Editorial

Integrative Cancer Therapies
Volume 7 Number 4
December 2008 223-225

10.1177/1534735408327252
http://ict.sagepub.com
hosted at
http://online.sagepub.com

Enzymes and Cancer: A Look Toward the Past as We Move Forward

Keith I. Block, MD

Several years ago, I was having lunch with a prominent German medical oncologist at a conference on cancer and CAM at the National Institutes of Health (NIH) in Washington, DC. I asked him what the most exciting thing in cancer CAM in Europe was at that time. "Enzymes," he said. A bit surprised by his instantaneous response, I asked him what the second most exciting thing was. Again with no hesitation he blurted out, "More enzymes!"

We did not pursue the conversation much further, but the incident has stuck in my mind for many years now, and I have both used and kept an eye on enzyme therapy ever since. I have observed some of my cancer patients who were using enzyme-based supplements, and I have explored how active enzyme supplements might be successfully formulated. I was thus quite intrigued when *Integrative Cancer Therapies* Corresponding Editor Ralph Moss proposed this special issue on enzyme therapy for cancer in honor of the birth anniversary of John Beard, the scientific founder of enzyme therapies. Ralph, in his guest editorial, summarizes the articles in this issue, to which he has contributed an impressive set of scholarly biographical and historical studies of Beard and the course of his studies on enzymes and cancer.

Oral systemic enzyme therapy for cancer is widely used in Europe, and a therapy based on pancreatic enzyme extracts has been the subject of an NIH-sponsored trial in the United States. As a clinician, I find myself most interested in the results of clinical trials. A group of especially interesting recent studies conducted in Europe are reviewed in this issue in the article by Beuth, but I would like to summarize, in this editorial, some other studies for our readers as well.

The enzyme preparations studied in Europe have typically been formulations of trypsin, chymotrypsin, and papain; there have also been studies of bromelain, an enzyme derived from pineapple. Wobe-Mugos is the most commonly studied product in cancer. It was formulated by MUCOS Emulsions GmBH, Munich, Germany, which also produced other enzyme products, such as Wobenzym, widely used for inflammation and sports injuries in Europe. The MUCOS group has since been purchased by Atrium Innovations, Inc, Canada. A number of early studies sponsored by MUCOS, not all of them published, are summarized in a 1996 publication.[1] Leipner and Saller reviewed clinical studies of oral systemic enzymes in oncology in 2000,[2] and they were allowed access to the MUCOS corporate files to obtain details of some of these trials. A number of the trials sponsored by MUCOS are in non-English journals, and this review has made useful details of these studies more accessible.

One of the characteristics of European evaluations of enzyme therapy is a predominance of retrospective designs. Enzyme therapy had become well established in European cancer centers before systematic attempts to evaluate its use were initiated. There is thus an effort among interested researchers to examine existing clinical data as a source for information regarding efficacy of the enzyme preparations. This has led to the use of retrospective study designs or, more specifically, retrolective designs. In retrolective studies, data are extracted from medical records of centers in which some patients used enzymes (or other therapies of interest) and others did not. Retrolective studies are essentially epidemiological, retrospective parallel group designs. As discussed by Beuth in this issue, these studies constitute level IIb evidence-based medicine and, as such, are acceptable to European Union nations as demonstrations of efficacy.

The major outcomes of most of these trials have concerned side effects of chemotherapy and radiation treatment, although some have also examined response and survival outcomes. Among the older studies summarized by Leipner and Saller, several concerned patients receiving chemotherapy. A randomized study in lung cancer patients, which was not statistically evaluated, employed oral or rectal administration of enzymes and suggested improved quality of life and reduced chemotherapy side effects. An open study of gastric cancer patients observed an increase in the ratio of T-lymphocytes to total lymphocytes in patients receiving enzyme therapy when compared

From the Block Center for Integrative Cancer Treatment, Evanston, Illinois, and the University of Illinois at Chicago College of Medicine and College of Pharmacy, Chicago, Illinois.

Address correspondence to: Keith I. Block, MD, Block Center for Integrative Cancer Treatment, 1800 Sherman, Suite 350, Evanston, IL 6020; e-mail: kblock@blockmedical.com.

with those receiving chemotherapy only. A post–marketing surveillance study (another retrospective design, of course) examined patients who had received hydrolytic enzymes along with bleomycin. A major side effect of bleomycin is pulmonary fibrosis. Because fibrosis is an inflammatory reaction, it would not be surprising to see it suppressed by enzymes that have anti-inflammatory properties. None of the 58 patients reviewed in this study experienced pulmonary toxicity. Data on response to chemotherapy are not available in this study. A randomized, single-blind study of ovarian cancer patients receiving chemotherapy observed a more rapid normalization of liver enzymes in the experimental group, but no differences in other common laboratory analyses were evident. An unpublished randomized, double-blind study in 60 colon cancer patients, obtained from the MUCOS files, observed lower levels of chemotherapy side effects and also suggested fewer metastases and a trend toward longer survival. In addition to this study, a later study by the same research group is available. This retrolective cohort study of 1242 colorectal cancer patients receiving chemotherapy, with or without enzyme therapy, showed a reduction in side effects of medications and disease symptoms.[3] More recent trials are reviewed in this issue by Beuth.

The most interesting chemotherapy study reviewed by Leipner and Saller, as well as by Beuth, is one conducted by Sakalova and colleagues in multiple myeloma (plasmacytoma).[4] In this retrolective study, data were gathered on patients with multiple myeloma. Some patients had received enzyme treatment (Wobe-Mugos) along with chemotherapy and others had not. The decision to use enzymes was made in what can be characterized as a quasirandomized fashion, according to the availability of enzyme medications at different times but without reference to prognostic factors. Kaplan–Meier and Cox regression analyses were performed. Survival of patients with stage III multiple myeloma who were treated with enzymes was 83 months, whereas that of patients who did not receive enzymes was 47 months, a significant difference. Sensitivity analysis of a variety of prognostic covariates indicated that age, sex, and known risk factors indicated no statistically significant differences in the covariates between the 2 groups.

On the basis of this study, an application was submitted to the US Food and Drug Administration, which resulted in the designation of Wobe-Mugos as an Orphan Drug for multiple myeloma. An initial Orphan Drug designation permits further research on a drug for potential approval in the US market, and a phase III trial was indeed begun for stage II or III patients to receive Wobe-Mugos in combination with chemotherapy.[5] However, the trial was never completed, apparently because of business disagreements between the German and US companies involved. Thus, Wobe-Mugos has never been submitted for actual approval as an Orphan Drug and, consequently, does not have regulatory status as a prescription drug in the United States.

Leipner and Saller review 3 early (1976-1992) trials of enzyme therapy given with radiation, in addition to 2 trials from the MUCOS files that were later published. A post–marketing surveillance study of patients with lung cancer receiving radiation observed that appearance of metastases was lowered and radiographic abnormalities were reduced in size among patients treated with enzyme therapy. Gastrointestinal cancer patients undergoing radiotherapy had a reduced duration of side effects with enzyme treatment in a prospective randomized trial. A randomized open trial in patients with oral cancers undergoing radiation observed a lower incidence of mucosal necrosis.

Published radiotherapy trials broaden the evidence base on enzymes and radiation. Two open randomized trials observed reductions in side effects of radiation therapy in head and neck cancers.[6,7] An open randomized trial in uterine cancer patients undergoing radiation indicated a reduction in side effects.[8] These trials and those in the preceding paragraph, however, suffer from defects in trial design, for example, lack of double-blinding. Two more recent trials, both double-blind trials, did not find such encouraging results. A double-blind randomized trial in patients receiving pelvic radiation did not show any reduction in side effects or treatment interruptions.[9] A 2007 randomized, placebo-controlled trial failed to find any effect of Wobe-Mugos in reduction of radiation-induced mucositis in patients with head and neck cancer.[10] It is somewhat concerning that the double-blind trials of enzyme therapy did not confirm the indications of the previous, less well-designed trials of enzymes in radiation therapy, although this cannot be taken as a final judgment of the efficacy of enzyme therapies in general. It is not clear from information available to me at this time, for instance, whether dosing was similar in all the trials or whether formulations of the product have remained the same over the years.

An interesting direction for research is highlighted by the work of Desser and colleagues on the effect of oral enzyme therapy on transforming growth factor-β (TGF-β).[11] Patients with rheumatoid arthritis, osteomyelitis, or herpes zoster, some of whom had elevated TGF-β, were given oral enzymes, as were a normal control group. No change in serum TGF-β levels was observed in normal controls or patients with normal TGF-β levels. However, TGF-β levels declined significantly in patients with initially elevated TGF-β levels.

TGF-β is associated with inflammatory conditions, as in the example of bleomycin-induced fibrosis mentioned above. Interestingly, TGF-β also plays a role in the very recent publication on genomic analysis of pancreatic cancer.[12] This study found that large numbers of genes are mutated or otherwise abnormal in pancreatic cancer cells, such that each pancreatic tumor had nearly 60 abnormal genes. These genes, however, could be grouped into 12 biochemical pathways that were considered highly

abnormal. One of these abnormal pathways was the TGF-β signaling pathway. This study obviously has major implications for multitargeted natural therapies, a topic that I have discussed before.[13] If enzyme therapies are able to help normalize the TGF-β pathway, as this study hints, they might play a role in such multitargeted therapy regimens. The possibility certainly deserves investigation.

There remains the more immediate question of the usefulness of enzyme therapies as adjuncts to conventional treatment or as anticancer or chemopreventive agents. Having observed cancer patients taking enzyme supplements for several years, I am convinced that they do effect a positive change in the internal biochemical environment. Suppression of inflammation is particularly noticeable. Under what circumstances they might be used most profitably in the clinic remains an open question. Certainly the contrasting results of the recent negative double-blind studies on radiation therapy and the prior, positive less well-designed studies is instructive. However, the intriguing data on TGF-β, and the equally interesting data discussed in the quantitative studies of Wald, Elzer, and Beuth in this special issue, as well as the interesting link Burleigh proposes to cancer stem cell theory suggest a need for further well-designed research that encompass a phase I to phase III model of study. Selection of what clinical outcomes would be best studied should be linked to the mechanistic information available on the various enzyme therapies rather than solely on existing nonrandomized studies. It may also be profitable to use enzymes in combination with other therapies for a truly multitargeted approach to cancer.

Enzyme therapies are, as Beuth points out in this issue, beginning to enter the realm of evidence-based medicine with the recent studies he reports, and those discussed in this editorial. But restricting our judgment about the usefulness of enzyme therapy to the existing trials may result in a limited and deceptive assessment of their ultimate contribution to clinical medicine. There is certainly a history of mechanistic theories about enzyme activity that are not in keeping with current understandings of cancer treatment. However, as recent work has shown, including the articles in this special issue, there is much more to be learned about oral enzyme therapy. Enzyme therapies in the future may indeed have many biologic and therapeutic roles for the cancer patient.

References

1. Klaschka F. *Oral Enzymes: New Approach to Cancer Treatment*. Gräfelfing, Germany: Forum Medizin; 1996.
2. Leipner J, Saller R. Systemic enzyme therapy in oncology. *Drugs*. 2000;59:769-780.
3. Popiela T, Kulig J, Hanisch J, Bock PR. Influence of a complementary treatment with oral enzymes on patients with colorectal cancers—an epidemiological retrolective cohort study. *Cancer Chemother Pharmacol*. 2001;47(suppl):S55-S63.
4. Sakalová A, Bock PR, Dedík L, et al. Retrolective cohort study of an additive therapy with an oral enzyme preparation in patients with multiple myeloma. *Cancer Chemother Pharmacol*. 2001;47(suppl):S38-S44.
5. Anonymous. Chemotherapy with or without Wobe-Mugos E in treating patients with stage II or stage III multiple myeloma. http://www.clinicaltrials.gov/ct2/show/NCT00014339?/term=wobe&rank=1. Accessed September 17, 2008.
6. Kaul R, Mishra BK, Sutradar P, Choudhary V, Gujral MS. The role of Wobe-Mugos in reducing acute sequelae of radiation in head and neck cancers—a clinical phase-III randomized trial. *Indian J Cancer*. 1999;36:141-148.
7. Gujral MS, Patnaik PM, Kaul R, et al. Efficacy of hydrolytic enzymes in preventing radiation therapy-induced side effects in patients with head and neck cancers. *Cancer Chemother Pharmacol*. 2001;47(suppl):S23-S28.
8. Dale PS, Tamhankar CP, George D, Daftary GV. Co-medication with hydrolytic enzymes in radiation therapy of uterine cervix: evidence of the reduction of acute side effects. *Cancer Chemother Pharmacol*. 2001;47(suppl):S29-S34.
9. Martin T, Uhder K, Kurek R, et al. Does prophylactic treatment with proteolytic enzymes reduce acute toxicity of adjuvant pelvic irradiation? Results of a double-blind randomized trial. *Radiother Oncol*. 2002;65:17-22.
10. Dörr W, Herrmann T; Study Group. Efficacy of Wobe-Mugos E for reduction of oral mucositis after radiotherapy: results of a prospective, randomized, placebo-controlled, triple-blind phase III multicenter study. *Strahlenther Onkol*. 2007;183:121-127.
11. Desser L, Holomanova D, Zavadova E, Pavelka K, Mohr T, Herbacek I. Oral therapy with proteolytic enzymes decreases excessive TGF-beta levels in human blood. *Cancer Chemother Pharmacol*. 2001;47(suppl):S10-S15.
12. Jones S, Zhang X, Parsons DW, et al. Core signaling pathways in human pancreatic cancers revealed by global genomic analyses. *Science*. 2008;321:1801-1806.
13. McCarty MF, Block KI. Multifocal angiostatic therapy: an update. *Integr Cancer Ther*. 2005;4:301-314.