Personalized Medicine Universe 1 (2012) 49–53

Contents lists available at SciVerse ScienceDirect

Personalized Medicine Universe

journal homepage: www.elsevier.com/locate/pmu

Original article

High-dose intravenous vitamin C improves quality of life in cancer patients

Hidenori Takahashi [a], Haruyoshi Mizuno [b], Atsuo Yanagisawa [c,*]

[a] Seren Clinic Tokyo, 2-10-2 Shiroganedai, Minato-ku, Tokyo 108-0071, Japan
[b] Mizuno Medical Clinic, 1-23-48 Tsukioka, Sanjo City, Niigata 955-0803, Japan
[c] The International Educational Center for Integrative Medicine, 3-17-19-701 Hirokane, Minato-ku, Tokyo 108-0072, Japan

ARTICLE INFO

Article history:
Received 6 March 2012
Accepted 8 March 2012

Keywords:
Cancer
Intravenous vitamin C
Riordan protocol
Quality of life

ABSTRACT

Purpose: High-dose intravenous vitamin C (IVC) therapy has been safely employed for at least 30 years as one form of complementary alternative medical treatments for cancer. We prospectively examined the effects of IVC on the quality of life (QOL) in cancer patients in a multicenter observational study.
Methods: This study involved 60 patients with newly diagnosed cancer who visited participating institutions in Japan between June and December 2010 for IVC as an adjuvant cancer therapy. Using the QOL questionnaire developed by the European Organization of Research and Treatment of Cancer (EORTC), EORTC-QLQ C30, QOL was assessed before, and at 2 and 4 weeks of IVC therapy.
Results: The global health/QOL score significantly improved from 44.6 ± 27.8 to 53.2 ± 26.5 ($p < 0.05$) at 2 weeks and to 61.4 ± 24.3 ($p < 0.01$) at 4 weeks. Patients also showed significant increases in physical, role, emotional, cognitive, and social functioning at 4 weeks after IVC ($p < 0.05$). In the symptom scale, significant relief was observed, especially in the score of fatigue, pain, insomnia, constipation, and financial difficulties.
According to the Clinical Global Impression of Change (CGIC), attending physicians evaluated the QOL of their patients as minimally to much improved in 46.7% (28/60) and 60.0% (30/60) at 2 and 4 weeks after IVC, respectively. Only 2 patients at 2 weeks and 3 patients at 4 weeks were evaluated as minimally worse. Moreover, all adverse events were mild, and none of the patients discontinued the therapy because of adverse reactions to IVC.
Conclusions: IVC can safely improve the QOL of cancer patients. These results warrant the conduct of prospective comparative studies to evaluate the usefulness of IVC for patients with advanced cancer.

1. Introduction

Various cancer symptoms cause profound changes in the quality of life (QOL) of patients. Because pain due to cancer is considered to occur in 70% or more of patients in the terminal stage, management of cancer pain is extremely important for maintenance and improvement of the QOL. Recently, "the World Health Organization (WHO) guidelines for cancer pain relief" have been accepted as the standard treatment for cancer pain, and many cancer patients seek alleviation from pain with appropriate use of opioids [1]. However, approaches to treating pain refractory to opioids and various distressing symptoms associated with cancer other than pain have not yet been sufficiently established.

While these limitations of conventional medical approaches are becoming widely recognized, there is a trend in seeking ideas to overcome limitations in complementary and alternative medicine (CAM) worldwide. The same trend has also been observed in Japan, and there is a high prevalence of CAM use in patients with advanced cancer, who expect that this therapy will help maintain and improve their QOL [2].

High-dose intravenous vitamin C (IVC) therapy, as a form of CAM for cancer, has been safely performed in the United States for at least 30 years [3,4]. Several clinical studies have previously shown the clinical usefulness of oral and intravenous administration of high doses of vitamin C to cancer patients and that IVC may confer a survival benefit [5,6]. However, because later studies have not confirmed the usefulness of vitamin C [7,8], IVC was rarely administered in cancer care [9].

However, with growing worldwide interest in CAM in recent years, the usefulness of IVC has been actively re-evaluated. In 2005, the National Institute of Health and the National Cancer Institute of

* Corresponding author. 1-4-33-105 Takanawa, Minato-ku, Tokyo 108-0074, Japan. Tel.: +81 90 4746 2012 (cell), +81 3 5795 1473; fax: +81 3 5795 1475.
E-mail addresses: bzr06263@nifty.com (H. Takahashi), mizuno@mail.com (H. Mizuno), atsuo@yanagisawa.com (A. Yanagisawa).

2186-4950/$ – see front matter
doi:10.1016/j.pmu.2012.05.008

the United States jointly published a high-quality basic study, which showed that high vitamin C concentrations selectively exert anti-tumor effects on various cancer cells [10].

Moreover, it has been shown that patients with advanced cancer tend to have low blood concentrations of vitamin C [11]. Mayland et al., showed that blood vitamin C concentrations were low in 72% of 50 patients with advanced cancer and that low blood vitamin C concentrations correlated highly with short survival times.

Therefore, to examine the clinical usefulness of IVC in terms of QOL, we conducted a prospective observational study on changes in QOL due to IVC and evaluated its safety in cancer patients.

2. Methods

This study was designed as a multicenter, open-label, prospective, observational study and conducted with the approval of the ethics review committee of The Japanese College of Intravenous Therapy with which the participating institutions are affiliated.

2.1. Study subjects

From 390 members of The Japanese College of Intravenous Therapy (Tokyo, Japan), 145 private clinics and hospitals were registered for participating in the study. Subjects were selected by consecutive sampling from the outpatient clinic of each participating institution from June 1st to December 30th in 2010. All subjects were new outpatients voluntarily requesting high-dose IVC for adjuvant cancer therapy and met all of the following inclusion criteria, and none of the exclusion criteria. All patients received sufficient explanation in either written form or orally and provided informed consent to participate in the study.

Inclusion criteria were as follows: (a) patients with malignant tumors, at least 18 years of age, (b) patients with no history of IVC therapy, (c) patients able to attend outpatient visits to co-operative doctors for at least 1 month, (d) before participating this study and undergoing high-dose IVC therapy, patients received sufficient explanation from co-operative doctors, adequately understood it, and consented in writing to participating in the study and undergoing IVC therapy of their own free will.

Exclusion criteria were as follows: (a) patients with impaired consciousness, (b) patients with serious systemic conditions for whom regular outpatient visits were difficult, and (c) patients considered to be inappropriate for this study by their doctors.

At each of the 145 participating institutions, IVC therapy was performed on an outpatient basis, twice a week, according to the standard method. The study period was set as the first 4 weeks, and we requested that the patients complete the QOL survey forms and that the co-operative doctors complete the case report forms.

2.2. High-dose IVC therapy

According to the Riordan IVC protocol [12], which is the standard IVC method, the initial IVC dose was set at 12.5–15 g, and blood samples were collected concomitantly to measure glucose-6-phosphate dehydrogenase (G6PD) activity levels. After the G6PD activity levels were confirmed to be normal, doses of vitamin C were increased to 25 g for the second and 50 g for the third administration. For the fourth treatment and thereafter, blood samples were collected to measure blood vitamin C concentrations as necessary, and the vitamin C doses were adjusted to achieve blood vitamin C concentrations of 350–400 mg/dL immediately after infusion. Vitamin C was diluted with distilled water to an osmolality of 1200 mOsm/kg H_20_2 or lower, and then mixed with magnesium sulfate as necessary, and slowly drip-infused at a rate of 0.5–1.0 g/min. While IVC therapy was performed, oral vitamin C was administered at a dose of 2–4 g/day.

In addition, no particular limit was set on basic therapy, concomitantly used drugs, or other treatments during the study period.

2.3. QOL assessments

For evaluating the primary endpoint, QOL assessment was conducted using the Japanese version of the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC-QLQ C30) version 3 [13,14] before initiating therapy, and at 2 and 4 weeks of IVC therapy. The secondary endpoint was the Clinical Global Impression of Change (CGIC; 1, much improved; 2, moderately improved; 3, minimally improved; 4, no change; 5, minimally worse; 6, moderately worse; 7, much worse), which was assessed by the doctors in-charge of care and treatment of the patients [15]. As to the safety assessment during the study, subjective symptoms were assessed weekly with patient diaries. For objective indices, blood samples were collected as often as possible, and results of blood tests were assessed.

2.4. Statistical analysis

For statistical analysis, EORTC-QLQ C30 data were first processed according to the EORTC-QLQ C30 Scoring Manual. The scores before initiating IVC therapy were separately compared to those at 2 and 4 weeks of IVC therapy by the Wilcoxon signed-rank test. A p value of less than 0.05 was considered to be a statistically significant difference.

3. Results

During the study period, 63 patients were enrolled. Three patients did not complete their participation in the study: 2 patients whose performance status (PS) was already 4 at enrollment became unable to continue outpatient visits because of disease progression and one patient was hospitalized to receive radiotherapy during the study period. Thus, only the data from 60 patients were used for the study. The characteristics of study patients are shown in Table 1.

In 57 of the study patients (95.0%), the primary lesions were solid tumors. When initiating IVC therapy, 37 patients (61.7%) had advanced cancer with metastatic lesions, of which 12 had postoperative recurrence.

During the study period, anti-cancer therapy was concomitantly administered in 34 patients (56.7%), many of whom received chemotherapy.

The initial IVC dose for 34 patients (56.7%) was 15 g or less and for 21 (35.0%) was 25 g. Because G6PD activity was confirmed to be normal in all patients, the doses of vitamin C were increased. At 4 weeks of IVC therapy, the median single dose was 50 g (range, 25–100 g), and 36 patients (60.0%) received doses ranging from 50 to 65 g, and 21 (35.0%) received doses of 75 g or more. The IVC target blood concentration of at least 350 mg/dL was achieved in only 47% (27 patients) at the third week and 54% (31 patients) at 4 weeks.

The results for QOL assessment by using EORTC-QLQ C30 before and after IVC are shown in Table 2.

In QOL assessment, the global health status scores showed significant improvement from 44.6 $\pm$ 27.8 before IVC therapy to 53.2 $\pm$ 26.5 at 2 weeks ($p < 0.05$) and 61.4 $\pm$ 24.3 at 4 weeks ($p < 0.01$) of IVC therapy. The functional scale scores also showed significant improvement in all 5 items, i.e., physical, role, emotional, cognitive, and social functioning.