria versus the current standard-of-care approach in cancer. This alternative approach can then be recommended as the basis for a Puerto Rico wide quality improvement initiative of patient outcomes in cancer therapy. Noteworthy, this pharmacokinetic information is currently limited or lacking, especially in the Puerto Rican population.

To address these important research questions on the pharmacokinetic of Vitamin C at high doses an optimal design is required. The present work describes the use of mathematical simulations in 12 patients by applying the Continual Reassessment Method (CRM) to determine operative characteristic of the experiment to be conducted in humans based on estimates of toxicity at high Vitamin C doses from previous reports and the expected number of subjects that need to be enrolled per dosage level [28,29].

Results and Discussion

The data of toxic episodes are in Table 1 and Table 2. The two curves are quite different but we amalgamate first all the data of the two experiments. In Figure 1 there is the regression of dosage versus percentage of incidents of toxicity. It should be noted that all except two of the episodes were either level 1 or 2. Only two of the episodes were level 3. In order to maximize previous information, all cases will be taken into account in the planned experiment with healthy volunteers. Since we take into account all cases, even the mild ones, we will target 80% of toxicity since only a small fraction of those cases are expected to be severe.

Dose	1	2	3	4
mg/Kg	1200	1800	2700	4500
% affected	20.0	0.0	29.0	17.0

Table 1: Data set taken from Hoffer [28].

Dose	1	2	3	4	5
mg/Kg	1050	2030	3010	3990	4970
% affected	33.3	42.9	50.0	66.7	80.0

Table 2: Data set taken from Riordan et al. [29].

In Figure 1, we present the regression line of the toxicity versus the weekly dosage of the two experiments together. The regression line is as follows:

$$Y = 9.351907 + 0.010088 * X \quad (1)$$

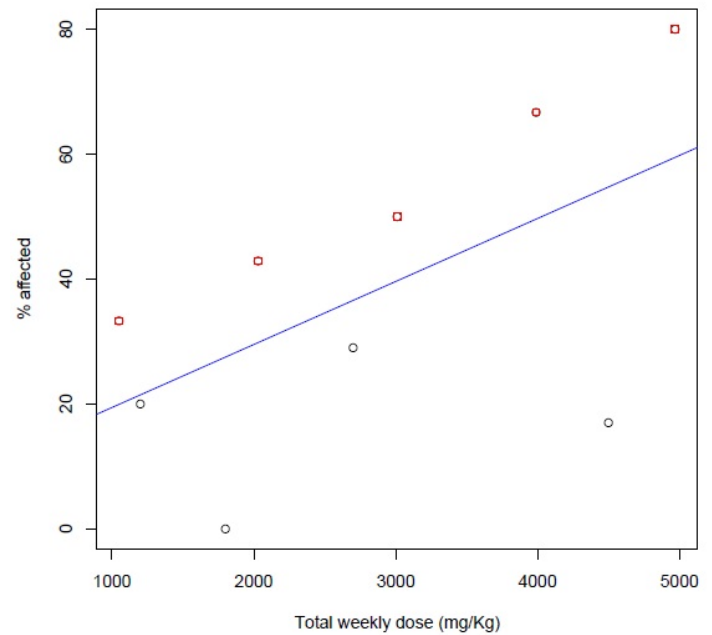


Figure 1. Linear regression model graph with all data included. Y-axis plots % affected with toxicity. The squares represent Riordan et al data set and circles represent Hoffer et al data set. Linear regression equation is presented by equation (1).

The estimates from overall toxicity based on the regression line are depicted in Table 3:

Level of Dosage	I: 2500	II: 3750	III: 4575	IV: 5000
Probability of Toxicity	0.346	0.472	0.555	0.598

Table 3: Estimation of overall toxicity probabilities for different dosages. The weekly doses are in mg/Kg.

According to the previous estimations and aiming for 80% of maximal toxicity (recall that 64 episodes were mild or moderate and only 2 severe), then the simulation gave the following distribution of patients (Table 4):

Level of Dosage	I: 2500	II: 3750	III: 4575	IV: 5000
Expected Number of Patients	3.09	3.09	3.03	2.79

Table 4: Expected number of patients per dosage according to CRM and maximal 80% of overall Toxicity.

This suggests a very balanced experiment over all the dosages (n=3 per dosage level) that will provide a balanced amount of information. We proceed in the next subsections to separate the two previous experiments.

Using only the data by Hoffer et al. [28] we have obtained the following linear regression equation:

$$Y = 12.188406 + 0.001691 * X \quad (2)$$

Figure 2 presents the regression line corresponding to this data points. Note that the levels of dosage in Table 3 are more conservative than Table 1 since the higher probability of toxicity assumes a 20%, which is almost 30% less. The estimates from overall toxicity based on the regression line using the data by Hoffer and co-workers are [28]:

Level of Dosage	I: 2500	II: 3750	III: 4575	IV: 5000
Probability of Toxicity	0.164	0.185	0.199	0.206

Table 5: Estimation of overall toxicity probabilities for different dosages using the regression model given in equation (2). The weekly doses are in mg/Kg.

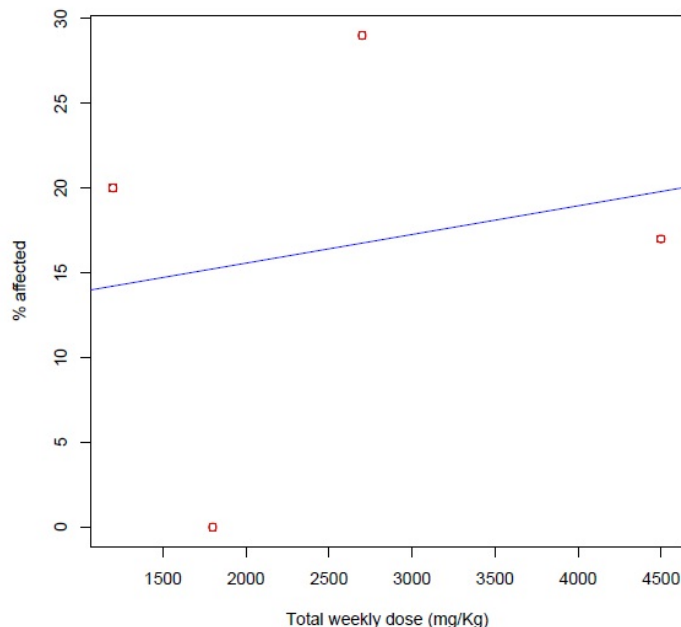


Figure 2. Linear regression model graph with data from Hoffer et al study [28]. Y-axis plots % affected with toxicity. Linear regression equation is presented by equation (2).

Whereas, the distribution of patients based on Hoffer data is [28]:

Level of Dosage	I: 2500	II: 3750	III: 4575	IV: 5000
Expected Number of Patients	3.00	3.00	3.00	3.00

Table 6: Expected number of patients per dosage according to CRM and maximal 80% of overall Toxicity. Hoffer et al. data was used [28].

By using the data provided by Riordan, we have the following linear regression equation (Figure 3) and estimates from overall toxicity as well as the expected number of patients [29]:

$$Y = 18.58286 + 0.01196 * X \quad (3)$$

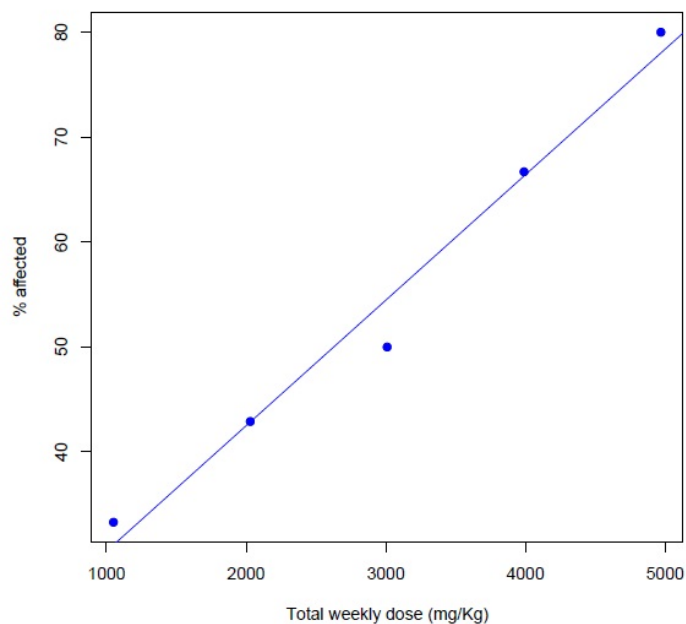


Figure 3: Linear regression model graph with data from Riordan et al study [29]. Y-axis plots % affected with toxicity. Linear regression equation is presented by equation (3).

Level of Dosage	I: 2500	II: 3750	III: 4575	IV: 5000
Probability of Toxicity	0.485	0.634	0.733	0.784

Table 7: Estimation of overall toxicity probabilities for different dosages using the regression model given in equation (3). The weekly doses are in mg/Kg.

Level of Dosage	I: 2500	II: 3750	III: 4575	IV: 5000
Expected Number of Patients	3.51	3.84	3.21	1.44

Table 8: Expected number of patients per dosage according to CRM and maximal 80% of overall Toxicity. Riordan et al. data was used [29].

As expected, the overall toxicity probabilities were higher from data by Riordan [29]. However, according to CRM, no significant differences in terms of the expected number of patients per dose level (i.e., approximately n=3) were observed after using either of the two sources of data.

The CRM methodology presented here has the advantage that it incorporates solid previous knowledge that comes in the form of two early studies. Since results from these two experiments were somewhat contradictory, we had to make three different analyses of the available data. Nevertheless, the conclusions are broadly convergent and predictions are comparable. Based on the probability of toxicity at the Vitamin C dosage range considered in this analysis, the CRM approach suggested the need of three

subjects (n=3) per dosage level in order to achieve the scientific goals of further trials. Accordingly, the CRM approach can thus minimize some dilemmas occurring with standard designs. That is, ethical pressure can be raised because larger than optimal number of patients are enrolled to be treated with doses that may be retrospectively predicted to be non-therapeutics or potentially toxic.

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