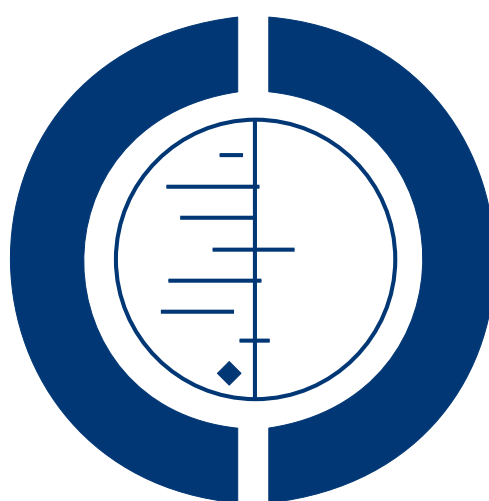


# Chemotherapy with Camptothecin compounds for metastatic colorectal cancer (Protocol)

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## TABLE OF CONTENTS

HEADER . . . . .	1
ABSTRACT . . . . .	1
BACKGROUND . . . . .	2
OBJECTIVES . . . . .	2
METHODS . . . . .	2
ACKNOWLEDGEMENTS . . . . .	5
REFERENCES . . . . .	5
WHAT'S NEW . . . . .	6
HISTORY . . . . .	7
CONTRIBUTIONS OF AUTHORS . . . . .	7
DECLARATIONS OF INTEREST . . . . .	7
SOURCES OF SUPPORT . . . . .	7

[Intervention Protocol]

# Chemotherapy with Camptothecin compounds for metastatic colorectal cancer

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## ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

1. To assess the effectiveness of adding one camptothecin compounds to other chemotherapy agents in the first line and second line treatment of metastatic colorectal cancer.
2. To assess the effectiveness of individual camptothecin compounds compared with each other (e.g. irinotecan, topotecan and homo-camptothecin).
3. To assess the effectiveness of different formulations, dose, route of administration and schedule of the same type of camptothecin compounds.

## BACKGROUND

Every year, more than 945,000 people will develop colorectal cancer (CRC) worldwide, and around 492,000 patients die (Weitz 2005). Nowadays, CRC has become the third most common cancer and the fourth most frequent cause of cancer death worldwide (Weitz 2005). Moreover, CRC is the fifth leading malignancy in China, and the morbidity produced by this disease is significant. Distant metastases are present in 15% of patients at the time of diagnosis (Cai 2006). Approximately 50% of patients will die of locally advanced or metastatic CRC, despite greater than 60% of them presenting with potentially curable disease (ACS 2002).

The treatment of patients with metastatic CRC has changed dramatically over the last 20 years. 5-Fluorouracil (5FU)-based therapies have been routinely included in treatment regimens for metastatic colorectal cancer for the past 40 years (Christopoulou 2004). The effectiveness of 5-FU-based chemotherapy has been relatively modest with on average an increase of 3.7 months in median survival compared to best supportive care (Best 2002).

In the mid-1990s the results had been improving following the increased availability of new drugs. The camptothecin compounds, which became available as new cytotoxic drugs in the mid-1990s, can inhibit topoisomerase I, thus impeding DNA uncoiling leading to double-stranded DNA breaks. The camptothecin compounds, such as irinotecan, topotecan and homocamptothecin, have been used in clinical practise in a number of cancers (Pizzolato 2003).

Irinotecan is one of the camptothecin compounds which have proven activity in 5FU refractory patients with metastatic CRC. A number of studies have shown that the patients with metastatic CRC can benefit from irinotecan as monotherapy (Hoeffken 1999, Pazdur 1997) or in combination with 5FU/ folinic acid (Seitz 1998, Rougier 2002) in second line treatment settings. In patients with metastatic CRC in whom 5FU had failed, those treated with irinotecan had a longer survival, fewer tumour-related symptoms, and a better quality of life than those managed with supportive care alone (Cunningham 1998). As a result irinotecan has been investigated as a first line treatment for metastatic CRC in combination with folinic acid in phase II (Maiello 2000) and phase III (Douillard 2000, Saltz 2000) trials. At the same time oxaliplatin combination regimens have emerged as another treatment option for patients with metastatic CRC (Goldberg 2004).

A large number of studies of the chemotherapy of camptothecin compounds for metastatic CRC have been published; some showing significant clinical benefits (Cunningham 1998, Douillard 2000, Saltz 2000, Köhne 2005).

Up to now there has been no Cochrane systematic review in this field. In this review, we hope to evaluate the effectiveness of camptothecin compounds and to collate the best evidence for the usage of camptothecins as single agents and in combination chemotherapy regimens in patients with metastatic CRC.

## OBJECTIVES

1. To assess the effectiveness of adding one camptothecin compounds to other chemotherapy agents in the first line and second line treatment of metastatic colorectal cancer.
2. To assess the effectiveness of individual camptothecin compounds compared with each other (e.g. irinotecan, topotecan and homocamptothecin).
3. To assess the effectiveness of different formulations, dose, route of administration and schedule of the same type of camptothecin compounds.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

Only randomized controlled trials will be included.

#### Types of participants

Patients with histologically proven metastatic and/or locally advanced colorectal cancer of any age or sex will be included. Patients with histology other than adenocarcinoma will not be included.

#### Types of interventions

We will include:

1. A single agent camptothecin compound chemotherapy or a camptothecin compound in combination with non-camptothecin compound based chemotherapy.
2. Comparison of different camptothecin compounds compared with each other (Irinotecan, Topotecan and homocamptothecin).
3. Comparison of different formulations, dosage, route and schedule of the same type of camptothecin compounds.

Additional interventions will be permitted provided they are common to both groups of the study.

#### Types of outcome measures

Primary: overall survival, progression-free survival

Secondary: complete and partial response rates (WHO 1979), quality of life, treatment toxicity (acute and late) and costs.

### Search methods for identification of studies

See: methods used in reviews.

A comprehensive and exhaustive search strategy will be formulated in an attempt to identify all relevant studies regardless of language or publication status (published, unpublished, in press, and in progress).

This review will draw on the search strategy developed for the Cochrane Colorectal Cancer Group as a whole. Relevant trials will be identified from:

## 1. Electronic databases

We will identify relevant trials from:

the Cochrane Colorectal Cancer Group Specialized Register, and the Cochrane Central Register of Controlled Clinical Trials (CENTRAL) in The Cochrane Library (latest update); MEDLINE (from 1966 to 2008), and EMBASE (from 1966 to 2008); Chinese Biomedical Database (from 1976 to 2008).

We will use the following search strategies, developed with help of Cochrane Colorectal Cancer Group, to search The Cochrane Library, EMBASE and MEDLINE, respectively, and adapt these search for use on other databases

### The Cochrane Central Register of Controlled Trials:

#1 (colorectal neoplasm) or (colorectal tumor) or (colorectal adenoma) or (colorectal cancer) or (colorectal carcinoma) or (colorectal disease) or (colorectal polyps) or (colonic) or (sigmoid neoplasms) or (adenomatous polyposis coli) or (hereditary nonpolyposis) or (rectal neoplasms) or (anus neoplasms)

#2 (camptothecin) or (CPT) or (Topotecan) or (Irinotecan) or (CPT-11) or (hCPT) or (homocamptothecin):ti

#3 (#1 AND #2)

### EMBASE (Webspirs 5.1, Silver Platter version 2.0)

#1 (colorectal neoplasm) or (colorectal tumor) or (colorectal adenoma) or (colorectal cancer) or (colorectal carcinoma) or (colorectal disease) or (colorectal polyps) or (colonic) or (sigmoid neoplasms) or (adenomatous polyposis coli) or (hereditary nonpolyposis) or (rectal neoplasms) or (anus neoplasms)

#2 (explode "colorectal-tumor" / all SUBHEADINGS in DEM,DER,DRM,DRR) or (explode "colorectal-adenoma" / all SUBHEADINGS in DEM,DER,DRM,DRR) or (explode "colorectal-cancer" / all SUBHEADINGS in DEM,DER,DRM,DRR) or (explode "colorectal-carcinoma" / all SUBHEADINGS in DEM,DER,DRM,DRR) or (explode "colorectal-disease" / all SUBHEADINGS in DEM,DER,DRM,DRR)

#3 (explode "rectum-adenoma" / all SUBHEADINGS in DEM,DER,DRM,DRR) or (explode "colon-polyposis" / all SUBHEADINGS in DEM,DER,DRM,DRR)

#4 (explode "anus-cancer" / all SUBHEADINGS in DEM,DER,DRM,DRR) or (explode "anus-carcinoma" / all SUBHEADINGS in DEM,DER,DRM,DRR)

#5 #1 or #2 or #3 or #4

#6 #5 not animal

#7 ((camptothecin) or (CPT) or (Topotecan) or (Irinotecan) or (CPT-11) or (hCPT) or (homocamptothecin)) in TI

#8 #7 not animal

#9 #6 and #8

#10 "RANDOMIZED-CONTROLLED-TRIAL"/ all subheadings

#11 "RANDOMIZATION"/ all subheadings

#12 "CONTROLLED-STUDY"/ all subheadings

#13 "MULTICENTER-STUDY"/ all subheadings

#14 "PHASE-3-CLINICAL-TRIAL"/ all subheadings

#15 "PHASE-4-CLINICAL-TRIAL"/ all subheadings

#16 "DOUBLE-BLIND-PROCEDURE"/ all subheadings

#17 "SINGLE-BLIND-PROCEDURE"/ all subheadings

#18 #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17

#19 (RANDOM\* or CROSS?OVER\* or FACTORIAL\* or PLACEBO\* or VOLUNTEER\*) in TI,AB

#20 (SINGL\* or DOUBL\* or TREBL\* or TRIPL\*) near ((BLIND\* or MASK\*) in TI,AB)

#21 #18 or #19 or #20

#22 HUMAN in DER

#23 (ANIMAL or NONHUMAN) in DER

#24 #22 and #23

#25 #23 not #24

#26 #21 not #25

#27 #9 and #26

### Medline (Webspirs 5.1, Silver Platter version 2.0)

#1 (colorectal neoplasm) or (colorectal tumor) or (colorectal adenoma) or (colorectal cancer) or (colorectal carcinoma) or (colorectal disease) or (colorectal polyps) or (colonic) or (sigmoid neoplasms) or (adenomatous polyposis coli) or (hereditary nonpolyposis) or (rectal neoplasms) or (anus neoplasms)

#2 explode "Colorectal-Neoplasms" / all SUBHEADINGS in MIME,MJME,PT

#3 #1 or #2

#4 #3 not animal

#5 ((camptothecin) or (CPT) or (Topotecan) or (Irinotecan) or (CPT-11) or (hCPT) or (homocamptothecin)) in TI

#6 #5 not animal

#7 #4 and #6

#8 clinical-trial in pt

#9 randomized in AB

#10 placebo in AB

#11 (clinical trials) in MESH

#12 randomly in AB

#13 trial in TI

#14 #8 or #9 or #10 or #11 or #12 or #13

#15 (animals) in MESH

#16 (humans) in MESH

#17 #15 not (#15 and #16)

#18 #14 not #17

#19 #7 and #18

### 2. Ongoing trials

We will also search the trial registers for ongoing trials:

Current Controlled Trials ([www.controlled-trials.com](http://www.controlled-trials.com)) The National Research Register

([www.update-software.com/National/nrr-frame.html](http://www.update-software.com/National/nrr-frame.html)) Clinical Trials ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)) Chinese Clinical Trial Register

([www.chictr.org](http://www.chictr.org)) The ISRCTN Register (<http://isrctn.org>) Australian Clinical Trial Registry (<http://www.actr.org.au/>) WHO IC-TRP Search Portal

### 3. Handsearches

We will handsearch the following Chinese medical journals: National medical journal of China; Chinese Journal of Surgery; Chinese Journal of General Surgery. References of identified studies will be searched to identify additional pertinent trials.

#### 4. Conferences

We will also search databases of conferences:

- (1) Gateway (<http://gateway.nlm.nih.gov/gw/Command>)
- (2) Psychinfo (<http://www.apa.org/psychinfo>)
- (3) BioMed Central  
(<http://www.biomedcentral.com/browse/abstracts>)
- (4) Medscape's Conference  
(<http://www.medscape.com/conferencedirectory>)
- (5) Gray Literature

We will also search gray literature in:

- (1) Centers for Disease Control (<http://www.cdc.gov>)
- (2) Health Canada (<http://hc-sc.gc.ca>)

#### 5. Adverse effects

A search for studies of side effects will be carried out and contact will be made with various adverse reaction reporting bodies. We will report any serious side effects from excluded studies and summarize them qualitatively in the discussion.

## Data collection and analysis

### Trials selection

Beibei Cui (CBB) and Yalun Li (YYL) will scrutinize the results of the search strategy for potentially relevant trials, and retrieve the full articles for all potentially relevant trials. CBB and YYL will independently assess each of these trials for inclusion in the review using an eligibility form based on the contents of the section 'Criteria for considering studies'. We will contact the original authors to retrieve the missing data. We will resolve any disagreements by discussion, with referral to a third reviewer Donghao Lv (LDH) if necessary. We will exclude studies that do not meet the inclusion criteria and state the reason in the 'Characteristics of excluded studies' table.

### Quality assessment of trials

Huan Song (SH) and Fan He (HF) will assess methodological quality of each trial in terms of generation of allocation sequence, allocation concealment, blinding, and loss to follow up. For each trial, we will classify each quality components as 'adequate', 'inadequate', or 'unclear' according to the guidelines of Cochrane Handbook 4.2.6 (Higgins 2006), and described by Wu 2007. The methods and performance both on generation of allocation sequence and allocation concealment, if the eligible studies from china, will be confirmed by telephone. We will display this information in an additional table and describe it in the section 'Methodological quality of included studies'. After including all eligible studies in the primary analysis, we aim to conduct sensitivity analyses for each of the quality factors using the subgroups adequate, inadequate, or unclear.

### Data extraction

LDH and SH will independently extract data using a piloted data extraction form. We will extract data on study characteristics including methods, participants, interventions, and outcomes. We will resolve any disagreements by referring to a third reviewer, Taixiang Wu (WTX), or the trial report and through discussion, or by consulting the Cochrane Colorectal Cancer Group. If data from the trial reports are insufficient or missing, we will contact the authors for additional information.

Where possible we will extract data to allow an intention-to-treat analysis (the analysis should include all the participants in the groups to which they were originally randomly assigned). If the number randomised and the numbers analysed are inconsistent, the percentage loss-to-follow-up will be calculated and reported in an additional table. For binary outcomes, we will record the number of participants experiencing the event in each group of the trial. For continuous outcomes, for each group we will extract the arithmetic means and standard deviations. If the data are reported using geometric means we will extract standard deviations on the log scale. Medians and ranges will be extracted and reported in tables.

### Data analysis

Review Manager (Version 4.1) will be used to analyze the data. We expect both event (dichotomous) data and continuous data. Different comparisons will be analysed separately. Risk ratios (RR) with 95% confidence intervals (CI) and control events rates will be used for reporting dichotomous data. We will calculate the number needed to treat (NNT) or the number needed to harm (NNH) for each remedy if a statistical significant difference appeared between two groups (Wu 2007b). Continuous data will be expressed as weighted mean differences (WMD) with 95% CI. In the case of outcome of continuous data with different scales, we will use standardised mean difference (SMD) with 95% CI. Pooled results will be estimated using random effect models (DerSimonin and Laird model). Tests for homogeneity will be carried out using Chi-square test with significance being set at  $p > 0.1$  and I-square will be used to estimate total variation across studies that is due to heterogeneity in percentage,  $<25\%$  is considered as low level heterogeneity, 25% to 50% as moderate level, and higher than 50% as high level (Higgins 2003). If moderate levels of heterogeneity ( $I^2 > 50\%$ ) are seen for the primary outcomes, we will explore possible sources of heterogeneity using sensitivity and subgroup analyses as described below. Potential publication bias will be assessed using the funnel plot or other corrective analytical methods depending on the number of included studies (Egger 1997).

### Subgroup analysis

We intend to explore the following potential sources of heterogeneity using subgroup analyses or meta-regression. Subgroup analyses may be based on the following:

- (1) Different interventions in treatment and control groups between studies;
- (2) Stages of patients at baseline;
- (3) Different formulations, dosage, route or schedule of camp-

tothecin compounds;

(3) Different lengths of follow-up;

(4) Age.

Sensitivity analyses:

We will explore reasons for heterogeneity in studies and, if necessary, use sensitivity analyses to examine the effects of excluding study subgroups, for example, those studies with lower methodological quality.

Clinical relevance tables

Clinical relevance tables will be compiled under additional tables to improve the readability of the review. For dichotomous outcomes, the number needed to treat will be calculated from the control group event rate and the relative risk (or odds ratio for beneficial events) using the Visual Rx NNT calculator (Cates 2003). Continuous outcome tables will also be presented under additional tables. Absolute benefit will be calculated as the improvement in the intervention group minus the improvement in the control group, in the original units. Relative difference in the change from baseline will be calculated as the absolute benefit divided by the baseline mean of the control group.

Non-randomised controlled studies will be listed but not discussed further. Studies relating to adverse effects will be described qualitatively.

## ACKNOWLEDGEMENTS

We thank Dr. Henning Keinke Andersen, and Cochrane Colorectal Cancer Group editorial board, for their comments on writing the protocol. And thank Dr. Karin Nielsen, Trial Search Co-ordinator, Cochrane Colorectal Cancer Group, for her help on development of search strategy.

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\* Indicates the major publication for the study

## WHAT'S NEW

Last assessed as up-to-date: 8 October 2008.

2 September 2008	Amended	1. Embellish the part of background; 2. Some minor changes on references; 3. Add non-first line therapy into objectives.
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## HISTORY

Protocol first published: Issue 1, 2009

20 December 2007	New citation required and major changes	Substantive amendment
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## CONTRIBUTIONS OF AUTHORS

All of the authors contributed to the development of the protocol.

## DECLARATIONS OF INTEREST

None Known.

## SOURCES OF SUPPORT

### Internal sources

- Dep. of Anal-Colorectal Surgery, West China Hospital, SCU, China.  
Expertise for suggestion and development.

### External sources

- No sources of support supplied