BioLogical NEWS

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Chemotherapy and Vitamin C

Chemotherapy is a first-line medical treatment in cancer treatment. Many people have asked the question: Does vitamin C interfere with chemotherapy, or does it enhance its effects? It turns out that this question is too complex for a one-liner, since what is meant by "chemotherapy" is a complex issue in itself. There are dozens of common drugs being used a chemotherapeutic agents, and of course each of these has a different pharmacodynamic profile and potential interaction with the various dose forms of vitamin C. Data are simply not available on the interactions in a clinical setting with all of these drugs and various doses of vitamin C or other antioxidants. However, the data that are available for some combinations show clearly that the clinical effects of vitamin C co-administered with chemotherapeutic drugs are in fact positive.

Studies supporting the use of Vitamin C with chemotherapy

Regardless of any theoretical objections to combining vitamin C with chemotherapy, in vitro trials and clinical trials overwhelmingly support the combination.

Reddy et al.[1] did an in vitro study to look at the effect of vitamin C on cervical carcinoma HeLa cells. They found a positive interaction - that vitamin C stabilized P53 enzymes making the cells more sensitive to cisplatin and etoposide. The effect was to increase the expression of genes coding for apoptotic proteins, leading to cell death.

Vitamin C has been shown to reverse vincristine resistance of human non-small-cell lung-cancer cells and improve the uptake of the drug[2]. Vitamin C has also been shown to improve the antineoplastic activity of doxorubicin, cisplatin and paclitaxel[3].

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Combined application of cyclophosphamide, methotrexate, 5-fluorouracil (CMF) may be used in the treatment of breast cancer. CMF may induce blood lipid abnormalities as a side effect. Muralikrishnan et al.[4] looked at the effects of vitamin C co administered with CMF on the lipid profiles of fibrosarcoma-bearing rats. "From the results, it becomes evident that the supplementation of vitamin C reverted the abnormally increased lipid and lipoprotein levels, due to fibrosarcoma itself and against its treatment with CMF. These results suggest that CMF treatment is more advantageous when administered together with vitamin C."

In a randomised clinical trial, Elsendoorn et al.[5] investigated the effects of an oral antioxidant mixture (Vitamins C, E and selenium) on cisplatin therapy in a variety of cancer patients. "A total of 27 patients with various types of cancer were treated with cisplatin-based combination chemotherapy. Out of these, 13 patients were randomized to receive supplementation treatment with a beverage containing the antioxidants vitamins C and E, plus selenium, during chemotherapy. The antioxidant mixture was administered to investigate whether it could reduce the potential genotoxic and nephrotoxic effect of the applied chemotherapy. A placebo group of 14 cancer patients received a beverage without selenium or antioxidants….Chemotherapy-induced frequencies of micronuclei after three cycles of chemotherapy correlated significantly with the cumulative dose of cisplatin (r=0.58, P=0.012) and the cisplatin-mediated loss of renal function (r=0.53, P=0.03). No consistent change in HPRT (hypoxanthine phosphoribosyl transferase) mutant frequency following chemotherapy was observed in the placebo and antioxidant group of patients. In conclusion, cisplatin-combination chemotherapy resulted in a cisplatin dose-related increase of the frequency of chromosomal damage. Supplementation with antioxidants did not prevent or reduce this effect."

Drisko et al.[6] reported the results of antioxidant therapy administered with chemotherapy in two cases of ovarian cancer. "For this preliminary report, two patients with advanced epithelial ovarian cancer were studied. One patient had Stage IIIC papillary serous adenocarcinoma, and the other had Stage IIIC mixed papillary serous and seromucinous adenocarcinoma. Both patients were optimally cytoreduced prior to first-line carboplatinum/paclitaxel chemotherapy. Patient 2 had a delay in initiation of chemotherapy secondary to co-morbid conditions and had evidence for progression of disease prior to institution of therapy. Patient 1 began oral high-dose antioxidant therapy during her first month of therapy. This consisted of oral vitamin C, vitamin E, beta-carotene, coenzyme Q-10 and a multivitamin/mineral complex. In addition to the oral antioxidant therapy, patient 1 added parenteral ascorbate at a total dose of 60 grams given twice weekly at the end of her chemotherapy and prior to consolidation paclitaxel chemotherapy. Patient 2 added oral antioxidants just prior to beginning chemotherapy, including vitamin C, beta-carotene, vitamin E, coenzyme Q-10 and a multivitamin/mineral complex. Patient 2 received six cycles of paclitaxel/carboplatinum chemotherapy and refused consolidation chemotherapy despite radiographic evidence of persistent disease. Instead, she elected to add intravenous ascorbate at 60 grams twice weekly. Both patients gave written consent for the use of their records in this report.

Patient 1 had normalization of her CA-125 (a cancer antigen test) after the first cycle of chemotherapy and has remained normal, almost 3 ½ years after diagnosis. CT scans of the abdomen and pelvis remain without evidence of recurrence. Patient 2 had normalization of her CA-125 after the first cycle of chemotherapy. After her first round of chemotherapy, the patient was noted to have residual disease in the pelvis. She declined further chemotherapy and added intravenous ascorbic acid. There is no evidence for recurrent disease by physical examination, and her CA-125 has remained normal three years after diagnosis. Because of the positive results found in these two patients, a randomized controlled trial is now underway at the University of Kansas Medical Center evaluating safety and efficacy of antioxidants when added to chemotherapy in newly diagnosed ovarian cancer."

"One of the most studied and, until recently, most controversial therapies is the use of high-dose ascorbic acid . Recent work has increased the understanding of the activity of vitamin C. This work has shown that vitamin C in doses many times over the RDA is a potent immunomodulator and has been found to be preferentially cytotoxic to neoplastic cells. Vitamin C enhances the activity of natural-killer cells in vivo and also enhances both B and T-cell activity. At doses in the gram range, it has been demonstrated to increase survival time of patients with malignancies. Golde and his group at Memorial Sloane Kettering demonstrated that vitamin C accumulates in some tumor cells via an increase in specialized cell surface transporters. Golde hypothesized that because vitamin C accumulates in some tumor cells at a greater rate than normal cells, vitamin C and possibly other antioxidants should be avoided during cancer treatment. The basis of this argument is the fact that increases in antioxidants in the cellular environment during treatment with radiation and/or chemotherapy would interfere with reactive oxidant species generation and cytotoxicity by these therapies. However, increasing evidence points to other mechanisms by which chemotherapeutic cytotoxicity is achieved (such as up regulating apoptotic gene expression); evidence supports cytotoxic synergism between chemotherapy and/or radiation and antioxidants when used appropriately."[7]

Vitamin C is known to augment the effects of arsenic trioxide in the chemotherapy treatment of multiple myeloma. "Patients with multiple myeloma (MM) invariably relapse with chemotherapy-resistant disease, underscoring the need for new agents that bypass these resistance mechanisms. We have reported that ascorbic acid (AA) enhances the activity of arsenic trioxide (As_20_3) against drug-resistant MM in vitro by depleting intracellular glutathione (GSH). These data led us to open a National Cancer Institute/Cancer Therapy Evaluation Program-sponsored Phase I/II trial of As_20_3 + AA for relapsed/refractory MM…. In conclusion, we have found that As_20_3 + AA has acceptable toxicity and that there is promising evidence of activity in refractory/relapsed myeloma."[8]

"The anthracycline antibiotic adriamycin (doxorubicin) is one of the most effective chemotherapeutic agents against a wide variety of cancers. However, its use is seriously limited by the development in the heart of acute and chronic toxic effects…Among followed strategies to attenuate adriamycin toxicity are dosage optimisation, synthesis and use of analogues or combined therapy with antioxidants. The most promising results come from the combination of the drug delivery together with an antioxidant in order to reduce oxidative stress."[9]

Recent studies showing that vitamin C is cytotoxic to various cancers

Vitamin C has also been shown to be cytotoxic to cancer cells in many other studies.

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Casciari et al[10] have reported in the British Journal of Cancer that "Vitamin C (ascorbate) is toxic to tumour cells, and has been suggested as an adjuvant cancer treatment. Our goal was to determine if ascorbate, in combination with other antioxidants, could kill cells in the SW620 hollow fibre in vitro solid tumour model at clinically achievable concentrations. Ascorbate anti-cancer efficacy, alone or in combination with lipoic acid, vitamin K3, phenyl ascorbate, or doxorubicin, was assessed using annexin V staining and standard survival assays. 2-day treatments with 10 mM ascorbate increased the percentage of apoptotic cells in SW620 hollow fibre tumours. Lipoic acid synergistically enhanced ascorbate cytotoxicity reducing the 2-day LC(50)in hollow fibre tumours from 34 mM (ascorbate) to 4 mM. Lipoic acid, unlike ascorbate, was equally effective against proliferating and non-proliferating cells. Ascorbate levels in human blood plasma were measured during and after intravenous ascorbate infusions. Infusions of 60 g produced peak plasma concentrations exceeding 20 mM with an area under the curve (24 h) of 76 mM h. Thus, tumoricidal concentrations may be achievable in vivo. Ascorbate efficacy was enhanced in an additive fashion by phenyl ascorbate or vitamin K3. The effect of ascorbate on doxorubicin efficacy was concentration dependent; low doses were protective while high doses increased cell killing."

Gonzalez et al.[11] tested the effect of different concentrations of ascorbic acid (AA), 50, 100, 250 mg/500 mg/dL) with copper sulfate (CS), 10 mg/dL) on human breast carcinoma (MDA-MB231) cell proliferation in vitro. "These results show that a combination of AA and CS inhibits human breast carcinoma cell proliferation in vitro. This cell proliferation inhibitory effect is directly proportional to the AA concentration with the exception of the 500 mg/dL AA dose. This chemotherapeutic effect was optimally enhanced when AA was added at a concentration of 250 mg/dL."

Bram et al[12] reported in Nature that vitamin C is preferentially toxic to malignant melanoma cells. "Saturation levels of ascorbate in tissues range from 1 to 2 mM. Such concentrations in our experiments inhibit malignant melanoma cells 20 to 500 times more than the other cells studied."

Zheng et al.[13] studied the effect of ascorbic acid and sodium selenite on human hepatoma cells. "After being treated with ascorbic acid (AA) 3 mM + sodium selenite (SS) 1.5 microM, the growth rate and mitotic index of human hepatoma cells BEL-7402 decreased remarkably. The indexes related to cell malignancy were improved… These results indicated that hepatoma cells had been successfully induced to redifferentiation by AA + SS." Zheng et al (different co-authors)[14] also studied the effect of the ascorbic acid – sodium selenite combination on gastric cancer cells. Their results indicated that a "combination of ascorbic acid and sodium selenite may induce the redifferentiation of human gastric cancer cells and inhibit cell growth by virtue of enhancing the activities of antioxidative enzymes and inducing the formation of H_2O_2, and altering the cell redox status. Combination of ascorbic acid and sodium selenite may be a potent anticancer agent for human gastric cancer."

The combination of ascorbate and hydroxocobalamin has been studied for its cytotoxic effect on cancer cells. In a study on epidermoid human larynx carcinoma cells, Akatov et al.[15] found that "The combination of hydroxocobalamin (vitamin B12b) and ascorbic acid (vitamin C) can cause the death of tumor cells at the concentrations of the components at which they are nontoxic when administered separately. This cytotoxic action on epidermoid human larynx carcinoma cells HEp-2 in vitro is shown to be due to the hydrogen peroxide generated by the combination of vitamins B12b and C."

Mechanisms of cell death induced by chemotherapy

It is useful is to consider some of the global mechanisms by which chemotherapeutics are thought to induce cell death. We can then ask the question: How does vitamin C interact with these mechanisms of cell death in conjunction with chemotherapy; positively, negatively, or not at all?

Each drug will produce a different effect, depending on the concentration of the drug at the tumor site and of course the nature of the tumor. By and large the major known mechanisms of cell death that may be initiated by chemotherapy are autoschizis and apoptosis[16]. Both these mechanisms can be triggered by oxidative damage from reactive oxygen species (ROS) or direct toxicity produced by chemotherapy. These reactions are enormously complex, involving genetic, mitochondrial and cytosolic responses and changes in affected cells, and may or may not include immune system responses[17]. The ultimate result of these mechanisms is the same – cell death. Apoptosis rarely induces an inflammatory response whereas autoschizis does; cell death by autoschizis is likely to produce significant inflammatory symptoms in affected areas. What is essential to realize however is that once these processes are started, they run to completion and are typically known as *programmed cell death*. Programmed cell death is largely under

genetic control. Programmed cell death will not occur if the genes coding for it in the cell are not expressed. Autoschizis is likely to decrease the affected cell population to a much greater extent than apoptosis; however the various forms of cell death occur in the same tissue at the same time.

In a study undertaken to examine the mechanisms of cell death in a human ovarian carcinoma cell line, the cells were exposed to a combination of vitamin C and vitamin K3 in high concentrations. A scanning electron microscope was used to examine the effects on cells. With the vitamin combination treatment, 43% of cells died from autoschizis and 3% from apoptosis[18]. Further research into this combination therapy has been conducted by Verrax et al[19] and Lasalvia-Prisco et al[20] showing clear cytotoxic effects of the high concentration vitamin combination on tumor cells. Of course, the precise mechanisms and percentage responses will vary depending on the tumor and the therapeutic agent(s).

Interactions between Vitamin C and Chemotherapy

There are numerous studies published that demonstrate that vitamin C can protect cancer cells from chromosome damage. In combination with certain chemotherapeutic drugs, vitamin C is anti-clastogenic (clastogenic means produces chromosome breaks) if in sufficient concentration[21]. Vitamin C in combination with cisplatin will reduce the chromosome damage that cisplatin would otherwise cause. It is assumed that the extent of chromosome damage produced by a drug is directly related to that drug's effectiveness - as a result there are many people who conclude that vitamin C interacts negatively with chemotherapy. It is clear from many clinical trials and observations however that vitamin C in general *improves* the effectiveness of these drugs and also decreases the side effects on normal tissue. Chromosome damage in itself is not a reliable predictor of the fate of the cell because chromosome damage in itself does not necessarily cause cell death. Cell death is largely mediated by the expression of genes that code for proteins that initiate programmed cell death events. Despite the anticlastogenic nature of vitamin C, vitamin C (if in sufficient concentration) has the effect of increasing the expression of these genes in cancer cells[22]. In fact it is reasonable to assume that gross damage to DNA might result in damage to the programmed cell death genes themselves, rendering the cell resistant to chemotherapy drugs[23].

Considerable research is being conducted into the role of telomeres and telomerase enzymes in cancer growth. Blasik et al[24] looked at the effect of vitamin C on a selenite – platinum conjugate drug used as a chemotherapeutic in their study on endometrial cancer cells. Sodium ascorbate at 10 and 50 microM reduced the extent of the DNA damage evoked by the drug, however the effect of the drug on telomerase activity and the overall effectiveness of the drug was not reduced by vitamin C. "Telomerase activation can be considered as a critical step in cell immortalization. The enzyme elongates or maintains telomere length by adding to its end tandem TTAGGG repeats by using its endogenous RNA template. Telomerase is not detectable in most somatic cells but is upregulated in germ line cells and in 85-90% of human cancers, which suggests an important role of telomerase in neoplastic transformation….mutagenic effects of the conjugate can be reduced by the well-recognized antimutagen, sodium ascorbate, but it can still retain ability to affect neoplastic transformation. The results obtained indicate that $(NH_3)_2Pt(SeO_3)$ may specifically inhibit telomerase activity in endometrial cancer cells."

Summary

Chemotherapy in general has clastogenic effects, i.e. it causes chromosome (DNA) damage in cancer cells and normal cells. It is reasonable to assume that the extent of this damage reflects the effectiveness of the drug, i.e. the more chromosomal damage in DNA in cancer cells the more effective the therapy is. Vitamin C is a known anticlastogen – it protects normal cells and cancer cells to some extent from this DNA damage. The anti-clastogenic effect of vitamin C depends on its concentration. At very high concentrations vitamin C is directly toxic to tumour cells[25]. Because of this anti-clastogenic activity it is also reasonable to assume that vitamin C will interact negatively with chemotherapy, i.e. it will reduce the effectiveness of chemotherapy. However it turns out that neither of these assumptions is reasonable because clinical and in vitro tissue culture research do not fully support these conclusions. There are many studies that show that although vitamin C decreases the DNA damage in target cells, the killing effect of the particular chemotherapy is increased. Cell death does not so much depend on gene damage, but rather depends on the expression of genes that code for programmed cell death events. Vitamin C in sufficient concentration is thought to initiate these events in damaged cells, certainly in cancer cells. Tumour drug resistance to chemotherapy has been related to the failure of programmed cell death mechanisms, because the genes that code for these mechanisms are themselves damaged. It is quite likely that chemotherapy itself may induce this damage, producing at once a highly drug resistant cell line.

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Vitamin C may be functioning to protect cancer cell DNA from this damage and also to increase the expression of cell death genes. Vitamin C may do this directly in high concentrations but it is also clear that in combination with certain chemotherapeutics that the combination has an increased lethal effect. Vitamin C is also acknowledged to be protective of normal tissue and can significantly decrease the side effects produced by chemotherapy.

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