JBUON 2017; 22(2): 530-534
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

ORIGINAL ARTICLE

Evaluation of complementary and alternative medicine trials registered in clinicaltrials.gov database

Omer Dizdar[1], Emre Bilgin[2], Serkan Akin[3], Saadettin Kilickap[1], Mutlu Hayran[1]

[1]Hacettepe University Cancer Institute, Department of Preventive Oncology, Ankara; [2]Hacettepe University Faculty of Medicine, Department of Internal Medicine, Ankara; [3]Hacettepe University Cancer Institute, Department of Medical Oncology, Ankara, Turkey

Summary

Purpose: *Complementary and alternative medicine (CAM) products are increasingly used because they are perceived as natural, relatively low-cost and probably effective therapies for various diseases including cancer. We aimed to determine the quantity and major characteristics of recent herbal/alternative medicine trials registered in clinicaltrials.gov in patients with cancer.*

Methods: *''Cancer AND (herbal OR complementary OR alternative)'' key words were used to query clinicaltrials.gov (access date 17 April 2015). From the results, 163 trials which have been conducted in patients with the diagnosis of cancer were identified and included in this analysis.*

Results: *At the date of access, 72 trials were completed, 37 trials were still recruiting patients and 10 trials had been withdrawn. Most common cancer type was breast cancer. Eighty-eight percent of trials were interventional and 60% of trials were randomized. The rate of new trial submission were similar for 5-year periods after 2000. The majority of the trials were conducted in United States of America (55%) and People's Republic of China (11%). Nine and 4 of 37 recruiting trials were recorded as phase II and phase III, respectively. When browsing was restricted to ''recruiting'' and 'interventional'' studies, the ratio of herbal/complementary treatment trials to all chemotherapy trials was 1.8 %.*

Conclusion: *CAM research in patients with cancer is currently limited, both in terms of quantity and quality. Until high quality scientific and clinical research establishes safety and efficacy of CAM practices, physicians should rigorously inform patients and the public on potential risks and caveats associated with CAM practices.*

Key words: *cancer, clinical trial, complementary alternative medicine, herbal*

Introduction

CAM refers to the use of non-mainstream practice together with (complementary) or in place of (alternative) conventional medicine. It includes the use of herbs, homeopathy, acupuncture, yoga, relaxation, meditation, massage, etc. The National Center for Complementary and Integrative Health (NCCIH) of USA uses the term "complementary health approaches" for practices and products of non-mainstream origin and "integrative health" for incorporating complementary approaches into mainstream health care [1]. Patients' demand on CAM products is increasing because they perceive these products as natural, relatively low-cost and probably effective therapies for their diseases. Sales of herbal dietary supplements in the United States increased by 7.5% in 2015, totaling an estimated 6.92 billion USD according to a new market report by the American Botanical Council [2]. In 2010, United States spent an estimated 125 billion USD on cancer care [3] while herbal supplement market was 5 billion USD at the same time [2], which is roughly 4% of cancer care expenditure. Worldwide expenditure is estimated to be 60 billion [4]. A recent study identified at least 300,000 CAM providers in the European Union (EU), 48% being medical doctors

Correspondence to: Omer Dizdar, MD. Hacettepe University Cancer Institute, Department of Preventive Oncology, Altindag, Ankara, Turkey. Tel: +90 312 305 43 29, Fax: +90 312 305 43 12, E-mail: omer.dizdar@hacettepe.edu.tr
Received: 02/01/2017; Accepted: 14/01/2017

and 52% non-medical practitioners. This number is the two thirds of the total number of general practitioners in the EU [5].

Patients with cancer also have a very high prevalence of herbal use. Most of the patients do not share information with their doctors on using CAM. Twenty-five to 47% of the cancer patients living in North America and 17 to 45% of those in various European countries report using CAM [6-8]. A recent survey in Turkey found that 68% of the patients with cancer reported using herbs, and only 24% of these users had consulted or discussed this with a physician [9].

On the other hand, the number and quality of clinical trials conducted with these remedies is disproportionally low. Most patients confidently use these products because they are labeled as ''natural'' and are effective as they have "stood the test of time". However, evidence showing their efficacy and safety, and fulfilling requirements of the contemporary medical research is limited for most of these practices, including insufficient number of randomized controlled trials and poor quality of conduct. In this analysis, we aimed to determine the quantity and major characteristics of recent herbal/alternative medicine trials registered in clinicaltrials.gov in patients with cancer.

Methods

ClinicalTrials.gov is affiliated to National Institutes of Health and is a registry and results database of publicly and privately supported clinical studies of human participants conducted around the world. ''Cancer AND (herbal OR complementary OR alternative) '' key words were used to query this database (access date 17 April 2015). From the results, 163 trials which have been conducted in patients with the diagnosis of cancer were identified and included in this analysis. Several characteristics of the trials, phase, patient group, sponsor, time period and interventions were analyzed with descriptive statistics using SPSS 20.0. Chi-square test was used to compare trial features in different time periods. A p value of less than 0.05 was considered statistically significant.

Results

Characteristics of the trials are shown in Table 1. At the date of access, 72 trials were completed, 37 trials were still recruiting patients and 10 trials had been withdrawn. Most common cancer type was breast cancer. Eighty-eight percent of trials were interventional and 60% were randomized. The rate of new trial submission was similar for 5-year periods after 2000. The majority of the trials were conducted in United States of America (55%) and the People's Republic of China (11%). Nine and 4 of 37 recruiting trials were recorded as

Table 1. Characteristics of the CAM trials in patients with cancer registered in clinicaltrials.gov

	All trials n (%)	*Recruiting trials n (%)*
Total trial number	163 (100)	37 (100)
Status		
Recruiting	37 (22.7)	
Terminated	8 (4.9)	
Completed	72 (44.2)	
Withdrawn	10 (6.2)	
Active, not recruiting	21 (12.80)	
Other	15 (9.2)	
Cancer type		
Breast	50 (30.2)	11 (29.7)
Lung	12 (7.3)	3 (8.1)
Colorectal	15 (9.2)	4 (10.8)
Other	46 (28.2)	9 (24.3)
General (not specified)	40 (24.5)	10 (27.1)
Phase		
1	12 (7.3)	0 (0.0)
1+2	15 (9.2)	3 (8.1)
2	45 (27.6)	9 (24.3)
2+3	3 (1.8)	1 (2.7)
3	13 (8.0)	4 (10.8)
4	4 (2.5)	0 (0.0)
Not stated	69 (43.3)	20 (54.0)
Age group		
Adult	143 (87.7)	31 (83.8)
Child	2 (1.2)	1 (2.7)
Adult+child	18 (11.1)	5 (13.5)
Sponsor		
NIH	61 (37.4)	9 (24.3)
Industry	10 (6.2)	2 (5.4)
Other	92 (56.4)	26 (70.3)
Type of trial		
Observational	18 (11.1)	5 (13.5)
Interventional	145 (88.9)	32 (84.5)
Design of trial		
Randomized	97 (59.5)	16 (43.3)
Other	66 (40.5)	21 (56.7)
Time of trial start		
<2000	5 (3.1)	1 (2.7)
2000-2005	53 (32.5)	2 (5.4)
2006-2010	46 (28.2)	13 (35.1)
>2011	49 (30.0)	20 (54.1)
Not stated	10 (6.2)	1 (2.7)
Intervention		
Drug/biologic/diet supplement	54-5-14 (33.1-3.1-8.5)	14-1-4 (37.8- 2.7- 10.8)
Behavioral	31 (19.0)	9 (24.3)
Device/Procedure	25 (15.3)	4 (10.8)
Other	24 (14.7)	1 (2.7)
Not stated	10 (6.2)	4 (10.8)

Table 2. Trial characteristics according to different time periods

	Trial start date			
	≤2005	*2006-2010*	*≥2011*	*p value*
Type of trial, n (%)				0.586
Interventional	50 (88)	40 (85)	45 (92)	
Observational	7 (12)	7 (15)	4 (8)	
Design of trial, n (%)				0.754
Randomized	37 (65)	31 (66)	29 (59)	
Other	20 (35)	16 (34)	20 (41)	
Intervention, n (%)				0.045
Drug/biologic/diet supplement	23 (44)	22 (51)	19 (40)	
Behavioral	11 (21)	9 (21)	11 (23)	
Device/Procedure	15 (29)	4 (9)	6 (12)	
Other	3 (6)	8 (19)	12 (25)	
Sponsor, n (%)				<0.001
NIH	40 (70)	9 (19)	11 (22)	
Industry	5 (9)	4 (9)	1 (2)	
Other	12 (21)	34 (72)	37 (76)	

phase II and phase III, respectively. In one of the phase III trials, acupuncture application for side effects of aromatase inhibitors was investigated. In the remaining 3 phase III trials, efficacy of melatonin, traditional Chinese medicine applications and a herbal mixture were investigated in lung cancer treatment. When browsing was restricted to ''recruiting'' and 'interventional'' studies, the ratio of herbal/complementary treatment trials to all chemotherapy trials was 1.8%.

Trial characteristics according to different time periods are shown in Table 2. No major alteration trend was observed considering trial design or type. The fraction of drug/biological/diet supplement trials and behavioral trials did not change over time but the number of device/procedure trials (which are mostly acupuncture trials) decreased and "other" trials (which are mostly reflexology/yoga/massage trials) increased from ≤2005 period to ≥2011 period. The number of trials sponsored by NIH or industry (as labelled) decreased while those sponsored by "Other" category (mostly consist of universities/academic centers) increased from ≤2005 period to ≥2011 period.

Discussion

In this analysis, we found that there are only few herbal/complementary treatment trials in patients with cancer registered in clinicaltrials.gov web site. The ratio of these trials to all cancer chemotherapy trials that have been registered in the same time point was 1.8%. The number of trials did not significantly change within 5-year periods from 2005 to 2015.

Cancer is the second leading cause of death after cardiovascular diseases. However, given the high mortality, morbidity, economical and emotional burden, it is probably the most fearsome disease for the patients. Patients with cancer frequently use herbal therapies with the intention to survive longer, or at least alleviate the pain and other sufferings. Furthermore, if you target "prevention of cancer" instead of "treatment of cancer", the number of potential consumers increases from millions to billions because cancer prevention using natural (and "naturally" harmless) plants and supplements is a very attractive offer for healthy individuals as well. One important motivation is seeking more than what modern medicine currently promises, which is not so satisfactory in terms of "cure", especially for advanced disease. High cost and fear of toxicity of conventional therapies, lack of adequate communication with the doctors, superstitions/religious beliefs are other reasons for using CAM.

Data on the comparative efficacy of these herbal compounds in specific cancers is limited. We also know little on whether the compound contains enough level of the active constituent we need, drug-herb interactions, toxicities etc. Herbal therapies are mostly used and advised in the treatment of complicated diseases with limited treatment options and low chance of cure. Had they been effective, such approaches would have been used more often for a more widespread and easy-to-treat symptoms instead of uncommon and difficult diseases, but the actual situation is the opposite. For a simple headache, you may (or may not) take an analgesic pill and it is mostly over, you don't need a natural herbal product for such an easily treatable condition with conventional medicine. However, if you have chronic persistent

headaches with no response to analgesics, herbal therapy is there. The same observation is valid for cancer patients, with higher rate of herbal use in the advanced settings [10,11].

The main obstacle for the acceptance of CAM by the medical community is the lack of robust scientific proof satisfying evidence-based medicine standards. As our study shows, physicians offering CAM, other non-medical CAM practitioners and CAM companies are not so interested in conducting or being involved in cancer research. Both the number and the quality of CAM research articles on cancer are far from what we expect from this huge client pool and market. In our study, we found that the number of registered trials did not increase proportional to the increase in sales from 2000 to 2010. Moreover, 6 % of the studies were sponsored by the industry while 40% was sponsored by NIH. The number of trials sponsored by the industry decreased over time while those sponsored by universities and academic centers (labelled as "other") increased (Table 2). This also shows the reluctance of the manufacturers for spending money on research for these products. Identification of all the components in the herbal product necessitates costly laboratory investment and success is not guaranteed. Although online scientific journal portals show hundreds of research papers on CAM, the quality of the studies is low and methodology is usually not appropriate. Most of the reviews and Cochrane analyses on CAM studies commented on the quality and methodology problems and the difficulty in drawing definitive conclusions from these studies [12,13]. Major criticisms include the lack of trials testing the same herbal medicine, lack of details on co-interventions, concomitant drugs and disease, unclear methods of randomization, poor reporting, high risk of bias and low number of participants [14]. In a recent review of controlled clinical studies published in Chinese, herbal medicine was the most frequently applied traditional Chinese medicine therapy (2677/2964 reports) The most frequently reported outcomes were clinical symptoms (56%), laboratory indices (43%), quality of life (38%), chemo/radiotherapy associated side effects (37%), tumor size (29%) and survival (15%). Among 2964 reports, only 5 relatively well designed RCTs showed positive findings, 2 with Traditional Chinese Medicine (TCM) alone and 3 with TCM plus conventional medicine [15].

Performing high quality trials with CAM products has some integral difficulties. Herbal treatment is made by prescribing formulae comprising various amounts of different herbs. A unified regimen is generally lacking. Even single products have batch to batch variations in chemical content. Studies on the quality of St John's wart preparations by high-performance liquid chromatography (HPLC) method showed hypericin content to be 47 to 165% of the label claim [16]. Another study showed that 26% of ginseng products did not meet the label claims of ginsenoside content [17]. Botanical quality is also affected by species differences, environment, cultivation methods, and adulteration with synthetic drugs, microbes, heavy metal and pesticide contamination, processing and manufacturing practices. This results in low quality and consistency of the products and low reproducibility [17]. Safety data including adverse reactions and drug-herb interactions is limited [18].

Legal and regulatory status is also not standard. In their comprehensive review on the legal and regulatory status of CAM in Europe, Wiesener et al. stated that the most striking finding across all 39 nations in EU was "the amazing difference in legislation and regulation in every single country" [19]. Seventeen nations had general CAM legislation, some countries had regulations on specific CAM treatments. CAM products are stipulated as food supplements in many countries and are not subjected to high quality control standards used for drug development. The distinction between food supplement and medicine is important and is determined by either the dose, the disease setting or just the intention to use. Dietary supplements contain dietary ingredients including vitamins, minerals, herbs, amino acids. They are used to supplement regular diet at physiological doses, with no claim to treat or prevent any diseases. As stated by the FDA, drugs are considered unsafe until proven safe, but dietary supplements are considered safe until proven unsafe. Treating diseases with food is an ancient method ("Let food be thy medicine", attributed to Hippocrates) and if something ancient is still present, some people put this forward as the evidence of efficacy, nullifying the need for further scientific research. Labeling the CAM products as food supplements gives manufacturers the opportunity to sell them with minimal regulation, so why would they allocate huge amount of money on research? Therefore, every country should implement regulations to prevent CAM manufacturers exploit this "legal gap".

In conclusion, current status of research on the use of CAM interventions in patients with

cancer is limited, both in terms of number of studies as well as the quality of research. In 1998, the National Institutes of Health set up the National Center for Complementary and Alternative medicine with the mission to "define, thorough rigorous scientific investigation, the usefulness and safety of CAM interventions and their roles in improving health care". Many other countries have launched homeopathic hospitals, undergraduate courses, MSc courses, post-graduate courses and compulsory curriculum of medical schools to increase CAM familiarization. Regulatory authorities should force providers to conduct laboratory and clinical trials to test the efficacy and toxicity of these products before licensing. The challenges of conducting CAM trials can be overcome with new technological advances for extraction and identification of putative active herbal components and adaptation of basic Good Clinical Practice principles. Good agricultural practice and good manufacturing practice standards should also be implemented by the herbal product industry to ensure safety and consistency. Until high quality scientific and clinical research establishes safety and efficacy of CAM practices, physicians should rigorously inform patients and the public on potential risks and caveats associated with CAM practices.

Conflict of interests

The authors declare no confict of interests.

References

1. https://nccih.nih.gov/health/integrative-health. Accessed in November 2016.
2. Smith T, Kawa K, Eckl V et al. Sales of Herbal Dietary Supplements in US Increased 7.5% in 2015 Consumers spent $6.92 billion on herbal supplements in 2015, marking the 12th consecutive year of growth. Am Botanic Council 2016: [VOL. NO?] 67-73.
3. Yabroff KR, Lund J, Kepka D et al. Economic burden of cancer in the United States: estimates, projections, and future research. Cancer Epidemiol Biomarkers Prev 2011;20:2006-2014.
4. WHO traditional medicine strategy 2002–2005. Geneva: WHO; 2002.
5. von Ammon K, Frei-Erb M, Cardini F et al. Complementary and alternative medicine provision in Europe--first results approaching reality in an unclear field of practices. Forsch Komplementmed 2012;19 (Suppl 2):37-43.
6. Johannessen H, von Bornemann Hjelmborg J et al. Prevalence in the use of complementary medicine among cancer patients in Tuscany, Italy. Tumori 2008;94:406-410.
7. Maskarinec G, Shumay DM, Kakai H et al. Ethnic differences in complementary and alternative medicine use among cancer patients. J Altern Complement Med 2000;6:531-538.
8. Laengler A, Spix C, Seifert G et al. Complementary and alternative treatment methods in children with cancer: A population-based retrospective survey on the prevalence of use in Germany. Eur J Cancer 2008;44:2233-2240.
9. Tuna S, Dizdar O, Calis M. The prevalence of usage of herbal medicines among cancer patients. J BUON 2013;18:1048-1051.
10. Mayadagli A, Aksu A, Goksel F et al. Determination of parameters affecting the use of complementary and alternative medicine in cancer patients and detection of prevalence of use. Afr J Tradit Complement Altern Med 2011;8:477-482.
11. Lam YC, Cheng CW, Peng H et al. Cancer patients' attitudes towards Chinese medicine: a Hong Kong survey. Chin Med 2009;4:25.
12. Ma LX, Ai P, Li H et al. The prophylactic use of Chinese herbal medicine for chemotherapy-induced leucopenia in oncology patients: a systematic review and meta-analysis of randomized clinical trials. Support Care Cancer 2015;23:561-579.
13. Guo Z, Jia X, Liu JP et al. Herbal medicines for advanced colorectal cancer. Cochrane Database Syst Rev 2012:CD004653.
14. Fung FY, Linn YC. Developing traditional chinese medicine in the era of evidence-based medicine: current evidences and challenges. Evid Based Complement Alternat Med 2015;2015:425037.
15. Liu J, Li X, Liu J et al. Traditional Chinese medicine in cancer care: a review of case reports published in Chinese literature. Forsch Komplementmed 2011;18:257-263.
16. de los Reyes GC, Koda RT. Determining hyperforin and hypericin content in eight brands of St. John's wort. Am J Health Syst Pharm 2002;59:545-547.
17. Fong HH. Integration of herbal medicine into modern medical practices: issues and prospects. Integr Cancer Ther 2002;1:287-293; discussion 293.
18. Alsanad SM, Williamson EM, Howard RL. Cancer patients at risk of herb/food supplement-drug interactions: a systematic review. Phytother Res 2014;28:1749-1755.
19. Wiesener S, Falkenberg T, Hegyi G et al. Legal status and regulation of complementary and alternative medicine in Europe. Forsch Komplementmed 2012;19 (Suppl 2):29-36.