Salvestrols

A natural, targeted approach to preventing and treating cancer

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The ultimate goal in cancer research is to find a way to kill cancer cells present as tumors, precancerous lesions, or circulating cancer cells, and to accomplish this with minimal systemic toxicity. Any realistic evaluation of the current status to cancer therapy suggests that this goal is far from being achieved, although for a small number of cancers, achieving a complete and durable cure is possible.

This article describes an alternative approach to cancer prevention and therapy based on the remarkable properties of an enzyme highly expressed at the protein level in cancer cells and present only in negligible amounts in normal cells. This statement applies to at least 26 different cancer types. The reason this is important is that naturally occurring substrates for this enzyme exist which when metabolized in the cancer cell yield a cytotoxin that kills the cell. Research over the past decade has identified extracts of certain fruits that have been demonstrated in cell culture studies to provide highly active cytotoxic metabolites generated by this enzyme. In addition, serum variations in substrate and metabolite have been demonstrated to provide evidence of the presence of cancer, to some extent its stage, and when the substrate is observed to

be metabolized and the metabolite detected, an indication of the success of the therapeutic intervention is evident. This provides compelling biological plausibility for the therapy and the action of this enzyme.

Human studies at this point in time involve case histories of 15 patients cured, in the opinion of the specialists involved, by the use of this oral therapy. The success of the therapy appears independent of the site. Given that this is a natural product, it is unrealistic at this time to expect more comprehensive clinical evidence, and to ignore this approach appears to be a serious mistake.

Introduction

The natural history of cancer indicates initiation via a modified cell is followed over a number of years by abnormal cell growth before there is any clinical evidence of the disease. Current technology involving either scanning or the use of biomarkers or reliance on clinical manifestation (e.g. a lump) has a threshold for detection of somewhere between 1/10th of a billion and one billion cells. The time from initiation to this tumor size ranges from a few years to as many as 20 years. An important feature of this process is that it is well advanced before diagnosis is currently possible (Burke 2009, O'Shaughnessy 2002). Multiple cancers may be present at a variety of stages of development, and patients may also already have established metastasis from the primary cancer prior to diagnosis or treatment. Millions of individuals currently have undetected, silent cancer that is somewhere between the initiation of a cancer cell and manifestation of the disease (Hyman 2007).

The challenge of primary prevention involves preventing the formation of the initial modified cells or detecting and destroying their progeny. Primary carcinogenesis appears to occur constantly due to mutations induced by natural background radiation or by cell changes induced by a variety of endogenous and exogenous factors. The fact that the human race is here today suggests the existence of one or more protective mechanisms. Put another way, why don't we all get cancer? For existing tumours, the challenge is targeting with a localized therapy with low or negligible systemic toxicity, an approach attracting intense research interest at present (NIH 2012).

It is well established that the consumption of fruits and vegetables offers protection from cancer, and various constituents such as polyphenols have been suggested as responsible, partially mediated through the ability to counteract, reduce and also repair damage resulting from inflammation and oxidative stress (Reiss 2012, Seeram 2008, Vainio 2006, Ware 2009a). However, there is another mechanism which may be much more important. This is based on the fact that cancer cells express at the protein level an enzyme that is capable of metabolizing chemicals found in fruits and generating cytotoxic metabolites within the same cell. The enzyme belongs to the large P450 class and is designated CYP1B1. Already in 2002 it was reported that this enzyme converted resveratrol into the anticancer agent piceatannol (Potter 2002). So far, there are 26 cancer types where tumour cell overexpression of CYP1B1 has been demonstrated, but its presence in normal cells is negligible. In Appendix 1 of his book *Linking Diet and Cancer. Salvestrols, Nature's Defence Against Cancer*, Dr. Brain Schaefer cites 62 studies (Schaefer 2012b). Taking advantage of this cytotoxin generating ability provides a targeted therapy independent of cancer type (Tan 2007).

The literature associated with exploiting the beneficial aspects of CYP1B1 is sparse and some appears in journals not covered by MEDLINE (PubMed). However, the book cited above provides a detailed, documented review of the issues being discussed here and also includes considerable unpublished information (Schaefer 2012b).

The search for the best CYP1B1 substrates

The remarkable property of CYP1B1 prompted two researchers, Professors Gerald Potter and Danny Burk in Leicester, U.K. to search for both synthetic and natural substrates using cancer cell culture techniques (Androutsopoulos 2008, Potter 2002, Potter 2006). A prodrug was developed and substrates for CYP1B1 yielding potent natural cytotoxic metabolites identified. In comparison with organically grown produce, produce grown with insecticides and from highly inbred varieties or hybridized to decrease bitterness had remarkably low levels of these substrates, an observation of great significance. The name Salvestrol was given to these

active compounds or extracts (Schaefer 2012b, Tan 2007). They are vastly more selective than conventional chemotherapy because they target CYP1B1.

Summary of case studies

The evidence for human efficacy derives from a number of case studies. (Schaefer 2012a, Schaefer 2012b, Schaefer 2007, Schaefer 2010, Schaefer 2012c). In all cases listed in the table below, the cancer was considered cured by the oncologists involved. Additional cases have been collected including lung and pancreatic cancer (Schaefer 2012a).

Salvestrols of various potency were used by the individuals in these case studies which spanned a considerable time. Complete success is not always achieved by individuals using salvestrols, and dose, potency and adherence may be among the responsible factors. European experience with dose escalation suggests that there is a range of a factor of about two in the dose that produces response (Schaefer 2012a). Also, the currently available commercial extract is much more potent than earlier formulations. Dismissing or ignoring these case studies because they are not proper clinical trials is unrealistic considering a natural product is involved.

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The author of this article attempted to give wider recognition to the remarkable property and potential of CYB1B1 and some of these results by publishing two articles, but there appears to be little interest (Ware 2009a, Ware 2009b). Instead, research interest is focused on inhibiting this enzyme because it is implicated in carcinogenesis, especially involving aromatic hydrocarbons and estrogen, or on research involving stimulating immune activity against CYP1B1 (McFadyen 2005, Swanson 2010). However, once one has cancer, this seems irrelevant. Inhibition of CYP1B1 would address only a very minor aspect of carcinogenesis while eliminating what appears to be a very important human defence mechanism against this disease. Also, smoking is an avoidable risk and the major source of exogenous aromatic hydrocarbons. Given the apparently universal phenomenon of CYTP1B1 overexpression in cancer cells, it is hard to see how this enzyme could have evolved to be anything other than mostly beneficial, and thus not a target for inhibition or a vaccine (which exists, incidentally).

Diagnosis by detecting CYP1B1 in serum

The original observation that CYP1B1 was not expressed in normal cells was found to be not universally true when highly sensitive detection methods were used, although the levels were still vastly lower than found in tumour tissue (Schaefer 2012b) Eventually the researchers developed a highly sensitive serum assay specific for human CYP1B1 protein. A proteomic approach was involved and it was possible to establish a baseline CYP1B1 level in individuals believed to be free of cancer which was minute but not zero. This background of CYP1B1 may reflect adventitious cancer cells constantly being generated. Based on thresholds derived from this background level, Schaefer estimates that the present level of sensitivity allows cancer detection about six years prior to clinical manifestation. For example, CYP1B1 at between 100 and 6000 times normal background was measured in lung cancer patients with levels providing a good correlation with the extent of disease (Schaefer 2012b).

Monitoring the success of therapy with serum CYP1B1 metabolites

Schaefer describes a second blood test termed the metabolic approach (Schaefer 2012b). A sensitive analytical method for testing in blood and urine for both the salvestrol (substrate) and its CYP1B1 metabolite was developed, and provided the opportunity to detect the presence of the enzyme and measure the extent of the cancer by the change in substrate concentration and the appearance of metabolite. A salvestrol was used that produced large amounts of metabolite with no confounding from

SUMMARY OF CASE STUDIES		
Site	Stage	Cases*
Squamous-cell carcinoma (lung)	2-3	1
Melanoma	4	1
Prostate (one Gleason 3+3)	3	3
Breast, (one aggressive)	3	2
Breast	1	1
Bladder		1
Liver	2	1
Colon		1
Hodgkin's Lymphoma	3B	1
Squamous cell carcinoma (anus)		1
Lymphocytic leukemia		1
Primary peritoneal carcinoma		1
**Cases considered cured or in total remission*		

dietary sources, and upon testing a group of healthy individuals it was found the salvestrol was recovered unmetabolized in the blood and urine. When cancer patients were given the salvestrol, the metabolite was found and the amount of substrate decreased with the magnitude of the effect dependent on the severity of the disease as estimated from the clinical presentation. For severe disease, the researchers were unable to detect any substrate, only the metabolite. These observations were made on individuals with breast, stomach, kidney, and prostate cancer with an array of stages but skewed towards more advanced cases. This approach does not yield site-specific information if the presence of cancer is indicated.

The metabolic approach obviously offers the opportunity to measure the effectiveness of any given salvestrol mixture, as well as the ability to examine and adjust for individual dose dependence. Finally a non-invasive judgment is possible regarding when a "cure" or significant regression has been achieved by this alternative approach. This can then be confirmed by conventional methods.

The proteomic approach is exquisitely sensitive and close to the state of the art for detection of a chemical in the circulation. Thus if screening is done and a positive result is obtained, where is the cancer? A serious problem since it may be small enough as to escape all modern attempts to locate it. Also, there is no non-specific anticancer treatment in so-called evidence based or officially sanctioned cancer therapy that could be used in the absence of knowledge of the identity of the tumour site. But the metabolic approach allows testing the most modern and powerful salvestrol on patients with cancer, even if not clinically evident, to determine if the metabolic markers change, thus potentially justifying and encouraging an alternative therapeutic program, independent of the lack of knowledge of the actual site.

The future

Mainstream medicine thinks only in terms of their holy grail, the randomized, controlled trial as evidence for even considering a new therapy. Held in high contempt is the case study. Consider the obstacles facing salvestrols. Naturally occurring chemicals generally cannot be patented. Companies selling products such as salvestrols are tightly regulated as to what claims can be made concerning efficacy. Clinical trials required for regulatory approval are very expensive. Only a synthetic salvestrol has a chance of becoming an approved prescription drug or approved "medicinal food." It would be hard to find a physician who would take the professional risk of recommending to a cancer patient a natural product rather than the conventional approach. Combining salvestrols with conventional treatment is interesting but probably would be hard to implement in the face of negative attitudes.

A trial can be visualized that might satisfy integrative physicians demanding more concrete evidence. It would involve patients who have rejected conventional treatment or found it failed them. These individuals could be recruited for an uncontrolled study or an old-fashioned study where the control is based on the average life expectancy or cancer progression of multiple matched untreated patients.

Taking low doses of salvestrols for cancer prevention also appears reasonable and this may be significantly superior to taking fruit extracts available at the health food store or online because salvestrols are selected extracts which have laboratory-proven cancer cell cytotoxicity. The above discussion provides justification for the role of salvestrols in prevention. However, the optimum dose is still unknown.

Conclusions

The underlying theory of salvestrols is that CYP1B1 represent a rescue enzyme that evolved in humans eons ago, partly in order to deal with cancer cells and destroy them with substances derived from the normal diet. The evidence is compelling that this enzyme is overexpressed in cancer cells and present only in minute and insignificant levels in normal cells. Furthermore, related to diagnosis and prognosis, the enzyme is present at vastly higher levels in the blood of individuals with cancer as compared to those who are cancer free. The observations based on cell culture studies involving cancer and normal cells confirm the presence of cytotoxic metabolites of CYP1B1 and the indifference of normal cells to the substrate. When

cancer patients are compared to normal controls, after dosing with salvestrols the serum salvestrol levels, rather than being unchanged, are lower and can be driven to near zero in advanced cancer patients, while evidence of toxic metabolites increases in step with these decreases. These observations significantly support the biological plausibility of the therapy. The modern salvestrols used in today's preparations contain fruit-derived CYP1B1 substrates proven in cell culture studies to yield high levels of cancer cell cytotoxicity, whereas commercially available fruit extracts and polyphenols mixtures sold as supplements have never been graded for efficacy by this standard.

Evidence of salvestrol induced remission or cure consists of 15 specialist verified human case studies covering 11 cancer types. More are about to be reported. At this stage in the evolution of salvestrol therapy, this is the only clinical evidence one should expect. These case studies along with serum metabolite and proteomic studies support the salvestrol concept. While it is understandable that practitioners would be less than happy about such a modest clinical evidence base, it must be remembered that this is a natural product. There are even restrictions on the extent to which it can be promoted as effective against cancer and represents a therapy resisted a priori by conventional medicine. There will no doubt be small clinical trials in the near future, but given the absence of side effects of, waiting for such trials seems unnecessary. There are fewer regulatory barriers to the acceptance of the metabolic and proteomic approaches to cancer detection and monitoring therapy. This in fact is a principal focus at present with research ongoing at University of Victoria and University of British Columbia (Schaefer 2012a).

Issues such as the use of salvestrols for primary and metastatic cancer prevention will no doubt remain theoretical for a long time, given the natural history of cancer and nature of the product, and the huge cost of human studies. Nevertheless, to ignore the possibility that this is a true magic bullet with minimal or no side effects may be to ignore one of the most important developments in cancer detection and therapy in decades.

Salvestrols are availble at www.salvestrol.ca. Dr. Schaefer's book can be ordered via this link: http://www.salvestrolbook.com.

Disclaimer and conflict of interests

The author of this article has no financial interest in any commercial or research aspect of salvestrols, does take daily low dose of Salvestrol "Platinum" for prevention, and emphasizes that the above review does not constitute a recommendation or advice but merely provides information. ■

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