中国临床肿瘤学教育专辑

(2002)

吴一龙 谷力加 王思愚 主编

中山大学出版社

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图书在版编目(CIP)数据

中国临床肿瘤学教育专辑 .2002/吴一龙,谷力加,王思愚主编.—广州:中山大学出版社,2002.6
ISBN 7-306-01941-4

Ⅰ.中…
Ⅱ.①吴… ②谷… ③王…
Ⅲ.肿瘤学-文集
Ⅳ.R73-53

中国版本图书馆 CIP 数据核字(2002)第 034858 号

中山大学出版社出版发行
(地址:广州市新港西路135号　邮编:510275
电话:020-84111998、84037215)
广东新华发行集团发行
新会市棠下中学印刷厂印刷
(地址:新会市棠下镇　邮编:529164　电话:0750-6522589)
787 毫米×1092 毫米　16 开本　20.5 印张　491 千字
2002 年 6 月第 1 版　2002 年 6 月第 1 次印刷
印数:1~3 500册　定价:50.00 元

主编： 吴一龙　谷力加　王思愚

编委：（按姓氏拼音排序）

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前　言

中国抗癌协会第六届临床肿瘤协作中心（CSCO）学术年会在美丽的羊城隆重召开，本次大会有两个鲜明的特点，一是美国临床肿瘤学会（ASCO）派出了阵容强大的代表团参会，众多国际上的知名专家如 ASCO 现任主席 Paul Bunn 教授、首席执行官 Chaeles Balch 教授、下任主席 Margaret Tempero 教授、东部肿瘤研究组（ECOG）部门主席 Rorbert Comis 教授和美国西南肿瘤研究组（SWOG）肺癌委员会主席 Gandara 教授、日本国立癌病中央医院院长兼胸外科上任 Tsuchiya 教授，还有国际上著名的肿瘤内科专家 Natale 和 Lynch 教授等共同加盟，无疑使这次会议具有了国际性。二是首次尝试了中国抗癌协会两个专业委员会联合举办学术会议的做法，使得 CSCO“团结、协作、务实”的口号有了更为深入的内涵。学术上临床肿瘤协作和肺癌单病种联合凸显了一般和特殊有机结合的特点。来自全国各地近千名肿瘤临床工作者、肿瘤学同道齐聚一堂，共同研讨新世纪防癌治癌大计。我们完全有理由相信，本次大会的圆满成功，必将达成肿瘤学某些研究领域的共识，有力地促进国内外肿瘤学研究的交流与合作，对我国的肿瘤学发展和肿瘤性疾病诊疗水平的提高起到积极的推动作用。

在本届大会即将召开之际，我们以循证医学基本思想为指导，特将来自国内外知名专家的 48 篇优秀论文编辑成《中国临床肿瘤学教育专辑（2002）》，力争从肿瘤学的各个领域全方位地为广大肿瘤学工作者提供学术参考，为研究、学习肿瘤学起到抛砖引玉的作用，为广大肿瘤学科研和临床工作者间的交流与合作起桥梁作用。

本专辑的内容涵盖了诊断、治疗、预后、分子生物学和基因工程等肿瘤学的各个领域，信息容量大，内容新颖，聚焦于肿瘤学特别是临床肿瘤学的最新发展动态，反映了当今肿瘤学的最新研究成果，既达成了某些共识，又产生了一些新的争鸣之处。这无疑是广大肿瘤学工作者脚踏实地挑战癌魔的智慧结晶，同时也集中体现了新世纪我国肿瘤学各个研究领域的强大活力。

21 世纪是生命科学的世纪，恶性肿瘤已成为人类健康的头号杀手。新世纪临床肿瘤学研究突出“从研究到临床（translation research to bedside）”和“循证肿瘤学”的特点。大量的基础研究特别是分子生物学的研究结果正逐渐转化为临床所应用的方法，新近出现的分子靶向治疗就是众望所期待的、不同于传统手术、放疗和化疗的恶性肿瘤的治疗方法。已有专家指出，靶向治疗有望使人类在攻克癌症的征途上向前跨出关键的一大步。循证肿瘤学重证据的思维方法，也将越来越深刻地影响着肿瘤学的临床研究，借此临床工作者能避免恶性肿

瘤的过渡治疗或治疗不足，使恶性肿瘤的治疗进入一个理性的阶段。CSCO 密切关注这些进展。我们相信，在党中央科教兴国战略方针的指引下，在我国卫生领导部门的统一部署下，在全社会的大力支持下，全国的肿瘤学工作者必将继续发扬团结一致的协作精神，再接再厉，全身心地投入到防癌抗癌的伟大事业中去，为人类最终战胜肿瘤做出更加积极的贡献！

本次学术年会由中山大学肺癌研究中心和中山大学附属第一医院共同承办，对于他们的艰辛工作特致以深深的谢意。由于时间较紧，错漏在所难免，也请读者见谅、指正。

孙燕　储大同　吴一龙

2002 年 6 月

目　录

CLINICAL TRIAL DESIGN: ENDPOINTS FOR CLINICAL TRIAL

Clinical Trials in Advanced Colorectal Cancer as a Paradigm for Clinical Trial Design Issues

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The views expressed herein do not necessarily reflect the views of the US Food and Drug Administration or the United States government.

The appropriate and valid selection of endpoints (outcomes) to measure in cancer trials is a point of ongoing debate. This lecture provides the definitions, advantages, and potential drawbacks of the major endpoints used in cancer trials. Factors in the design of a clinical trial include the patient population to be studied (e.g., metastatic setting versus adjuvant trial), the trial's purpose, the phase of the trial, the type of agent being studied, and the selection of a control arm. Traditional endpoints, such as survival, time-to-progression, disease-free survival, response rate, and palliation of symptoms will be discussed. Examples from recent clinical trials in advanced colorectal cancer will be used to illustrate these endpoints.

Survival

Survival is defined as the time from randomization to death. Analysis should include an intent-to-treat population with all randomized patients included. This is an unambiguous endpoint that is not subject to investigator interpretation or bias. Survival can be assessed daily. Survival trials usually require large sample sizes and longer follow-up periods than endpoints discussed below. Methodological debates continue as to the effect of cross-over therapy on survival. An example of the use of survival as an endpoint in clinical trial design is the clinical development of irinotecan (CPT-11) in the treatment of metastatic colorectal cancer.

Time – to – Progression (TTP)

TTP is defined as the time from randomization to the time progressive disease is documented. The TTP endpoint usually requires a smaller sample size than a survival endpoint and also has a shorter follow-up period. TTP will not be obscured by subsequent therapies prescribed at the time of progression. TTP may be suhject to assessor, physician, and investigator bias. This can be problematic in unblended trials. TTP is measured relatively infrequently compared to the continuous assessment of survival. The clinical significance of small changes in TTP may be of questionable value

To minimize bias, tbe assessment of TTP should be based on the date of last tumor evaluation. All patients on treatment arms should be evaluated on the same schedule and these evaluations should be on regular intervals. All disease sites should be measured at baseline and follow-up. The same type of assessment tool should be used at each follow-up.

A trial performed in advanced colorectal cancer using the agent, oxaliplatin, will be discussed to illustrate problems associated with TTP. In this trial, oxaliplatin plus 5-fluorouracil was compared to 5-fluoruracil plus leucovorin. Although the trial demonstrated a positive effect on TTP associated with the use of oxaliplatin, a survival advantage was not observed with this agent.

Time – to – Treatment Failure (TTF)

TTF is defined as the time from randomization to documentation of any of the following: progressive disease, death, withdrawal due to adverse events, lost to follow-up, patient refusal, and/or the initiation of new anti-tumor therapy. Because this endpoint is a composite of efficacy and toxicity determinations, confusion regarding efficacy conclusions can occur. In general, toxicity and efficacy determinations should be separate analytical endpoints. Therefore, TTF should be avoided as a primary study endpoint.

Response rate (RR)

RR is defined as a reduction of tumor size by a pre – specified determination. The prescribed treatment is "entirely" responsihle for the RR (tumor reduction.) In contrast, survival and TTP have an effect of the natural history of the disease PLUS treatment effect. The RR is comprised of partial responses and complete responses. Patients with stable disease are not included in RR since stable disease may reflect the disease's natural history rather than a treatment effect.

Single – agent Phase II trials of irinotecan in metastatic colorectal cancer will be discussed. These trials demonstrated response rates for irinotecan in a patient population refractory to 5 – fluorouracil. Subsequent randomized trials have confirmed a survival advantage associated with irinotecan compared to best supportive care. In this instance, RR was a surrogate for the subsequent demonstration of survival improvement.

Health – related Quality of Life (HRQOL)

HRQOL is defined as the extent to which one's usual or expected physical, emotional, and social well – being are affected by a medical condition or treatment. This endpoint is persuasive only in randomized, blinded trials. In the absence of blinding, a striking difference between treatment arms must be demonstrated. The major advantage of QOL studies is the patient's perspective on treatment is provided by the measurement. Missing data may make interpretation of HRQOL endpoints problematic. In addition, multiple endpoints and comparisons to baseline must be adjusted for in the statistical analysis plan. Blinding is frequently difficult in oncology trials due to differences in toxicities between treatment arms.

Disease – Free Survival (DFS)

DFS is defined as the time from randomization to the time of documented relapse. Disease – free survival is frequently used in adjuvant trials as an endpoint. In certain diseases (e.g., breast cancer) DFS may correlate with overall survival. This endpoint requires careful serial follow – up to detect recurrence and/or new primaries.

Palliation

Palliation of tumor – related symptoms in combination with response rate is a valid endpoint.

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APPLYING GCP GUIDELINE ON CLINICAL TRAILS OF TRADITIONAL CHINESE MEDICINE

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Introduction

Traditional Chinese medicine (TCM) is currently, de facto, an integral part of the health care system in China. The majority of the population uses TCM and western medicines interchangeably for health problems ranging from influenza to advanced malignant disease. The China Government has endorsed a dual system and therefore TCM accounts for around 40% (by cost) of all delivered health care[1]. Whilst western medicine is moving towards the application of evidence-based health care, there is less formal evidence for either the efficacy or safety of TCM. Many cancer patients, particularly patients with end stage disease, have utilized both western and TCM during course of their illness, but get confused about the validity of therapy. Western medicine is based on scientific principle and supported by evidenced-based clinical research. In short of scientific evidence, therapies are considered to be complementary and alternative medicine (CAM). The National Cancer Institute (NCI) has described CAM as a broad range of healing philosophies, approaches, and therapies that are used in addition to (complementary) or instead of (alternative) conventional medicine. The distinctions are clearly made to the patient and most are adequately informed of their choice. Cancer patients would understand the nature of conventional oncology therapies and accept that a therapy would have generally been studied extensively for safety and effectiveness through a rigorous scientific process. They would also accept that less is known about the safety and effectiveness of complementary and alternative methods. However, such distinctions are less clearly defined in China. There are conventional medicine hospitals that provide TCM service, and vice versa. Patients, while receiving conventional therapy, may wrongfully presume the TCM therapy to be evidence-based.

TCM is enjoying a "free – ride" with conventional western medicine in China. We earn patients' trust by rigorous clinical research to assure safety and efficacy and we devote time, money and effort to perform clinical trial for conventional treatment according to Good Clinical Practice Guideline (GCP)[2]. In order to practice a truly integrated dual system in China, we should encourage GCP standard clinical research on TCM. Many cancer patients found conventional can-

cer therapy expensive partly because of the high quality clinical research. In contrast, TCM may be cheaper simply because they did not allocate research funding to support the claims towards efficacy and safety. In order to optimize patients' benefit from both approaches, more clinical research done according to GCP is needed. Once the quality of research in TCM is being raised, we may find the cost between CHM and conventional medicine not to be as different as we thought.

The health care insurance industry is rapidly developing in China since the entrance to World Trade Organization. Medical services would have to be proven efficacious by scientific evidence for insurance coverage. Conventional medicine and TCM will compete for the same pool of funding in future. Thus, it will be important to define the efficacy of TCM by GCP standard clinical research[3]. In this article, we explore the philosophy behind GCP guideline and TCM, identify the fundamental differences and propose research methodology that may be adopted by serious clinical researcher on TCM.

Philosophy of TCM

Traditional Chinese Medicine (TCM) is an ancient multidisciplinary practice of disease prevention and healing. Around 3500 BC when Chinese civilization started to take shape herbal medicine was primarily practiced by tribal shaman. They believed that "Qi" is the "vital essence" of life that interacts and flows between humans and nature. As the Chinese civilization and language flourished in the Han dynasty, TCM was integrated into the Chinese culture. Drawn on the Taoist theory the body was viewed as a microcosm interacting continuously and closely with the universe. During this era the major chronicles, *Huang Di Nei Jing* (*The Internal Book of Huang Di*) *and Shen Nong Ben Cao Jing* (*The Pharmacopoeia of Shen Nong*), were composed. The principles of Yin and Yang and the Five Elements (water, wood, fire, earth, metal) have since been established as the foundation of TCM. Over the past centuries CHM has been developed into a comqlex system with these principles appearing in all disciplines of practice.

TCM is a practice of selecting a combination of herbal or natural items to reinstall the balance of yin and yang, and the five elements in a "diseased" body. Illness and symptoms are a manifestation of imbalance of the universal principles that are applicable to both humans and nature. Based on this theoretical framework the yin herb is used to counterbalance the yang illness, and vice versa. The medicinal herbs are classified by their four energies (hot, warm, cold, cool) and five flavors (hot, sweet, sour, bitter, salty). The four energies correspond to the yin and yang principles and five flavors to the five elements. The plants are also categorized as ascending-descending and elevating-suppressive. This refers to its movement of the Qi (energy) in the body: up and down, in and out. Seemingly the buman body is composed of four vital bodily humors, five solids and six hollow organs. Each of these organs is dominated by one or a combination of the five elements and classified as either a yin or yang organ. Thus the function of each organ, despite what its name may imply, does not always correspond to the anatomical structure in Western medicine. Diseases are attributed to a disturbance of the balance by external cosmological factors,

the six excesses (wind, cold, summer-heat, dampness, dryness, fire). The body reacts to the "six excesses" differently depending on the internal condition. A healthy body with strong Qi may prevent illness by its strong flow of blood and energy. In contrast a weakened body with exhausted Qi is susceptible to the six excesses. The role of the CHM is to strengthen the Qi and re-establish the balance.

The herbs are grouped according to its function. The *Ben Cao Gang Mu* (*General Outlines and Divisions of Herbal Medicine*), by Li Shizhen (1517 ~ 1593AD), is an enormous pharmacopoeia that lists 1892 types of medicinal items ranging from common herbs to exotic animal parts. Among these about three hundreds items are commonly used by the modern CHM practitioners. A prescription is usually composed of 10 to 15 types of herbs. There are 6 basic approaches in the application of herbs for treatment of diseases; perspiration method, neutralizer method, stimulation method, heat-clearing method, deflection method and tonic method. The knowledge on the function of a single herb or combination of herbs, which was usually past from one generation to the next, was based on years of experience through trial and error. Special formulations may be kept as a family secret for many generations. Its efficacy may have been claimed but never proven. The reason that it was not proven may not due to its lack of efficacy, but the major reason was because that clinical research methodology has not been fully developed until mid twentieth century in the West.

The practice of TCM has changed little over the centuries. The standard approach involves a TCM practitioner assessing the patient by seeing, smelling, questioning and examining (the four diagnostic methods). Similar to western medicine a diagnosis is made upon completion of assessment. A prescription of Chinese berbs is then written up, which is processed by herbalist who has expertise in recognizing and weighing the herbs. The standard method of administration is in the form of broth extract. The herb mixture is "cooked" with 3 to 4 bowls of water until over half of the liquid has evaporated. The broth (or tonic extract) is ingested in 2 to 3 portions over the day when the stomach is empty. Tbis cumbersome procedure usually takes hours of slow boiling and the smell may be offensive. Other methods of administration in form of pills, dan, gum and medicinal wine are also popular.

Philosophy of GCP guideline

Careful design, good quality control and reproducibility are the foundations of credible clinical research. The rules of Good Clinical Practice (GCP) have been formulated to assure patient safety and creditability of clinical trial[2]. At the International Conference of Harmonization in 1996 the European Union, Japan and United States accepted GCP as the standard guideline for their regulatory authorities. Although the GCP was developed with conventional medicine in mind, its objectives and principles can also be applied to TCM:

1. Clinical research in TCM should be conducted in accordance with all relevant ethical guidelines, consistent with the principles described in the Declaration of Helsinki;

2. A clinical trial in TCM should be initiated if benefits justify the risks;

3. The rights, safety and well-being of the trial participants should prevail over interest of science and society;

4. The available non-clinical and clinical information on an investigational product or intervention should be adequate to support the proposed study;

5. A scientifically sound, clear and detailed protocol should be developed;

6. The study should be conducted in compliance with the protocol that has received prior approval from the Ethics Committee;

7. The clinical care given to participants should be the responsibility of a qualified and registered practitioner;

8. All individuals involved in conducting the study should be qualified by training, education, and experience to perform his or her respective tasks. This includes the TCM practitioners who should be certified in an accredited institution for CHM training;

9. Written informed consent should be obtained from every participant;

10. All study information should be recorded, handled, and stored in a way that allows accurate reporting, interpretation and verification. For safety reason, timely reporting of adverse event is also important;

11. The confidentiality and privacy of records that could identify participants should be protected;

12. Investigatioual products should be manufactured, handled and stored in accordance with Good Manufacturing Practice (GMP) or equivalent standards. Quality control of herbs should also be implemented in the study;

13. System with procedures that ensure the quality of every aspect of the study should be implemented.

Fundamental problems

Western medicine is founded on a structured concept and fixed quantification, while TCM is based on Taoist theory that emphasizes the continuous fluctuation of the natural cosmic energy. To many TCM practitioners it would be senseless to explain how TCM works using the western concepts of anatomy and medicine since five thousand years of history to millions of people has established its merits. Researcher must overcome the fundamental philosophical differences between western and Chinese medicine in order to conduct GCP-standard research on TCM. Science is found on observation from experiments with controlled variables. Clinical study on efficacy is structured on the impact of a specific therapy on clinical outcomes of a group of patients with homogenous illness. In contrast, herbal concoctions are usually variable from patient to patient and from time to time. If researchers specify treatment to a single concoction for all patients, the essence of TCM will not be fully utilized.

Treatment endpoints for western medicine and TCM are different. The objective of TCM is

to re-install the balance of Yin and Yang and with such improve the well being of patient. A positive outcome can be highly subjective to patients 'feeling and healers' interpretation of symptoms and signs. While in western medicine, the defined endpoints of tumor response and survival are highly objective. To select and capture specific endpoints that are important to hoth western and Chinese medicine has proven to be difficult.

TCM is not a standardized therapy. Quality of botanical product depends on the origin of plantation and soil quality. In short of formal agricultural cultivation it will be impossible to assure quality of the plant. Also there are the issues with storage, contamination and processing, the standard of which would not be amendable or acceptable for scientific study. Assuming the berbs to be grown and processed in a standardized manner, method of preparation may still be highly variable. In other words researchers will have difficulty to standardize the quality of prescribed herbal therapy for clinical trial.

The ultimate test for TCM is a double blind randomized placebo-controlled trial because placebo effect may play a significant role in subjective improvement that is frequently claimed by patients. However, placebo herbs do not practically exist. All substances, plants and animal products alike, carry either a therapeutic or toxic value to the body. Beside it would be impossible to blind either the healer or patient from the therapy options as most of the plants carry a distinct smell, color and taste.

Compliance problem is not unique to TCM clinical research but researchers may expect a high level of non-compliance. Unless the researchers provide both western and Chinese medicine within the same institutes the patient may likely seek medical attention from various sources. It is a routine practice to document all concurrent medications used by study subjects but it will not be feasible if the study subject is receiving care from another herbalists.

GCP standard research methodology for TCM clinical trial

Recent publications from Western countries have confirmed that it is possible to conduct TCM clinical research according to GCP guidelines[4,5]. Bensoussan et al conducted a randomized double-hlinded study on the benefit of TCM in irritable bowel syndrome. Patients in the treatment arm received individualized formulations of Chinese herbal medicine dispansed in a gelatin capsule. The placebo was designed to taste, smell and look similar to the active treatment. TCM was shown to improve symptoms for some patients. Limited by a small sample size (78 patients only) the study results are not definitive. However, their methodology offered the first evidence that conducting high quality clinical research on TCM, according to internationally agreed standards, was practicable.

A common drug discovery process usually begins at the basic research level for the development of drugs target to a specific disease mechanism. Pre-clinical data are needed before an Investigational New Drug Application can be made. Phase I trials for determining safety and dosage of the drug and phase II trials for determining anti-tumor activity are usually needed before a larger

phase III randomized trial is being planned. However, TCM development is considered a special case for the following reasons:

1. The roots of TCM span over 2, 500 years, the system has been established and is stable among the Chinese herbalists. Although it continues to evolve as new techniques, theories, and substances are incorporated, the basic method and prescriptions are well established.

2. Unlike conventional medicine, TCM focuses on patterns of disease rather tban cause and effect. TCM doctors treat patients according to the chief complaint and discrimination of patterns of symptoms associated with imbalance in the body system.

3. A new drug for western medicine is usually a well define molecule while TCM is more a practice than a molecular drug. The phase I and II trials design is specific for development of a molecule but not necessarily applicable when multiple herbs are involved in routine TCM practice.

4. Herbs are rarely prescribed individually because a symptom pattern requires formulas of multiple herbs. Each herb plays a specific role in order to obtain a balance to treat various obstruction or stagnation in the body system and would consist of adding or subtracting TCM constituents according to the patient's actual condition.

In order to overcome the common problems and produce GCP standard clinical research, there must be compromises between the two schools of philosophy. However, tbe essence and ethics of both practices must be maintained. The following suggestion will help to develop a mutual acceptable guideline for development of CHM researches:

1. Research should be conducted on the practice of TCM and not just on the herbs or combination thereof. Since TCM is not a practice of one drug for one disease/

2. Phase I and II studies for determination of safety and dosage may not be necessary before conduct of randomized trials in most circumstances. The knowledge of adverse effects of herbs has been past from one generation to the next and according to the first principle a fixed dosage is not warranted. However, patients' safety is being closely monitored in a well conducted clinical trial setting.

3. The basic principle of study design, data management, monitoring and analysis (according to Good Clinical Practice Guidelines) for a randomized study must be closely followed to sustain the scientific merit of study.

4. Randomized phase III study should be double－blind as much as possible to avoid assessment bias. TCM carries a mythical appeal to most patients, which may potentate the placebo effect.

5. The blinding process sbould be designed carefully with properly prepared placebo herb or combination of herbs that have similar look, smell and taste. In order to standardize and control the quality of treatment and placebo herb must be prepared as extract form (granules or capsules) centrally, and dispensed in quantified portions.

6. In TCM, where all natural substances are potentially therapeutic, researcher may face tbe problem of defining placebo substance (s). We propose that the placebo substance (s) should be