VOLUME 26 · NUMBER 34 · DECEMBER 1 2008

JOURNAL OF CLINICAL ONCOLOGY

CELEBRATING 25 YEARS OF JCO

Retinol, Vitamins, and Cancer Prevention: 25 Years of Learning and Relearning

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Twenty-five years ago, we published a phase I trial of retinol in cancer patients.[1] By today's standards, this phase I trial left much to be desired. The sample size of 13 patients, the methods to evaluate adverse effects (remember radionuclide liver-spleen scans?), and the lack of pharmacokinetics are just a few areas that make it seem naive. However, although deficient by today's standards, the unique aspects of that trial remain—the potential target population and the agent being studied, retinol (ie, vitamin A).

In 1983, the retinoids, vitamin A and its family of naturally occurring and synthetic analogs, were just entering the realm of clinical investigation. In 1979, Sporn and Newton[2] published their landmark article on the retinoids and introduced the concept of chemoprevention—the possibility that we could prevent, arrest, or reverse carcinogenesis by the administration of exogenous agents. At the time, simple in vivo and in vitro experiments suggested that retinoids could act as chemoprevention agents. In addition, *trans*- and *cis*-retinoic acid had shown some activity in patients with established cancers.[3,4] The group at the University of Arizona Cancer Center led by Dr Frank Meyskens initiated studies to investigate the potential of the retinoids for treating cancer and as cancer prevention agents. The 1983 phase I trial was one of a series of trials testing retinol, retinyl palmitate, and 13-*cis*-retinoic acid. These phase I and II trials were among the first studying potential chemoprevention agents and set a precedent for their clinical evaluation.

Another important aspect of this trial was the recognition of dietary micronutrients and vitamins as biologically active agents that deserved laboratory and clinical investigation. In the late 1970s and early 1980s, the study of vitamins in cancer prevention and treatment was more in the realm of alternative treatment. A re-evaluation was supported by the increase in nutritional epidemiology and the findings of inverse associations between the intake of foods rich in certain vitamins and cancer incidence. Over time, epidemiologic studies became more sophisticated in analyzing dietary constituents and included serum concentrations of micronutrients. The inverse associations with specific cancers held. Although plagued with potential confounders, these studies suggested that low serum concentrations of retinol and its precursor (β-carotene) were risk factors for many cancers.[5,6] In parallel, work by Lotan and Clifford[7] and others describing additional synthetic retinoids, retinoid receptors, and their role in cancer and normal cellular differentiation gave the area a strong basic science foundation. It was clear that the retinoids had an important biologic role (they are vital amines are they not?) and that their manipulation may result in clinical benefit.

In 1983, literature describing the clinical use of the retinoids was scant. None of the newer retinoids were available for clinical use, and toxicity reports were anecdotal and consisted almost exclusively of accidental or health enthusiast overdosing with retinol or retinyl palmitate. Because these agents had a potential for use in cancer treatment as well as cancer prevention, we decided that they should be treated like any biologically active drug. Their potential for use in a healthy but high-risk population made it imperative to have a clear understanding of the dose-toxicity relationship. Hence, we studied the retinoids as we would any phase I cancer agent. Our phase I trial of retinol was closely followed by a phase II trial in cancer patients[8] and later used in a large phase III chemoprevention trial (Carotene and Retinol Efficacy Trial [CARET]).[9]

Since those early days, many years have passed, and we have learned much. In the area of therapeutics, retinoids are now approved for clinical use and are part of standard treatment protocols—*trans*-retinoic acid for acute promyelocytic leukemia, 13-*cis*-retinoic acid for acne, and bexarotene for cutaneous T-cell lymphoma.

In the area of chemoprevention, retinoids and their dietary precursor (β-carotene) were some of the first agents to be tested in large population-based trials. In the National Cancer Institute-sponsored trials in Linxian, China, both β-carotene and retinol were part of the nutritional combinations tested. In this nutritionally deficient population, the combination of β-carotene, α-tocopherol, and selenium showed a decrease in cancer incidence and a survival advantage.[10] The Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) trial in Finland and our CARET trial in the United States studied β-carotene along with α-tocopherol (ATBC) and retinol (CARET) in cigarette smokers.[11] These studies in a nutritionally adequate population did not show benefit from either retinol or β-carotene supplementation; both ATBC and CARET found a significant increase in lung cancer incidence in the retinol/β-carotene–containing arms within 1 to 2 years of administration.

That first generation of chemoprevention trials taught us much. Our enthusiasm of intervening with harmless micronutrients or vitamins has been tempered by a better understanding of the complexity of carcinogenesis and the complexity, but still poor understanding, of the mechanism and scope of biologic activity of vitamins and micronutrients. The findings of increased lung cancer incidence in both the

DOI: 10.1200/JCO.2008.19.0884; published online ahead of print at www.jco.org on November 3, 2008

ATBC trial and the CARET trial were unexpected. Micronutrients were clearly complex interventions with many potential adverse effects. These were not pharmaceutical interventions such as finasteride or tamoxifen, where the synthetic drug had a specific target and a relatively predictable effect on normal and malignant tissues expressing the target receptor. In addition, both of those agents had a long history of use in the general population and had undergone extensive testing for US Food and Drug Administration approval. Their toxicities were well known. Trials using these agents have been one of the great successes of chemoprevention, decreasing the target cancer incidence rate with the expected toxicities.[12,13]

The use of micronutrients and vitamins must be viewed differently from the use of synthetic drugs. Over the millennia, human physiology has evolved to optimally function with dietary micronutrients and vitamins concentrations within a narrow range. Dietary micronutrients are active in many metabolic functions, and deficiency affects many organ systems. Taking supraphysiologic doses for prolonged time may also affect many organ systems; our understanding of the pharmacology and physiologic effects at these high doses is incomplete. Perhaps it was naive to expect that increasing the intake of a micronutrient 10-fold would modify cancer incidence and cause few adverse effects. Perhaps it is not surprising that the first generation of trials testing high-dose vitamin supplementation found unexpected adverse effects, including an increased incidence of cancer and cardiovascular disease in ATBC and CARET (likely as a result of β-carotene), lung cancer and cardiovascular disease in a trial of 13-*cis*-retinoic acid,[14] and perhaps cardiovascular disease in multiple studies studying α-tocopherol. A recent meta-analysis of mortality in 68 randomized trials of antioxidant supplements found increased mortality in the treatment arms.[15] Like other prescribed pharmacologic interventions, increasing the dosage 10-fold does not necessarily lead to better results; it can be fatal.

Back in 1983, we started with the right idea, carefully studying a proposed intervention to define its dose-toxicity relationship, pharmacology, and then efficacy in areas where activity was found or suggested. In the realm of cancer treatment, this phase I/II approach has worked well. Cancer prevention, however, is dramatically different from cancer treatment; our target populations are, in general, healthy, and our tolerance of toxicity and adverse effects is low. Duration of treatment may be in years and not the usual shorter duration of the standard phase I, II, or III cancer treatment trial. End points are not response in a patient with a measurable tumor but change in the incidence of cancer (a rare event even in high-risk populations), and where the true onset may occur up to 10 years before clinical detection. The search for markers or surrogate end points both to shorten trial duration and lower the sample size requirements remains allusive and is an area of intense research. These features of chemoprevention research have resulted in continual modification and refinement of the design of phase I/II trials for prevention agents.

Regardless of the modifications of future phase I/II trials, we clearly need to continue to define the dose-toxicity relationship of an agent before starting phase III trials, be it a pharmaceutical or a micronutrient/vitamin. US Food and Drug Administration restrictions require pharmaceuticals to have extensive evaluation before they are administered to patients. However, because of the lack of both US Food and Drug Administration oversight and pharmaceutical industry interest and the general assumption that vitamins are safe, vitamins have had inadequate investigation before being administered to healthy populations in high doses for long periods of time. We should not be surprised at unexpected events because these agents have never had the careful evaluation that is part of a large, randomized, placebo-controlled trial. Our experience over the last 25 years has made us relearn the importance of carefully completing phase I and II trials of any agent before starting a large, long-term, population-based trial. This point becomes especially critical in cancer prevention research, where the target populations are healthy and the chances of doing harm can outweigh the benefits.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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Provision of study materials or patients: Gary E. Goodman
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REFERENCES

1. Goodman GE, Alberts DS, Ernest DL, et al: Phase I trial of retinol in cancer patients. J Clin Oncol 1:394-399, 1983
2. Sporn MB, Newton DL: Chemoprevention of cancer with retinoids. Fed Proc 38:2528-2534, 1979
3. Bollog W, Matter A: From vitamin A to retinoids in experimental and clinical oncology: Achievements, failures and outlook. Ann N Y Acad Sci 351:9-23, 1981
4. Meyskens FL, Gilmartin E, Alberts DS, et al: Activity of isoretinoin against squamous cell cancers and pre-neoplastic lesions. Cancer Treat Rep 66:1315-1319, 1982
5. Bertram JS, Kolonel LN, Meyskens FL: Rationale and strategies for chemoprevention of cancer in humans. Cancer Res 47:3012-3031, 1987
6. Peto R, Doll R, Buckley JD, et al: Can dietary beta-carotene materially reduce human cancer rates? Nature 290:201-208, 1981
7. Lotan R, Clifford JL: Nuclear receptors for retinoids: Mediators of retinoid effects on normal and malignant cells. Biomed Pharmacother 45:145-156, 1991
8. Goodman GE, Christofferson E, Kaplan HG, et al: Phase II trial of retinol in patients with advanced cancer. Cancer Treat Rep 70:1023-1024, 1986
9. Omenn GS, Goodman GE, Thornquist MD, et al: Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. N Engl J Med 334:1150-1155, 1996
10. Blot WJ, Li JY, Taylor PR, et al: Nutrition intervention trials in Linxian, China: Supplementation with specific vitamin/mineral combinations, cancer incidence, and disease-specific mortality in the general population. J Natl Cancer Inst 85:1483-1492, 1993
11. The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group: The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. N Engl J Med 330:1029-1035, 1994
12. Thompson IM, Goodman PJ, Tangen CM, et al: The influence of finasteride on the development of prostate cancer. N Engl J Med 349:215-224, 2003
13. Fisher B, Costantino JP, Wickerham DL, et al: Tamoxifen for prevention of breast cancer: Report of the National Surgical Adjuvant Breast and Bowel Project P-1 study. J Natl Cancer Inst 90:1371-1388, 1998
14. Khuri FR, Lee JJ, Lippman SM, et al: Randomized phase III trial of low-dose isotretinoin for prevention of second primary tumors in stage I and II head and neck cancer patients. J Natl Cancer Inst 98:441-450, 2006
15. Bjelakovic G, Nikolova D, Gludd LL, et al: Mortality in randomized trials of antioxidant supplements for primary and secondary prevention: Systematic review and meta-analysis. JAMA 297:842-857, 2007

