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Review

Antioxidants as precision weapons in war against cancer chemotherapy induced toxicity – Exploring the armoury of obscurity

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ABSTRACT

Cancer is the leading cause of mortality worldwide, accounting for almost 13% of deaths in the world. Among the conventional cancer treatments, chemotherapy is most frequently carried out to treat malignant cancer rather than localised lesions which is amenable to surgery and radiotherapy. However, anticancer drugs are associated with a plethora of side effects. Each drug, within every class, has its own set of adverse reactions which may cause patient incompliance and deterioration of the quality of life. One of the major causes of adverse reactions, especially for drugs targeting DNA, is the excessive production of reactive oxygen species (ROS) and subsequent build up of oxidative stress. To curb these undesired side effects, several dietary supplements have been tested, amongst which antioxidants have gained increasing popularity as adjuvant in chemotherapy. However, many oncologists discourage the use of antioxidant rich food supplements because these may interfere with the modalities which kill cancer by generating free radicals. In the present review, all studies reporting concomitant use of several antioxidants with chemotherapy are indiscriminately included and discussed impartially.

The effect of supplementation of thirteen different antioxidants and their analogues as a single agent or in combination with chemotherapy has been compiled in this article. The present review encompasses a total of 174 peer-reviewed original articles from 1967 till date comprising 93 clinical trials with a cumulative number of 18,208 patients, 56 animal studies and 35 *in vitro* studies. Our comprehensive data suggests that antioxidant has superior potential of ameliorating chemotherapeutic induced toxicity. Antioxidant supplementation during chemotherapy also promises higher therapeutic efficiency and increased survival times in patients.

Contents

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1. Introduction

Antioxidants prevent cellular damage by reacting and eliminating oxidizing free radicals thereby finding relevance in adjuvant chemotherapy. The use of antioxidant supplements by patients with cancer is estimated to be between 13 and 87% (VandeCreek et al., 1999; Block et al., 2008). Such broad range of percentage might be attributed to the difference in cancer types, age, education, complementary medicines and ethnicity in the group undertaken for the study. The use of supra-dietary doses of antioxidant has attracted increasing interest as a possible primary and secondary cancer deterrence strategy. Higher levels of endogenous antioxidant may protect against chemotherapy induced oxidative stress especially in some cancer patients having impaired capacity to deal with oxidative insult (Conklin, 2004). However, in cancer chemotherapy, a mode of action of certain antineoplastic agents involves generation of free radicals further leading to cellular damage and necrosis of malignant cells. Hence use of antioxidant during chemotherapy is criticized due to fear of causing interference with efficacy of the drug. On the contrary, many integrative practitioner converse uses of antioxidant supplements allowing patients to tolerate possibly higher effective doses of chemotherapy thereby increasing the chance of better tumor response and improved survival rate. Thus concomitant use of antioxidant during chemotherapy is been highly controversial topic. The questions repeatedly put forth are "Do antioxidants increase or decrease the efficacy of anticancer agent? Do antioxidants protect normal tissue and ameliorate toxicity or protect cancer cells from the effect of chemotherapy". This review intends to give a succinct idea about chemotherapy induced toxicity; ROS and oxidative damage followed with clarification on the major issue surrounding this controversy by reviewing the current state of understanding about potential and established interaction between antioxidant and conventional oncological therapies.

1.1. Chemotherapy

Chemotherapy is used primarily to treat systemic disease rather than localized lesions that are amenable to surgery or radiation. It uses antineoplastic agents in an attempt to destroy tumor cells by interfering with cellular function including replication. These drugs result in causing lethal injury to DNA which further leads to malignant cell death via apoptosis. In cancer treatment, mode of action of certain chemotherapeutic agents involves generation of free radicals to cause cellular damage and necrosis of malignant cells (Lamson and Brignall, 1999; Potmesil, 1994). Drugs with free radical mechanism include but are not limited to alkylating agent (alkylsulfonates, ethyleneamines and hydrazines), anthracyclines (doxorubicin and doxorubicin), platinum coordination complexes (cisplatin, carboplatin), podophyllin derivatives (etoposides) and camptothecins (irinotecan, topotecan). These ROS often are sources of atrocious side effects which remains as long as the duration of chemotherapy treatment (Joensuu, 2008).

1.2. Chemotherapy induced systemic toxicity

By its very nature, anti-cancer chemotherapy is cytotoxic that means it is designed to damage human cells. Because anti-cancer drugs are cytotoxic for normal as well as neoplastic cells, the range of unwanted effects that accompanies their use is broad. Many of the side-effects are potentially life-threatening or seriously debilitating. The precursor cells of the hemopoietic system, sited in the bone marrow, undergo cell division more rapidly than those of any other organ system and thus are particularly vulnerable to damage from cytotoxic drugs, since most chemotherapeutic agents act principally on dividing cells. Accordingly, bone marrow depression is a side-effect of nearly all such drugs and is the dose-limiting side effect of most. Red blood cell macrocytosis is a common effect of hydroxyurea, methotrexate, cytarabine and other antimetabolites.

Nausea and vomiting which usually occurs within 24 h of drug administration can be amongst the most disturbing and unpleasant side effects induced by chemotherapy. If persistent, vomiting may lead to dehydration, electrolyte disturbances, metabolic alkalosis, weakness, weight loss, cachexia, nutritional impairment and physical injury such as esophageal tears and fractures (Tortorice and Connell, 1990). Diarrhea and constipation in cancer patients may be due to many factors that include age, anticholinergics, narcotics, low fibre diet, decreased appetite and inability to eat and drink due to oral mucositis or esophagitis apart from the side-effects of cytotoxic drugs.

Cardiac damage is the dose-limiting toxicity of the anthracycline group of antitumor antibiotics related anthraquinones and can cause cumulative cardiomyopathy (Von Hoff et al., 1979). Damage to the liver is a complication of many drugs. Since patients receiving chemotherapy often are very ill and simultaneously receiving other medications that may impair liver function, it is often impossible to determine which of their treatments is responsible for the liver abnormality. Furthermore, septicemia, parenteral nutrition, viral and fungal infections and metastatic disease itself also commonly cause hepatic disturbance.

Pulmonary complications and kidney toxicity are being increasingly recognized and may be dose-limiting. Lung toxicity induced by methotrexate is said to occur in 5–8% of patients and includes pulmonary edema, pulmonary fibrosis, capillary leakage and hypersensitivity reaction (Bannwarth et al., 1994). The kidneys are vulnerable to damage from chemotherapeutic agents as they are the elimination pathway for many drugs and their metabolites. Cisplatin primarily causes proximal and distal tubular damage, although a rare hemolytic-uremic syndrome has also been reported (Daugaard et al., 1988).

Fertility problems can be an unfortunate delayed side effect of chemotherapy. Cytotoxic drugs damage the germinal epithelium resulting in reduced testicular volume and sperm count (Miller, 1971). The degree of dysfunction depends on the dose of drug as well as age and pubertal status of the patient at the time of treatment (Sherins, 1993). Often chemotherapy mediated toxicities are related to generation of ROS leading to oxidative stress in cell.

1.3. Chemotherapy induced ROS and their intracellular sources

Most of the oxygen taken up by the cells is converted to water by the action of cellular enzymes. However, some of these enzymes leak electron into oxygen molecules and lead to the formation of free radicals. They are also formed during normal biochemical reactions involving oxygen. ROS is a collective term used for a

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