Clinical Evaluation of Vitamin C and other Micronutrients in the Treatment of Cancer

Gerald Batist, M.D.[1]

Introduction:

Over the great expanse of time during which therapies of various sorts were applied to cancer treatment, micronutrients and small molecules of various types have been used. In the early 1950's two clinical investigators in the United States exposed children with acute leukemia to selenium of unknown specific form, and published measured declines in leukemia cell number in the circulation. They stopped therapy due to inordinate toxicity. Vitamin C was studied at the Mayo Clinic in patients with advanced colorectal cancer, and the published reports showed no change in tumor size or its natural history. Important points of criticism and clarification are required in interpreting these two examples, without which they may well be far from definitive trials of these particular agents as therapies.

On the other hand, beyond the context of formal clinical trials, many of these chemicals are used by a variety of practitioners on a regular basis. There is a large literature of published anecdotal cases claiming anti-tumor efficacy in a variety of settings. Although far from conclusive and although important details are missing, these observations cannot be dismissed.

The details of the cases in these two contexts, as well as the manner in which they are described and publicized, expose a significant rift within the world of alternative therapists that may be hampering ultimate determination of the efficacy and optimal use of Vitamin C and other micronutrients. Although attitudes are difficult to change, factual information and conventions of investigation (i.e. rules that are commonly accepted in order to prove something) may be a starting point. I begin with some definitions of clinical oncology settings, of clinical trials, and observations about the biology of the actual cancers described in many of the anecdotal cases.

1. McGill Centre for Translational Research in Cancer. Sir Mortimer B. Davis-Jewish General Hospital, Montreal, PQ

Definitions

Cancers are defined histologically by their tissue of origin and by their stage, which defines the extent to which detectable tumours have grown beyond the initial tumor mass, i.e. metastases. There may be great differences between the natural histories of various tumor types, and the prognosis is intimately linked to the stage.

The process of tumor metastasis is presently understood to be a very active one, requiring the participation of a number of gene products that enable the tumor cell to digest its surrounding normal matrix of tissue, mobilize into lymphatics or blood vessels, and colonize somewhere and finally multiply and grow into a secondary tumor. During the past 20 years many trials have demonstrated that for a number of cancer types, giving adjuvant chemotherapy following removal of the original tumor can result in a significant reduction in the appearance of metastases and in significantly increased cure rates.

New Cancer Treatment Development

Most novel therapeutic agents are studied first in patients with metastatic disease, since one wishes to show some antitumor efficacy in this setting before mounting what are by necessity (for statistical reasons) large trials involving many hundreds of patients. Phase I studies are performed in patients with cancers for whom there is no therapy of proven value, or in whom standard therapy has proven ineffective. By definition, the initial studies of new agents are performed with the aim of determining the nature, intensity, and reversibility of toxicity. Also pharma-

cokinetics are performed to be able to define an optimal dose and schedule. A structured module places three patients at a given dose level, and in the absence of significant toxicity, a subsequent group of three receive a slightly higher dose. This escalation continues until a maximally tolerable dose is defined. For molecules with minimal toxicity but known biological mechanisms of action, it may simply be enough to determine a biologically effective dose.

Phase II studies make use of the information learned in phase I (dose and schedule) in studying a specific tumor type in 20-30 patients. These patients as well have advanced measurable cancers. A 1 cm tumor mass contains approximately 100 million tumor cells, so by the time it becomes detectable it already has a large tumor volume. Here the principal interest is in anti-tumor efficacy. In the classical paradigm, only if a minimum of efficacy is demonstrated here does the new drug go on to a phase III randomized study comparing it to the current standard. It could even be performed in the adjuvant setting.

The basic rules of clinical trials that are observed to assure patient safety and ethical concerns are:

1. Review and approval of the protocol by a duly constituted Ethics Committee composed of medical, laypersons, patients advocates and legal experts. The result should be a consent form outlining risks and benefits that the patient would be willing to sign.

2. Review and approval by an appropriate governmental regulatory agency.

3. A commitment to publish the results of the study, whether positive or negative.

4. No direct exchange of money between the patient and investigator.

Currently Used Chemotherapy

Both cancer patients and clinicians are eager for new therapeutic approaches. The use of cytotoxic drugs often appears limited by the modest degree of selectivity towards cancer cells they are intended to eradicate, and by resistance mechanisms developed by these cells after only a few cycles of chemotherapy. There is therefore a great need and interest to develop new drugs of high efficacy and low toxicity with the potential to increase survival, without the deleterious effects on quality of life due to toxicity of treatment. Yet at the same time it must be recognized that:

1. Standard cytotoxic chemotherapy presently saves millions of lives (e.g. adjuvant breast and colon cancer treatments), and prolongs the survival of hundreds of thousands.

2. Since the 1950's a very sophisticated industry has developed devoted to finding ways to limit chemotherapy-induced toxicity, and many of them work very well (e.g. new effective classes of anti-emetics, bone marrow-specific colony-stimulating factors).

3. All of the biological or immunological therapies with proven efficacy in published clinical trials have toxicity, not necessarily less, but different.

4. Many of the non-toxic cancer treatments being examined have been found to work best in pre-clinical models in combination with certain chemotherapy drugs, so their clinical development may need to be performed in combination.

Do We Need New Paradigms for New Treatment Development?

One must face the possibility that the optimal evaluation and therapeutic potential of a novel class of drug may not be optimally tested in the classical schema for new treatment development. We may require novel paradigms to test and then eventually use these. This is becoming increasingly clear for a number of biological agents which act through mechanisms distinct from cytolysis. For example anti-angiogenesis targeting treatments are not likely to cause tumors to shrink, but rather

just to stop their further growth. These drugs would (and have) been called inefficacious in the classical large volume advanced disease setting of the typical phase II trial. Furthermore, these agents, along with a number of other new approaches, are clearly demonstrated in preclinical animal models to be most effective when there is a very small volume of cancer cells. They may correspond in humans to the post-surgical adjuvant setting, rather than the metastatic setting. These realizations suggest that for some agents the appropriate approach to test their possible benefit should be:

1. A phase I-type trial designed to find the best dose and schedule, and to define toxicity alone and possibly combined with cytotoxic chemotherapy if it is appropriate. If the mechanism of action is known, e.g. depleting a growth factor level in blood, or activating cytotoxic T cells, then the goal would be to find the minimum bioeffective dose.

2. Skipping phase II trials and even phase III trials in patients with advanced disease, and examining the new treatment in the adjuvant setting. There are a number of possible variations on this. Randomized trials vs. placebo may require a large number of patients. Treating all patients in the study for disease where optimal therapy is initially very effective (e.g. surgery in pancreas cancer or chemotherapy in small cell lung cancer), yet is almost uniformly followed by tumor recurrence within a reasonable short time. In this setting the recurrence rate is so high and so certain, that a randomized study may not be necessary to make the case, if vitamin C resulted in a significant change in results at perhaps 1-2 years.

What is the Proposed or Testable Mechanism of Action of Vitamin C?

The best starting option for a successful clinical investigation is to address the unique nature of a new agent. Some of the literature demonstrates an *in vitro* cytotoxic effect of vitamin C, at doses that may not be easily achieved in humans. Furthermore this effect may depend on non-protein bound vitamin C, so that plasma serum level determination may require some sophistication.

If direct cytotoxicity is thought to be the principal mechanism of action of vitamin C as a potential cancer therapeutic, it may be crucial to determine how it works. Since combining cytotoxics that work through different pathways could result in synergy, one would consider these facts in testing vitamin C as a therapeutic agent.

On the other hand, vitamin C may have an immunomodulatory effect, though much of the immunologic research suggesting such a mechanistic pathways is now known not to be critical for tumor immunity. These studies require *in vivo* experimentation, but as well the capacity to examine antigen presenting function or generation of cytotoxic lymphocytes. The question is open as to whether these should first be explored in pre-clinical animal models, or can be performed in the context of a dose-finding clinical trial.

Several *in vivo* models for solid tumors (allografts, xenografts, transgenic mice) have been validated by classical chemotherapy. Many are used in preclinical studies together with a large battery of *in vitro* tests, in order to evaluate the relative efficacy (and toxicity) of a cytotoxic agent in comparison to others. Specific endpoints have been established and are routinely used. In the case of non-classical or non-cytotoxic agents new measures of efficacy and biological activity are necessary (e.g. anti-angiogenic agents or signal transduction inhibitors). Conventional cytotoxic drugs are designed to respond to well-defined efficacy criteria such as reduction of tumor mass or decrease of metastatic nodules.

What Cancers to Test? To Treat?

I have alluded to a number of tumor types whose natural history and current treatment offer opportunities to investigate

most efficiently new approaches including vitamin C. These will have to be carefully considered with respect to the number of subjects and the design of the trials.

It is also worth commenting about the types of cancers frequently cited in anecdotal cases of vitamin C anti-tumor efficacy. In particular we must be especially aware of the unpredictable natural history of nodular (follicular) lymphoma, with a prolonged waxing and waning history; renal cell carcinoma which can do the same, including long periods of quiescence and rare spontaneous regressions; ovarian and small cell lung cancer, which respond dramatically to chemotherapy, which is also being given by some accounts. Furthermore there are other potentially complex scenarios which require detailed information on concurrent treatments and mode of disease evaluations.

The hurdles that are on the path to testing vitamin C as a cancer therapy are not unique, and it is hoped that consideration of other examples noted above will be of some assistance in this task.