BRIEF COMMUNICATION

The Trials (and Tribulations) of Complementary and Alternative Medicine in Oncology

Ethan B. Ludmir, Amit Jethanandani, Walker Mainwaring, Austin B. Miller, Timothy A. Lin, Andres F. Espinoza, Vivek Verma, Noam A. VanderWalde, Aaron J. Grossberg, B. Ashleigh Guadagnolo, Albert C. Koong, Reshma Jagsi, Charles R. Thomas, C. David Fuller

See the Notes section for the full list of authors' affiliations.

Correspondence to: C. David Fuller, MD, PhD, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Unit 97, Houston, TX 77030 (e-mail: cdfuller@mdanderson.org).

Abstract

Two decades following the creation of the Office of Cancer Complementary and Alternative Medicine at the National Cancer Institute, the status of complementary and alternative medicine (CAM) research within oncology remains opaque. To better understand the landscape of CAM studies in oncology, we identified CAM-related phase III randomized controlled trials (RCTs) through ClinicalTrials.gov and compared these CAM trials to all non-CAM oncologic RCTs. Pearson χ^2 testing was used to compare proportions across groups; all tests were two-sided. Comparing the 25 identified CAM RCTs with 739 non-CAM RCTs, CAM studies were more likely to be sponsored by a cooperative group (64.0% vs 28.6%, $P < .001$) and less likely to be industry funded (8.0% vs 76.5%, $P < .001$). CAM trials disproportionately excluded disease-related outcomes as endpoints (8.0% vs 84.6%, $P < .001$), were unsupported by prior early-phase data (55.0% vs 96.1%, $P < .001$), and did not meet the primary endpoint (8.7% vs 53.0%, $P < .001$). Given the observed relationship between encouraging pilot data and subsequent phase III trial success, we contend that future CAM RCTs may yield more promising findings if better supported by appropriately designed and well-characterized early-phase signals.

In 1998, spurred by rising interest in the use of complementary and alternative medicine (CAM) for cancer patients, the National Cancer Institute (NCI) created the Office of Cancer Complementary and Alternative Medicine (OCCAM) and has supported OCCAM with more than \$100 million annually since 2005 (1). Two decades following the inception of OCCAM, we sought to better define the status and impact of CAM-related research in clinical oncology (2). We specifically compared characteristics and outcomes of CAM- and non-CAM-related phase III randomized controlled trials (RCTs) for cancer patients. Understanding the landscape of CAM RCTs during the last 20 years may afford insight into the strengths and weaknesses of CAM-related research in oncology as well as a framework for next-generation study design.

To identify CAM- and non-CAM-related RCTs in oncology, ClinicalTrials.gov was queried on November 19, 2017. The

following search parameters were used: other terms: "cancer"; study type: "All Studies"; status: excluded "Not yet recruiting"; phase: Phase III; and study results: "With Results." This yielded 1239 trials. Trials were then screened for cancer-specific phase III randomized multi-arm trials addressing a therapeutic intervention (Figure 1). A total of 764 trials met inclusion criteria; of these, 25 (3.3%) were RCTs evaluating a CAM-related intervention using a previously published definition of CAM interventions (2). All CAM trials incorporated the CAM intervention in a complementary manner in addition to non-CAM oncologic therapies. Pearson χ^2 testing was used to compare proportions across groups; statistical analyses were performed using SPSS (Version 22.0) (3). All tests were two-sided, and a P value of less than .05 was considered statistically significant.

Compared with non-CAM trials, CAM trials were less likely to be industry funded (8.0% vs 76.5%, $P < .001$) and more likely to

Received: March 29, 2019; Revised: May 6, 2019; Accepted: May 29, 2019

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Figure 1. Flowchart of clinical trial screening, eligibility, and inclusion. CAM = complementary and alternative medicine; RCT = randomized controlled trial.

be sponsored by a cooperative group (64.0% vs 28.6%, $P < .001$; Table 1). Only two CAM trials (8.0%) included a disease-related outcome (eg, overall survival, progression-free survival) as either a primary or secondary endpoint. By contrast, 84.6% of non-CAM trials included a disease-related outcome as either a primary or secondary endpoint ($P < .001$; Table 1). A total 80% of CAM trials enrolled patients exclusively in the United States, whereas 71.6% of non-CAM RCTs enrolled patients in multiple nations ($P < .001$; Table 1).

Trials were then analyzed for whether the phase III RCT was supported by prior prospective data, typically phase I/II trials supporting subsequent phase III investigation. These preceding trials were identified by examining peer-reviewed publications from each included phase III trial; generally, prospective pilot data supporting the RCT were noted in the publication. For the few trials where this was not the case, we conducted a PubMed literature search and reviewed the RCT protocol (if available) to identify supporting prospective studies. CAM trials were less likely to be supported by antecedent prospective results than non-CAM trials (55.0% vs 96.1%, $P < .001$; Table 1).

Trial success, defined by whether the primary endpoint was met, was markedly lower among CAM trials (8.7% vs 53.0%, $P < .001$; Table 1). Both of the two positive CAM RCTs (4,5) were supported by preceding phase I/II data, both were NCI sponsored, neither was industry funded, and neither evaluated a disease-related outcome endpoint. Examining all trials (CAM and non-CAM), prior positive prospective data were associated with subsequent positive phase III RCT results. Trial success rates for phase III RCTs with or without preceding prospective results were 54.6% and 17.9%, respectively ($P < .001$).

These results highlight substantial differences between CAM and non-CAM RCTs in oncology. CAM trials are more likely to rely on government sponsorship than non-CAM interventions but less likely to evaluate disease-related outcome endpoints, be supported by prior prospective data, or succeed at meeting the

primary objective. Furthermore, exploratory analyses confirmed that CAM trials were statistically significantly less likely to be supported by prior pilot data or succeed at meeting the primary endpoint even when only nondisease-related outcome endpoint trials or only government-funded trials were examined. With continued rising interest in CAM among patients (6–10), ensuring that CAM interventions are rigorously evaluated in high-quality trials becomes increasingly imperative (11,12). During the initial 5 years following the establishment of OCCAM, investigators at the NCI reported on research-design issues observed among CAM trial applications (2). Examining 46 trial proposals aiming to utilize CAM interventions for symptom management, the NCI team described a fundamental deficit in pretrial data to justify support for many studies and stated at that time that “[b]ecause the usual preclinical data found in research on new pharmaceutical agents are generally not available for many CAM interventions, researchers may want to consider conducting pilot studies before moving into phase III efficacy trials” (2). Fourteen years following this recommendation for trial applications, we observe a substantial deficit in prospective pilot data justifying CAM-related RCTs that went beyond the application stage and were opened for patient enrollment. Furthermore, our results support a relationship between preceding early-phase data and subsequent odds of phase III trial success. This may explain, at least partially, the poor success rate of cancer-related CAM RCTs to date.

One of the chief strengths of this study is the scope of trials included. Collectively, the 764 trials represented in this study enrolled a total of 462 449 patients (including 5330 patients enrolled in the 25 CAM RCTs). The 739 non-CAM trials provide a robust comparator group; to our knowledge, this is the first analysis of CAM trials involving comparisons with a large pool of non-CAM studies. This allows for evaluation of the landscape of CAM RCTs in the broader context of oncologic research as a whole, demonstrating stark differences between CAM and non-

Table 1. Factors associated with CAM vs non-CAM trials

Trial factor	CAM trials No./total (%)	Non-CAM trials No./total (%)	P*
Industry funding of trial			
Yes	2/25 (8.0)	565/739 (76.5)	<.001
No	23/25 (92.0)	174/739 (23.5)	
Cooperative group trial			
Yes	16/25 (64.0)	211/739 (28.6)	<.001
No	9/25 (36.0)	528/739 (71.4)	
Disease-related outcome as endpoint			
Yes	2/25 (8.0)	622/735 (84.6)	<.001
No	23/25 (92.0)	113/735 (15.4)	
Accrual goal met			
Yes	8/14 (57.1)	366/548 (66.8)	.45
No	6/14 (42.9)	182/548 (33.2)	
Location of enrollment†			
United States only	20/25 (80.0)	147/730 (20.1)	<.001
Multinational	2/25 (8.0)	523/730 (71.6)	
Non-US single country	3/25 (12.0)	60/730 (8.2)	
Pretrial prospective results‡			
Yes	11/20 (55.0)	518/539 (96.1)	<.001
No	9/20 (45.0)	21/539 (3.9)	
Trial success (PEP met)			
Yes	2/23 (8.7)	302/570 (53.0)	<.001
No	21/23 (91.3)	268/570 (47.0)	

*Pearson χ^2 test P values are provided. CAM = complementary and alternative medicine; PEP = primary endpoint.

†Location of enrollment refers to the geographic countries in which patients were enrolled for a given trial; enrollment regions were divided by those that enrolled exclusively in the United States, those that enrolled in multiple countries, and those that enrolled in single countries other than the United States.

‡Pretrial prospective results include those phase III randomized controlled trials with positive prospective data before phase III trial initiation; typically this includes trials with positive phase I/II data supporting initiation of a subsequent phase III study. Only trials with peer-reviewed publication of PEP results were included in analysis of pretrial prospective results. Trials with insufficient data regarding accrual goals or PEP success were excluded from analysis.

CAM studies. A limitation of this analysis concerns the source of trials pooled for this analysis (ClinicalTrials.gov); the mandate of ClinicalTrials.gov has evolved since its creation in 2000, and older trials, particularly those that do not test systemic chemotherapeutics (including CAM trials), may be underrepresented (13,14).

Collectively, our results present an opportunity for improvement in CAM-related oncologic research. Instruction on best practices in the pragmatic design, execution, and reporting of pilot CAM trials is recommended. This is especially critical as OCCAM funding continues to shift away from clinical trials toward mechanistic laboratory-based research, and non-NCI bodies within the National Institutes of Health are declining to fund oncology-specific CAM work. By ensuring that appropriate early-phase signals are identified for CAM interventions in can-

cer care, we hope that subsequent phase III RCTs will yield more promising findings.

Funding

The authors report no funding for this work.

Notes

Affiliations of authors: University of Texas MD Anderson Cancer Center, Houston, TX (EBL, AJ, ABM, TAL, BAG, ACK, CDF); University of Tennessee Health Science Center, Memphis, TN (AJ, NAV); Baylor College of Medicine, Houston, TX (WM, TAL, AFE); University of Texas Health Science Center, Houston, TX (ABM); Allegheny Health Network Cancer Institute, Pittsburgh, PA (VV); Oregon Health and Science University, Portland, OR (AJG, CRT); University of Michigan, Ann Arbor, MI (RJ).

The authors report no financial disclosures or conflicts of interests related to this work.

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