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VITAMIN C, EDTA & ULTRAVIOLET IN CANCER TREATMENT

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EXECUTIVE SUMMARY

Cancer has fast becoming one of the leading cause of morbidity and mortality in the world. Adjunctive therapies such as vitamin C and chelaters are said to have powerful healing properties in the treatment of cancer.

Vitamin C is a highly effective and least toxic anti-oxidant i.e. protecting body against oxidative stress including free radicals. On the other hand, EDTA has been approved by US FDA for chelation therapy for lead and heavy metal poisoning. As for UV radiation, the beneficial effects include vitamin D production and treatment of certain skin conditions.

There was insufficient strong evidence retrieved to support the effectiveness and safety of vitamin C on treatment of cancer. However, there was no evidence retrieved on the effectiveness and safety EDTA and ultraviolet on the same issue.

Based on this review, more clinical research is required to provide evidence to support the effectiveness, safety and cost-effectiveness of vitamin C, EDTA and ultraviolet in the treatment of cancer.

VITAMIN C, EDTA & ULTRAVIOLET IN CANCER TREATMENT

1. INTRODUCTION

Cancer has fast becoming one of the leading cause of morbidity and mortality in the world. World Health Organization reported that the condition accounted for 7.9 million deaths (around 13% of all deaths) in 2007.[1] In fact, such deaths worldwide are projected to continue rising, with an estimated 12 million deaths in 2030. Most of the cancer deaths yearly are due to lung, stomach, liver, colon and breast cancer. In the United States of America, one of every four deaths is due to cancer.[2] According to Malaysian Burden of Disease and Injury Study, cancer ranks sixth in the overall burden of disease and is responsible for 6.5% of the total DALYs[3]. Health Facts 2004 of Malaysia also stated that malignant neoplasms was the 10th principal cause of hospitalisation and the 3rd principal cause of death in the Ministry of Health hospitals.[4]

Cancer arises from mutated normal cell in a multistage process.[1] These are due to interaction between a person's genetic factors and external agents i.e. physical, chemical and biological carcinogens. Treatment-wise, apart from curing and prolonging life, the aim of cancer treatment includes improving quality of life of the patients. Principal treatment methods of this condition are surgery, radiotherapy and chemotherapy. Palliative care is provided to those who are not able to have a curative treatment.

Adjunctive therapies on cancer are said to have powerful healing properties of their own.[5] They include vitamin C, chelaters, ozone, etc. Vitamin C, taken as supplementary antioxidants against free radicals, is postulated to help in cellular defense in the prevention and treatment of certain diseases like cancer. This can be done via increasing intake of it either through increasing the dietary intake of antioxidant-rich foods or taking its supplements. On the other hand, some alternative practitioners claim that chelation can be used as a cancer treatment in removing 'environmental toxins' from the body or blocking the production of free radicals.[6] Other method advocated in cancer treatment includes photodynamic therapy (PDT) which photosensitises drugs used for such treatment.[7]

This technology review was done following Minutes of Post-Cabinet Meeting.

2. OBJECTIVE

To assess the effectiveness, safety and cost-effectiveness of vitamin C, Ethylenediaminetetraacetic acid (EDTA) and ultraviolet in the treatment of cancer

3. TECHNICAL FEATURES

3.1 Free radicals

Atoms consist of a nucleus, neutrons, protons and electrons.[8] When the bonds between these parts split, free radicals are formed. They are very unstable and react quickly with other molecules/compounds to gain stability. This may lead to a chain reaction which eventually results in the disruption of a living cell. Some free radicals arise normally during metabolism and immunity. However, environmental factors such as pollution and radiation can also produce free radicals. Normally, the body can handle free radicals but if antioxidants are unavailable or if the free-radical production becomes excessive, damage can occur. Antioxidants are thought to protect the body against the destructive effects of the free radicals by neutralizing the free

radicals. They themselves don't become free radicals by donating an electron because they are stable in either form.

3.2 Vitamin C

Vitamin C or L-ascorbate is an essential nutrient in a range of essential metabolic reactions in the normal growth and development of humans.[9,10,11] It plays an important role in the synthesis of collagen, promote wound healing and influence many immunological and biological reactions in the body. It is also a highly effective and least toxic anti-oxidant particularly in protecting body against oxidative stress including free radicals, and also toxic chemicals as well as pollutants. Proponents of megadose combination vitamin therapy, including vitamin C for cancer, based their recommendations on laboratory studies indicating that these substances cause immune modulation, tumour suppression and promotion of cell differentiation.[11] They also recommend that megadose vitamin C administered either intravenously or orally and can be given concurrently with chemotherapy.

When attached to a hydrogen ion, L-ascorbate ion forms ascorbic acid.[10,11,11] Humans have no enzymatic capability to manufacture the vitamin and therefore obtain it from dietary sources especially the green vegetables and fruits. The North American Dietary Reference Intake recommends 90 milligrams Vitamin C per day and not more than 2 grams/day. This can be achieved through well-balance diet. However, the body requirement for it increases in physical or chemical stress and in elderly people. This belief has led to the widespread use of vitamin C supplements. Lack of the vitamin is rare but may results in scurvy.

The biological half-life for Vitamin C is short that is 30 minutes only.[9] As it a water-soluble vitamin, it is not stored in the body and excreted in the urine.[9,11,11] Due to this, humans need a continuous supply of the vitamin. Vitamin C exhibits remarkably low toxicity based on animal study. It is chemically decomposed under certain conditions for example at temperature of 190^{o}C. Vitamin C supplements are generally well-tolerated. High doses may cause stomach irritation, diarrhoea and others. It may also acidify the urine, alter the results of urine tests, affect iron metabolism and possibly increase risk of oxalate deposits in kidney or bladder.[11]

3.2 EDTA

EDTA is a widely used abbreviation for the chemical compound_ethylenediaminetetraacetic acid[12,13] The chemical is not found naturally and mostly synthesised from 1,2-diaminoethane (ethylenediamine), formaldehyde (methanal), water and sodium cyanide. This polyamino carboxylic acid is widely used to sequester di- and trivalent metal ions. It is not degraded or removed during conventional wastewater treatment. But adjustment of pH and sludge residence time may result in almost complete mineralization of EDTA.

The important uses of EDTA are in the cleaning industry, food industry (approved by US Food and Drug Administration/US FDA as a preservative in packaged foods and vitamins), medical treatment particularly in chelation therapy for lead and heavy metal poisoning (approved by US FDA), as anticoagulant in medical and laboratory chemicals/equipment.[12,13,14] It has been found to be both cytotoxic and weakly genotoxic in laboratory animals.[12] EDTA is available as an injection (150mg/ml) and tablet (poor absorption at 3-8% only). In lead and heavy metal poisoning, EDTA is given in infusions in a 1 to 5 hours treatment with a minimum of 20 treatments.[13,14] IV infusion of EDTA typically costs US$75-150 each (20 treatments cost about

$3000) and oral testament of 180 tablets between US$37-86.[14] The treatment should not be given during pregnancy, in severe renal failure or hypothyroidism.

Common side-effects reported include burning sensation at injection site, allergic reaction, hypoglycaemia, hypotension, etc. It may also diminish desirable nutrients e.g. calcium and zinc.[13,14] EDTA also increases effect of insulin and may decrease the insulin requirement.[14]

3.4. Ultraviolet

Ultraviolet radiation is a form of electromagnetic energy and found in sunlight.[15,16] As an ionizing radiation, it can cause chemical reactions and many other health effects, both beneficial and damaging. The radiation is classified according to wavelength in nanometers (nm). There are three categories of it i.e. ultraviolet A with wavelength between 320 and 400 nm, ultraviolet B with wavelength between 280 and 320 nm and ultraviolet C with wavelength between 200 and 280 nm. The shorter the wavelength, the more energetic and more biologically damaging the radiation is. In this case, the ultraviolet C is potentially the most damaging but fortunately, it is being absorbed by oxygen and ozone in the stratosphere and could not reach the surface of the earth. In fact, because of the absorption, 98.7% of the ultraviolet radiation that reaches the surface is ultraviolet A.

The beneficial effects of ultraviolet radiation include vitamin D production and treatment of skin conditions e.g. psoriasis and vitiligo. The harmful effects of ultraviolet radiation are like sunburn, skin cancer, phokeratitis or arc eye, cataract, etc.

4.METHODOLOGY

4.1Search Methods

Literatures were searched through electronic databases specifically PubMed/Medline, Cochrane, INAHTA and also in general databases. The search strategy used the terms, which are either singly or in various combinations: ("Neoplasms"[Mesh] AND "Therapeutics"[Mesh]), (Cancer OR neoplasms), "cancer treatment", "Ascorbic Acid"[Mesh], vitamin C, "Edetic Acid"[Mesh], (“ethylene diamine tetraacetic acid” OR EDTA), "Ultraviolet Therapy"[Mesh], ultraviolet treatment. In Pubmed/Medline database, limits applied were Humans, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Review, English.

4.2 Selection of studies

Any primary and secondary papers pertaining to Cancer Treatment with vitamin C, EDTA or ultraviolet will be included in this technology review. Literatures discussed solely on prevention, those without abstract, and those that full text could not be obtained were excluded. A critical appraisal of the retrieved relevant papers was performed and the evidence level was graded according to the US/Canadian Preventive Services Task Force (Appendix 1).

5. RESULTS AND DISCUSSION

5.1 Effectiveness

5.1.1 Vitamin C

The potential role of vitamin C in the prevention of cancer has been the subject of a great of research.[11] On the other hand, there are not many articles retrieved from the scientific databases that study on its safety and effectiveness in the treatment of cancer.

A total of five online articles discussing on the effectiveness of vitamin C in the treatment of cancer have been retrieved. They consist of one Health Technology Assessment (HTA), one large randomised controlled clinical trial (RCCT) and three small non-randomised, non-controlled clinical trials. The HTA, RCCT and one of the non-randomised, non-controlled trials studied a combination of vitamin C with other vitamins. The ability to infer from the findings to attribute the reported efficacy to vitamin C specifically is limited because of the multi-component intervention used. In fact, type of cancer patients participated in the studies was diversified from all types to either Prostate Cancer or Non-Small Cell Lung Cancer.

In the HTA report of clinical trials on human subjects, extraction on the supplemental use of vitamin C for the treatment of cancer involved only four studies.[17 level I] Only the fatal and development of new tumours outcomes were related to this technology report. The HTA could not pool the related data due to heterogeneity. However, it was reported that there was no significant decrease in risk of all-cause mortality for vitamin C as a treatment for advanced cancer (Recommended Daily Allowance/RDA doses of combined vitamins to megadoses of these vitamins in Bladder Cancer, RR=0.86, 95% CI 0.37 to 2.01; daily 10 gm vitamin C to placebo in advanced Rectum and Colon Cancer, RR=1.04, 95% CI 0.69 to 1.57; and daily 3 gm vitamin. C to placebo in Breast Cancer, RR= 1.52, 95% CI 0.72, 3.23).

From the same HTA mentioned above, vitamin C was beneficial in reducing occurrence of new tumours in a single trial on patients with Bladder Cancer having bacillus Calmetee-Guerin (BCG) vaccination.[17 level 1] The RR of megadoses of combined vitamin to RDA doses was 0.50, 95% CI 0.32 to 0.78. From these findings, the HTA concluded that there was little evidence to support that vitamin C can beneficially affect survival. The assessment did not support the use of supplements of vitamin C to treat cancer. This was in contrast to the numerous observational studies reporting benefits in persons consuming diets that were high in vitamin C. The limitation of this 2003 HTA report was that it involved studies from 1984 – 1994.

The above negative findings were supported by a large RCCT involving 136 patients conducted on the effectiveness of chemotherapy plus high dose of multiple antioxidants (vitamins C, E and beta carotene) against those without the antioxidants in advanced Non-small Cell Lung Cancer.[18 level I] The difference in response rates between the two arms was not significant (p=0.28). In fact, the overall survival between the two arms was also not significant (p=0.20). It was proposed that larger trials are needed to demonstrate whether high-dose multiple antioxidants in conjunction with chemotherapy increase the response rates and/or survival time in advanced lung cancer.

A recent study used intravenous (IV) vitamin C (ascorbic acid) in advanced malignancy instead.[19 level II-3] The vitamin C was given in infusion with 0.4, 0.6, 0.9 and 1.5 g ascorbic acid/kg body weight 3 times weekly in a specified escalation manner. Average duration of

participation was 10 weeks with a maximum of 30 weeks. The study demonstrated that no patient had an objective anticancer response although no statistical result was given on this finding.

On contrary, Tareen B et. al. recently found that oral Apatone showed promise in delaying biochemical progression in the end stage prostate cancer patients.[20 level II-3] Apatone consisted of 5,000 mg of Vitamin C and 50 mg of Vitamin K. In a 12 weeks follow-up of the small study, Prostate Specific Antigen (PSA) Velocity decreased and Prostate Specific Antigen Doubling Times increased in 13 of 17 patients (p<0.05). In fact, patients terminating Apatone therapy experienced sharp increase in PSA levels.

In terminal cancer patients, the quality of life is important and the treatment focuses on patient's well-being in addition to minimizing symptoms. In a study on health-related quality of life in terminal cancer patients after high dose intravenous and oral vitamin C administration using self-administered questionnaire, significant improvement was noted in global health/quality of life scale (p=0.001), functional scale (p<0.05) and certain variables in symptom scale i.e. fatigue, nausea/vomiting, pain, and appetite loss (p<0.005).[21 level II-3] Although the author concluded that vitamin C was an effective therapy to improve quality of life of terminal cancer patients, the study was only conducted in a very short duration (one week). Further study is required to compare effects of vitamin C in between placebo and vitamin C group in terminal cancer patients in a longer duration.

5.1.2 EDTA

There was no retrievable evidence on effectiveness of EDTA from the scientific databases.

5.1.3 Ultraviolet

There was no retrievable evidence on effectiveness of ultraviolet from the scientific databases.

5.2 Safety

5.2.1 Vitamin C

The safe use of vitamin C was found in four retrieved studies. In a large RCT using high dose multiple antioxidants including vitamin C, toxicity profiles were similar in both arms (with/without the antioxidants).[18 level I] However, no statistical result was given in for the finding. Main cumulative toxicities reported were peripheral neuropathy and alopecia but these could not be attributed to vitamin C alone due to the multiple antioxidants used as the intervention.

Vitamin C was also found to be safe for use in three non-randomised, non-controlled clinical trials. The vitamin was well tolerated or having minimal adverse events and toxicity in high doses when administered orally and intravenously. [19, level II-3, 20 level II-3, 21 level II-3] This include no dose-limiting adverse effects in treatment of Prostate Cancer patients who had failed standard therapy.[20 level II-3] In a study by Hoffer LJ et. al., intravenous vitamin C appeared to be safe and sustained plasma level of >10 mmol/l for more than four hours in patients with normal renal function.[19 level 11-3] Yeom CH et. al. concluded the safety findings in their short study based on significant reduction in certain symptoms of their study subjects namely fatigue, nausea/vomiting, pain and appetite loss after administration of vitamin C (p<0.005).[21 level II-3]

5.2.2 EDTA
There was no retrievable evidence on safety of EDTA from the scientific databases.

5.2.3 Ultraviolet
There was no retrievable evidence on safety of EDTA from the scientific databases.

5.3 Cost-effectiveness
No evidence addressing cost-effectiveness of vitamin C, EDTA or ultraviolet retrieved.

6. CONCLUSION
Compared to articles on the role of vitamin C in the prevention of cancer, there were not many articles that study its safety and effectiveness in the treatment of the condition.

Based on the above review, there was insufficient strong evidence to support the effectiveness and safety of vitamin C on the treatment of cancer. On the other hand, there was no evidence retrieved on the effectiveness and safety for EDTA and ultraviolet in the treatment of cancer.

7.RECOMMENDATION
More clinical research is required to provide evidence to support the effectiveness, safety and cost-effectiveness of vitamin C, EDTA and ultraviolet in the treatment of cancer. Hence, the use of vitamin C, EDTA, and ultraviolet in the treatment of cancer is not recommended.

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1. APPENDICES

9.1 Appendix 1 - Level of Evidence Table

Level	Study design
I	Evidence obtained from at least one properly designed randomized controlled trial
II-1	Evidence obtained from well-designed controlled trials without randomization
II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group
II-3	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence
III	Opinions or respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees

Source: US/CANADIAN PREVENTIVE SERVICES TASK FORCE (HARRIS 2001)