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Opinion

Should Sézary Disease Patients Take Glutathione Supplementation?

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Many anticancer chemotherapeutic agents are capable of generating reactive oxygen species (ROS) and reactive nitrogen species (RNS) that could lead to oxidative damage in both normal and malignant cells [1]. While antioxidants may alleviate chemotherapy-induced adverse effects associated with oxidative stress, it is also possible that antioxidant may impede the efficacy of anticancer chemotherapy by scavenging ROS/RNS. For example, Cascinu., *et al*. have reported that glutathione supplementation significantly reduced neuropathy in advanced colorectal cancer patients receiving oxaliplatin, leucovorin and 5-fluorouracil regimen [2]. In contrast, it has been shown that glutathione and glutathione precursor N-Acetylcysteine, or desferrioxamine (iron chelating agent) effectively inhibited cell death in cutaneous T-cell lymphoma cell lines and T lymphocytes isolated from Sézary syndrome patients [3]. There is an ongoing clinical debate on whether cancer patients should consume antioxidant supplements (e.g., N-acetylcysteine, glutathione, vitamin E, resveratrol) during the course of cancer chemotherapy. Based on published studies, the answer to the question remain inconclusive. Most of these reported, however, primarily include solid tumors. Few studies involve hematologic malignancies and none of these studies include Sézary syndrome [4-6].

The World health organization and the European organization for Research and Treatment of Cancer have classified the cutaneous lymphomas into three major categories: 1) cutaneous T-cell and NK-cell lymphomas (CTCL), 2) cutaneous B-cell lymphomas, and 3) precursor hematologic neoplasm [7]. Sézary syndrome is an aggressive type of T-cell lymphomas, and it belongs to the CTCL category. Sézary syndrome is accounted for 1% of all CTCL cases examined, and they carry a poor prognosis.

Methotrexate (MTX) or the alkylating agents (e.g., chlorambucil) are the most frequently used for the treatment of Sézary syndrome. However, due to the fact that Sézary syndrome is refractory to standard cancer chemotherapy, several novel agents have been developed and introduced into the treatment regimens for Sézary syndrome to improve the disease prognosis. These novel agents include retinoid X receptor agonists e.g., bexarotene [8], histone deacetylase (HDAC) inhibitors e.g., vorinostat [9], a monoclonal antibody that targets CD52 (alemtuzumab), and a recombinant interleukin-2 (IL-2) that is fused to the diphtheria toxin (denileukin diftitox), and targets CD25. Despite availability of classic chemotherapeutic and newly developed agents, the survivals of patients with Sézary syndrome remain poor with a median survival from initiation of therapy of 55 months [10] and 5-year relative survival rates below 40% [11]. Therefore, the development of novel treatment modalities remains warranted.

Gemcitabine is a deoxycytidine analogue that has been used off-label for relapsed or refractory patients with Sézary syndrome. The main mechanism of action of gemcitabine is to inhibit DNA replication by incorporation the phosphorylated form of gemcitabine into DNA as a false deoxycytidine analogue and through inhibition of ribonucleotide reductase, which depletes nucleotides required for DNA synthesis, thereby inducing cell apoptosis. Current knowledge has revealed that glutathione is essential for the process of cell cycle progression. Inhibition of glutathione synthesis arrests cell cycle in the S phase [12,13] whereas accumulation of glutathione in the nucleus is observed at the S-phase of proliferating cells [14]. These data suggest that increased nuclear glutathione level is responsible for a successiveness of cell cycle progression. Therefore, increased glutathione availability may promote cancer cell proliferation. An *in vivo* study

in mice has demonstrated that N-acetylcysteine increased melanoma metastasis, supporting an involvement of glutathione in cancer cell growth and a disease progression [15].

So, should Sézary syndrome patients consume N-acetylcysteine or glutathione while receiving an antimetabolite, gemcitabine? Gemcitabine must be incorporated into DNA chain during the S-phase of cell cycle to exert its cytotoxicity. Therefore, blocking glutathione uptake into the nucleus may compromise gemcitabine cytotoxic activity, whereas promoting glutathione transport into the nucleus may enhance gemcitabine activity. Whether this hypothesis is true, one need to examine and verify such theory. Nevertheless, it does raise a question whether Sézary syndrome patients (as a matter of fact, all cancer patients) should take an antioxidant supplement such as glutathione or N-acetylcysteine during cancer treatment. To date, there is no consensus recommendation on whether antioxidant should be taken during anticancer chemotherapy. Theoretically, should Sézary syndrome patients chosen to take glutathione supplements along with gemcitabine therapy, the possible outcomes could fall into some of the following possibilities: (1) glutathione may decrease adverse effects associated with gemcitabine, (2) glutathione may diminish anticancer activity of gemcitabine, (3) glutathione may enhance anticancer properties of gemcitabine and (4) glutathione may have no effect on gemcitabine. Until there is a definite proof otherwise, it is going to be just a theory.

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