Therapeutic Nutrition

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Beyond Chemoprevention: Nutraceuticals
That Abrogate or Delay the Onset of Cancer and
Enhance Conventional Cancer Treatments

Introduction

Conventional cancer treatment has been in place for over 50 years with little change in the overall strategy. Resectable tumors are removed surgically, while remaining inoperable sites are treated with radiation, chemotherapy or both. These latter modalities nonspecifically target all tissues, the only differentiation being their rapidity of growth and the focusing possible with directed radiation and certain methods of chemotherapy delivery. As a result, collateral damage and adverse side effects are the rule. The severity of these adverse effects has stimulated a continuing search for ways to reduce them.

As the research has progressed, there has developed a growing consensus that a variety of nutraceuticals can complement the effects of standard cancer treatment. Their contributions are several:

• Nutraceuticals can decrease the side effects of conventional cancer treatment.
• Nutraceuticals can protect normal cells from the indiscriminate damage done by cancer treatment.
• Nutraceuticals can enhance the effects of cancer treatment.
• Nutraceuticals can abrogate or delay the onset of cancer.
• Nutraceuticals can destroy cancer after it appears.

A single admonition and three specific caveats accompany such recommendations. There is a fear that the antioxidant supplements that protect normal cells from chemotherapy will also protect cancer cells. Research has identified only three potential antagonistic interactions among the many nutraceutical and chemotherapeutic agent combinations studied. Beyond these three, the results have been universally benign, both in the laboratory and in clinical trials.

Antioxidants

Radiotherapy and some forms of chemotherapy function by creating oxidizing free radicals that damage malignant cells. The chemotherapeutic agents most noted for creating cellular damage by generating free radical oxidants are the alkylating agents (e.g., cyclophosphamide, ifosamide), the tumor antibiotics (e.g., doxorubicin, bleomycin), and the "platinum" compounds (e.g., cisplatin). Since antioxidants are free-radical scavengers, their use in combination with these agents must be explored before being recommended. Sufficient evidence from research has justified the practice, although the mechanism by which these nutraceuticals exert opposite effects on normal and malignant cells has yet to be fully elucidated. Two theories have been proposed, both of which require an exploration of the mechanisms of action of cancer treatments.

Traditionally it has been thought that DNA damage leading to cell necrosis is the way radiation and chemotherapy kill cancers. More recently evidence suggests, however, that damage of a lesser severity, perhaps to cell membranes by lipid peroxidation, arrests mitosis and initiates apoptosis. Since many antioxidant treatments stimulate apoptotic pathways, such an effect might override any potential antagonism. This effect is likely to be further enhanced by an intrinsic deficit in malignant cell repair mechanisms. A dramatic deficiency of catalase has been identified in many cancers. When cells with this deficiency are treated with vitamin C, hydrogen peroxide accumulates, and the cells die. Adding catalase to these cell cultures completely nullifies the effect.

In the laboratory, cancer cell cultures have demonstrated a variety of beneficial results from the addition of a mixture of antioxidants. Numerous tumor growth inhibitory signals have been generated, among them inhibited expression of c-myc, N-myc and H-ras and the activity of protein kinase C and increased expression of transforming growth factor (TGF) mRNA, TGF protein and its secretion, and the expression of p21 and wild-type p53. Specific nutraceuticals have by themselves generated many other beneficial effects, although the results have not been entirely benign. Certain individual antioxidants at low doses have been shown to stimulate the growth of some cancers. Others, given individually even at high doses, have had no effect whatsoever. And the effects of many agents at both low and high doses have yet to be defined. Therefore, carefully designed regimens, usually involving multiple agents at tested dosages, have been advocated, rather than individual supplements used alone or indiscriminately combinations in poorly controlled doses.

One clinical study compared standard paclitaxel and carboplatin chemotherapy for non-small-cell lung cancer with and without ascorbic acid 6100 mg/day, dl-alpha-tocopherol (vitamin E) 1050 mg/day and beta-carotene 60 mg/day. A tendency to favor the combined regimen appeared but was statistically insignificant at p = 0.20.

Maitake Mushrooms

A particular mushroom native to Japan has generated substantial interest for its ability to inhibit tumor growth. Maitake (Grifola frondosa) is so rare and so delicious that folks dance when they find it, hence the literal translation "dancing mushroom." It was singled out after 15 years of mushroom research by one investigator using MM46 mice with breast cancer. Mice receiving either oral or
intraperitoneal Maitake extract had either complete or >75% remission of their tumors.11

Powders and extracts of this mushroom, identified as Maitake D-fraction (Maitake Products, Inc.) and Maitake crude powder, have produced remarkable improvements in advanced breast, lung and liver cancers and some suggested benefits in leukemia, stomach and brain cancer patients. It appears to increase immune cell activity, generating increases in TNF-alpha and IFN-gamma from spleen cells and TNF-alpha expressed in NK cells. It also increases macrophage-derived interleukin-12, which serves to activate NK cells.12-15

In the laboratory, D-fraction, a beta-glucan, was tested in combination with carbustine (BCNU), 5-fluorouracil (5-FU), methotrexate (MTX), etoposide, cisplatin and mitomycin C on prostate cancer cell cultures. BCNU, 5-FU and MTX produced a 50% reduction in cell viability. Only the combination of BCNU and D-fraction increased the death rate to ~90%. The increased death rate was accompanied by ~80% reduction in the activity of glutathione-dependent detoxifying enzyme glyoxalase-I, suggesting a mechanism for the observed effect.16

Proteolytic Enzymes
Among the proteolytic enzymes of interest to oncology, trypsin and chymotrypsin from cattle or pigs, papain from papaya sap, and bromelain from pineapple stems are the most studied. Bromelain contains nine active proteases. They reduce the adverse effects caused by radiotherapy and chemotherapy and, prolong survival. One study of patients with inoperable lung cancer treated with fluorouracil, vinblastine, methotrexate and cyclophosphamide found a reduction in leukopenia, mucusitis and uremia in patients who received in addition a combination of papain, trypsin and chymotrypsin. The mean survival also increased by 25%.17 The same combination reduced the elevation in liver enzymes caused by carboplatin, epirubicin and prednimustine treatment of ovarian carcinoma18 and prolonged survival by 76% in patients treated with a variety of regimens for multiple myeloma.19 Several studies augmenting radiotherapy with the same combination of proteolytic enzymes produced improvements in radiation side effects or disease progress.20

The effects of proteolytic enzymes are not well understood as yet, but they appear to be based on induction of antiproteinases and on alterations of cytokine composition inducing anti-inflammatory effects.20

Curcumin
Curcumin (diferuloylmethane), a polyphenol derived from the turmeric plant, is a potent antioxidant and anti-inflammatory agent. During 50 years of research it has shown an ability to suppress initiation, proliferation and metastasis of a wide variety of tumor cell lines. Its many mechanisms of action include down-regulating the expression of COX2, LOX, NOS, MMP-9, uPA, TNF, chemokines, cell surface adhesion molecules, cyclin D1 and growth factor receptors (such as EGFR and HER2). It also inhibits the activity of c-Jun N-terminal kinase, protein tyrosine kinases and protein serine/threonine kinases. Even at high doses it has demonstrated no dose-limiting toxicity and thus offers considerable promise as a cancer treatment, although human cancer studies should be completed and published to further validate its effects and initiate widespread implementation of this cancer treatment strategy.21

Quercetin
Quercetin, a flavonoid antioxidant present in many yellow vegetables, has been studied extensively in the laboratory and occasionally in human cancer trials. It is able to alter the concentration of chemotherapeutic agents inside cancer cells, affect cell cycle regulation, interact with type II estrogen binding sites, and inhibit tyrosine kinase, frequently, but not always, generating an anticancer effect.22,23 It is also able to overcome anti-apoptotic mutations that result in drug resistance in human tumors.24

Graviola (Annona Muricata)
The leaves, bark, and stems of Graviola, an evergreen indigeneous to tropical areas in South and North America including the Amazon, show remarkable cytotoxicity and selectivity against cancer cells. The phytochemical group, Annonaceous acetogenins, seems to play a significant role in this tree's antitumor properties.25-28

The group of compounds found in Graviola are potent inhibitors of NADH:ubiquinone oxidoreductase, which is an essential enzyme in complex I leading to oxidative phosphorylation in mitochondria. They also inhibit the ubiquinone-linked NADH oxidase enzyme, which is specific to the plasma membranes of cancerous cells.29

Much of the recent research done on extracts of this tree has been conducted by Purdue University, supported by grants from the National Cancer Institute and the National Institutes of Health. What they have found is that Annonaceous acetogenins can selectively inhibit the growth of cancerous cells and also inhibit the growth of adriamycin and other drug-resistant tumor cells.27 Not only are the compounds effective in killing tumors that have proven resistant to anti-cancer agents, but they also have a special affinity for such resistant cells.28

And we know the mechanism of action of at least one compound in the Annonaceous acetogenin group, bullatacin, which preferentially kills multi-drug resistant cancer cells by inhibiting ATP production, and thus removing the cancer's energy source.27

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Caveats
The three adverse experiences with combination treatment (chemotherapy plus select nutraceuticals) are all in vivo decreases or suspected decreases in the effectiveness of the chemotherapeutic agent.\(^2^\)
- N-acetylcysteine has reduced adverse effects from radiation and chemotherapy, but it is also suspected of decreasing the therapeutic effect of doxorubicin.\(^2^,^3\)
- There is one report of beta-carotene inhibiting the effect of 5-fluorouracil in fibrosarcoma, and, although it has demonstrated beneficial effects in other studies, the information available is not yet sufficient to recommend its use over vitamin A.\(^4,^5\)
- Tangeretin, a bioflavonoid, is reported to decrease the growth factor expression, cyclooxygenase-2, matrix regulation of antiapoptotic proteins; and downregulation of metalloproteinase-9, urokinase-type plasminogen activator angiogenesis through inhibition of vascular endothelial growth factor expression, cyclooxygenase-2, matrix metalloproteinase-9, urycrinase-type plasminogen activator and adhesion molecules. Furthermore, phytochemicals can modulate these molecular targets with considerably greater safety than standard radiation and chemotherapeutic agents.

This article has covered some of these chemicals but there are more. Genistein, resveratrol, dially sulfide, isothiocyanates, 3-ally cysteine, allicin, lycopene, capsaicin, are more. Genistein, resveratrol, dially sulfide, isothiocyanates, 3-ally cysteine, allicin, lycopene, capsaicin, and other well-researched phytochemical agents can be used alone or in combination with standard chemotherapy to treat cancer, and alone, to prevent its onset.

References
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