Published in final edited form as:

J Soc Integr Oncol. 2007 ; 5(3): 125–129.

Which botanicals or other unconventional anticancer agents should we take to clinical trial?

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Abstract

There is significant public and scientific interest as regards unconventional anticancer agents (“CAM agents”). This paper describes five principles pertaining to the question of which CAM agents should be taken to clinical trial: 1) Very many CAM agents have been proposed as cancer treatments, far more than could possibly be studied in clinical trials; 2) Claims by patients or practitioners are generally unhelpful in choosing which CAM agents to test; 3) Laboratory studies can help determine which CAM agents to take to trial, and with which co-interventions; 4) Preliminary laboratory studies are essential to confirm safety before trials can be considered; 5) The vast majority of anticancer CAM agents will be ineffective: our aim should be to discard agents from consideration as rapidly as possible.

Keywords

botanicals; herbs; herb-drug interactions; antioxidants

Introduction

This is the seventh in a series of papers in which I give an informal, personal perspective on methodological issues in integrative oncology research.[1–6] Most of the previous papers have concerned complementary therapies for symptom control, including issues such as randomization, assessment of quality of life, and accrual. This paper concerns the other major area of integrative oncology research: agents such as botanicals or vitamins for cancer control. For the sake of brevity, I will call these CAM (complementary and alternative medicine) agents. The current paper also differs in that, instead of dealing with issues of clinical trial design or analysis, I focus on a question that should be addressed before a trial is even considered, namely which CAM agents should even be taken to trial.

My basic premise is that research on anticancer CAM agents is qualitatively different from research on CAM for symptom control. In the course of my work at Memorial Sloan-Kettering Cancer Center, I have been involved in a variety of symptom control trials, including studies of music therapy for mood disorder; massage for pain; acupuncture for hot flashes; and acupuncture for neck pain. I will use these studies, and other well known trials, as counterexamples as I develop five general principles for anticancer CAM research. These principles are as follows:

1. Very many CAM agents have been proposed as cancer treatments, far more than could possibly be studied in clinical trials.
2. Claims by patients or practitioners are generally unhelpful in choosing which CAM agents to test.
3. Laboratory studies can help determine which CAM agents to take to trial, and with which co-interventions
4. Preliminary laboratory studies are essential to confirm safety before trials can be considered.
5. The vast majority of anticancer CAM agents will be ineffective: our aim should be to discard agents from consideration as rapidly as possible.

Principle 1: Very many CAM agents have been proposed as cancer treatments, far more than could possibly be studied in clinical trials

In March 2007, I conducted a Google search for “anticancer herbs”. Over 50 different botanicals were mentioned on the first three pages retrieved. I then searched Medline for “(herbs OR herbal OR botanical) AND cancer” and again read the first three pages, a total of 60 abstracts. Every single abstract concerned a different agent, and only two or three were in the Google pages I looked at.

There is clearly very little possibility that we could take to clinical trial even just those CAM agents found by the most cursory search of Google and Medline: we simply do not have the time, money or human resources. This means that the first task for research on anticancer CAM is to determine which agents to take to trial, knowing that this will be a small proportion of the total.

Now compare other areas of CAM research: if we were to write out a list of the main CAM therapies (acupuncture, massage, hypnosis, chiropractic etc) and the main indications for each (e.g. for acupuncture: musculoskeletal pain, fatigue, nausea, mood disorder, obesity, smoking cessation; for massage: pain, anxiety for massage; etc.), the total number of trials would not be completely disproportionate to the resources available. We obviously need to prioritize, but in general we can look at any particular claim (e.g. acupuncture can help treat fatigue) and have a reasonable chance of testing it in a clinical trial. This is not the case with anticancer CAM: the existence of a therapeutic claim is not, in itself, justification for a clinical trial.

Principle 2: Claims by patients or practitioners are generally unhelpful in choosing which CAM agents to test

When I first started at Memorial Sloan-Kettering Cancer Center, I asked some of the music therapists about their daily clinical work. They told me that they often worked on patients undergoing high dose therapy with autologous stem cell rescue (“bone marrow transplant”). These patients were in hospital for weeks at a time undergoing extremely harsh and dangerous treatments. The music therapists told me that the patients on the bone marrow transplant wards were often very anxious and depressed, but that music therapy was generally very helpful and improving the patients’ moods. This was particularly because the therapists could visit the patients throughout the course of their stay and develop a relationship with them. As a result, we developed a study of music therapy for mood disorder in patients undergoing bone marrow transplant. We completed the trial and published the results a few years ago [7]: mood disorder during was lower in patients randomized to receive music therapy as compared to controls receiving standard psychosocial care.

What is interesting about this story is that we went through the enormous trouble and expense of designing and conducting a randomized trial on the basis of a practitioner's say-so. But this doesn't seem terribly unreasonable because a good music therapist should be able to tell, more or less, whether or not patients feel better after treatment.

Perhaps the most dramatic example of a CAM clinical trial being based on a clinical observation is the studies of traditional Chinese medicine for eczema conducted in the UK[8]. A dermatologist at a major London hospital had been treating a boy with severe eczema, when, one day, he turned up pretty much cured. The boy's parents told the dermatologist that they had taken him to see a Chinese herbalist and that the herbs seemed to be having some benefit. This led the dermatologist to investigate further and, eventually, conduct a randomized trial.

Cancer isn't like eczema: you can't just look at someone and tell that a treatment is working, you have to evaluate how long a patient has survived. As it turns out, however, survival is a very tricky endpoint. A common type of story we hear about is a patient being told he has "only a few months to live", but then he takes a CAM agent and is still alive several years later. The essence of this type of story is that the patient survived longer than expected, and that the CAM agent must be the reason. But of course many cancer patients will indeed live longer than expected regardless of what agents they use. Indeed, assuming an exponential distribution for survival time, about 5% of patients will survive at least five times longer than average and about 1% will survive 10 times longer or more. Now approximately 500,000 Americans die of cancer each year, and we know from patient surveys and that a high proportion of cancer patients use CAM agents[9]. Using a conservative estimate that 20% of cancer patients use CAM agents, we might assume that, each year, there are 100,000 new cases of Americans with incurable cancer who use CAM. From our survival distributions, we would estimate that 1000 of these patients will live 10 times longer than expected. So every year we should be able to find large numbers of people who took CAM and have remarkable survival stories.

The other problem with using case histories as a basis for clinical trials in cancer is that of attribution. The British dermatologist was offering treatment to help control eczema symptoms and he would not expect this to lead to a dramatic improvement in the boy's skin condition. Cancer patients, on the other hand, rarely take only CAM treatments; typically, they undergo conventional treatments such as surgery or chemotherapy and use CAM agents as an additional approach. As a result, it is extremely difficult to know whether an anticancer CAM approach was responsible for any particular patient's unusually long survival, and might therefore be worth investigating in a clinical trial, or whether the patient was responding to a conventional treatment given concurrently.

Accordingly, the only good basis for a claim of an unusual clinical effect from a CAM agent would be to have: a) pathological documentation of cancer; b) clear evidence that a CAM therapy was used; c) clear evidence that no other treatment was used; d) radiographic evidence (e.g. an X ray or CAT scan) of cancer remission. This is pretty much the basis of the National Cancer Institute's "Best Case Series"[10]. But remarkably few CAM agents have been submitted for evaluation through this mechanism.

Principle 3. Laboratory studies can help determine which CAM agents to take to trial and with which co-interventions

I am not a laboratory scientist, but I do find many laboratory studies of CAM to be very interesting. In our own institution, for example, we have been studying acupuncture using fMRI: preliminary data suggest that acupuncture, but not placebo acupuncture, is associated with predictable patterns of stimulation in areas of the brain that correlate with the functional effects of the acupuncture prescription under study. I have seen similar work on music examining, for example, brain functioning in musicians listening to Bach[11]. That said, I can't

think of many scenarios where I would use a laboratory study to determine what CAM treatment to study, or in which patients to study it.

Quite the reverse is true for anticancer CAM agents: I suggest that laboratory studies should be the primary determinant of our clinical research on such agents. As an illustration, let's imagine that we were interested in conducting some research on anticancer mushrooms. There are a large number of these agents including Maitake, *Cordyceps*, Reishi, Shiitake and Enoki. There are few human data on these agents and so I can't see any reasonable way of choosing between them other than by laboratory study, for example, by giving each agent to a group of mice inoculated with cancer and seeing which group survived longest. We could refer to prior literature, but that would not necessarily give us a direct comparison, we would merely find data on each mushroom separately.

Before we compared the agents head-to-head, however, we might think about how they would be used in clinical practice. It would be unusual to use a mushroom product as a sole treatment for cancer, it is more likely to be combined with chemotherapy or immunotherapy. Moreover, we might to take a more standard drug development approach to our CAM agents, trying to understand their mechanism of action and then choosing co-interventions appropriately. At Memorial Sloan-Kettering Cancer Center, for example, we have studied the mechanism of action of glucan-containing botanicals and found that they promote the action of antibodies. Accordingly, we hypothesized that they would enhance the effects of therapeutic antibodies such as Herceptin or Rituxan. We confirmed this hypothesis in a mouse model, compared different glucans to see which was most effective and then moved forward to an early phase clinical trial[12].

Principle 4. Preliminary laboratory studies are essential to confirm safety before trials can be considered

I don't normally spend much time worrying about the safety of CAM. There is a lot of it around, and if it was dangerous, I guess we would have heard about it by now. Moreover, it is difficult to imagine how CAM therapies such as massage or music therapy would lead to important harm. For others CAM approaches where risk is more plausible, such as acupuncture, there have been large outcome studies suggesting a good safety record[13,14].

There are two reasons why anticancer CAM agents may be unsafe. The first is that although CAM agents are widely used in the community, what is safe for a relatively healthy individual might be far less safe for a sick cancer patient undergoing concurrent conventional therapy. I have discussed this point previously in a paper on the design of Phase I trials of anticancer CAM agents[2].

The second reason why anticancer CAM may be unsafe is something that needs to be evaluated before such agents are taken to clinical trial. This point concerns interactions with conventional CAM agents. It is known, for example, that some botanicals have metabolic interactions with chemotherapy agents such that use of the botanical dramatically lowers blood concentrations of the chemotherapy[15]. There is also evidence that some antioxidants might interfere with cytotoxic therapy[16] and that botanicals with estrogenic properties might compromise the efficacy of therapies such as Tamoxifen[17]. The key issue here is that such effects will not be clinically obvious: patients taking St John's wort during Irinotecan treatment don't display unusual adverse events, they just put themselves at risk of an earlier death from cancer by reducing the effectiveness of their treatment[15].

I would argue, therefore, that we should only take to clinical trial those CAM agents that have proven to be safe in laboratory studies. A suitable panel of investigations might include metabolic studies, to determine whether the CAM agent affects the blood concentration of

chemotherapy or other agents given concurrently; cell line studies, to determine any direct interactions at the cell surface; animal studies as an *in vivo* investigation of interactions before human use.

Principle 5. The vast majority of anticancer CAM agents will be ineffective: our aim should be to discard agents from consideration as rapidly as possible

I once acted as statistician on a grant for a novel screening method for anticancer botanicals. In brief, laboratory studies had indicated that botanicals containing glucans, which includes mushroom and fungal products such as Maitake, Reishi and PSK, act through a mechanism involving complement receptor 3[12]. The idea was to use an *in vitro* system to test the effects of a large number of botanicals on this receptor in order to identify the most promising candidates for clinical trial.

Our grant was rejected. One of the main criticisms was that our model system might be “unfair” to some botanicals: it is quite possible that one of the botanicals we screened might have little effect on complement receptor 3, but be active against cancer through an unrelated mechanism.

In our view, this criticism inverts the standard rationale for anticancer CAM research. We are not interested in studying anticancer CAM agents because we want to find out more about them, we are interested in finding agents that will helping cancer patients live longer, healthier lives. I am perfectly prepared to be “unfair” to any number of anticancer CAM agents if I could show that just one had important clinical activity against cancer. This is because I believe that the vast majority of the CAM agents proposed as treatments for cancer are ineffective: I’d say the same for most conventional agents currently in early phase testing.

Let’s imagine that, with all our work on anticancer CAM, we were able to contribute to finding a *single* treatment that became routinely used to treat cancer. In my view, that would be pretty extraordinary, and a vindication of everything we had done. So let’s focus our energies on finding that one treatment. If our preliminary studies of an agent don’t blow our socks off, forget it and move on: there are too many CAM agents to look at, and too little time to study them.

Conclusion

In this paper I have argued that there are more anticancer CAM agents than could possibly be studied in clinical trials and that we therefore face a major challenge in choosing which to take forward to early phase study. I have also argued that patient or practitioner opinion is of little value in choosing between agents and that we should rely heavily on laboratory studies. Our aim in such studies should be rapid assessment, aiming to discard as many agents as fast as possible so as to concentrate on those with the most unusually promising results.

I do think that there is one general exception to these principles. Some CAM agents become so widely used by cancer patients that appropriate trials become a public health issue. Examples include laetrile[18], shark cartilage[19], vitamin C[20] and Di Bella therapy[21]: I believe that research was warranted in each of these cases, despite the lack of good laboratory data, on the grounds that cancer patients needed information on which to base real-life decisions.

In general, however, we are interested in anticancer CAM agents because we wish to develop effective therapies that could be made widely available to cancer patients throughout the world. For this goal, we have little alternative but to turn to the laboratory to guide our choice of agents for clinical trial.

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