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

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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

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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.

Table 1
Baseline characteristics of the study subjects.

	No. of patients	(%)
Age		
Median (range, years)	61 (37–88)	
Sex		
Male	34	56.1
Female	26	43.9
ECOG Performance status		
0	14	23.3
1	34	56.7
2	5	8.3
3	6	10.0
4	1	1.7
Cancer diagnosis		
Lung	14	23.3
Breast	8	13.3
Stomach	8	13.3
Colon	6	10.0
Uterus	4	6.7
Liver	3	5.0
Prostate	3	5.0
Ovary	3	5.0
Pancreas	2	3.3
Malignant lymphoma	2	3.3
Others	7	11.7
Metastasis		
Positive	37	61.7
None	18	30.0
Unknown	5	8.8
Anti-cancer therapy during study period		
Cx	33	55.0
RT	1	1.7
None	26	43.3
Previous anti-cancer therapy		
Surgery only	8	13.3
Surgery + Cx	18	30.0
Surgery + Cx + RT	1	1.7
Cx only	20	33.3
Cx + RT	3	5.0
RT only	1	1.7
None	2	3.3
Unknown	7	11.7

ECOG: Eastern Co-operative Oncology Group; Cx: chemotherapy; RT: radiation therapy.

Table 2
Effects of intravenous vitamin C therapy on the quality of life (as assessed using the EORTC-QLQ C30 questionnaire) in 60 cancer patients.

	Before	2 weeks	4 weeks
Global health status/QOL			
Global health status	44.6 ± 27.8	53.2 ± 26.5*	61.4 ± 24.3**
Functional scales			
Physical functioning	74.0 ± 27.7	78.3 ± 23.7*	79.9 ± 24.1*
Role functioning	64.2 ± 33.0	71.2 ± 31.1*	75.4 ± 30.2**
Emotional functioning	76.4 ± 21.1	82.2 ± 19.0*	87.4 ± 15.3**
Cognitive functioning	74.3 ± 26.1	81.6 ± 23.9	84.2 ± 22.1**
Social functioning	70.9 ± 30.4	81.3 ± 25.2*	82.4 ± 21.7**
Symptom scales			
Fatigue	42.4 ± 28.7	31.8 ± 25.3**	28.4 ± 25.7**
Nausea and vomiting	8.9 ± 22.1	9.3 ± 20.6	7.6 ± 17.6
Pain	17.8 ± 25.7	13.8 ± 23.6	10.0 ± 13.9*
Dyspnea	27.2 ± 29.8	23.2 ± 27.2	16.4 ± 23.7
Insomnia	31.1 ± 32.1	23.2 ± 27.2*	16.4 ± 23.7**
Appetite loss	26.1 ± 36.4	30.5 ± 32.9	20.5 ± 28.0
Constipation	21.1 ± 31.3	13.6 ± 22.4*	11.7 ± 22.3*
Diarrhea	10.7 ± 24.3	9.2 ± 19.5	10.1 ± 20.0
Financial difficulties	34.5 ± 32.1	26.4 ± 29.8	26.2 ± 28.2*

$N = 60$; Values shown are mean ± standard deviation (SD); *$p < 0.05$ and **$p < 0.01$, compared to values before intravenous vitamin C (IVC) therapy; QOL, quality of life.

Regarding the symptom scales, fatigue scores, which were the highest before IVC therapy, showed significant improvement from 42.4 ± 28.7 before the IVC therapy to 31.8 ± 25.3 at 2 weeks of IVC therapy ($p < 0.01$); further, the improvement was maintained at 4 weeks with a score of 28.4 ± 25.7 ($p < 0.01$). The insomnia score, the second highest, showed an improvement from 31.1 ± 32.1 before IVC therapy to 23.2 ± 27.2 at 2 weeks ($p < 0.05$) and 16.4 ± 23.7 at 4 weeks of IVC therapy ($p < 0.01$). The scores of pain, constipation, and financial difficulties also showed significant improvement after 4 weeks of IVC therapy ($p < 0.05$).

For evaluating the secondary endpoint, the QOL was assessed by using the CGIC by doctors who were in-charge of care and treatment of the patients. Forty-six percent (28/60) and 60.0% (36/60) of the patients showed "minimally" to "much improved" conditions at 2 and 4 weeks after IVC, respectively. Only 2 patients (3.3%) at 2 weeks and 3 patients (5.0%) at 4 weeks showed "minimally worse" conditions (Table 3).

No patients discontinued their participation in the study because of adverse reactions to IVC. The observed subjective symptoms included headache in 5 patients (8.3%), nausea in 5 (8.3%), angialgia in 2 (3.3%), dry mouth in 1 (1.7%), tumor site pain (breast cancer) in 1 (1.7%), and dysuria in 1 (1.7%). All symptoms were mild, at Grade 1. Angialgia was relieved by applying warm compress to the sites, and all the other symptoms were managed by follow-up palliative treatment. Although 33 patients (55.0%) received concomitant anti-cancer drugs, no adverse events were reported in 45 (75.0%) throughout the study period.

4. Discussion

With the objective of examining the usefulness of high-dose IVC in improving the QOL of cancer patients, we conducted a multicenter prospective observational study and found that administration of IVC twice a week for 4 weeks significantly improved the QOL for cancer patients.

In recent years, the importance of providing palliative care to cancer patients in the early stage has been advocated worldwide, and clinical studies confirming the utility of this approach have also been reported [17]. However, specific approaches central to palliative care are presently limited to pain management. Although global studies on palliative care approaches have been conducted since the WHO issued guidelines for cancer pain relief in 1996 [1], management strategies for symptoms other than pain have not yet been established fully [18]. Most notably, for fatigue associated with cancer, which is described as the sixth vital sign, no effective therapy has been found.

Our results suggest that simple administration of high-dose vitamin C, an essential nutrient, can improve the QOL for cancer patients, especially in terms of various subjective symptoms, including fatigue.

There are several potential mechanisms by which vitamin C may improve the QOL for cancer patients. First, vitamin C deficiency is

Table 3
Effect of high-dose intravenous vitamin C on clinical global impression of change (CGIC) in 60 cancer patients.

Clinical judgment	2 weeks	4 weeks
Very much improved	2% (1/60)	2% (1/60)
Much improved	8% (5/60)	10%(6/60)
Minimally improved	37%(22/60)	48%(29/60)
No change	50%(30/60)	35%(21/60)
Minimally worse	2% (1/60)	5% (3/60)
Much worse	0% (0/60)	0% (0/60)
Very much worse	0% (0/60)	0% (0/60)

present in many cancer patients [11]. Supplementation may improve QOL by relieving fatigue and various other symptoms caused by a state of chronic vitamin C deficiency in these patients. While IVC therapy approach consists mainly of intravenous infusion of high-dose vitamin C approximately twice a week, concomitant oral administration of vitamin C at a high-dose is recommended [12]. In fact, oral administration of vitamin C may be more helpful for patients with a chronic deficiency of vitamin C than intravenous infusion of high-dose vitamin C. The clinical studies conducted in the 1970s to assess oral administration of vitamin C showed no significant difference in survival benefit, but the QOL was not assessed in those studies [7,8]. In future studies, clinical usefulness of oral vitamin C supplementation in cancer patients with vitamin C deficiency need to be evaluated. Further, opioid doses for cancer pain may vary among individual patients, and optimal doses of vitamin C may differ depending on tumor types and individual differences among patients. For example, patients with advanced lung cancer are reportedly exposed to very high oxidative stress [19]. According to the results of our present study, relief of subjective symptoms, such as fatigue, may serve as an index to determine the most appropriate doses for individual patients. Future studies should focus on method to determine the optimal vitamin doses C for individual cancer patients.

The second mechanism we must consider is the possibility that a direct anti-cancer activity of vitamin C improved QOL for cancer patients. At present, vitamin C is known to exert anti-cancer activity selectively on cancer cells by generating pro-oxidant activity, depending on blood concentrations, without affecting normal cells [10,20,21]. Moreover, in order to achieve blood vitamin C concentrations high enough to exert anti-cancer activity, high doses of vitamin C need to be administered intravenously rather than orally [4]. Thus, IVC is regarded as a treatment in which high doses of vitamin C are deliberately administered via intravenous infusion to achieve blood concentrations of vitamin C that can exert anti-tumor effects [22–28]. As a result of IVC therapy, the target blood concentration of vitamin C was achieved in approximately half of the patients in this study and most patients showed QOL improvement.

In another study on QOL changes induced by administration of vitamin C to cancer patients [29], vitamin C was intravenously infused at 10 g/session only twice during the 1-week study period, and oral vitamin C was concomitantly administered at a dose of 4 g daily during the same period. The QOL before versus after the study period was assessed using the EORTC-QLQ C30. As in our study, significant improvement was observed in several indices, including the global health status scale and fatigue scale. Because it is apparent that the intervention strategy used by Yeom et al. did not achieve blood vitamin C concentrations high enough to exert anti-tumor effects, improvement of the QOL and relief of subjective symptoms, such as fatigue, might have been attributable to mechanisms other than the direct anti-tumor effects of IVC.

As to other anti-tumor mechanisms, vitamin C was recently shown to be involved in anti-angiogenesis [30–32]. Because subjective symptoms were relieved in a relatively short period of 1–2 weeks in both our study on QOL in cancer patients and the study by Yeom et al. [33], we consider it probable that QOL improvements might have been caused by mechanisms other than direct anti-tumor effects of vitamin C. The clinical significance of the original objective of IVC, which is "to achieve high blood concentrations of vitamin C via intravenous infusion," should be determined by assessing direct anti-tumor effects instead of whether the QOL improvement or subjective symptom relief is rapidly achieved. Further long-term studies may be necessary to assess this possibility. At present, clinical studies on the anti-tumor effects of IVC are ongoing in various regions and the results are awaited.

A third possible mechanism of improvement of the QOL by IVC is the suppression of the effects of anti-cancer drugs by vitamin C, resulting in reduction of adverse reactions to these drugs, thereby improving QOL. The complex biokinetics of vitamin C has sparked numerous discussions on whether vitamin C reduces the effects of anti-cancer drugs [27,34–37]. However, because IVC is already in widespread use, mainly in the United States, clinical studies on the usefulness of IVC in combination with anti-cancer therapy have been started [16,38]. The advantages and disadvantages of combining IVC and anti-cancer drugs may well be revealed in the future.

Although subjective symptoms, such as angialgia during IVC therapy and headache/nausea after treatment, occurred in a few patients, all subjective symptoms were quite mild. These are known adverse reactions caused by the relatively high osmotic pressure of IVC, and are considered to be treatable on an outpatient basis. Moreover, there were 46 patients (80.7%) who answered that they would request continuation of IVC after study completion, indicating extremely high adherence. As shown in an IVC Phase I study recently conducted in the United States [16], we believe that IVC can be safely performed for cancer patients on an outpatient basis.

The present study has certain limitations. The study is a prospective rather than a comparative study. Further, the QOL scores used as the primary endpoint are extremely subjective indices. In addition, no particular limit was set on concomitant anti-cancer therapy and various other therapies, including CAM. The anti-tumor effects of IVC were not assessed, because of the relatively short study period. Although the target blood vitamin C concentration for the original IVC therapy was achieved in approximately half of the study patients, it is noteworthy that QOL, especially regarding fatigue and insomnia, was significantly improved within as low as 1 month after initiating IVC therapy. However, further long-term clinical studies are required to evaluate the clinical effectiveness of intravenous vitamin C therapy.

5. Conclusion

We conducted a multicenter prospective observational study to examine the effects of high-dose IVC therapy on the QOL of cancer patients. Scores for both the global health status and functional scales of the EORTC-QLQ C30 showed significant improvement at 4 weeks of IVC therapy; further, subjective symptom scores, especially those for fatigue and insomnia, showed significant improvement. On the basis of these results, we propose that IVC can safely improve the QOL of cancer patients. IVC has drawn attention as one of the anti-cancer therapies expected to safely exert anti-tumor effects, and clinical studies combining IVC with anti-cancer drugs are currently underway. Meanwhile, it may also be important to conduct prospective clinical studies on the usefulness of IVC as a palliative care procedure that improves the QOL of cancer patients, focusing particularly on the relief from fatigue. In addition, future studies on the IVC protocol need to focus on the effects of repetitive intravenous infusion of high-dose vitamin C and regular oral supplementation of vitamin C in the IVC protocol.

Conflict of interests

The authors have no potential conflicts of interest relevant to this study.

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