Alternative Cancer Cures: “Unproven” or “Disproven”?

Andrew Vickers, PhD

ABSTRACT Oncology has always coexisted with therapies offered outside of conventional cancer treatment centers and based on theories not found in biomedicine. These alternative cancer cures have often been described as “unproven,” suggesting that appropriate clinical trials have not been conducted and that the therapeutic value of the treatment is unknown. Contrary to much popular and scientific writing, many alternative cancer treatments have been investigated in good quality clinical trials, and they have been shown to be ineffective. In this article, clinical trial data on a number of alternative cancer cures including Livingston-Wheeler, Di Bella Multitherapy, antineoplastons, vitamin C, hydrazine sulfate, Laetrile, and psychotherapy are reviewed. The label “unproven” is inappropriate for such therapies; it is time to assert that many alternative cancer therapies have been “disproven.” (CA Cancer J Clin 2004;54:110–118.) © American Cancer Society, 2004.

INTRODUCTION

Oncology has always coexisted with therapies offered outside of conventional cancer treatment centers and based on theories not found in biomedicine. An example is Laetrile, which is provided at alternative clinics in Mexico and elsewhere. The rationale for Laetrile therapy is that cancer is caused by deficiency of a vitamin called “B-17”; providing vitamin B-17 in the form of Laetrile therefore leads to cancer remission. Needless to say, vitamin B-17 has not been described in the general biomedical literature.

Cancer treatments such as Laetrile are often described as “unproven” cancer treatments. Probably the best-known example is the American Cancer Society (ACS)’s previous Committee on Unproven Methods of Cancer Treatment that investigated treatments such as Laetrile and published a series of articles in this journal in the 1980s. The difficulty with the term “unproven” is that it does not distinguish unusual and implausible alternative cancer cures from, say, a novel targeted therapy yet to be subject to Phase III trial. This has led some to use terms such as “unconventional” cancer treatments or complementary and alternative medicine (CAM) cancer treatments. The latter is particularly popular and was recently adopted by the ACS. When using this term, however, it is important to distinguish between “alternative” treatments used as cancer cures instead of oncologic therapy and “complementary” therapies used alongside conventional medicine, typically to treat symptoms and improve quality of life.

In this article, we will address the question of whether “alternative” and “unproven” are really interchangeable terms. We will argue that contrary to much popular and scientific writing, many alternative cancer treatments have been investigated and found ineffective in good quality clinical trials. In other words, alternative cancer cures generally are not just “unproven,” they have often been “disproven.” This is not merely a semantic issue; the advice we give to patients concerning a therapy should differ importantly if it has been shown not to be of benefit, compared with if its benefit is simply unknown.
As in all areas of science, research on alternative cancer therapies involves a continuum of proof and disproof. For some alternative therapies, there is strong negative evidence from multiple studies; for other therapies, the weight of data suggesting lack of benefit is not as decisive. This is at least partly because investigators feel no need to duplicate negative results of an improbable treatment hypothesis. Indeed, it is arguable that it would often be unethical to accrue patients for such trials. Regardless, “unproven” appears an inappropriate term for a treatment if there are good data suggesting that it is ineffective.

A REVIEW OF CLINICAL TRIALS ON ALTERNATIVE CANCER CURES

We review the data from clinical trials of alternative cancer cures below. Several of the therapies are no longer readily available to cancer patients in the United States; others are no longer popular. We are including such therapies in the review, even though this will not be of direct practical value to the clinician. This is to demonstrate that, when tested, alternative cures have been shown not to work, regardless of where and when they were being used.

Livingston-Wheeler

Livingston-Wheeler is a classic example of an alternative cancer cure, because it is practiced in a specialist clinic, not a traditional cancer center, and is based on a belief located outside of biomedical knowledge. The founder of the therapy, Virginia Wheeler, believed that all cancer is caused by a bacterium, Progenitor cryptoides, an entity that has not been described outside of her work. The cancer treatment offered at the Livingston-Wheeler Clinic in San Diego, California consists of efforts to strengthen the immune system by “detoxification” through diet and enemas and by the administration of special vaccines. Cassileth et al. matched 78 patients treated at Livingston-Wheeler to control subjects treated with standard anticancer therapies and supportive care and/or investigational agents (interleukin-2, for example) at the University of Pennsylvania under the care of a conventional oncologist. Matching variables included race, sex, age, disease site, and date of diagnosis. All subjects had advanced colorectal cancer, nonsmall cell lung cancer, pancreatic cancer, or melanoma. All had a predicted survival of no more than one year and were felt to have no standard conventional treatment options of proven efficacy. Many of the patients at Livingston-Wheeler also received conventional chemotherapy, radiotherapy, and/or surgery before and after enrollment in the study in addition to their unconventional therapy.

There was no difference in survival between groups; median survival in both groups was close to a year, with 85% of patients surviving for fewer than two years. Patients treated at Livingston-Wheeler had significantly poorer quality of life as measured by the Functional Living Index–Cancer.1 Whatever one believes about the relative merits of the nonrandomized design, the study is, at the very least, a well-controlled cohort study examining survival in patients treated at Livingston-Wheeler. The results of the study refute the often repeated claim that the clinic has an 82% cure rate, even in advanced cancer.2

Di Bella Multitherapy

Di Bella multitherapy was developed by Luigi Di Bella, an Italian physician. Provided at a private outpatient clinic, the therapy consists of a large number of different drugs, including many not traditionally used as anticancer agents. The most recent versions of the therapy incorporated melatonin, bromocriptine, octreotide, mixed retinoids, and cyclophosphamide. Although Di Bella claims that his approach was developed through empirical testing, there appears to be an emphasis on agents that modulate the production of growth hormone, clearly an unusual rationale for a cancer therapy. Di Bella multitherapy was systematically evaluated in the late 1990s following controversial court rulings, intense media exposure, and public demonstrations. Eleven separate Phase II trials were conducted in lymphoma, lymphoid leukemia, breast cancer
(both good and poor performance status), lung cancer (both chemotherapy treated and chemotherapy naïve), colorectal cancer, pancreatic cancer, head and neck cancer, glioblastoma, and advanced solid tumors. An additional trial on early-stage breast cancer failed to accrue and was stopped. The number of patients on each trial ranged from 20 (glioblastoma) to 65 (lung cancer patients with prior chemotherapy treatment). A total of 395 patients were accrued on the 11 trials with 386 eligible for evaluation of response. No patients experienced a complete response to treatment and only three (less than 1%) showed a partial response. At a follow-up three to eight months, 57% of patients had died, and only 4% of patients were still receiving treatment. In addition to the prospective Phase II trials, researchers conducted a retrospective evaluation using Di Bella’s clinic records. The analysis was restricted to patients living in areas of Italy with a cancer registry so that the cancer site and date of diagnosis could be confirmed. Clinic records for nearly half of the eligible patients did not include adequate documentation of treatment, and a further 10% were lost to follow-up. Analysis therefore focused on 248 patients. Survival in these patients was poorer than in cases matched from a cancer registry. For example, only 21% of children with leukemia treated by Di Bella survived five years, compared with 70% of those in the national registry. Although there are obvious biases in these kinds of comparisons (patients who do not do well after initial therapy may turn to Di Bella therapy) there was certainly no evidence that Di Bella therapy was active, with poor five-year survival probabilities for all diagnoses. The authors also reported that the number of patients treated by Di Bella was far less than he had claimed (approximately 1,500 compared with 10,000) and the treatment regimen used varied over time and between patients, contrary to Di Bella’s public pronouncements.4

Revici

Like Di Bella multitherapy, Revici treatment is named after the physician who developed and provided the method of treatment. Emanuel Revici’s therapy is based on an unusual theory of pathophysiology: all conditions, including cancer, result from an imbalance of metabolism. Patients may either have a “catabolic” or “anabolic” type imbalance and are treated with antianabolic or anticatabolic agents, for the most part regardless of presenting signs and symptoms. The type of imbalance is determined by analysis of urine, blood, and body temperature. For example, high urine pH, low serum potassium, and high body temperature are associated with anabolic imbalance; low urine surface tension, low blood calcium, and low body temperature are associated with an imbalance of the catabolic type. The agents used by Revici are quite unlike those used in traditional oncology, including glycerol, n-butyl alcohol, and sulfurated vegetable oil. In 1965, the Journal of the American Medical Association published a cohort study of 33 patients with histologically-confirmed, advanced solid tumors who received treatment from Revici.5 Twenty-two of these patients died while receiving treatment, eight left the trial, and three remained under Revici’s care at the end of the study. Of the eight who left the trial, four died and two were lost to follow-up. The researchers claimed that no patient exhibited evidence of objective tumor response and that all three patients still under treatment by Revici showed signs of tumor progression. Although Revici disputed the tumor response data, it is clear that only 15% of patients survived until the end of the trial. This contradicts the claim that, in the words of a favorable book, Revici is the “doctor who cures cancer.”6

Burzynski and Antineoplastons

Stanislaw Burzynski treats patients at a private clinic using what he terms antineoplastons, mixtures of peptides, amino acids, and other simple organic substances that are said to promote the body’s natural defenses against cancer. Although he has published several studies of his own, these are of a rather unclear design.7 A Phase II trial in glioma conducted under the auspices of the National Cancer Institute was halted due to poor accrual, after Burzynski failed to agree with the investigators on possi-
ble expansion of the eligibility criteria. Nine patients were accrued, six of whom were able to be evaluated for response. There were no objective responses, and all six showed evidence of tumor progression after treatment durations of between 16 to 66 days. The mean time to treatment failure (progression or discontinuation due to toxicity) was 29 days. All nine patients died before the study closed, all but one death being due to tumor progression. Although the authors of the article claimed that the small sample size precluded “definitive conclusions,” the results of the patients in the trial are clearly extremely disappointing.8

**High-dose Vitamin C**

High-dose vitamin C was popularized as a cancer therapy by Linus Pauling. Pauling published a nonrandomized trial reporting that patients treated with vitamin C lived longer than those treated at a neighboring hospital that did not provide vitamin C therapy.9 He speculated that vitamin C improved “host resistance” to cancer.10 Given overwhelming public interest in vitamin C as a cancer cure, a randomized trial was conducted in which 150 patients with advanced cancer received either vitamin C or placebo. Survival was short in both groups—over 80% of patients died within 12 weeks—and there were no significant differences between groups.11 The trial was criticized by Pauling, who claimed that the inclusion of patients who had prior chemotherapy and who might thus be immunosuppressed invalidated the evaluation of a therapy thought to act by means of an immune mechanism. A further trial was therefore conducted with 100 patients with advanced colorectal cancer who had no previous chemotherapy. Again the results failed to find differences between groups, with all patients in the vitamin C group dying within two years. The 95% confidence intervals excluded the possibility that vitamin C could improve survival by 25% or more.12 Recently, some workers have argued that the negative results might have resulted from the use of oral rather than intravenous vitamin C.13 However, it is generally the oral form that is promoted and sold as an alternative cancer cure and, given the current state of the scientific literature, it appears highly unlikely that this is of benefit.

**Chaparral**

Extracts from chaparral, a desert shrub, were used as a general cure-all by Native American healers. It became a popular anticancer medicine in the 20th century, at least partly on the basis of theories that it could remove cancer-causing “toxins” from the liver and pancreas. Following presentation of a case in which an 87-year-old man experienced regression of a facial melanoma after chaparral treatment, Smart et al. accrued patients with advanced cancer to a Phase II trial of chaparral. The report of the trial included the initial patient, suggesting that accrual was not entirely prospective. Excluding this patient from analysis, three of the 44 patients who were evaluated experienced tumor regression, although this was defined liberally (a 25% reduction in tumor size), and included one patient whose response lasted only 10 days. This low response rate prompted the authors to advise against the use of chaparral as a self-treatment for cancer.14

**Hydrazine Sulfate**

Although hydrazine sulfate is a synthetic drug, it is included here because it is taken by cancer patients as an alternative therapy and because it is based on a therapeutic rationale quite unlike any other currently licensed cancer drug. Several early clinical trials seemed to indicate possible benefit from hydrazine sulfate. Chlebowski et al., for example, randomized 65 patients with advanced nonsmall cell cancer to receive hydrazine sulfate plus chemotherapy or chemotherapy alone. Overall survival was non-significantly higher in the hydrazine sulfate group (median survival, 292 versus 197 days; P = 0.11). There were statistically significant differences for some secondary endpoints, such as caloric intake, but not others, such as weight gain.15 On the basis of the trend toward increased survival seen in this study, three randomized, placebo-controlled trials were conducted to determine whether hydrazine sulfate could improve survival or quality of life.
The studies included, respectively, 243 patients with newly diagnosed nonsmall cell lung cancer concurrently treated with etoposide and cisplatin, 1,6 128 patients with advanced colorectal cancer receiving no other oncologic therapy, 17 and 291 patients receiving cisplatin and vinblastine for advanced nonsmall cell lung cancer. 18 Hydrazine sulfate did not improve survival in any of these settings. The survival curves were essentially overlapping in the two lung cancer trials; the colorectal cancer trial was stopped early because of excess deaths in the hydrazine arm (P = 0.034). Survival was poor in all three trials, with over 90% of patients dying during a one- to two-year follow-up.

Laetrile

Laetrile is a naturally occurring glycoside derived from apricot pits that became a popular alternative cancer treatment in the 1970s. In a single arm, Phase II trial, 179 patients with advanced, untreatable cancer and measurable lesions were treated with Laetrile. As was common practice at the time, patients also received vitamins and pancreatic enzymes. Only one patient met the criteria for a partial response; 90% of patients had disease progression within three months. Median survival was only 4.8 months. 19

Shark Cartilage

Shark cartilage was popularized as an anticancer treatment in the early 1990s. This followed the publication of a book Sharks Don’t Get Cancer and a documentary on the television program “60 Minutes” purporting to show good results from shark cartilage in Cuban cancer patients. 20,21 By the mid-1990s, it was estimated that 50,000 Americans were using shark cartilage as a treatment for cancer. This prompted the development of a Phase II trial that accrued 60 patients with tumors of the brain, breast, colon, lung, lymphoma, prostate, and unknown primary. All but two patients had Stage IV disease. Fifty patients could be evaluated. No patient experienced a complete or partial response; five died while on therapy, five withdrew for toxicity, 27 progressed while on therapy, and 13 had stable disease. The median time to progression in the group as a whole was 50 days; 90% had progressed within six months, and no patient experienced a progression-free interval of more than a year. No improvement was observed in quality of life. 22

The shark cartilage story does, however, have an interesting twist. There is a biologic rationale for the use of cartilage products as anticancer agents: cartilage is an avascular tissue and contains antiangiogenic substances. Indeed, the ability of cartilage to inhibit neovascularization was first demonstrated over 25 years ago. 23 The antiangiogenic properties of cartilage are not species-specific, as extracts from the cartilage from a range of different animals have been shown to inhibit the formation of blood vessels. 24 A Canadian pharmaceutical company has developed a method to extract fractions from shark cartilage that have potent antiangiogenic properties (the shark is a good source of cartilage because a high percentage of body weight is cartilaginous). These various fractions have been compared in laboratory models and the most promising fraction identified. Known as Neovastat (AEterna Laboratories, Inc., Quebec, Canada), this liquid formulation contains a high concentration of biologically relevant molecules, unlike the products available in health food stores and over the Internet, and has been entered into clinical trials. Batist et al. have reported a Phase II trial of Neovastat. Although the initial aim was to determine the long-term safety profile of this agent, the dose was increased during the trial following safety data from a separate trial becoming available. This gave the authors the opportunity to assess dose-response with respect to survival. The authors reported the results for 22 patients with renal cell carcinoma. It is not clear from the published report if other patients were accrued. Patients receiving high-dose Neovastat survived significantly longer (14.4 versus 7.1 months) than those receiving low doses. 25 The trial was nonrandomized, and the results cannot be taken as definitive. Several Phase III trials are currently underway to determine whether Neovastat is of benefit for lung and kidney cancer. 24
Metabolic Therapies: Gerson and Gonzalez

Alternative cancer therapies are often practiced in Mexico so that clinics can avoid US regulations. Many of the Mexican clinics, including that established by German physician Max Gerson, offer “metabolic” therapy. Treatment is based on the belief that cancer is a symptom of the accumulation of toxins. “Detoxification,” a prime treatment goal, involves coffee enemas or high colonics, special diets, raw juices, enzymes, and supplements. A retrospective study of melanoma patients treated at a Gerson clinic, which was conducted by physicians working at that clinic, concluded that five-year survival of patients receiving Gerson therapy were higher than those reported in large cohort studies. This analysis was flawed by subgroup analyses (“Stage IIIA/B males had exceptionally high survival rates”), the use of unadjusted comparisons to nonrandomized controls, and exclusions (40% of the patients undergoing Gerson therapy were excluded from analysis). In response to detailed criticisms, the authors accepted that a nonrandomized study such as the one published did not provide strong evidence of a treatment effect.

A more promising result has been reported from a cohort study of 11 pancreatic cancer patients treated by Nicholas Gonzalez, a physician in private practice in New York, who uses a metabolic regimen that includes pancreatic enzymes. Gonzalez reported 81% survival at one year and 45% survival at two years and claimed such results were far superior to national averages. The study was small and obviously prone to several biases. Not only is the comparison with national averages unadjusted for confounders, but the principal results are based on patient selection; 12 patients who did not comply with treatment were excluded from analysis. Nonetheless, the generally positive results reported by Gonzalez were enough to prompt a National Institutes of Health-funded Phase III trial, which is currently accruing patients.

The Risberg Cohort Study

In 1992, Risberg and colleagues surveyed close to 1,000 Norwegian cancer patients about alternative treatments for cancer. Their initial purpose was to determine the prevalence and determinants of alternative medicine use. The investigators later realized that it would be possible to link their data to the Norwegian Statistical Registry to obtain information on survival. They found that alternative medicine use was associated with poorer survival; 79% of alternative medicine users died during follow-up compared with 65% of nonusers. This analysis was confounded by the poorer clinical status of users at the time of the survey. As might be expected, a patient with a treatable early cancer might be less likely to turn to an alternative cure than a patient with advanced disease and few remaining conventional treatment options. A multivariable Cox regression was used to control for baseline differences in stage, performance status, time since diagnosis, and other prognostic variables. There was a trend for alternative medicine users to have shorter survival (hazard ratio 1.30, 95% CI, 0.99–1.70; $P = 0.056$), a result that was robust to various sensitivity analyses. The authors hypothesized that shorter survival might be explained by “patients’ correct perception of the gravity of their disease.” Whatever the explanation, the study certainly finds no evidence that use of alternative medicine improves survival.

Psychotherapy as a Cancer Cure

The theory that changing mental state can affect the course of cancer has been popularized by authors such as Bernie Siegel and Deepak Chopra. In best-selling books aimed at the general public, these authors make claims such as that patients can “control the course of [cancer], using thoughts” or that by becoming an “exceptional cancer patient,” patients can develop a strong will to live and beat cancer. Even stronger claims are made by authors, such as Louise Hay, who propose psychologic state as an important causal factor. Hay, for example, claims that the “probable causes” of cancer include “deep hurt; long-standing resentment ... grief eating away at the self; carrying hatreds.”

Bernie Siegel’s Exceptional Cancer Patients (ECaP) program has been evaluated in a matched cohort study. Thirty-four women with breast cancer attending the ECaP program
were matched in a 1:3 ratio with comparable patients identified from tumor registries. At 10 years of follow-up, there were no differences in survival between the two groups, with approximately 40% of patients in both groups alive at the end of study.31

Several studies do, however, appear to show survival advantages in cancer patients receiving psychologic treatment. In the late 1970s, David Spiegel conducted a randomized trial that aimed to examine the effects of a psychosocial support group on quality of life and symptoms in women with metastatic breast cancer. As a post hoc analysis, the investigators looked at survival differences and reported a statistically significant prolongation of survival in the group receiving psychosocial support.32 This trial has been widely publicized and extensively cited; a search on Science Citation Index in November 2003 finds over 800 citations for the Spiegel study (interestingly, the “negative” ECaP trial has been cited only 65 times). Only rarely has it been pointed out that that the survival analysis was unplanned and, as such, should be treated as hypothesis generating. A subsequent randomized trial found no impact of psychosocial treatment on survival33 but was criticized by Spiegel as a “nonreplication,” primarily on the grounds the intervention varied between trials.34 A trial by Goodwin et al. cannot be prone to the same criticism. Spiegel was involved in the training of the individuals providing the psychosocial treatment and played a key role in the planning of the trial as a whole. In the study, 235 women with metastatic breast cancer were randomized in a 2:1 ratio to weekly group therapy or to usual care. Although, as expected, the support group had benefits for pain and mood, there was no difference between groups for survival. Median survival was close to 18 months in both groups, with a hazard ratio in favor of control of 1.06, or 1.23 after adjustment for predictors such as estrogen receptor status.35

DISCUSSION

There is increasing interest in CAM among oncologists. It is important to distinguish, however, between complementary therapies that are used alongside conventional medicine for symptom management and quality of life and alternative therapies that are used instead of oncologic therapy for the purposes of cancer cure.

Where alternative cancer cures have been tested, they have generally been shown not to work. That said, an extraordinary number and variety of different alternative cancer cures have been described,36 and clearly only a minority have been subject to clinical trial. What then should we believe about alternative treatments that have yet to be evaluated? We would argue against being agnostic in the absence of clinical trials; other evidence can be used to come to reasonable, if provisional, conclusions. For example, it would be rational to have more faith in a new targeted therapy for which there is a good understanding of mechanism, cell line studies, and promising animal data than in an alternative therapy based on an entirely fanciful notion that is without any substantive evidence at all.

It is not straightforward to evaluate alternative cancer cures. Alternative clinics often have poor documentation. Di Bella, for example, documented treatment for only half of his cancer patients. Relationships between investigators and alternative practitioners are often strained, at least in part because the practitioners are generally distrustful of the investigators’ motives. Indeed, it is noteworthy that the typical reaction of the alternative cancer medicine community to negative results has been to take these merely as proof of the bias of conventional researchers. In many cases, this has extended to accusations of deliberate suppression or falsification of data. The motive generally given is that the researchers are protecting the vested interests of the pharmaceutical industry, which would be threatened were it to become known that an inexpensive alternative treatment could cure cancer.

There are also inherent methodologic problems in research on alternative cancer cures. Alternative cancer treatments that aim to support the body’s own response to cancer might not be expected to bring about the rapid regression of tumors required by Phase II designs
with a response endpoint. Phase II designs that measure survival are common but require implicit or explicit nonrandomized comparisons that are open to criticism. Randomized trials require patients to be willing to accept treatment choices that are determined by chance. This becomes problematic if the treatment choices are very different, such as chemotherapy versus a dietary regime. Indeed, the ongoing Phase III trial of metabolic therapy versus chemotherapy was changed from a randomized to a nonrandomized “preference” design due to a lack of patients willing to have their treatment decided by chance.

Complementary therapies for cancer-related symptoms were not part of this review. There is now emerging evidence that therapies such as hypnosis, relaxation therapy, massage, music therapy, and acupuncture can be of benefit for cancer-related symptoms. This developing research base is at least partly responsible for the establishment of programs that provide complementary therapies at major cancer centers such as Memorial Sloan-Kettering, Dana–Farber, University of California at San Francisco, and MD Anderson. Such programs integrate conventional and complementary medicine clinically and academically, and, as such, they can be described as “integrative oncology.”

This review did not include most botanical (herbal) treatments for cancer. This is on the grounds that just like conventional anticancer pharmaceuticals, most botanicals are thought to act either by direct cytotoxicity or by immunomodulation. While the best evidence suggests that some popular botanicals, such as mistletoe, are ineffective against cancer, there is good evidence that others, such as lycopene or polysaccharide-K (PSK) (from Coriolus versicolor), may be of benefit. Furthermore, the mechanism of action of several anticancer botanicals is being elucidated, leading to rational development of combinations with conventional agents. For example, PSK and similar botanicals contain β-glucans, which have been shown to promote antitumor immunity by activating complement receptor 3. This suggests that they would act synergistically with therapeutic antibodies such as trastuzumab or rituximab, an effect that has been demonstrated in a mouse model. Phase I clinical trials are currently underway at Memorial Sloan–Kettering Cancer Center to investigate the therapeutic potential of β-glucan/antibody combinations.

The incorporation of biomedical knowledge in the therapeutic development of popular anticancer botanicals is of great promise. Alternative cancer therapies that have abandoned biomedical knowledge, for example, by trying to treat deficiencies of nonexistent vitamins, have been shown not to be of benefit. The label “unproven” is inappropriate for such therapies. It is time to assert that many alternative therapies have been “disproven.”

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