The Interaction of Vitamins with Cancer Chemotherapy

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The role that vitamins play in the growth and development of the cancer cell is understood only in certain instances. For example, methotrexate—which is actually a folate antivitamin—is effectively used as a chemotherapeutic agent and its toxic actions are well controlled by leucovorin, a folate vitamin. However, there is conflicting evidence and relatively little known about the importance of such critical vitamins as cholecalciferol, ascorbic acid, niacin, pyridoxine, thiamine and riboflavin, to mention only a few. Many studies on nutrition in cancer make special efforts to relate the protein content of the diet to cancer growth and immune capacity of the host, but fail to investigate the specific influence of vitamin content or deficiency, which may be of equal importance. 

The great improvement in the technology of performing vitamin serum level assays—mostly as a result of the development of radioimmune assays—has placed a powerful tool in the hands of clinicians and researchers. It is now possible to assay serum levels of vitamins present in only minute amounts, such as B12. This provides exact information on the presence of deficiency or excess. 

The purpose of this article is to report on the role of vitamins in: (1) the induction of cancer by carcinogens; (2) the enhancement or inhibition of chemotherapy; and (3) the course of malignant disease. Contrary to popular opinion, vitamins can be quite toxic and cannot be used indiscriminantly. In cancer chemotherapy their use is especially critical and we need more information.

Vitamin A

Because vitamin A has a natural role in the preservation of the function of cell membranes—particularly epithelium—it and other retinoic acid analogues have been widely used with some success in the therapy of such diseases as leukoplakia. More recently retinoic acid has been used topically in skin diseases such as acne, psoriasis and ichthyosis. Promising results have been obtained in cystic and anglobate acne with 13-cis-retinoic acid. However, caution is necessary because it has been demonstrated that in

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nude mice retinoic acid causes sensitization of the skin to ultraviolet light and an increased susceptibility to epidermal cancers.11

Far more important is the development of a concept of "chemoprevention," which involves certain lung neoplasias and vitamin A analogues, or retinoids.4 (See also Sporn MB: Retinoids and Cancer Prevention. CA; 29:120-125, 1979). This therapy attempts to block key metabolic pathways during the period of pre-neoplasia rather than attempting to destroy developed and established cancer cells. There is a balance between the induction of neoplasia by carcinogens and its inhibition by nutritive agents. The problem becomes one of "selective toxicity," a familiar one in pharmacology.12,13 Additional data come from an epidemiologic study of 8,000 male smokers in Norway that relates the incidence of lung cancer to a low dietary intake of vitamin A.14

Considerable experimental evidence clearly demonstrates that retinoids, like hormones, control cell differentiation and growth in target organs such as bronchi, trachea, stomach, intestine, uterus, kidney, bladder, testis, prostate, pancreatic ducts and skin.15 In organ cultures of prostate glands, hyperplastic and anaplastic epithelial lesions induced by chemical carcinogens can be reversed by retinoids.16,17 Retinoid deficiency may enhance the binding of the carcinogens or their metabolites to epithelial DNA.18

Unfortunately, vitamin A itself cannot be used in large enough doses for a sufficient period of time to be therapeutically effective without causing hypertoxinosis A.8 Fortunately, synthetic retinoids that modify the basic molecule, either in the hydrocarbon ring, the side chain or the polar terminal group, retain their antineoplastic properties and are much less toxic systemically.4 Some of these derivatives show great promise experimentally and it is likely that controlled human studies will be undertaken (at least one is underway now in the study of bladder cancer) with the best available compounds.

Vitamin C
The so-called "Orthomolecular Therapy" of cancer with "megadoses" of vitamin C (up to 10 grams a day) has received a great deal of popular attention. The beneficial actions claimed are:
- relief of pain from skeletal metastases;
- reduction of opiate dosage;
- correction of high urinary hydroxyproline;
- tumor regression and prolonged life expectancy.19-22

However, evidence for benefit is based on uncontrolled and non-randomized clinical trials. While therapeutic actions remain unconfirmed by other researchers or by a well-conducted clinical trial, there has been considerable effort expended to discover a secure experimental basis. It is claimed that vitamin C either slows down or stops the growth of malignant cells by inhibiting the action of hyaluronidase, the substance necessary for cell division, proliferation and migration.23 Recently, all the possible mechanisms of potential beneficial action have been reviewed.24

In lung cultures, the addition of either L-cysteine or ascorbic acid to the medium protects against the abnormal growth and malignant transformation induced by exposure to smoke from tobacco or marijuana cigarettes. This protection was afforded to both young and old cultures.25 Decrease of DNA synthesis and neoplastic cell proliferation have been observed for ascorbic acid in tumor cell lines in culture.26 A mutagenic action of vitamin C has been demonstrated in fibroblast cultures.27 Tumor bearing guinea pigs require ascorbic acid for tumor growth.28 Thus, it is seen even in
this brief review that at least experimentally there is ample evidence of an interaction of vitamin C with both neoplastic cells and carcinogenic agents.

It is not entirely true that vitamin C therapy is without risk. When taken in daily gram amounts for prolonged periods, vitamin C can be toxic.8 Perhaps its most serious reaction is the depression of B₁₂ serum levels that may lead to bone marrow changes.29-31 The utilization and distribution of B₁₂ is a factor in carcinogenesis. Consequently, the effect of vitamin C upon Vitamin B₁₂ may be indirectly involved in the problem of carcinogenesis.

The relationship of vitamin C therapy to the radiosensitivity of neoplastic tissues is also significant because inhibition of cellular oxidation protects tumors against radiation to a considerable degree. The chemical reaction of ascorbate with radiation induced radicals and the resulting additional oxygen consumption may produce a greater degree of hypoxia and subsequent radioprotection. Drugs such as metronidazol and Flagyl (which inhibit cellular oxygen consumption) cause reoxygenation of tumor tissue and hence increase radiosensitivity.32 Obviously, patients taking large amounts of ascorbic acid are subject to an inhibiting interaction with radiosensitizing drugs and this should be guarded against.

Vitamin B₁₂

In rat leukemia therapy with cis-diamine-chloroplatinum, the addition of vitamin B₁₂ and the citrovorum factor greatly increased the life span of the animals.33 In humans it has been found that a high serum B₁₂ level usually implies a poor prognosis in a patient with hepatic cancer.34 In hepatocellular carcinoma, serum B₁₂ unsaturated binding capacity provides a simple method of following the course of chemotherapy. This is related to the production of high serum levels of a B₁₂ binding glycoprotein by such tumors as malignant hepatoma.35,36

In the experimental production of hepatic tumors with aflatoxins there is some evidence that B₁₂ potentiates chemical carcinogenesis and tumor formation.37 Of greater importance in this study was the protein level of the diet. B₁₂ increases the excretion of urinary N-formino-L-glutamic acid, as do several chemical carcinogens (e.g., diethylnitrosamine), which similarly interfere with enzymes involved in the metabolism of carbon compounds.38 This may partially explain the results of the study.

While the exact role of vitamin B₁₂ in chemical carcinogenesis is still obscure, there is little doubt that it is involved. In hepatocellular carcinoma, B₁₂ is clinically useful as a diagnostic and prognostic tool in the form of serially followed serum levels. In some instances, its administration may accelerate the course of the disease, while in others it may increase survival time.

Pyridoxine, B₆

Pyridoxal phosphate is the essential coenzyme for biosynthetic reactions concerned with antibody production and cell-mediated immunity. In advanced metastatic carcinoma of the breast and other tissues, there is a substantially lower pyridoxal phosphate level as compared to normal controls. It is still unknown whether the anergic state of advanced breast cancer patients is due to B₆ deficiency or if it can be reversed by B₆ therapy.39

A comparative study of the effectiveness of placebo, topical thiopeta and pyridoxine in preventing recurrence of stage 1 bladder cancer showed that oral pyridoxine was significantly more effective than the placebo. Indeed, it equaled local thiopeta in effectiveness.40 In the therapy of primary and metastatic liver carcinoma with intrahepatic arterial infusion of Mitomycin-c and 5-fluorouracil, the addition of pyridoxine led to a lower incidence of toxicity.41

There have been attempts to produce B₆ antivitamins such as 4-halovinyl and
Vitamin E

The exact requirements for this fat soluble vitamin in human metabolism and its mechanism of action remain an enigma. Most explanations of its action are based on the fact that it is an antioxidant and the belief that it is a general protector of structural lipoproteins or of oxidizable lipid components. Recent work considers selenium an essential component of glutathione peroxidase, which destroys H₂O₂ and organic hydroperoxides, which in turn protects cell membranes against oxidative damage. Selenium works in conjunction with vitamin E; the latter prevents the formation of liquid hydroperoxides.⁴³

The drug adriamycin (doxorubicin) is an effective chemotherapeutic agent whose mechanism of action is suppression of DNA synthesis. Unfortunately, it also causes peroxidation of cardiac lipids and as a result, along with its other toxic side-effects, it is specifically cardiotoxic. Prior therapy of mice with alpha tocopherol greatly reduces the cardiac toxicity of adriamycin without inhibiting its antitumor effects.⁴⁴ The administration of selenium-vitamin E to weaning rabbits treated chronically with adriamycin results in decreased incidence of cardiomyopathy and increased survival time.⁴⁵ Clinical studies are now in progress that indicate that vitamin E does afford protection against adriamycin cardiotoxicity. However, this does not obviate the need for careful monitoring and follow-up of the cardiac status of patients receiving adriamycin.

Vitamin K

It is now known that vitamin K is a component of a microsomal carboxylase system. Studies of this system have uncovered a new amino acid, gamma carboxyglutamic acid (Gla), which is a component of prothrombin and phylogenetically related proteins that are found in bone and renal tissue. It is suspected that vitamin K dependent proteins—which have strong calcium and phospholipid binding properties—are involved at the membrane level in the metabolism of calcium.⁴⁶

The carcinogen 4-nitroquinoline-1-oxide and its metabolites have properties similar to vitamin K at the subcellular level.⁴⁷ The mean number of spontaneous lung metastases from Lewis lung carcinomas was reduced in three groups of C57BL mice when vitamin K deprivation was induced by adding the vitamin K antagonist phenprocoumon to the drinking water.⁴⁸ It is believed that fibrinolysis and prevention of platelet aggregation are important elements in preventing metastasis; in light of this, intravenous chemotherapy with adjunctive coumadin anticoagulants may represent a new approach to the prevention of metastases.⁴⁹,⁵⁰ There is growing evidence and conviction that vitamin K has a role in chemical carcinogenesis.⁵¹-⁵³ Vitamin K antivitamins may prove beneficial clinically, especially in the prevention of metastasis.⁵⁴

Miscellaneous Vitamins

Riboflavin deficiency has been shown to stimulate azo dye carcinogenesis and to inhibit tumor growth in man and animals. Other work with riboflavin demonstrates an inhibition of uptake of methotrexate by neoplastic cells and also a slight inhibitory effect in 3, 4-benzopyrene-induced skin tumors.⁵⁴,⁵⁵
About one-third of patients receiving 5-fluorouracil therapy were found to have thiamine deficiency as compared to normal controls. When the thiamine was replaced there was rapid progression of the tumor and such therapy may be detrimental.\(^5\)

Niacin is crucial to the function of the pyridine nucleotides NAD and NADP and could be expected to have a significant role in carcinogenesis but this relationship has not been thoroughly studied. However, in one of the few studies that have been conducted niacin appeared to promote the development of kidney neoplasias induced by diethylnitrosamine. It is known that niacin will increase the incidence of pancreatic islet-cell tumors after the administration of streptozotocin. On the other hand, niacin will prevent the depletion of NAD coenzymes by alkylating agents.\(^6\) Thus, the role of niacin in chemical carcinogenesis remains obscure and requires further inquiry.

Comment

It is obvious that no blanket recommendations can be made with respect to the use of either vitamins or antivitamins as adjunctive cancer therapy, except where the clinical therapeutic benefit has been substantiated. However, this subject has been neglected too long and what is needed are more accurate and detailed observations of carcinogenesis and its course in humans, with particular emphasis on diet and crucial dietary factors such as vitamins and the quality of protein intake. There are areas in which further study of the interaction of vitamins with cancer chemotherapy may bring improvement to what is currently a bleak therapeutic outlook:

- Smokers may be able to protect themselves with vitamin A derivatives.
- There may be dietary factors in the development of stomach cancer that interact with environmental carcinogens to either enhance or prevent the disease.
- The incidence of metastatic disease may perhaps be minimized by dietary manipulation.

Examination of most patient charts shows little or no reference to detailed and accurate dietary history; a more thorough approach to the dietary history of cancer patients is urgently needed. Are we missing important clues to the causation or prevention of cancer that could be discovered if more attention was paid to a thorough documentation of the intake of vitamins?

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THE ROAD NOT TAKEN

When Otto Hahn stumbled upon the discovery of nuclear fission in Berlin in 1938, he had no inkling of nuclear weapons, no premonition that he was treading on dangerous ground. When the news of Hiroshima came to him seven years later, he was overcome with such grief that his friends were afraid he would kill himself. Science and technology, like all original creations of the human spirit, are unpredictable. If we had a reliable way to label our toys good and bad, it would be easy to regulate technology wisely.

From: Reflections: Disturbing the Universe-I, Freeman Dyson, The New Yorker, August 6, 1979, p 39.