DEVELOPMENT OF AN ONCOLOGY DATABASE FOR DRUG INTERACTIONS OF ANTI-CANCER DRUGS WITH COMPLEMENTARY AND ALTERNATIVE MEDICINE

Kuo En Yi[1], Lee Jun Jie Jonathan[1], Yap Yi-Lwern Kevin[2], Chan Alexandre[2]
[1]Science Research Programme, Hwa Chong Institution, 661 Bukit Timah Road, Singapore 269734
[2]Department of Pharmacy, Faculty of Science, National University of Singapore,
Block S4, 18 Science Drive 4, Singapore 117543

SCIENCE RESEARCH PROGRAMME 2008/09

Introduction

Cancer is a prevalent health problem with increasing incidences worldwide.[1] Many cancer patients consume complementary and alternative medicines (CAMs) in addition to their cancer therapy for treatment, prevention, or supportive care therapy.[2,3] Cancer patients are at high risk of suffering from anti-cancer drug (ACD)-CAM interactions due to the narrow therapeutic indices of the ACDs. This can lead to sub-therapeutic effects or increased toxicities which may compromise the efficacy and safety of their chemotherapy treatments.[4] Thus, it is important for clinicians to have quick access to information regarding ACD-CAM interactions so that they can make better informed decisions in clinical practice. Clinicians currently use a variety of resources for information on ACD interactions. However, these sources have limited information on ACD-CAM interactions. This project aims to engineer a comprehensive oncology database that documents ACD-CAM interactions. This database will provide clinicians with a user-friendly interface and easy access to ACD-CAM interaction information.

Materials and Methods

Drug information regarding ACDs and CAMs was collated from 11 sources (Figure 1).[5-15] CAMs were classified into 8 categories based on their indications in cancer therapy: (a) cancer treatment or prevention, (b) immune system-related, (c) alopecia, (d) nausea and vomiting, (e) peripheral neuropathy and analgesics, (f) anti-inflammatory, (g) fatigue syndrome and (h) non-cancer related. A database engine with a programming interface was constructed using a combination of softwares and programming scripts. The graphical user interface was created with various web elements such as forms, drop down menus and lists.

Figure 1. Flowchart showing the creation process of the oncology database

Compilation of ACDs and CAMs
- Sources: Chinese Material Medica, Aetna Intelihealth, TCM Assistant, Memorial Sloan-Kettering, Micromedex, Natural Medicines Comprehensive Database, Drugs.com, Caremark, DoubleCheckMD, British National Formulary and Drug Information Handbook
- Exclusion criteria: Alternative therapies, commercial supplements
- Classification of CAMs based on indications in cancer therapy

ACD- and CAM-related Information
- Names of ACDs and CAMs
- Mechanisms of action and pharmacokinetic data
- CAM characteristics based on TCM principles

ACD-CAM Interaction Information
- Interaction effects and severities
- Substantiating evidences
- Proposed management plans

Creation of database engine and web documents
- Softwares: Adobe Dreamweaver CS4, XAMPP (*v2.5*), Filezilla (*v3.2.0*), SQL Manager 2007 for MySQL (*v4.4*)
- Programming scripts: HTML, XHTML, PHP, javascripts, MySQL

Uploading into web server
- Designed in tabular format with forms, drop down menus and lists
- Graphics and content inserted into cells

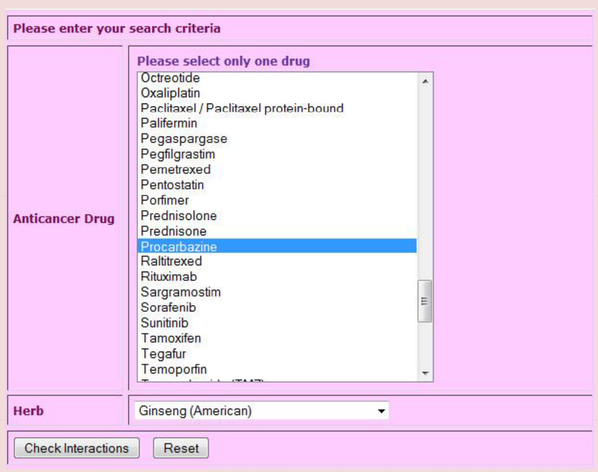
Results and Discussion

Classes of CAMs	No. of CAMs in each class	No. of interacting CAMs	No. of interactions
Cancer treatment and prevention	65	17	339
Immune system-related	17	7	145
Alopecia	3	0	0
Nausea and vomiting	1	0	0
Peripheral neuropathy and analgesics	14	4	103
Anti-inflammatory	39	9	247
Fatigue syndrome	5	4	64
Non-cancer related	67	11	354

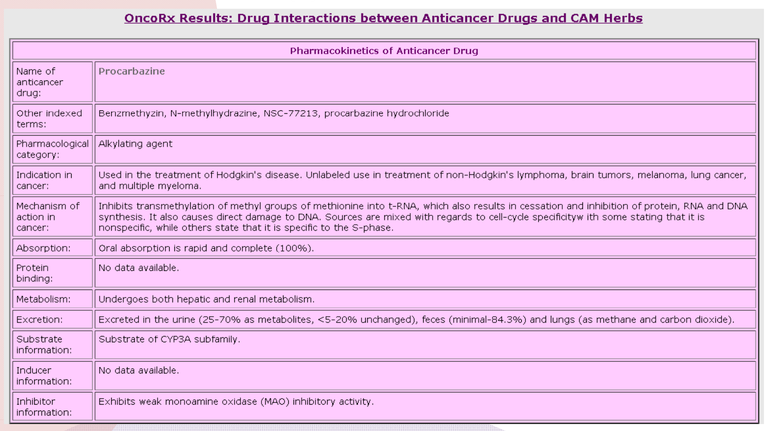
Table 1. Summary of CAMs and ACD-CAM interactions

Figure 2. Interaction search between procarbazine and American ginseng

(a) Graphical user interface of the search engine



(b) Search results



OncoRx Results: Drug Interactions between Anticancer Drugs and CAM Herbs

Pharmacokinetics of Anticancer Drug

Name of anticancer drug:	Procarbazine
Other indexed terms:	Benzmethyzin, N-methylhydrazine, NSC-77213, procarbazine hydrochloride
Pharmacological category:	Alkylating agent
Indication in cancer:	Used in the treatment of Hodgkin's disease. Unlabeled use in treatment of non-Hodgkin's lymphoma, brain tumors, melanoma, lung cancer, and multiple myeloma.
Mechanism of action in cancer:	Inhibits transmethylation of methyl groups of methionine into t-RNA, which also results in cessation and inhibition of protein, RNA and DNA synthesis. It also causes direct damage to DNA. Sources are mixed with regards to cell-cycle specificityw ith some stating that it is nonspecific, while others state that it is specific to the S-phase.
Absorption:	Oral absorption is rapid and complete (100%).
Protein binding:	No data available.
Metabolism:	Undergoes both hepatic and renal metabolism.
Excretion:	Excreted in the urine (25-70% as metabolites, <5-20% unchanged), feces (minimal-84.3%) and lungs (as methane and carbon dioxide).
Substrate information:	Substrate of CYP3A subfamily.
Inducer information:	No data available.
Inhibitor information:	Exhibits weak monoamine oxidase (MAO) inhibitory activity.

(i) Pharmacokinetic information of ACD

Characteristics of Herb

Name of herb:	Ginseng (American)
Scientific name(s):	Panax quinquefolius
Other common names:	Xi yang shen, western ginseng, five-fingers, hua qi shen
Main constituents:	Saponin glycosides (panaquilon, ginsenosides)
Flavors and properties according to TCM practice:	Flavor: Sweet, slightly bitter Property: Data not available
Herb indication in cancer:	Cancer prevention, cancer treatment, immunostimulation Mode of action: Exact mechanism of action unknown. Ginsenoside Rg1 is associated with improvements in humoral and cell-mediated immune response in mice. Anticancer activity has been shown in vitro for several ginsenosides
Metabolism:	Data not available
Elimination:	All ginsenosides are primarily eliminated unchanged in the urine. Elimination half-lives range from 20-500 minutes
Substrate information:	Data not available
Inducer information:	Data not available
Inhibitor information:	Data not available
Herb data references:	[1] Chen SE, et al. American ginseng. III. Pharmacokinetics of ginsenosides in the rabbit. Eur J Drug Metab Pharmacokinet 1980;5(3):161-8. [PMID: 7202434] [2] Ginseng (American). Memorial Sloan-Kettering Cancer Center. URL: http://www.mskcc.org/mskcc/html/69236.cfm. Accessed 07 Aug 2008. [More details] [3] Shin HR, et al. The cancer-preventive potential of Panax ginseng: a review of human and experimental evidence. Cancer Causes Control 2000;11(6):565-76. [PMID: 10880039]
Adverse drug reactions:	No significant reactions reported
Adverse drug reaction references:	[1] Ginseng (American). Memorial Sloan-Kettering Cancer Center. URL: http://www.mskcc.org/mskcc/html/69236.cfm. Accessed 07 Aug 2008. [More details]

(ii) CAM characteristics

Detected Herb-Drug Interaction

Interaction:	**Effect:** American ginseng may interfere with MAOI therapy. **Level of significance:** Moderate [Natural Medicines] **Summary:** With concommitant phenelzine and unspecified ginseng use, there is one case report of insomnia, headache and tremors; and another of hypomania.
Proposed management (if applicable):	Therapy involving the concommitant use of procarbazine and American ginseng should be avoided.
References:	[1] Shader RI, Greenblatt DJ. Phenelzine and the dream machine--ramblings and reflections. J Clin Psychopharmacol 1985;5:65. [2] Jones BD, Runikis AM. Interaction of ginseng with phenelzine. J Clin Psychopharmacol 1987;7:201-2.

(iii) Details of detected interaction

A total of 117 ACDs and 166 CAMs are included in the database. The database can detect up to 943 interactions, of which majority are predominantly pharmacokinetic in nature. Among CAMs used for cancer related purposes (Table 1), those indicated for cancer treatment and prevention are the most (39%), followed by those indicated for anti-inflammation (24%). CAMs in these categories also exhibit the highest proportion of drug interactions (27% and 20% respectively). CAMs indicated for nausea and vomiting, and alopecia have the least number of CAMs and they do not have any interactions with ACDs.

Users are able to search for interactions based on the CAM indications in cancer therapy. Search results consist of information regarding the ACDs, CAMs and detected drug interactions (Figure 2). ACD- and CAM-related information include their names, mechanisms of actions, and pharmacokinetic properties. In addition, characteristics based on traditional Chinese medicinal (TCM) principles are also included for CAMs. Details of the drug interaction, such as interaction effects, severities, substantiating evidences and proposed management plans, are also shown to users.

Conclusion

A computerized oncology database for drug interactions has been created. This database provides users with easy access to drug interaction information between ACDs and CAMs. Users are able to refine their searches based on various CAM indications in cancer therapy. This database is intended to complement the resources that are currently available for clinicians in the oncology setting, so as to provide better patient care in their practice.

References

1. American Cancer Society. Global Cancer Facts and Figures 2007. Available from http://www.cancer.org/downloads/STT/Global_Facts_and_Figures_2007_rev2.pdf. Accessed 11 December 2008.
2. Boon HS, Olatunde F, Zick SM. Trends in complementary/alternative medicine use by breast cancer survivors: comparing survey data from 1998 and 2005. *BMC Women's Health* [serial online] 2007;**7**:4. Available from http://www.biomedcentral.com/1472-6874/7/4.
3. Bressler R. Herb-drug interactions: interactions between kava and prescription medications. *Geriatrics* 2005;**60(9):**24-25.
4. Miller LG. Herbal medicinals: selected clinical considerations focusing on known or potential drug-herb interactions. *Archives of Internal Medicine* 1998;**158(20):**2200-2211.
5. Chang H-M, But PP-H, Yao S-C, Wang L-L, Yeung SC-S. Pharmacology and applications of Chinese materia medica. Singapore: World Scientific Publishing Co., 2001.
6. Aetna InteliHealth Inc. Index of herbal medicines and supplements. Available from http://www.intelihealth.com/IH/ihtIH/WSIHW000/8513/31402.html. Accessed 11 December 2008.
7. e-MS Inc. TCM Assistant. Available from https://www.tcmassistant.com/index.html. Accessed 11 December 2008.
8. Louis V. Gerstner J. Memorial Sloan-Kettering Cancer Center - cancer information. Available from http://www.mskcc.org/mskcc/html/58481.cfm. Accessed 11 December 2008.
9. Thomson Healthcare. Micromedex® Healthcare Series [internet database]. Available from http://www.micromedex.com. Accessed 10 December 2008.
10. Jellin JM, Gregory PJ. Natural Medicines Comprehensive Database. 10th ed. Stockton, CA: Therapeutic Research Faculty, 2007.
11. Drugsite Trust. Drugs.com™: drug information online. Available from http://www.drugs.com. Accessed 11 December 2008.
12. Gold Standard Inc. Caremark Drug Interactions. Available from http://cpref.gsm.com/inter.asp?r=8084. Accessed 11 December 2008.
13. Enhanced Medical Decisions Inc. DoublecheckMD.com™. Available from http://www.doublecheckmd.com. Accessed 11 December 2008.
14. British Medical Association, Pharmaceutical Society of Great Britain. British National Formulary. 53rd ed. London, UK: BMJ Publishing Group Ltd & RPS Publishing, 2007.
15. Lacy CF, Armstrong LL, Goldman MP, Lance LL. Drug Information Handbook with International Trade Names Index. 15th ed. Hudson, OH: Lexi-comp, 2007-2008.