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Original Paper

How Useful are Unconventional Cancer Treatments?

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Unconventional cancer treatments are used frequently. Therefore, oncologists need to know about them. This article gives an overview of current knowledge on the most prevalent complementary or alternative cancer therapies. A distinction is made between alleged cures, preventive and adjunctive measures. Shark cartilage, mistletoe, thymus therapy, essiac, hydrazine sulphate, 714-X, dietary regimens, green tea and Panax ginseng are all covered specifically. None of these treatments offer reasonable hope for a cure. Some strategies are promising in terms of cancer prevention. The true potential of unconventional therapies might lie in adjunctive and palliative care. It is concluded that good evidence in this area is scarce. *Vis-à-vis* the high prevalence of unconventional cancer treatments, rigorous investigations are mandatory, not least for increasing the safety of future patients.

Key words: complementary medicine, alternative medicine, cancer, palliative therapy, unconventional drugs, diet
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INTRODUCTION

COMPLEMENTARY/ALTERNATIVE MEDICINE (CAM) can be defined as ''diagnosis, treatment and/or prevention which complements mainstream medicine by contributing to a common whole, by satisfying a demand not met by orthodoxy or by diversifying the conceptual frameworks of medicine'' [1]. CAM is immensely popular: the 1 year prevalence in general populations is 40% in the U.S.A. [2], 50% in Australia [3] and 65% in Germany [4]. In patient populations this figure can be even higher (for example [5]). Patients with acute, serious, life-threatening conditions have different motives for trying CAM than those with chronic, benign diseases. For cancer patients the most powerful motivations are the wish to leave no option untried and dissatisfaction with mainstream oncology [6, 7].

Oncologists are often fiercely opposed to the usage of CAM by their patients, while general physicians are usually more open and express a desire to be supportive of patient choices [8]. This tension is reflected in the content of several recent review articles on CAM use for cancer (for example [9–12]).

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These differing reactions may well be attributable to the type of unconventional therapies used by patients with cancer versus those used by others: cancer patients may be drawn to remedies promoted as *alternatives* to mainstream cancer care. Such regimens are typically unproved or disproved, and they can cause harm by delaying needed mainstream treatment or causing physiological problems. Conversely, healthy people or those with minor or self-limiting illnesses do not use remedies promoted as 'cancer cures'. Rather, they are likely to try *complementary* therapies that enhance well-being or relieve the symptoms of short-term illnesses. Although complementary therapies are also used by cancer patients, oncologists are typically more familiar with—and opposed to—the alternatives to mainstream cancer treatment.

In this article, we will briefly review the prevalence of CAM for cancer and provide an update on the various therapeutic, preventive and palliative approaches. Because the material on this topic is voluminous, our focus is recent literature and currently popular therapies.

PREVALENCE

The use of CAM for cancer is extremely widespread. A recent systematic review of all data in this area located 26 surveys from 13 countries, including four surveys of paediatric

patients [13]. The analysis of these data suggested (but by no means proved) a substantial increase of usage during the last 20 years. The average prevalence across all studies was 31%. The most popular therapies were dietary treatments, herbalism, homeopathy, hypnotherapy, imagery/visualisation, meditation, megavitamins, relaxation and spiritual healing.

A particularly revealing recent survey originates from Norway [14]. It followed 252 cancer patients for 60 months of their illness. There was a slight increase of CAM-use during this period. At the conclusion of the investigation, 27% of all patients were using some form of CAM. Interestingly, the 5-year survival rate of CAM users was not significantly different from non-users.

UNCONVENTIONAL CANCER TREATMENTS

Those complementary treatment modalities for which sufficient data exist—or which are important through their high prevalence—will be evaluated in the following section. This will be based on systematic reviews when they are available, rather than on single trials. If positive, single trials are rarely acceptable to sceptics; if negative they are usually rejected by proponents of that particular therapeutic method. Therefore, systematic reviews seem to offer an adequate solution and methodology. Currently popular CAM therapies for which no investigative data exist will also be reviewed. A distinction will be made between: (1) treatments claimed to offer a potential cure or prolongation of life; (2) modalities promoted as preventative measures and; (3) therapies used in palliative or adjunctive care.

Complex therapies promoted to cure cancer or extend remission

Unfortunately, few rigorous, controlled trials exist in this area. Indeed, few studies have been conducted, and many investigations are methodologically flawed. The Bristol Cancer Help Centre Study [15] is an example of the damage and confusion that seriously flawed studies can cause; although this particular study involved a complementary, adjunctive regimen and not a treatment aimed at destroying cancer. It apparently demonstrated that survival of those women with breast cancer who were treated by an adjunctive package of CAM had a significantly poorer survival rate than those not receiving the additional treatment. These results were probably due to selection bias and would have been avoided had the study been properly randomised.

Cassileth and colleagues [16] conducted a matched-pair comparison of survival times of cancer patients receiving standard care with those receiving an additional alternative treatment package (autogenous immune-enhancing vaccine, bacille Calmette-Guérin, vegetarian diets and coffee enemas). There were no differences in survival times, but patients on the alternative had significantly poorer quality of life.

Cancer treatment that applies traditional Chinese herbal remedies alone or with mainstream care is under modern investigation. Some promising preliminary results have been reported. For example, a Chinese researcher randomised 102 patients with lung cancer into one group treated conventionally and one receiving additional individualised treatments according to the principles of traditional Chinese medicine [17]. In the latter group, the 2-year survival rate was 56%, significantly greater than the 2-year survival in the control group (16%).

Laetrile and other previously popular alternatives

Laetrile, a popular alternative cancer cure in the 1970s, has been tested in rigorous clinical trials (see [18]). No substantial benefit was found, either in terms of cure, survival or stabilisation of cancer, or improvement of symptoms.

Each decade since the early years of this century has been associated with a cancer 'cure' that achieved great prominence, only to fade away as new therapies arose. Koch Antitoxins (1940s), the Hoxie Treatment (1950s), Krebiozen (1960s), Laetrile (1970s), metabolic therapy from Mexico and immunoaugmentative therapy from the Bahamas (1980s), are prominent examples [19]. More recently, other 'cures' have become widespread. Only some have been tested for efficacy.

Shark cartilage

Two glycoproteins, sphyrnastatin 1 and 2, have been isolated from cartilage of the hammerhead shark. Strong anti-angiogenic activity and inhibition of tumour neovascularisation have been demonstrated in animal models [20]. This mechanism could, in principle, be helpful in the treatment of human cancer [21].

Shark cartilage is administered orally and one might ask whether the two large glycoproteins allegedly responsible for the anti-angiogenic activity reach the bloodstream of those who take shark cartilage in the recommended dose. Macromolecules are not normally absorbed by the intestinal tract, and proteins that did enter the body would cause immune responses with potentially serious allergic reactions. Yet the gut may not be a totally impermeable barrier: some macromolecules do seem to cross the human gastro-intestinal tract [4]. Small amounts of sphyrnastatin 1 and 2 could, therefore, escape digestion and find their way to a solid cancer via the blood circulation [22].

Many of the formulations commercially available contain only binding agents or fillers without any anti-angiogenic activity [23]. No reliable dose–response data exist and bioavailability studies are not available.

To date, no good clinical studies have been published. The U.S.A. National Cancer Institute (NCI) initiated a trial of shark cartilage in 1994. It was discontinued when it was found that each batch (provided by advocates) was contaminated [24]. One study seems to have been carried out in Cuba. Its results have not been published but were described by NCI officials as 'unimpressive' [25]. Preliminary results were reported from a trial in the U.S.A. Apparently 50% of cancer patients felt an improvement in quality of life, better appetite and less pain [5]. The dose was approximately 100 g of dried shark cartilage powder per day. This dose is far in excess of the recommended dosage printed on many commercially available products [26].

One also ought to question whether shark cartilage products are safe. No systematic investigations on this topic have been published. One case of shark cartilage-induced hepatitis was recently reported [27]. Thus, at present, one can only conclude that no convincing data exists for advocating the usage of shark cartilage in cancer. The same is true for bovine cartilage, a long-term topic of study for a U.S.A. investigator.

Mistletoe (Iscador)

Extracts of mistletoe were introduced in the early part of this century. These extracts have become a popular remedy in Europe during recent decades and are presently gaining

ground in North America. The preparations are injected subcutaneously according to a complex schedule that may be adjusted individually. Mistletoe extracts contain viscumin (mistletoe lectin) and viscotoxin. Both have biological activity in various *in vitro* and *in vivo* modules. These include modification of intracellular protein synthesis [28]; stimulation of cytokine production [29]; inhibition of tumour colonisation [30]; and inducing cell necrosis [31].

Two recent systematic reviews on mistletoe are available [32, 33]. Both found only a few clinical trials, none of which was conclusive due to significant methodological flaws. Furthermore, the injectable preparations are burdened with potentially dramatic allergic reactions. Kleijnen and colleagues therefore conclude: ''we cannot recommend the use of mistletoe extracts in the treatment of cancer patients with an exception for patients involved in clinical trials'' [33].

Thymus therapy

The thymus, as we know, plays a key role in the immune defence system. The idea to stimulate the body's defensive mechanisms against malignant growth through injections of thymus extracts may, therefore, seem plausible.

Preclinical studies have demonstrated that thymus extracts restore lymphocyte function and improve immunological variables [34]. *In vitro* experiments have shown an activation of natural killer cells [35] as well as an increase in cytotoxic activity [36]. Thymopentin also increases mitogen-induced interferon levels in human lymphocytes [37]. Moreover, animal experiments have suggested that thymus extracts inhibit tumour growth in rats [38] and mice [39]. Notwithstanding these findings, the mechanism of action remains speculative [40] and our knowledge regarding the pharmacology of the various compounds used is incomplete.

A recent systematic review of the data from randomised clinical trials [41] located 13 such studies. Five of these suggested that thymus therapy might convey some benefit but, overall, the verdict was not positive. The low average methodological quality of the trials and overt contradictions in outcomes prevented firm conclusions. It should also be mentioned that injectable thymus preparation can cause severe allergic reactions.

Essiac

This herbal mixture was originally formulated by a Canadian Ojibwa healer. Over the past 70 years, it has become increasingly popular in North America. The formula consists of four herbs: *Arctium lappa*, *Rheum palmatum*, *Rumex acetosella* and *Ulmus fulva*. A recent systematic review did not find a single published clinical trial [42]. Several unpublished investigations were identified but their validity remains doubtful. Furthermore, there was some evidence for anticancer effects of several of the constituent herbs. The author concluded that ''some weak evidence of its (Essiac's) effectiveness existed''; that there is no definitive evidence; and that ''Essiac is unlikely to cause serious side-effects when used as directed'' [42].

Hydrazine sulphate

Based on Warburg's notion that cancer cells are characterised through their anaerobic (rather than aerobic as in normal cells) glucose metabolism, Joseph Gold sought to find a way of blocking this pathway with a view of inhibiting cancerous growth. In his experiments the substance which apparently proved most effective in achieving this aim was hydrazine sulphate [43]. This *in vitro* result has been confirmed repeatedly.

A recent systematic review [44] found numerous clinical trials including three randomised U.S.A. studies. The author noted that Russian investigations tended to reach positive conclusions, but that their work was methodologically weak. With the exception of Gold's own and an affiliated research group, the US studies yielded negative results [45–47]. In particular, these randomised trials did not suggest that hydrazine sulphate inhibits gluconeogenesis. Therefore it ''*may* play a role in reducing the severity of cachexia and in improving the quality of life of cancer patients. The value of hydrazine sulphate as an antitumour agent—specifically its capacity to stabilise tumour size, cause tumour regression and improve survival—remains uncertain'' [44]. However, according to each of the three prospective, randomised, placebo-controlled U.S.A. trials, hydrazine sulphate produced ''no benefit''.

714-X

This anticancer formula was analysed by the Canadian Government and found to contain camphor, ammonium chloride and nitrate, sodium chloride, ethyl alcohol, and water. The inventor of 714-X, Canadian Gaston Naessens, recommends (usually three) treatment cycles of daily injections for 21 days followed by 3 days of rest. 714-X is used in North America and Europe, particularly for prostate cancers. Numerous testimonials have been published in its support. A recent systematic review found few animal studies and no human trials that supported its benefit [48]. Kaegi concluded that ''side-effects appear to be minimal, but evidence of its effectiveness is limited''. The Canadian Expert Advisory Committee also reports no scientific data to support claims that 714-X can cure cancer or AIDS, but it warned of possible adverse effects from the combination of its various constituents.

Dietary regimens

Some diets may have potential for cancer prevention (see below), others claim that prolongation of life is an achievable goal. A recent review found no convincing evidence in support of the latter hypothesis [49]. In particular, unreplicated data apparently showing a 6-fold increase in 5-year survival rates of melanoma patients treated with the Gerson diet [50] do not stand up to scrutiny.

For the Macrobiotic diet no evidence from clinical trials was found. It should be pointed out that complementary dietary regimens are burdened with significant adverse effects. Downer and colleagues [51] found that one-third of those on a Macrobiotic diet experience problems due to weight loss, the restrictive and unpalatable nature of the regimen, time spent preparing the food and the expense and inaccessibility of some ingredients. No diet has been shown to cure cancer.

Other currently popular treatments

A characteristic of promoted alternative cancer treatments is their transitory nature [52]. The dozens of recently and currently popular alternative therapies preclude mention of them all. A few that are now in vogue are noted briefly here.

Antineoplastons, a biological cancer treatment manufactured by a physician in Houston, Texas, retains substantial

popularity. Patients from North America and Europe attend the clinic where this treatment is obtainable at great cost. Because it is an experimental, unproved treatment, insurance does not reimburse patients. No data support the efficacy or safety of antineoplaston therapy.

In 1998, hundreds of cancer patients sought prescriptions for the untested DiBella 'cancer cure'. Dr DiBella in Modena, Italy, produced a treatment that includes the natural hormone somatostatin plus vitamin A derivatives. The public demand for this therapy was so great that the Italian government permitted and paid for its use. Recently, Canadian and Italian scientists conducted clinical tests and found no evidence that the treatment cures cancer. In 75% of patients studied the cancer worsened or the patient died, according to the Italian news agency ANSA.

Fresh cell therapy, also called live cell therapy or cellular therapy, has become increasingly popular. Offered in Mexico and Europe (it is illegal in the U.S.A.), it uses injections of animal embryo cells from the organ that corresponds to the patient's cancerous organ or tissue. Advocates believe that the injected cells go through the patient's body to the target organ. There they repair the cancer cells. No data support the value of fresh cell therapy. It has no proven benefit and can cause serious side-effects such as infections and death.

Oxygen therapies, also called hyperoxygenation, bio-oxidative therapy and oxidative therapy, are used to treat cancer and AIDS. The incorrect belief behind this therapy is that cancer is caused by oxygen deficiency. Proponents believe that overwhelming the cancer cells with more oxygen than they can manage will kill them. There is no evidence that oxygen therapies effectively treat any serious disease, and they have potential for harm.

PREVENTIVE MEASURES

In the context of CAM, measures to prevent cancer almost invariably relate to nutrition. As such, most are not strictly CAM, but mainstream medicine. Those often promoted by proponents of CAM are discussed here.

Vegetarianism

The notion that cancer mortality is highest in countries with large average meat consumption is not new [53]. Recently it has been supported by good evidence. In a prospective study from the U.K., 6000 non-meat-eaters and 5000 meat-eaters were followed for 12 years [54]. At the end of this period all-cause mortality in the former population was approximately half of that of the latter group. After controlling for smoking, body mass index and socio-economic status, the all cancer death rate ratio was 0.61 (95% confidence interval (CI) 0.44–0.84) for non-meat-eaters compared with omnivores. These results confirm and expand the available evidence to suggest that a high fibre, fruit and vegetable intake conveys some protection against colon and breast cancer [55]. The point here is that it is not necessarily the avoidance of all meat that is protective. One ought furthermore to stress that strict vegetarianism carries the risk of malnutrition [56].

Allium vegetables

There are several lines of evidence to suggest that the regular consumption of onion or garlic is tumour-protective. Diallyl sulfide, abundant in garlic and onion, has repeatedly been shown to inhibit chemically induced stomach cancer in experimental animals [57]. The effect could be due to the elevation of glutathione *S*-transferase, which contributes to the detoxification of carcinogens [58]. Diallyl sulfide may also exert antineoplastic effects by modulating glutathione *S*-transferase-dependent detoxification enzymes [59].

Recent animal experiments suggest that several components of the diet may interact leading to an inhibition in the occurrence of DNA adducts in tissues [60]. Another possible mechanism could lie in the antinitrosating and nitrite scavenging action of sulphur compounds of garlic and onion. N-Nitroso compounds are powerful carcinogens. Endogenously formed nitrosamines seem to be inactivated by constituents of garlic and onion.

A further mechanism could be provided by the antibacterial actions of allicin [61]. These may firstly reduce the bacterial conversion of nitrate to nitrite in the stomach, thereby limiting the formation of potentially carcinogenic nitrosamines [62]. Secondly, garlic has been shown to kill *Heliobacter pylori in vitro* [63]. *Heliobacter pylori* infection is a major risk factor for stomach cancer. The antibacterial action of garlic could well convey some protection against this form of cancer.

A systematic review [64] was aimed at summarising existing epidemiological data on this topic. Twenty studies were located. With one exception, they suggest that allium vegetables convey protection against cancers, particularly those of the gastro-intestinal tract. Even though these data are encouraging, one ought to remember that epidemiological studies of this type are prone to bias. The hypothesis would seem to be worthy of testing in an intervention trial that minimises the danger of bias and confounding.

Green tea

There is a body of evidence to suggest that the polyphenols in green tea exhibit anticancer effects. For instance, given orally to experimental animals, green tea inhibits the growth of transplanted tumours [65], reduces the incidence of tumours in animals exposed to carcinogens [66] and reduces the metastatic potential of cancer cells [67].

Black tea is produced by fermenting green tea leaves. The process partly depletes it of polyphenols, which are thought to be the tumour-protective principle in green tea. Epidemiological studies suggest that the regular consumption of green tea conveys a moderate reduction of cancer risk, particularly cancers of the upper digestive tract [68–70]. A recent systematic review of the data concluded that: ''there is some evidence that green tea may prevent the occurrence of some cancers'' [71].

Panax Ginseng

Recent research implies that Panax Ginseng, also known as Korean, Chinese or Asian Ginseng, is tumour-protective through stimulation of the immune system [72, 73]. Perhaps the most compelling evidence in support of this hypothesis was published recently [74]. This study was carried out in a Ginseng-growing region in Korea, where 4634 inhabitants were assessed by questionnaire on Ginseng intake. During the 5 years of follow-up, 137 cases of cancer occurred. Those individuals who regularly consumed fresh Ginseng had a cancer risk ratio of 0.31 (95% CI 0.13–0.74). Although there was a dose–response relationship, the data are not ultimately convincing owing to the possibility of confounding.

ADJUNCTIVE (COMPLEMENTARY) TREATMENTS

Few oncologists would object to their patients seeking reassurance and comfort from complementary treatments aimed at symptom control or enhancing the quality of patients' lives [75]. This does not mean, however, that any form of CAM claiming to achieve this aim should be adopted uncritically. Such claims represent testable hypotheses and, before dedicating time and money to such treatments (obviously leaving less time and money for other interventions), good evidence is required [76]. This seems of particular importance when adjunctive complementary therapies are used for palliation.

In contrast to 'alternative' treatments, adjunctive therapies are minimally or non-invasive, non-toxic, inexpensive, simple to use and often self-administered. They are soothing and have the added virtue of permitting patients to assume control of some aspects of their care, with all of the psychological benefits such control conveys.

Many research-supported complementary therapies can improve the well-being of patients with cancer. These include meditation, yoga and other mind–body programmes for stress, acupressure or ginger for nausea, Tai Chi and other gentle exercise techniques for gaining strength, therapeutic massage, mint and other teas for indigestion, certain herbs for depression and anxiety, acupuncture for pain and nausea, and other approaches [24].

Some published evidence in this area, however, is anecdotal, inconsistent in conclusions, and unconvincing [77–79]. Other studies show that relaxation programmes can reduce cancer patients' pain [80, 81].

Complementary adjunctive treatments seem an important and fruitful area of future research, particularly in the realm of palliative care. We urgently need to know the value of these treatments in comparison with conventional palliative techniques.

CONCLUSION

Many cancer patients use CAM. Therefore, it is mandatory to ensure that more good than harm results. Treatments promoted as cures or that claim to prolong life carry the greatest risk of harm. None of the treatments reviewed above offer a reasonable hope for cure. Some strategies seem promising in terms of cancer prevention. The largest potential of CAM lies in complementary, adjunctive, palliative care. It is important to continue investigating the specific merits and mechanisms of complementary therapies, and to subject them to proper scientific scrutiny.

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