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ROLE OF ANTIOXIDANTS IN CANCER PATIENTS TREATED WITH EITHER CHEMOTHERAPY OR RADIOTHERAPY OR BOTH: PAST, PRESENT, AND FUTURE

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ABSTRACT

Oxidative stress is a key component in the carcinogenesis process stimulated by endogenous and exogenous factors, reactive oxygen species (ROS), etc. inducing cellular damage. Because complete recovery of cancer patients following a single treatment is quite difficult, therefore many integrative practitioners converse use of antioxidant supplements, allowing cancer patients to tolerate possibly higher effective doses of chemotherapy, thereby increasing the chance of better anti-tumor response and improving survival rate. As chemotherapy reduces serum levels of antioxidant vitamins and minerals due to lipid peroxidation and thus produces a higher level of oxidative stress. This may reflect a failure of the antioxidant defense mechanism against oxidative damage induced by commonly used anticancer drugs as well as by radiotherapy. Therefore, supplementation of certain antioxidants and nutrients can help to enhance the health status of patients undergoing a continuous regime of chemotherapy and thus can decrease the duration of chemotherapy regimens. Although there are many opinions about the risks or benefits of antioxidant supplementation, the only supportable conclusions based on the present research are that it is difficult to demonstrate definitively that antioxidants ameliorate therapeutic toxicities and that there is no evidence of antioxidant supplementation causing harm to cancer therapy, except for smokers undergoing radiotherapy. In the future, we are focusing on more disease-specific, target-directed, and highly bioavailable antioxidants along with nanotechnology delivery of antioxidants leading to increased therapeutic index and higher drug concentration in tumor tissues.

KEYWORDS: Oxidative stress, cancer, chemotherapy, antioxidant.

INTRODUCTION

Cancer is the leading cause of death worldwide. Although outcomes of cancer therapy have improved, cancer becomes a systemic disease beyond a particular point. Oxidative stress is a key component in the carcinogenesis process stimulated by endogenous and exogenous factors, reactive oxygen species (ROS), etc. inducing cellular damage.[1] Because complete recovery of cancer patients following a single treatment is quite difficult, a multidisciplinary approach combined with surgery, chemotherapy, radiotherapy, and immunotherapy is usually utilized.[2] Many integrative practitioners converse use of antioxidant supplements, allowing cancer patients to tolerate possibly higher effective doses of chemotherapy, thereby increasing the chance of better anti-tumor response and improving survival rate. At present antioxidants prescribed among cancer patients are estimated to be between 13 and 87%.[3]

Antioxidants are often described as ‘‘mopping up” free radicals, meaning they neutralize the electrical charge and prevent the free radical from taking electrons from other molecules.[4] Some endogenous antioxidant defense mechanisms, such as superoxide dismutase, glutathione peroxidase, and catalase, can counter-balance oxidative microenvironments. Nonenzymatic exogenous antioxidants such as vitamins, minerals, and polyphenols also can quench ROS activity.[5,6] They prevent cellular damage to normal organs and tissues by reacting and eliminating oxidizing free radicals[7] and thereby finding relevance in adjuvant chemotherapy. Also, these higher levels of endogenous antioxidants may protect against chemotherapy-induced oxidative stress, especially in some cancer patients having impaired capacity to deal with oxidative insult.[7] Such a broad range of percentages might be attributed to the difference in cancer types, age, education, complementary medicines, and ethnicity in the group undertaken for the study.

The role of antioxidants is controversial in cancer therapy because of two very imperative features ‘‘First, there are two different kinds of antioxidants doses used based on which the data on the role of antioxidants in cancer therapy can be categorized: **a preventive dose**, which is a low dose, and **a therapeutic dose**, which is a high dose. Preventive dose or Lower-dose antioxidant supplementation may protect normal cells and reduce the toxicity of radiation and chemotherapy.[8] For the therapeutic dose, the data shows that it inhibits the growth of cancer cells but not the normal cells. Therefore, researchers are looking at data for preventive doses, which is perplexing.

Numerous original research articles have focused on the topic of whether supplemental antioxidants administered during chemotherapy can protect normal tissue without adversely influencing tumor control. Due to variation in study design, intervention protocol, cancer type, the timing of observation, inclusive criteria, and statistical analysis, the chemotherapy regime develops uncertainty to make a definitive conclusion regarding the risk of decreased tumor control as a consequence of administering supplemental antioxidants during chemotherapy. On the contrary, a certain recent review concludes that antioxidants when given concurrently

(a) do not interfere with chemotherapy,

(b) enhance the cytotoxic effect of chemotherapy,

(c) protects normal tissue, and

(d) increases patient survival and therapeutic response.[9]

Some antioxidants are useful for restoring the natural antioxidants in the body, which are often depleted after the completion of chemotherapy, resulting in decreased side effects and increased survival time in patients undergoing chemotherapy.

Cancer patients suffer from vitamin deficiencies, particularly in folic acid, vitamin C, pyridoxine, and other nutrients because of poor nutrition and treatment. Chemotherapy reduces serum levels of antioxidant vitamins and minerals due to lipid peroxidation and thus produces a higher level of oxidative stress. Therefore, supplementation of certain antioxidants and nutrients can help to enhance the health status of patients undergoing a continuous regime of chemotherapy.[10]

Vitamin E has been shown to decrease chemotherapy-mediated toxicity, and omega-3 fatty acids increase survival time in terminal cancer patients. Other than suppressing the free radical-induced progression of lipid peroxidation in normal cells, vitamin E is also known to induce apoptosis in experimental tumor lines and increase the efficacy of chemotherapy.[11]

It is generally recognized that adequate levels of antioxidants are a precondition for optimal health. In addition to having tumoricidal effects, the free radicals generated by radiotherapy may upset the oxidant-antioxidant equilibrium, causing acute, intermediate, and long-term damage that can result in, among other things, second cancers.[12] Despite recent comprehensive review articles concluding that supplemental antioxidants do not undermine

the effectiveness of cytotoxic therapies, the use of antioxidants during cancer treatment remains controversial.

Many oncologists take the position that antioxidants by their nature undermine the free radical mechanism of chemotherapy and radiotherapy and should therefore generally be avoided during treatment. Until recently, research attention had focused primarily on the interaction of antioxidants with chemotherapy; relatively little attention has been paid to the interaction of antioxidants with radiotherapy.

Studies have shown that both chemotherapy and radiotherapy decrease plasma antioxidant levels. This "may reflect a failure of the antioxidant defense mechanism against oxidative damage induced by commonly used anticancer drugs"[13] as well as by radiotherapy.[14-16]

The preponderance of evidence supports a provisional conclusion that dietary antioxidants do not conflict with the use of chemotherapy and radiotherapy in the treatment of a wide variety of cancers, and may significantly mitigate the adverse effects of that treatment and targeted nutrient therapies using antioxidant or their precursors can prove to be beneficial in reducing the toxic effect of medications thereby improving the therapeutic efficacy.

Therefore, antioxidant therapies may alleviate the adverse effects of chemotherapy and/or radiotherapy but interaction among them may antagonize antitumor effects by reducing oxidative damage. Hence use of antioxidants during chemotherapy is criticized due to fear of causing interference with the efficacy of the drug.

DISCUSSION

The advent of modern cancer treatments has substantially improved the survival rate of patients. The enhancement in survival reflects progress in early-stage diagnosis and the use of a multidisciplinary approach. However, chemotherapeutic agents are associated with toxicity due to their potential to target rapidly dividing normal cells in the body. The prime concern of chemotherapy is drug-associated oxidative stress, which results in many side effects. The use of antioxidants can be beneficial in this respect as they minimize the burden of free reactive radicals in cells and thus can decrease the duration of chemotherapy regimens.

Despite nearly two decades of research investigating the use of dietary antioxidant supplementation during conventional chemotherapy, controversy remains about the efficacy and safety of this complementary treatment.

Several randomized clinical trials have demonstrated that the concurrent administration of antioxidants with chemotherapy reduces treatment-related side effects. Some data indicate that antioxidants may protect tumor cells as well as healthy cells from oxidative damage generated by some chemotherapeutic agents. However, other data suggest that antioxidants can protect normal tissues from chemotherapy-induced damage without decreasing tumor control. The lack of enthusiasm among clinical oncologists for using high doses of antioxidant vitamins in combination with chemotherapy is primarily based on the fear that antioxidant vitamins may protect both normal and cancer cells against free radicals which are generated by most chemotherapeutic agents.

Often there is disagreement on how could antioxidant therapy protect normal cells against damage from cancer therapies, while not affecting or increasing their cytotoxic effect against malignant cells? The answer to this question is not entirely figured out, but certain concepts might help us to understand.

One is that if the generation of Reactive Oxygen Species by a cancer chemotherapeutic agent or a free radical intermediate of the drug plays a role in its cytotoxicity, the antioxidant may interfere with the drug's antineoplastic activity. However, if the reactive species are responsible only for the drug's adverse effects, the antioxidant may reduce the severity of such effect without interfering with the drug's antineoplastic activity. Thus, it is important to distinguish between a drug's ability to induce oxidative stress in a biological system and the role, if any, that reactive oxygen species or free radicals intermediate play in the mechanism of action of the drug.

The **second** concept why antioxidants are found to increase the drug's cytotoxic effect against malignant cells is that chemotherapy often harms DNA, which causes the cells to undergo **apoptosis, rather than necrosis.** Since many antioxidant treatments stimulate apoptotic pathways, the potential exists for a complementary effect with chemotherapy and antioxidants.

The **third** view is that the defensive mechanisms of many cancer cells are known to be impaired. This presumably makes tumor cells unable to use the extra antioxidants in a repair capacity.

Several randomized controlled trials, some including only small numbers of patients, have investigated whether taking antioxidant supplements during cancer treatment alters the effectiveness or reduces the toxicity of specific therapies.[17]

Moss et al. in the year 2007, investigated articles and reviewed them to find out the use of alpha-tocopherol for the amelioration of radiation-induced mucositis; pentoxifylline, and vitamin E to correct the adverse effects of radiotherapy; melatonin alongside radiotherapy in the treatment of brain cancer; retinol palmitate as a treatment for radiation-induced proctopathy; a combination of antioxidants and the use of synthetic antioxidants like amifostine and dexrazoxane, as radioprotectants. With few exceptions, most of the studies draw **positive conclusions** about the interaction of antioxidants and radiotherapy.[18]

In the **year 2012**, the same group published data investigating the associations between antioxidant use after breast cancer diagnosis and breast cancer outcomes in 2264 women. Antioxidant supplement use after diagnosis was reported by 81% of women. **Among antioxidant users**, frequent use of vitamin C and vitamin E was associated with decreased risk of breast cancer recurrence, vitamin E use was associated with decreased risk of all-cause mortality but conversely, frequent use of combination carotenoids was associated with increased risk of death from breast cancer and all-cause mortality.[19]

Kushwaha V et al. in the year 2013 conducted a study on the Role of free radical scavengers in oral malignancies treated with radiotherapy and concluded that the free radical scavenger significantly reduces the oxidative stress in patients with oral cancer after radiotherapy by limiting lipid peroxidation and/or scavenging reactive oxygen species generated due to irradiation. When antioxidants are used in combination with radiotherapy in oral malignancies as a treatment it not only contributes to a favorable outcome and better survival but it also decreases the propensity of side effects and toxicities of radiotherapy and increases its tolerability in cancer patients.[20]

Yasueda A et al. in 2015 among the 49 studies reviewed, 46 showed the reduction of adverse effects by antioxidant supplementation. On the other hand, only 1 randomized control trial, using vitamin A, reported that supplementation possibly increased chemotherapy-induced toxicities. Chemotherapy and radiotherapy cause various adverse effects, which may be caused by free radicals. In 18 randomized control trials in which platinum was used as the therapeutic agent, the effects of melatonin,[21-27] selenium,[28-31] and vitamin[32-38]

supplementation on chemo-toxicities were reported. Among 7 trials using melatonin, 6 reported that melatonin supplementation significantly improved myelosuppression, weight loss, and neurotoxicity. Selenium supplementation was used in 4 trials. In 2 trials selenium supplementation was reported to be significantly effective for nephrotoxicity and Quality of Life. Vitamins were used in 7 randomized control trials, showing a significant improvement in Quality of Life in 1 trial and a significant decrease in various chemo-induced toxicities in 5 trials. Similarly, they found 7 randomized control trials studying the effects of melatonin[22-24,26,27,39] or vitamin E[40] on relieving toxicity of plant alkaloid–based chemotherapy, although these regimens were not considered to exert cytotoxicity by generating free radicals. All of them reported that melatonin or vitamin E supplementation was significantly effective in reducing toxicities. Furthermore, we found 5 studies[27,29,41,42] that researched the interaction between antioxidants and alkylating chemotherapy (cyclophosphamide). In 3 trials[27,29,41] out of 5 using cyclophosphamide regimens, there was a significant effect of antioxidants on chemo-induced toxicity. One trial[42] using busulfan reported improvement in chemo-induced toxicities for more patients in the vitamin A supplementation group than in controls.

As described above, a significant relief in chemotherapy-induced toxicities was reported in many trials using various antioxidant supplements. However, among trials in which the same combination of chemotherapeutic agent and antioxidant was used, some reported effective outcomes.

Radiation In total, 19 radiotoxicity prevention trials were investigated, which specifically aimed to reduce toxicities affecting the mucosa, skin, salivary glands, and taste. Four of 19 trials reported no significant differences in toxicity between groups. Antioxidant supplements such as vitamin E,[43,44] multivitamin combination,[33,45,46] polyphenol,[47,48] and zinc[49-55] were effective in preventing radiation-induced toxicities in the skin, mucosa, and salivary glands.

Singh K et al. in 2017 reviewed articles, out of the total cases reported in 174 research articles, 138 research papers have reported consequences of antioxidant supplementation during or after the chemotherapeutic setting of which 122 articles (88%) state that antioxidants mitigate the toxicities induced by chemotherapeutic agents. Out of 130 papers, 91 articles (70%) reports that the therapeutic efficiency of chemotherapy increases in the presence of antioxidants. Conjugate antioxidant supplementation was also seen to increase the survival time in the patients according to 26 reports (63%) of 41 research articles. Thus,

our comprehensive data, therefore, suggest that antioxidants do not interfere with chemotherapy and can be prescribed in a clinical setting to increase the standard of life.[56]

In pathological conditions and cancer therapy, examining the viability and safety of antioxidants trials should be performed with a single regimen, a single type of cancer, and a single antioxidant. Only such investigations would adequately describe the safety and effectiveness of antioxidant use by cancer patients during therapy. Therefore, we are unable to judge the effectiveness and safety of antioxidants definitively.

CONCLUSION

We concluded that in the past free radical scavengers in cancer patients treated either with Chemotherapy or Radiotherapy or Both ameliorate the action of free radicals generated by chemotherapy and Radiotherapy on normal cells. But some research showed that antioxidant interacts with Chemotherapy and reduces the effect of chemotherapy on cancer cells. In the current scenario role of free radical scavenger are beneficial in both Chemotherapy and Radiotherapy.

In the future, we are focusing on more disease-specific, target-directed, and highly bioavailable antioxidants because one of the major obstacles is in the delivery of these agents to their intended site of action. We may use nanotechnology in the delivery of antioxidants leading to increased therapeutic index and higher drug concentration in tumor tissues.

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