

Understanding the Business Value of Flexible Studies for Traditional Chinese Medicine Trials in China



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Multilingual Focus Group

Session 17



Acknowledgements

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- Many thanks to the OHSUG Planning and Review Committee and OHSUG Multilingual Focus Group Chairs for their infinite patience in receiving and expeditious review of this presentation.
- Many thanks to everyone who participated in the development of presentation.



Assumptions/Scope/Disclaimer

- Assumptions: Audience has a basic understanding of RDC 4.6 OnSite and Multi-Arm study design and Crossover Study Design
- Scope: RDC 4.6.



Basic Chinese medicine theory

- According to Chinese medicine theory, a syndrome is a group of associated signs and symptoms described in terms of Yin and Yang, *Qi*, and *Xue* (blood)
- Acupuncture is also based on Chinese medicine, where nerves located at specific points in the human body can represent places where “Qi” can circulate and enter/leave the body.
 - These points are also associated with specific herbal treatments, or Traditional Chinese Medicines are used to re-balance Qi and Xue
- Chinese medicine has always regarded cancer as several different diseases rather than a single disease.
 - In some cases, Western physicians are beginning to recognize this as well (e.g. Andrew Weil, M.D.)



High-Level Background of Traditional Chinese Medicine.

- TCMs or Traditional Chinese Medicines are any kind of medical treatments which are known historically in China, but are generally classified as “alternative medicine” in conventional (sometimes called “Western”) medical terms.
 - Can include Acupuncture, Moxibution, Chinese Massage, Qigong
 - Purposes of this discussion are around Chinese Herbal Medicines
- Chinese medicine remains popular in China where traditional herbal preparations are estimated to account for 30–50% of the total medicinal consumption.



High-Level Background of TCMs: Use and Controversy in US

- Chinese medicine has also been gaining popularity in the West.
 - Mostly marketed as dietary supplements; not as strictly regulated by FDA in US.
- Also questions about safety and proper use of TCMs
 - Ephedra, Ginseng. Note that US FDA ban on Ephedra specifically excludes TCM preparations of Ephedra.
 - <http://www.quackwatch.com>
- Historically, there has not been a large amount of funding for TCM double-blind trials to prove efficacy. This leads to some controversy over the use and usefulness of TCMs.
- Also controversy over use of endangered animals in the preparation of TCMs.
 - This practice is not legal in China and most of the world, but still occurs illegally.



High-Level Background of TCMs: Alternative Medicines

- However, some “alternative medicine” theories do support a correlation between the use of TCMs when used in conjunction with conventional medical treatments.
 - According to Dr. Andrew Weil: “[A common denominator among those HIV-infected individuals who never get AIDS is] the commonest thing is the use of Chinese herbal medicines.... Specifically Chinese. Not necessarily one thing, but a variety of Chinese herbal therapies that are believed to enhance immunity. ... Of the people that I've seen who have done very well, a common theme is that they've used TCM -- especially combinations of Chinese herbs.”
 - http://findarticles.com/p/articles/mi_m0ISW/is_2002_April/ai_84211120/
 - Andrew Weil, MD, on Chinese Medicine for HIV & AIDS - Interview with Andrew Weil
 - Townsend Letter for Doctors and Patients, April, 2002 by Lily G. Casura



High Level Background of TCMs: Commercially developed Drugs

- According to wikipedia: Chinese wormwood (qinghao) was the source for the discovery of Artemisinin, which is now used worldwide to treat multi-drug resistant strains of falciparum malaria, and is also under investigation as an anti-cancer agent.
- From this, Novartis was developed Coartem, first registered in 1998, which contains artemether and lumefantrine. The Active Ingredient Arthemether was developed by the The Shanghai Institute of Materia Medica, a subsidiary of the Chinese Academy of Sciences.
- **REFERENCE:** <http://www.knowledgeatwharton.com.cn/index.cfm?fa=viewfeature&articleid=1802&languageid=1>



High Level Background TCMs: Commercially developed “Botanical” Drugs (2)

- In 2004, US FDA published “Guidance for Industry for Botanical Drugs”, which is an herbal medicine that has been successfully modernized and has a clear pharmacokinetic profile.
 - Significant because this allowed Botanical Drugs to contain MORE THAN ONE Active Ingredient. This means the ingredients could be extracted as a whole, and not individually isolated and tested.
- In 2006, MediGene, a German biotech firm, obtained US FDA approval for Veregen, a botanical drug that is extracted from green tea leaves for genital wart treatment. This proved it was possible to get Botanical (multi AI) herbal drugs approved and commercially marketed in the US.
- **REFERENCE:** <http://www.knowledgeatwharton.com.cn/index.cfm?fa=viewfeature&articleid=1802&languageid=1>



High Level Background TCMs: Commercially developed “Botanical” Drugs (3)

- Hutchison MediPharm has 2 drugs based on TCMs:
 - HMPL-004 for the treatment of Crohn's disease and Ulcerative Colitis, expected 2011 in US
 - HMPL-002, a treatment for head and neck cancer, expected 2013 in US
- Tasley Pharmaceutical has 1 drug based on TCMs:
 - Compound Danshen Dripping Pill, (CDDP), Derived from Danshen (the dried root of *Salvia miltiorrhiza*) and two other plant ingredients for cardiovascular diseases.
 - Danshen is a TCM which has been used in China for increased blood circulation and relieving chest pain.
- **REFERENCE:** <http://www.knowledgeatwharton.com.cn/index.cfm?fa=viewfeature&articleid=1802&languageid=1>



High-Level Background: Chinese government Funding in TCM

- Lot of focus/funding on promoting the TCM study recently.
- Created great opportunities in Clinical DM market in China.



Challenge of evaluating efficacy of TCMs in standard clinical trial designs

- Chinese medicine practitioners prescribe herbal medications to rectify disharmony in a patient's system.
 - This means prescribing something to increase something positive in the human body, not necessarily to offset a specific symptom or disease
- A study of 19 different Ginseng trials with both positive and negative efficacy results shows that the clinical trials did not consider Qi-deficiency or Qi-tonic (increase) as a factor of the actual trial result.
 - Possible these are EXPECTED results of Ginseng, but not necessarily positive results from a clinical trial perspective.
- REFERENCE: Study designs of randomized controlled trials not based on Chinese medicine theory are improper 25 February 2009; *Chinese Medicine* 2009, 4:3 [doi:10.1186/1749-8546-4-3](https://doi.org/10.1186/1749-8546-4-3)
- <http://www.cmjournal.org/content/4/1/3>



Challenge of evaluating efficacy of TCMs in standard clinical trial designs

- This is a different approach than identifying a specific compound/AI, administering a precise dose, then measuring a direct effect on a specified lab test measurement, checking for AEs and performing patient Follow-up for some specified time after.
 - Dr. Weil: “Traditional Chinese Medicine is all about expelling evil and supporting good. Modern western medicine is mainly about expelling evil. I think my role as an integrative oncologist is to support the good as well as expelling the evil.”
 - <http://www.drweil.com/drw/u/ART03060/Treating-Cancer-With-Integrative-Medicine.html>
- Possibly, the efficacy of TCMs in clinical trials could be evaluated more accurately if the Qi and Xue conditions of the patients could be considered in the trial conditions or randomizations themselves (group together like Qi and Xue patients and then apply treatments, for example).



Multi-Arm Crossover Trial Designs which may be useful for TCMs: Dosing for Botanical Medicines

- Given the number of different factors driving TCM-based research, Crossover trial designs could be useful (beyond pure Longitudinal Designs) in the following scenarios:
- 1) Conventional Clinical Trials to identify dosing levels for Botanical Medicines based on direct extract of TCM core ingredients:
 - These are the conventional trials being performed today for the commercial drugs based on TCMs already sited.
 - Multi-Arm crossover could allow patients to increase dosing in different arms in the same study depending on whether or not there is an directed measured improvement
 - Example: reduction of tumor sizes with increased dosing over time with HMPL-002



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 - Multi-Arm crossover could allow patients to increase dosing in different arms in the same study depending on whether or not there is an directed measured improvement
 - Example: reduction of tumor sizes with increased dosing over time with HMPL-002 without significant AEs



Multi-Arm Crossover Trial Designs which may be useful for TCMs: Oncology Trials

- 2) Oncology based trials where symptoms of chemotherapy are treated by TCMs
 - Crossover from ARM with conventional treatment to TCM treatment, where conventional treatment is not effective (or reversed)
 - Crossover to combination treatment where one treatment is not effective
- 3) Oncology based trials where TCMs are used as potential combination therapy with conventional treatments
 - Crossover from ARM with only conventional treatment where there is not a significant reduction in tumor size to combination treatment with TCMs.



Multi-Arm Crossover Trial Designs which may be useful for TCMs: Comparison of TCMs to each other

- 4) In considering the cases with Qi and Xue both have to managed at the same time, combinations of TCMs need to be studied together
 - Crossover one TCM which treats Qi conditions with another that treats Xue conditions, for patients which exhibit BOTH symptoms midstream in a trial.



Crossover Scenarios Possible in OC/RDC 4.6

- Include screenshots with DCI Book Rules for each of the 4 scenarios described in the previous slides



Are Oncology Trials with TCMs Happening Already in 2010

- Yes. See ASCO (American Society of Clinical Oncology). From 2010 Conference (famous conference for Biotech/Pharma where new therapies are introduced, also watched very closely by industry/financial analysts)
 - Scenario 2: Study on external Chinese herbal medicine LC09 treating hand-foot skin reaction associated with the multitargeted kinase inhibitors.
 - Scenario 3: A prospective, randomized, controlled, multicenter trial of Chinese herbs by stages combined with chemotherapy for advanced non-small cell lung cancer.
 - Scenario 4: Effects of Chinese herbal medicine on cytochrome P450, a systematic review.

Phase II randomized study of compound Chinese herbal extract LC09 for external treatment of hand-foot syndrome induced by anticancer therapy.

Sub-category:

Quality of Life Mgmt

Category:

Patient and Survivor Care

Meeting:

2010 ASCO Annual Meeting

Session Type and Session Title:

Trials in Progress Poster Session, Trials in Progress Poster Session

Abstract No:

TPS322

Citation:

J Clin Oncol 28:15s, 2010 (suppl; abstr TPS322)

Author(s):

L. Jia; Department of TCM Oncology, China-Japan Friendship Hospital, Beijing, China

Abstract:

Background: Hand-foot syndrome (HFS) and hand-foot skin reaction (HFSR) induced by anticancer therapy can impact quality of life (QoL) and may lead to dose modification or treatment interruption, even when the therapy may prove beneficial. The earlier-phase data of compound Chinese herbal medicine LC07 on treating capecitabine-induced HFS in metastatic breast cancer has shown significant effective. LC09 is an advanced Chinese herbal extract based on LC07. The objective of this clinical trial is to evaluate the efficacy and safety of LC09 external treatment on HFS/HFSR. The research is funded by the Ministry of Science and Technology of China (No. 2008BAI53B023), and designed by the China-Japan Friendship Hospital. Trial start date is 20 Aug 2009, and the completion date is 20 Dec 2011 (estimated). **Methods:** Entry Criteria: Diagnosis of cancer, with HFS/HFSR grade ≥ 1 (NCI-CTCAE version 3.0) after anticancer therapy, including chemotherapy and molecular targeted therapy. Age: 18 to 85. Able to participate in study procedures and QoL evaluations. No history of hand and foot skin diseases. No concurrent other treatment for HFS/HFSR. Expected Enrollment: 204 pts. Outline: This is a phase II, double-blind, randomized, multicenter study. Patients are randomized to 1 of 2 treatment arms. Patients soak their hands and feet in the Chinese herbal extract LC09 lotion (Arm I) or placebo lotion (Arm II) for 20 minutes, twice daily for 7 days. Anticancer treatment continues until the end of therapy in the absence of disease progression or unacceptable toxicity. Physical examination, NCI grade of HFS/HFSR, NRS scale of pain and Skindex-16 (a dermatologic QoL patient reported questionnaire) are assessed at baseline, and at 1 week. Patients also complete a daily diary to document side effects and medication compliance. After completion of study therapy, patients are followed at 3 weeks.

- http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abstract_detail_view&confID=74&abstractID=50651

01 A prospective, randomized, controlled, multicenter trial of Chinese herbs by stages combined with chemotherapy for advanced non-small cell lung cancer.

Sub-category:

Metastatic

Category:

Lung Cancer - Metastatic

Meeting:

2010 ASCO Annual Meeting

Session Type and Session Title:

This abstract will not be presented at the 2010 ASCO Annual Meeting but has been published in conjunction with the meeting.

Abstract No:

e18000

Citation:

J Clin Oncol 28, 2010 (suppl; abstr e18000)

Author(s):

Z. Xu, C. Jin, Z. Wang, H. Deng, D. Shen, M. Zhang, M. Li, J. Wang, Z. Zheng, Y. Gong; Department of Oncology, Longhua Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai, China; Department of Integrated Chinese and Western Medicine, Thoracic Hospital, Jiaotong University, Shanghai, China; Department of Thoracic Surgery, Longhua Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai, China; Department of Oncology, Traditional Chinese Medicine Hospital, Shanghai, China; Traditional Chinese Medicine Cancer Institute, Shanghai University of Traditional Chinese Medicine, Shanghai, China

Abstract:

Background: Chemotherapy plays an important role in the treatment of advanced non-small cell lung cancer (NSCLC), but the overall survival (OS) and the median survival time (MST) are not satisfactory. Chinese herbs (CH) is a popular treatment for NSCLC in china. Our purpose was to observe the efficacy of CH by stages combined with chemotherapy versus chemotherapy alone for NSCLC (stage III/IV). **Methods:** A prospective, randomized, controlled, multicenter, clinical trial was conducted on 115 patients assigned to treatment group (60) and control group (55). The control group was treated by chemotherapy (cisplatin and gemcitabine [GP]/cisplatin and vinorelbine [NP]) alone, while the treatment group was treated by chemotherapy (GP/NP) combined with CH and was administered Kangliuzengxiao decoction (KLZX) during chemotherapy course and Feiyanning decoction (FYN) maintenance after chemotherapy. End points were OS, MST, response rate, toxicity, and Karnofsky score. **Results:** MST was 14.47 months (95% confidence interval, 10.37 to 18.57) in treatment group compared with 10.97 months (95% confidence interval, 9.35 to 12.59) in control group ($p = 0.001$). 1 year, 2 years, 3 years, 5 years survival rates in treatment group were 54.8%, 24.6%, 13.2%, 5.7%, compared to control group 35.6%, 3.7%, 0%, 0% ($p = 0.001$). The response rates (CR+PR) were 28.3% (treatment group) and 18.2% (control group), there was no statistically significant difference in response rate between the two groups. The toxicities mainly were gastrointestinal dysfunction and myelosuppression of different degrees. Remission rate of nausea/vomiting symptoms was high after patients treated with CH in treatment group ($p < 0.05$), myelosuppression was more significant in control group than in treatment group ($p < 0.05$). Karnofsky score of treatment group was higher than that of control group ($p < 0.01$) ($p < 0.01$).

Conclusions: In this trial, chinese herbs by stages combined with chemotherapy could prolong the MST and OS, still improve Karnofsky score, while the toxicity was not enhanced. Chinese herbal medicine was a promising maintenance treatment for advanced NSCLC.

- http://www.asco.org/ASCOv2/Meeting/Abstracts?&vmview=abstract_detail_view&confID=74&abstractID=48493



Sub-category:

Pharmacology/Pharmacokinetics

Category:

Developmental Therapeutics - Clinical Pharmacology and Immunotherapy

Meeting:

2010 ASCO Annual Meeting

Session Type and Session Title:

This abstract will not be presented at the 2010 ASCO Annual Meeting but has been published in conjunction with the meeting.

Abstract No:

e13150

Citation:

J Clin Oncol 28, 2010 (suppl); abstr e13150

Author(s):

S. Bhowmik, W. Lu, D. S. Rosenthal; The George Washington University School of Medicine and Health Sciences, Washington, DC; Osher Research Center, Dana-Farber Cancer Institute/Harvard Medical School, Boston, MA; Dana-Farber Cancer Institute/Harvard Medical School, Boston, MA

Abstract:

Background: Interactions of cytochrome P450 (CYP), especially CYP3A4, between chemotherapy agents and other xenobiotics can cause potential adverse effects during cancer treatment. Furthermore, Chinese herbal medicine (CHM) has been increasingly used by cancer patients during chemotherapy. The purpose of this study is to systematically examine available literature on the effects of CHM on CYP3A4. **Methods:** Relevant research articles published prior to May 31, 2009 in PubMed and The Natural Medicines Comprehensive Database were searched using the MeSH terms "Cytochrome P-450 CYP3A", "Drugs, Chinese Herbal", and "Medicine, East Asian Traditional", and CHM names obtained from "Chinese Herbal Medicine: Materia Medica", a widely used CHM textbook. Articles in non-English languages and herbs infrequently used in practice were excluded upon review. Full texts were obtained for further analysis and effects on CYP450 of each studied herb were evaluated.

Results: Of the 483 herbs/herbal mixtures searched, 47 (10%) have been studied for their interactions with CYP450 in 42 research articles, consisting of 30 in vitro and 25 in vivo tests in all. Among these herbs, 38 (81%), 10 (21%), and 15 (32%) exhibited inhibition, induction, and no effect on CYP450, respectively. Ten herbs (Ginkgo biloba, Pueraria lobata, Saposhnikovia divaricata, Citrus aurantium fruit, Curcuma longa, Panax ginseng, Glycyrrhiza uralensis, Glycyrrhiza glabra, Evodia rutaecarpa, Schisandra chinensis) and 2 mixtures (PC-SPES and Shoseiryuto) showed conflicting results with CYP450. Among the 26 herbs and mixtures studied with CYP3A4, 15 (58%), 5 (19%), and 8 (31%) exhibited inhibition, induction, and no effect, respectively. Three herbs (Ginkgo biloba, Evodia rutaecarpa, Schisandra chinensis) showed conflicting results with CYP3A4.

Conclusions: Chinese herbs and their mixtures may alter functions of CYP450, and the majority of studied herbs show a potential inhibitory effect on CYP3A4. Future studies are needed to further understand the impact of using CHM on the safety of patients undergoing chemotherapy.

- http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abstract_detail_view&confID=74&abstractID=41500



Conclusion

- Tremendous interest in TCMs, from conventional medicine, alternative medicine, Botanical medicine commercial development and China-based internal studies are driving new and more sophisticated clinical trials around TCMs.
- OC/RDC 4.6 has the ability to handle multi-arm crossover scenarios which will become increasingly more relevant to TCM trials, especially their Oncology-related indications.
- Advanced clinical research IS happening with TCMs.
- Enabling RDC Interface in Simplified and Traditional Chinese (as demonstrated in Session S15 by DBMS Consulting) will also increase and facilitate these types of trials.



Question and Answers

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Biographies

Sunil G. Singh, President & CEO, DBMS Consulting, Inc.

- Sunil is a Global Oracle Health Sciences deployment expert for DBMS Consulting. He has been an active member of the OHSUG community since 1996 and is extremely grateful for this opportunity to make these presentations at OHSUG 2010.

Dr. Letian Liu, VP DBMS APAC, DBMS Consulting, Inc.

- Dr. Liu has recently moved back after 16 years in the US to Shanghai, to head the Asia Pacific operations for DBMS Consulting. Dr. Liu brings in 20 years of experience with clinical trials and data-management, Pharmaceutical R&D and applied chemistry.
- Prior to joining DBMS Consulting, Dr. Liu was technical lead for Oracle Clinical/ePower with Covance, and Senior Architect for Oracle Clinical/TMS/RDC/ePower/AERS/IRReview at Ingenix(i3); and as research scientist at REVLON. Dr. Lucy Liu holds a Ph.D. in Analytical Chemistry from The City University of New York, a BS degree in Engineering from Zhejiang University in China.