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Unconventional Anticancer Agents: A Systematic Review of Clinical Trials

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Abstract

Purpose—A substantial number of cancer patients turn to treatments other than those recommended by mainstream oncologists in an effort to sustain tumor remission or halt the spread of cancer. These unconventional approaches include botanicals, high-dose nutritional supplementation, off-label pharmaceuticals, and animal products. The objective of this study was to review systematically the methodologies applied in clinical trials of unconventional treatments specifically for cancer.

Methods—MEDLINE 1966 to 2005 was searched using approximately 200 different medical subject heading terms (eg, alternative medicine) and free text words (eg, laetrile). We sought prospective clinical trials of unconventional treatments in cancer patients, excluding studies with only symptom control or nonclinical (eg, immune) end points. Trial data were extracted by two reviewers using a standardized protocol.

Results—We identified 14,735 articles, of which 214, describing 198 different clinical trials, were included. Twenty trials were phase I, three were phase I and II, 70 were phase II, and 105 were phase III. Approximately half of the trials investigated fungal products, 20% investigated other botanicals, 10% investigated vitamins and supplements, and 10% investigated off-label pharmaceuticals. Only eight of the phase I trials were dose-finding trials, and a mere 20% of phase II trials reported a statistical design. Of the 27 different agents tested in phase III, only one agent had a prior dose-finding trial, and only for three agents was the definitive study initiated after the publication of phase II data.

Conclusion—Unconventional cancer treatments have not been subject to appropriate early-phase trial development. Future research on unconventional therapies should involve dose-finding and phase II studies to determine the suitability of definitive trials.

INTRODUCTION

Despite considerable improvement in survival rates, more than 500,000 Americans die each year from cancer, and prognosis remains poor for many cancer diagnoses.[1] Therefore, a substantial number of patients turn to a one or more of a wide variety of unconventional agents and treatments used as anti-cancer therapies. Many agents, such as PC-SPES (BotanicLab, Brea, CA), Reishi mushroom, or Essiac, are derived from botanicals. High doses of nutritional supplements, such as vitamin C, also are included in many unconventional approaches. Other agents include off-label pharmaceuticals (eg, hydrazine sulfate), animal products (eg, shark cartilage), and substances found naturally in the human body (eg, melatonin and coenzyme Q10). A final category of unconventional anticancer therapy consists of treatment systems that

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use several modalities concurrently. For example, metabolic therapy includes dietary changes, supplements, saunas, and enemas in an effort to reduce cancer-promoting "toxins." Unconventional therapies are sometimes described as complementary and alternative medicine; here, we use the term unconventional in preference because most complementary therapies, such as acupuncture or massage, aim to relieve symptoms of cancer, rather than extend survival.

We are examining clinical trial methodology for unconventional anticancer therapies. The first step in our investigation is to document early-phase methodologies applied in such trials. Here, we present a systematic review of clinical trials of unconventional anticancer therapies. Our aims are to describe the number of such trials, the agents studied, the study end points, and the methodologies used. We are particularly interested in the degree to which research on unconventional therapies has followed the standard development trajectory from phase I to phase II to phase III.

METHODS

Search Strategy

We searched MEDLINE (1966 to January 2005) using medical subject heading terms for unconventional therapy (eg, "complementary therapies" or "plants, medicinal") along with a large number (n = 187) of free text terms (eg, "laetrile," "Mistletoe," or "melatonin"). The results were then combined with cancer terms (eg, "neoplasms [MeSH] " or "cancer*"). Full details of the search are available from the authors. Searches were supplemented by scanning lists of review articles, such as the Office of Technology Assessment report on Unconventional Cancer Treatments.[2] Our search strategy was designed to maximize sensitivity rather than precision. We initially intended to repeat these searches using a variety of other bibliographic databases such as EMBASE and the Cochrane library. However, initial analyses of the many thousands of references retrieved from these databases recovered zero additional references.

Criteria for Including Studies

Type of intervention. We included reports of unconventional cancer treatments that involved administration of an agent to patients diagnosed with cancer. The aim of the treatment must have been to extend life, rather than to control symptoms. Lacking a sharp dividing line between conventional and unconventional, we used the following guidelines: any botanical extract that contained more than one chemical constituent was included, except when other constituents were considered impurities; any treatment explicitly mentioned in the search strategy was included; and any treatment described as antineoplastic in the Physician's Desk Reference (2003) was excluded.

Type of study participants. Trials were included if they studied cancer patients at any stage. Trials of participants without cancer were included if the rationale of the study explicitly concerned development of a treatment for active cancer (eg, pharmacokinetic studies in healthy volunteers).

Type of study. Trials were included if they met any of the following criteria: the trial was explicitly described as phase I, phase I and II, phase II, or phase III; the trial end point was survival, disease progression, disease recurrence, tumor marker, or tumor response; different doses, schedules, or routes of administration were compared; the primary end point was toxicity; or the primary rationale given for the study was to determine safety. Only trials that prospectively accrued patients to the experimental treatment arm were included. Studies of regimens that included both unconventional and conventional agents were included if they compared two groups of patients receiving similar treatment other than the addition of the

unconventional agent in one group; were single-arm trials in which patients had received standard treatment, had not responded, and had then received the unconventional agent in addition to the standard treatment; or were trials that compared different doses of the unconventional agent. We excluded trials from China on the grounds that, in our experience of reading such trials translated into English, these trials have been of unclear design; moreover, we felt that the methodology of Chinese research has little bearing as to the design of early-phase trials in the West.

Reasons for excluding an article were categorized as follows: treatment not unconventional, not human subjects, not a prospective clinical trial, not cancer patients, no clinical outcome (eg, immune end points), symptom study, effects of unconventional treatment not estimable, and Chinese study. If a study met more than one exclusion criterion (eg, a laboratory study of a chemotherapy agent), the first criterion on the list was used (in this case, treatment not unconventional).

Data Extraction

The study sample was described in terms of sample size, diagnosis (single cancer site or mixed), and stage (early, late, or all stages). The end points for phase I trials were categorized as toxicity, efficacy (eg, tumor marker), and pharmacokinetics. Efficacy end points were not considered for phase I trials unless they contributed to determining optimal dose. For phase II and III trials, efficacy end points were categorized as tumor response, tumor marker, disease-free survival, overall survival, alive at fixed time after entry, and event free at fixed time after entry.

Each study was categorized as phase I if it was explicitly described as phase I or phase I/II; if different doses, schedules, or routes of administration were compared; or if the primary rationale given for the study was to determine safety. Trials were classified as phase II if the study was explicitly described as phase II or phase I/II; if the rationale was to determine whether a controlled trial was warranted; or if the trial was a single-arm study with survival, disease progression, tumor marker, or tumor response as the primary end point. Some trials were classified as both phase I and II. Trials were classified as phase III if they were explicitly described as such or if the trial incorporated a control arm and did not meet the criteria for a phase I or II study, as just described.

Design was further categorized as follows. For phase I, we documented whether the rationale concerned dose finding, safety, or another explicit purpose or was unclear. For phase II, we documented whether a rationale was given for the sample size and whether the design incorporated a formal decision rule (eg, a certain proportion of responses) for continuation to phase III. For phase III, we categorized design as randomized, concurrent cohort, historical cohort, or case control.

For phase II and III trials, we documented the rationale for the dose and schedule of the experimental agent using the following criteria: formal dose-finding study, common practice, preclinical data, and no rationale given/unclear. Common practice is when the rationale for the dose is based on clinical practice or public use; preclinical data is when the rationale for the dose is based on animal or in vitro studies extrapolated to humans. If a phase I trial had been completed before the phase II or III trial and the dose used in the subsequent trial was the dose recommended in the phase I trial, then the later trials were classed as having a prior dose-finding study, even if they did not make explicit reference to the phase I data.

For each phase III trial, we documented whether it had been preceded by a phase II trial. Where an agent had been subjected to several phase III trials, the phase II trial had to be completed before the start of the first phase III trial.

Review Methods

We read the title and abstract of all articles in an initial screen, obtaining full text unless there was clear evidence that the article would not be eligible. The initial screen was conducted by J.K.; A.J.V. checked all possibly eligible articles and a random sample of excluded articles. Data were extracted from full text by both A.J.V. and J.K. for English language articles. For foreign language articles, J.K. worked interactively to obtain appropriate information with a reviewer fluent in the appropriate language (see Acknowledgment).

RESULTS

Study Sample

We screened 14,735 articles; 14,392 were deemed clearly ineligible on initial screen, and full text was obtained for 343. Of these 343 articles, 214 met eligibility criteria, giving a total of 14,521 that were excluded. The reasons for exclusion are listed in Table 1. The most common reasons were treatment not unconventional (49%; typically a study of a plant-derived chemotherapy agent such as a taxane), not human subject (30%; usually a cell line or animal study), and not clinical trial (15%; most often an epidemiologic study or a review).

The 214 eligible articles described a total of 198 separate trials, including 20 phase I, 70 phase II, 105 phase III, and three that met criteria for both phase I and II. There are more articles than trials because several phase III studies were reported on more than one occasion as data matured. Table 2 lists the treatments assessed in these trials; the treatments total more than 198 because some trials compared more than one unconventional treatment. Nearly half of the trials addressed mushroom and fungal products, particularly polysaccharide Kureha (PSK), which is an extract from the fungus *Coriolus versicolor*. The next most commonly studied agent was melatonin, although almost all trials came from a single author. The pharmaceuticals studied included hydrazine sulfate, laetrile, dimethyl sulfoxide, and antineoplastons.

Trial Design

Phase I. The most common rationale for the phase I trials was safety (nine trials). One trial compared two different types of botanical extract; the rationale was unclear for two trials. Only eight of the 20 phase I trials were classified as dose finding. These included trials on the following six agents: soybeanextract, green tea extract (two trials), PSK, lentinan (an extract from the Shiitake mushroom, two trials), curcumin, and Neovastat (Aeterna Laboratories Inc, Quebec City, Canada), a patented cartilage preparation. Not all of these trials can be described as efficient designs to obtain optimal dose. In the PSK trial, for example, 22 patients received PSK either daily or every other day at the discretion of their doctors, and various immune parameters were compared between groups.[3] There is no clear link between the findings of this trial and the dose schedule for PSK used in phase III trials.

Phase II. The design of phase II trials was generally unclear. Only 16 of the 73 phase II trials had a decision rule, and 11 of these trials were associated with a single treatment; in the late 1990s, an unconventional cancer therapy known as the Di Bella regimen gained enormous public attention in Italy, and the Italian government instituted a rapid and systematic evaluation. Excluding this somewhat unique event, only five (8%) of 62 trials included a statistical design. Only six phase II trials of three agents (green tea extract, lentinan, and Neovastat) had prior dose-finding trials. Moreover, one of the lentinan trials used 4 mg/d when the prior phase I trial recommended 2 mg/d. The most common end point was tumor response (45 trials, 62%); 21 trials assessed overall survival, nine assessed progression-free survival, and 15 assessed a tumor marker, predominantly prostate-specific antigen. Tumor response was the only end point for approximately half (n = 34) of the phase II trials, which is a some what surprising finding given that the agents studied did not seem to be strongly cytotoxic.

Phase III. Most of the 105 phase III trials were randomized (90 trials, 86%) and assessed overall survival (88 trials, 84%). Of the 27 different agents studied in phase III trials, only one agent had a prior phase I study (lentinan, 13 trials). The definitive study was initiated after the publication of phase II data for only three agents (schizophyllan, six trials; melatonin, 10 trials; and arginine, one trial).

Dose finding. Table 3 lists the rationales given by the investigators for the doses used in phase II and III trials combined. Twelve trials studied multi-intervention packages of treatment, and hence the question of dose finding was not applicable. Of the remaining 166 trials, the majority (112 trials, 67%) either provided no rationale or the rationale was unclear. Thirty trials (18%) either simply copied a dose used in a prior trial or used common clinical practice as a justification. Only approximately 10% of effectiveness trials of unconventional agents had a prior dose-finding trial in cancer patients.

DISCUSSION

We have systematically identified and analyzed a large number of clinical trials of unconventional cancer treatments. Our review provides little evidence that these treatments have been subject to appropriate early-phase trial development. This is first seen in the combined number of phase I and II trials (n = 93), which is slightly lower than the number of phase III studies (n = 105). This is a marked distinction to conventional agents, for which there is a preponderance of early-phase trials and relatively few agents are studied in phase III. For example, a search for cancer trials on Medline finds approximately 12,000 phase I and II trials, but only approximately 1,000 phase III trials.

The near complete absence of dose-finding studies is a particular concern. In the majority of cases, investigators gave no justification at all for the dosages administered to study patients. In other studies, a rationale was given but was clearly inadequate. For example, a trial of PC-SPES[4] cited “common [use] in the community” for choice of dose. Leaving aside the issue of adulterants,[5] it is possible that a lower dose of PC-SPES might have been equally effective while reducing the incidence of endocrine side effects or, alternatively, that a higher dose could have increased the duration of response.

There is a similar lack of phase II trials of unconventional cancer treatments. We take the view that far more agents are proposed as active againstcancerthancanpossiblybestudiedinthesortoflarge,lengthy,and expensive phase III study required for definitive evaluation of effectiveness. The phase II trial remains a valuable, if imperfect, method of screening agents to pick those most worthy of further study. It hardly seems optimal that only three of the agents tested in phase III studies, representing less than 20% of trials, were previously tested in phase II studies.

Moreover, the methodology of early-phase trials that have been conducted is open to criticism. In the case of phase II trials, only a small minority of the trials we identified had a statistical plan or a decision rule. Most typically, investigators stated that they accrued a certain number of patients without justifying the number chosen, reported patient outcomes without reference to a prespecified plan for statistical analysis, and drew conclusions based on a general impression of the data. Examples of conclusions drawn from studies with no statistical plan include the following: “the prolonged survival [reported] warrants . . .large, placebo-controlled, randomized trials”[6] and “[the results] warrant further studies.”[7] Approximately half of the phase II studies reported only tumor response, which is a poor choice of end point for agents unlikely to bring about rapid tumor regression.

Conversely, at least some of these early-phase studies have used traditional designs in an arguably inappropriate manner. A phase I trial of green tea extract[8] attempted to determine

dose by the conventional method of escalating doses in patients who had failed prior therapy until severe acute toxicities were reported. The problem with such a study design is that green tea is not a strong cytotoxic and is unlikely to be used as a single agent against bulky disease. A more plausible role is preventing progression of premalignant lesions (as the authors themselves suggest) or possibly preventing recurrence after resection. Unlike cytotoxics, green tea can be taken daily over many months and years. Therefore, the maximum-tolerated acute dose is arguably of limited interest.

It has been suggested that low-toxicity agents with a history of human use do not require early-phase trials. We believe that, even if safety does not need to be demonstrated, early-phase trials can help determine optimal dosing and target populations. Research on megadose vitamin C provides an excellent example where failure to undertake early-phase trials has led to controversy and suboptimal research. When a phase III trial of vitamin C, initiated without prior phase I or II trials, found no evidence of benefit,[9] proponents countered that the trial included patients who had received prior chemotherapy and claimed that this negates the effects of vitamin C.[10] A second phase III trial was conducted with prior chemotherapy as an exclusion, but results were again negative.[11] Subsequently, however, it has been argued that both prior trials used insufficient oral doses and that further research on intravenous vitamin C should be conducted.[12] We believe that such controversies might have been avoided by appropriate early-phase research.

We also accept that not all phase III trials of unconventional agents need to be preceded by phase II trials or that phase II trials need to be preceded by phase I trials. For instance, widespread public use might mandate that a definitive study be rapidly conducted. A good example is the recent phase III trial by Loprinzi et al[13] of shark cartilage, which was published after our searches were completed. This trial was initiated in response to massive public use, and given the nature of the product studied, it is hard to argue that the investigators would have gotten a better or quicker answer had they started with a phase I or II study.

We also accept that there are inherent methodologic difficulties in early-phase research on unconventional agents. For example, an immunostimulant botanical is unlikely to induce rapid tumor regression in a patient with late-stage disease. Yet the same is true of many novel conventional agents, such as antiangiogenics, vaccines, or targeted therapies. A considerable methodologic literature has developed describing solutions to the challenge of phase I and II design for such agents,[14,15] and this literature is a useful source for investigators of unconventional therapies. Given the findings of this systematic review, that early-phase trials of such therapies are sparse and of poor quality, appropriate use of sound methodology is the least we can expect on behalf of the many patients who are interested in unconventional approaches.

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Table 1.

Reasons for Exclusion From Study

Reason	No. of Patients	%
Treatment not unconventional	7,175	49
Not human subject	4,310	30
Not a clinical trial	2,179	15
Not cancer patients	373	3
No clinical outcome	176	1
Symptom study	112	1
Effects of unconventional treatment not estimable	60	< 1
Chinese study	130	1
Other	6	< 1
Total	14,521	100

Table 2.

Description of Agents Studied in the Included Trials

Agent	No. of Trials
PSK	45
Other fungal products	33
Iscador/mistletoe	14
PC-SPES	6
Other botanicals	23
Vitamins	13
Other supplements	9
Melatonin	19
Treatment packages*	15
Pharmaceuticals†	22
Other‡	6

NOTE. Total number is greater than the number of trials because some trials studied more than one type of agent.

Abbreviation:

PSK

polysaccharide Kureha.

* Treatments such as metabolic therapy that include multiple interventions

† Includes hydrazine sulfate, dimethyl sulfoxide, laetrile, and antineoplastons.

‡ Includes unconventional vaccines and cartilage products.

Table 3.

Rationale for Dose Used in Phase II and III Trials of Unconventional Cancer Therapies

Rationale	No. of Trials	%
No rationale given	95	53
Unclear	17	10
Dose used in a previous trial	19	11
Formal dose-finding study in cancer patients	19	11
Not applicable	12	7
Common practice	11	6
Preclinical data	5	3
Formal dose-finding study in healthy volunteers	0	0
Total	178	