

Elevate the ROS Level to Kill Cancer Cells during Chemotherapy

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Chemotherapy and radiotherapy are an essential treatment for many cancers, sometimes in combination with cytoreductive surgery. While radiotherapy destroys cancer cells by ionizing radiation that directly damages DNA, most of the chemotherapeutic agents generate Reactive Oxygen Species (ROS) that lead to oxidative damage in various molecules of the cell [1]. However, both processes mainly induce apoptosis to kill cancer cells. Any cancer cells that are not killed by these therapies could proliferate again, resulting in the relapse of cancer.

The clinical benefit of using antioxidant supplements along with chemotherapy and radiotherapy is highly debatable, and not conclusive. This is either due to incomplete investigations, lack of enough samples for suitable statistical analysis, or failure to correlate wide ranges of different parameters used in different studies [2]. However, some of the clinical studies suggest that the antioxidant supplemented group had a worst survival rate, than the group who did not use antioxidant supplements [3]. Although in some cases, use of antioxidant has fewer side effects leading to less damage to normal tissues, but with a decrease in the overall survival rate. The ROS generated by anticancer agents, although effective in killing cancer cells, also alters other cellular pathways leading to various side effects [4]. The serious side effects encountered in chemotherapy include nephrotoxicity, ototoxicity or cardiotoxicity [2]. However, it is also believed that antioxidant supplemented reduction of side effects depends, mainly on using specific anticancer drugs for certain cancers.

Thus, the intriguing question is whether antioxidant should continue to be used along with chemotherapy, or should be avoided. Also, the question arises whether cancer cells should be killed completely to cure cancers, without considering side effects. Logically, complete cure of cancer by overcoming drug resistance with minimal side effects should be the first priority.

A systematic search including chemotherapy and ROS generation yielded more than 13,000 publications in the PubMed database, including mainly clinical studies. Searching anticancer agents mediated ROS generation yielded 307 studies in most recent years, demonstrating an intense focus shift towards understanding the mechanism of drug-mediated cancer cell death, through ROS generation. This shift could be attributed to the use of current genomic and molecular biology tools, to help understand adverse outcomes of chemotherapy and drug resistance that are observed in decades of clinical treatments. Arguably, as most of the recent studies have pointed out, if those anticancer agents generate ROS to kill cancer cells, then why antioxidant would be used along with chemotherapy? Instead, elevation of ROS should be the most effective way to supplement anticancer drugs. In addition, it has been observed in several recent reports that a reduced ROS level is attributed to drug resistance in certain cancer cells for some anticancer drugs [1,5], and indirectly supported by other studies [6,7]. Thus, increase of ROS level along with the drug could help in overcoming drug resistance during chemotherapy.

Now what are the means to elevate ROS level in the cancer cell for effective killing with chemotherapy? The simple answers are by manipulating antioxidant genes or ROS maintaining genes/enzymes, or by conjugating nanoparticles that generate ROS, or by introducing

external ROS to the tumor sites. Although, several antioxidant genes are known such as SODs (superoxide dismutases), catalase, GSH (glutathione), thioredoxins and peroxiredoxins, the ROS maintaining genes (e.g. ARHGEF6, p53, APEX1 etc.), and their mechanisms are largely unknown. Nanoparticles-mediated ROS generation technologies are also being developed [8].

The most important question is how effective overall would it be to overcome drug resistance by elevating the ROS level? At this point, extensive investigations could be initiated to assess the effect of elevated level of ROS to overcome drug resistance for many anticancer drugs in different types of cancers. After successful characterization in cellular and mouse models, the results could be implemented in systematic clinical trials. Thus, in the coming years, advanced chemotherapeutic treatments could be supplemented by means of ROS elevation, rather than with antioxidants.

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