• REVIEW ARTICLES •

Vitamin C and Cancer: What can we Conclude - 1,609 Patients and 33 Years Later?

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In 1976 an article co-authored by Linus Pauling described that 100 terminal cancer patients treated with intravenous vitamin C, followed by oral maintenance, lived four times longer than a control group of 1,000 patients who did not receive vitamin C. The study was strongly criticized because the control group was very different from the group treated with vitamin C. The latter were declared terminally ill much sooner than the control group thus resulting in an artificially longer survival for the vitamin C group. Three double blind placebo controlled randomized trials performed at Mayo Clinic using oral vitamin C for cancer patients were negative. In a phase I-II trial performed by Riordan et al, none of 24 cancer patients treated with IV vitamin C responded. At this point we don't have information as to which is the actual plasma level of vitamin C that can produce tumor shrinkage. We don't have consistent information either regarding what is the clinical dose necessary to yield therapeutic plasma levels. In view of this lack of data after trials which have included at least 1,591 patients over 33 years, we have to conclude that we still do not know whether Vitamin C has any clinically significant antitumor activity. Nor do we know which histological types of cancers, if any, are susceptible to this agent. Finally, we don't know what the recommended dose of Vitamin C is, if there is indeed such a dose, that can produce an anti-tumor response. [*P R Health Sci J 2010;3:215-217*]

Key words: Vitamin C, Cancer, Dose, Plasma level

In 1976, Dr. Cameron, a Scottish physician, published in collaboration with Linus Pauling an article in the prestigious journal PNAS describing that 100 terminal cancer patients treated with intravenous vitamin C for 10 days followed by oral maintenance, lived four times longer than a control group of 1,000 patients who did not receive vitamin C (1). The study was retrospective in nature but nevertheless it stirred a great deal of excitement in many scientific minds as well as in the lay public, some of which still persists. However, the study was strongly criticized by Dr. William Dewys who discovered that the control group was very different from the group treated with vitamin C because the latter were declared terminally ill much sooner than the control group (2). Because survival was measured from the time the patients were declared terminally ill to the time when they died, that resulted in an artificially longer survival for those assigned to receive Vitamin C. Dr. DeWys noticed this bias when he discovered that the time that elapsed from the diagnosis of cancer to becoming terminally ill was shorter for patients receiving Vitamin C as compared with controls when it should have been similar for both groups.

In order to verify these findings, Creagan et al. from the Mayo Clinic, decided to investigate further this issue in a rigorous double-blind randomized prospective study in which half the patients received high doses of oral Vitamin C and the other half an oral placebo. The patients were all terminal and had failed prior chemotherapy. The results were published in 1979 in the New England Journal of Medicine (3). The control group and the vitamin C group were very comparable regarding age, performance status and other important prognostic factors. Sixty patients were treated with Vitamin C (experimental group) and 63 with placebo (control group). There was no difference in survival between the two groups with survival curves virtually overlapping. No difference was found either in relation to symptomatic improvement, weight loss or performance status.

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Although patients in Cameron's original study were similar to those from the Mayo Clinic, Linus Pauling criticized the latter study, alleging that the Mayo Clinic patients had received prior chemotherapy, and thus their immune system was deficient. For this reason, Moertel et al. from Mayo Clinic, decided to repeat the study limiting it to patients who had not received prior chemotherapy. The results, published in 1985, were equally poor (4). A third double-blind study conducted by Tschetter et al. also arrived at similar conclusions (5).

In 1994 Robinson et al. published a study conducted in nude mice transplanted with squamous cell carcinoma and treated with high doses of intravenous Vitamin C. The findings were somewhat worrisome because they showed that high doses stimulated the growth of these tumors and only megadoses had an antitumor effect (6). For vitamin C to be effective, the doses had to be so high that it was not certain whether they could be achieved in humans without intolerable toxicity. However, Casciari et al. in 2001 published results of a study (7) aimed at determining which Vitamin C levels in blood were necessary to produce an antitumor effect on colon cancer cells growing in vitro. They found that levels of 10 mM/L or higher were required for this purpose. To determine which doses of vitamin C were needed to achieve such a level in blood, they studied a single patient to whom they first administered 30 and later on 60 gm of intravenous vitamin C. They found that a dose of 60 gm was capable of producing a plasma level above 10 mM/L. In a more recent dose finding and pharmacokinetic phase I clinical trial (8), Hoffer et al. entered 18 patients with advanced cancer. The aim of that study was to explore the safety of i.v. ascorbic acid administered in a dose sufficient to sustain plasma ascorbic acid concentrations >10 mmol/l for several hours. Pharmacokinetic studies were obtained for six patients infused with 0.1, 0.2, 0.4, 0.6 and 0.9 g/kg and five patients infused with 1.5 g/kg. They determined that intravenous ascorbic acid, administered at a dose of 1.5 g/kg three times weekly, appears to be safe and is capable of achieving plasma ascorbic acid concentrations >10 mM/L for >4 h in patients with normal renal function. They recommend a dose of 1.5 g/kg for future phase II trials. No antitumor response was observed in these 18 patients.

The latter study aimed at obtaining plasma ascorbic acid concentrations >10 mM/L for several hours since that appeared to be the required concentration to attain antitumor effects. However, in another study performed by Casciari et al. in guinea pigs, they found that a much lower plasma level of 1 mM/L was capable of inducing antitumor effects in L-10 transplanted cells (9). The quality of this research study has to be questioned in view of the fact that essential information such as the number of guinea pigs in each experiment was missing from their report.

Based on the first study by Casciari (7), Riordan et al. criticized the Mayo Clinic studies arguing that treatment with oral vitamin C can not achieve the plasma levels of 10 mM/L required for the antitumor effect of Vitamin C. According to him, only doses of 50 gm or higher (equivalent to ~0.7 gm/kg in an average adult) are capable of achieving such a plasma level. He chose to ignore the second study by Casciari in which L10 tumor cells (9) were sensitive to much lower levels of Vitamin C. Riordan ignored this study in spite of the fact that he had actually co-authored that study with Casciari. Riordan then decided to administer high doses of vitamin C intravenously to 24 patients with terminal cancer (10). As it was unknown whether high doses could be tolerated intravenously, they started treatment at a dose of 10 grams and gradually escalated the doses to reach 50 grams. The drug was given as a continuous infusion over 8 weeks. In general, these doses were well tolerated except for one case who developed renal calculi and two who developed anemia. It was disappointing that none of the 24 cancer patients responded to treatment (10). The mean plasma level was 1.1 mM/L which is in the range of the necessary therapeutic levels according to the L-10 study (9) although below the range of 10 mM/L thought to be necessary in the colon cancer in vitro model (7). It is very disconcerting to find that the vitamin C levels in Riordan's clinical trial in patients with cancer didn't correlate with the dose administered (10). No explanation was given for this unusual finding. Another unknown piece of information is what is the intratumoral vitamin C level necessary to achieve cytotoxicity. It is possible that malignant tumors might be more avid for vitamin C than normal tissues and that a relatively low plasma level might be enough to produce cytotoxicity. In fact that is exactly what Casciari's study with the L-10 model showed. Most patients in Riordan's clinical study were treated at doses below 50 gm and therefore according to him, did not receive optimal treatment. Five patients did receive treatment at the 50 gm dose and all of them failed to respond.

In conclusion, assuming that 1.5 g/kg three times weekly of intravenous vitamin C is the recommended dose, then this agent has not received a fair and adequate trial. However, we have contradictory information as to which is the actual dose that can produce tumor shrinkage. It is very likely that such dose might vary according to the type of tumor treated.

After trials which have included at least 1,609 patients over 33 years, we have to conclude that we still do not know whether Vitamin C has any clinically significant antitumor activity. Nor do we know which histological types of cancers, if any, are susceptible to this agent. Neither do we know with certainty what is the required plasma ascorbic acid level that will result in antitumor effects. Assuming that this level is 10 mM/L then the recommended dose of Vitamin C appears to be in the range of 1.5 g/kg three times weekly.

Dr. Riordan's followers and collaborators, now close to 5 years after his death, have failed to generate convincing scientific evidence that this drug is clinically effective. They should concentrate their efforts in answering all of these so far unanswered questions. From the clinical standpoint, a phase II study using 1.5 g/kg three times weekly would be in order so as to establish if there is any hint of antitumor activity. Clearly high dose intravenous Vitamin C is not without its side effects, some

of which can be very serious, including renal failure (11-12). At this time it is not acceptable or ethical to recommend this treatment to anyone with cancer, except within the framework of a clinical trial.

Resumen

En 1976, un artículo co-escrito por Linus Pauling describió que 100 pacientes con cáncer terminal tratados con vitamina C endovenosa seguido por mantenimiento oral, vivieron cuatro veces más que un grupo control de 1,000 pacientes que no recibieron vitamina C. El estudio fue duramente criticado porque el grupo control era muy diferente al grupo tratado con vitamina C. Los pacientes tratados con Vitamina C se declararon terminales mucho antes que el grupo control, resultando así en una supervivencia artificialmente más larga para el grupo de vitamina C. Luego de esto, tres ensayos doble ciego aleatorios realizados en la Clínica Mayo exploraron el uso oral de la vitamina C comparándola con un placebo en pacientes terminales con cáncer. Los tres fueron negativos. En un estudio fase I-II realizado por Riordan et al., ninguno de los 24 pacientes con cáncer tratados con vitamina C endovenosa respondieron. Mas aun, en este momento no tenemos información en cuanto a cual es el nivel en plasma de vitamina C capaz de producir una respuesta antitumoral. Tampoco tenemos información consistente con respecto a cuál es la dosis clínica necesaria para obtener dichos niveles plasmáticos terapéuticos. En vista de esta falta de datos luego de varios ensayos clínicos que han incluido al menos 1,591 pacientes por un periodo de 33 años, tenemos que concluir que todavía no sabemos si la vitamina C tiene actividad antitumoral clínicamente significativa. Tampoco sabemos que tipos histológicos de cáncer, si es que hay alguno, son susceptibles a este tratamiento. Por último, no sabemos cuál es la dosis terapéutica recomendada de vitamina C, si realmente existe tal dosis, que pueda producir una respuesta antitumoral.

References

1. Cameron E, Pauling L. Supplemental ascorbate in the supportive treatment of cancer: Prolongation of survival times in terminal human cancer. Proc Natl Acad Sci U S A 1976;73:3685-3689.
2. DeWys W. How to evaluate a new treatment for cancer. Your Patient and Cancer 1982;2:31-36.
3. Creagan ET, Moertel CG, O'Fallon JR, et al. Failure of high-dose vitamin C (ascorbic acid) therapy to benefit patients with advanced cancer. A controlled trial. N Engl J Med 1979;301:687-690.
4. Moertel CG, Fleming TR, Creagan ET, Rubin J, O'Connell MJ, Ames MM. High-dose vitamin C versus placebo in the treatment of patients with advanced cancer who have had no prior chemotherapy. A randomized double-blind comparison. N Engl J Med 1985;312:137-141.
5. Tschetter. A community based study of vitamin C (ascorbic acid) in patients with advanced cancer. Proc ASCO 1983;2:abstr 92.
6. Robinson AB, Hunsberger A, Westall FC. Suppression of squamous cell carcinoma in hairless mice by dietary nutrient variation. Mech Ageing Dev 1994;76:201-214.
7. Casciari JJ, Riordan NH, Schmidt TL, Meng XL, Jackson JA, Riordan HD. Cytotoxicity of ascorbate, lipoic acid, and other antioxidants in hollow fibre in vitro tumours. Br J Cancer 2001;84:1544-1550.
8. Hoffer LJ, Levine M, Assouline S, et al. Phase I clinical trial of i.v. ascorbic acid in advanced malignancy. Ann Oncol 2008;19:1969-1974.
9. Casciari JJ, Riordan HD, Miranda-Massari JR, Gonzalez MJ. Effects of high dose ascorbate administration on L-10 tumor growth in guinea pigs. P R Health Sci J 2005;24:145-150.
10. Riordan HD, Casciari JJ, Gonzalez MJ, et al. A pilot clinical study of continuous intravenous ascorbate in terminal cancer patients. P R Health Sci J 2005;24:269-276.
11. McAllister CJ, Scowden EB, Dewberry FL, Richman A. Renal failure secondary to massive infusion of vitamin C. JAMA 1984;252:1684.
12. Wong K, Thomson C, Bailey RR, McDiarmid S, Gardner J. Acute oxalate nephropathy after a massive intravenous dose of vitamin C. Aust N Z J Med 1994;24:410-411.