出國報告（出國類別：進修）

進階癌症藥物研發臨床研究員訓練

服務機關：國立台灣大學醫學院附設醫院腫瘤醫學部

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出國期間：98 年 12 月 15 日至 100 年 11 月 15 日

報告日期：100 年 12 月 27 日

單位主管核章：

摘要:

這是出國進修主要的目的就是學習癌症藥物的研發。學習主要分為三個面相: 第一期臨床試驗的設計與執行、藥物動力學與藥物基因學對於藥物發展的影響、臨床試驗的設計與資料分析的統計學。第一期臨床試驗的學習包括了門診見習，計畫書的設計與修改，計畫送審與審查，受試者收案與試驗執行的審核(audit)。藥物動力學與基因學的部分包括了見習試驗檢體分析並參與討論，小動物影像實驗室觀摩，參與研究所藥物動力學小組課程並於期末提出研究計畫的報告。試驗的設計與資料分析的部分包括與癌症中心的統計師合作設計試驗與分析試驗資料，參與研究所統計課程並於期末提出研究報告。此外，這次進修中擬定了一個雙邊的合作研究，目前正在推動。

目次:

本文:

目的:

這是出國進修主要的目的就是學習癌症藥物的研發。台大醫院腫瘤部成立十多年來，臨床研究逐漸在亞洲的醫學中心展露頭角，在不少重要的跨國臨床試驗中扮演主導的角色。為了深化本院在癌症藥物研發的根基，本部近年來積極的發展早期臨床試驗。威斯康辛州立大學綜合癌症中心與本部甚至是台灣的腫瘤醫學發展的淵源很深，二十多年前威斯康辛大學癌症中心執行長卡本教授造訪亞洲許多新興國家，協助成立癌症中心，台大醫院腫瘤部即是其中之一。數年前卡本教授過世之後，為了紀念他，癌症中心改名為卡本癌症中心。威斯康辛卡本癌症中心是美國國家癌症中心底下主要的六家協和臨床研究中心，而現任的執行長 Dr. Wilding 是卡本教授的得意門生，在癌症藥物的產業界有很高的名望，所以卡本癌症中心擁有豐富的臨床研究資源，尤其是第一期臨床試驗中心更是資源的主要支配者。此外，癌症中心的背後有一家全美排名前十的綜合大學強力的支援。因此，學習早期臨床試驗，卡本癌症中心是首選之一。

過程:

1. 參與臨床試驗計畫的設計，受試者同意書的編寫，倫理委員會的送審。

Topic：**A Phase I Study of ABT-888 in Combination with Oxaliplatin and Capecitabine in Advanced Solid Tumors** （合併使用 **ABT-888, oxaliplatin** 和 **capecitabine** 治療嚴重固態惡性腫瘤的第一期臨床試驗）

試驗的內容蓋要：

This is a phase I dose escalation study of ABT-888 in combination with fixed-dose capecitabine and oxaliplatin. Patients will be treated with ABT-888 orally twice daily for 7 consecutive days every 2 weeks. Capecitabine will be administered orally once daily for 7 consecutive days every two weeks, and oxaliplatin will be given intravenously once every two weeks. Cycle length is 28 days.

Patients are eligible for this trial if they have the following malignancies: any BRCA-mutated malignancy, first or second line metastatic colorectal cancer, metastatic mucinous ovarian cancer, and any other gastrointestinal malignancy where oxaliplatin has been shown to have activity.

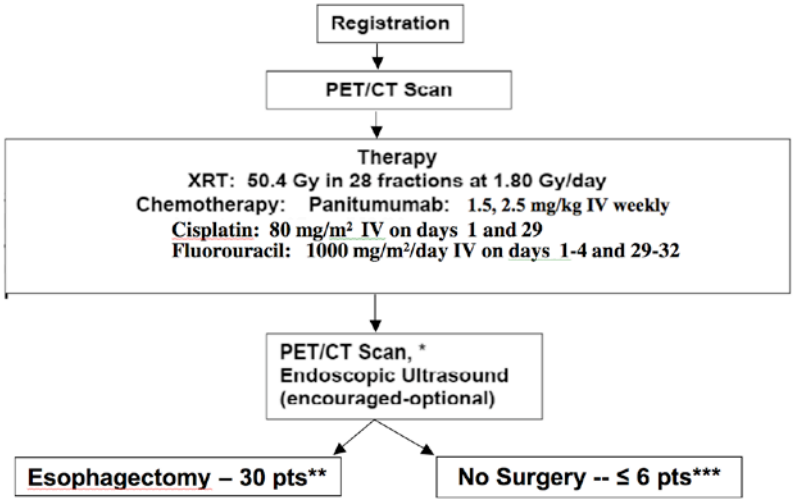
The dose of ABT-888 will be escalated using a 3-patient cohort design based on first cycle toxicities until dose limiting toxicities (DLT) and maximum tolerated dose (MTD) are defined. We will reserve one position at each dosing level for patients with known BRCA mutations. Should this position not fill within two weeks of cohort opening, it will be opened to other eligible patients.

說明: 這個試驗是用一種新機轉的藥物，抑制用於修復受損 DNA 的酵素 PARP，合併一種常用的化療處方（CAPOX），治療對象包括適用 CAPOX 的癌症種類，例如：大腸直腸癌，卵巢癌，胃癌，胰臟癌等，以及有 BRCA 突變的癌症。試驗的設計使用傳統的 3+3 模式，試驗的主要目的是決定 ABT-888 在此試驗的主要毒性以及最高可以忍受劑量。次要目的包括了療效，藥物動力學等。

Current status:
The dose of ABT-888 failed to escalate because of DLT of myelosuppression.
Discussion is ongoing about whether to have a dose level between level 1 and 2.

Topic: A PHASE I/II STUDY OF PANITUMUMAB/CISPLATIN/FLUOROURACIL COMBINED WITH RADIATION PREOPERATIVELY FOR PATIENTS WITH LOCALLY ADVANCED ESOPHAGEAL CANCER. (合併使用 panitumumab, cisplatin, fluorouracil 與放射線治療於局部嚴重性食道癌術前治療的第一，二期臨床試驗)

試驗的內容蓋要：



說明：本試驗主要是要測試食道癌術前 CCRT 使用 panitumumab, cisplatin, 和 5-FU 的可行性，同時決定 panitumumab 比較適合的劑量。此外，此試驗的目的也包括治療的效果與正子掃描用於預測療效的可行性。

Current status:

The dose of panitumumab failed to escalate because of DLT of mucositis. The discussion is ongoing about the amendment of the protocol to restart enroll patients.

Topic:

A Phase I Pharmacokinetic Study of Belinostat for Solid Tumors and Lymphoma in Patients with Varying Degrees of Hepatic Dysfunction (針對肝功能不全的惡性固態腫瘤與淋巴瘤患者做的 belinostat 第一期藥物動力學臨床試驗)

試驗內容概要:

Background:

Belinostat is a histone deacetylase (HDAC) inhibitor. HDACs are frequently deregulated in cancer cells, leading to an increase in deacetylation and the silencing of genes that normally control cell cycle arrest and apoptosis. Belinostat has growth inhibitory activity in several malignancies in vitro and in vivo, both as a single agent and in combination with chemotherapeutic agents. Several Phase I and II clinical trials have been conducted to date

in patients with solid tumor and hematologic malignancies; belinostat has been generally well tolerated.
Belinostat is metabolized in the liver and therefore, the safety and dosing of belinostat needs to be established in patients with varying degrees of hepatic dysfunction.

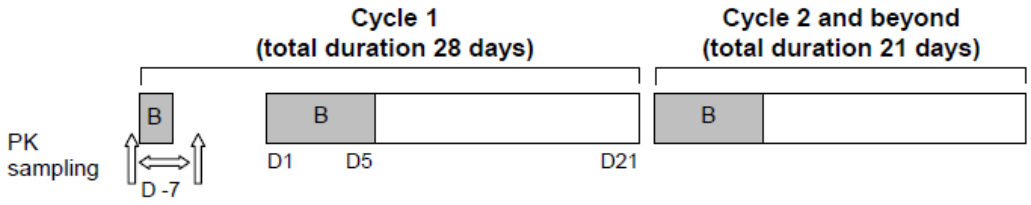
Objectives:
Establish the safety and tolerability of belinostat given on days 1 - 5 of 21-day cycles to patients with varying degrees of liver dysfunction.
Define the maximum tolerated dose (MTD) and recommended dose of belinostat given on days 1 - 5 of 21-day cycles to patients with varying degrees of liver dysfunction.
Evaluate the pharmacokinetics (PK) of one dose of belinostat (400 mg/m2) in patients with varying degrees of liver dysfunction
Obtain preliminary evidence of anti-tumor activity at tolerable doses of belinostat in patients with varying degrees of liver dysfunction.
Determine polymorphisms in the UGT1A1*28 allele and correlate these with the observed toxicities and the PK of belinostat in patients with varying degrees of liver dysfunction.
Measure direct versus indirect bilirubin levels and correlate these with observed toxicities, PK, and UGT1A1 polymorphisms.

Eligibility:
• Adults with histologically confirmed solid tumors or lymphomas whose disease has progressed after standard therapy or who have no acceptable standard treatment options. Patients with normal and varying degrees of hepatic dysfunction (mild, moderate, and severe) are eligible.

Study Design:
Patients will be divided into 4 cohorts based on their level of liver dysfunction. Belinostat will be administered IV over 30 minutes. On day -7 (Cycle 1 only), all patients will receive a single dose of 400 mg/m2 belinostat. On days 1 - 5 of each cycle, patients will receive belinostat at a dose dependent on the level of hepatic dysfunction (see below). The total length of Cycle 1 will be 28 days; all other cycles will be 21 days. No more than 12 patients with normal hepatic function will be accrued.

CTEP #8846
Clinical Center #11-C-0060

SCHEMA



B = Belinostat, administered IV over 30 minutes. On Day -7 (Cycle 1 only), **all patients** will receive a single dose of 400 mg/m^2 belinostat.

Starting on Day 1, patients will receive the assigned dose of belinostat, according to the dose escalation scheme, for Days 1–5 of each cycle.

Blood samples for correlative PK studies will be collected from all patients on Cycle 1 D-7 before the administration of belinostat, 15 minutes after starting infusion, and then at the following time points after the end of infusion: 5, 10, 15, 30, 60, 90 minutes, 2, 4, 6, 8, and 24 hours

Liver Dysfunction Groups

Cohort 1: Normal hepatic function: bilirubin ≤ upper limit of normal (ULN) **and** AST ≤ ULN

Cohort 2: **Mild hepatic dysfunction**: bilirubin > ULN but ≤ 1.5 x ULN **and/or** AST > ULN

Cohort 3: Moderate hepatic dysfunction: bilirubin > 1.5 x ULN to ≤ 3 x ULN and any AST

Cohort 4: Severe hepatic dysfunction: bilirubin > 3 x ULN but ≤ 10 x ULN and any AST

Topic:

A phase I, open-label, multi-center, randomized, crossover study to assess the bioequivalence of 2 formulations of TKI258, FMI capsule and FMI tablet, in patients with advanced solid tumors (這個第一期試驗主要的目的是要比較 TKI258 膠囊(舊型)和錠劑(新型)的藥物動力學，以利之後臨床試驗劑型的轉換)

TKI258 (dovitinib) is a broad, targeted inhibitor of RTKs: FGFR , VEGFR, PDGFRβ, CSF 1R, c-Kit, RET, TrkA, and FLT3 that mediate tumor cell proliferation and survival. Therefore, it is expected that therapy with TKI258 would inhibit cellular proliferation and/or induce apoptosis resulting in an anti-tumor effect.

Based on its potency as an inhibitor of these RTKs both in vitro and in vivo, and the compound's oral availability, TKI258 is being investigated as a single agent in metastatic renal cell carcinoma (mRCC), metastatic breast cancer (mBC), advanced urothelial cancer (mainly bladder cancer), advanced melanoma, multiple myeloma (MM), AML, and other solid tumor studies. TKI258 is currently in early stage clinical development and efficacy data are

preliminary. In phase I and phase II trials, objective responses and/or prolonged disease stabilizations have been observed in pre-treated patients failing standard of care therapies for cancers, including renal cancer, breast cancer, melanoma and multiple myeloma
The maximum tolerated dose (MTD) of TKI258 is 400 mg/day for the continuous once daily dosing regimen and 500 mg/day for the 5 days on/2 days off dosing regimen, which is the recommended phase II dose and schedule.

Primary objective
・ To assess the bioequivalence of 2 formulations of TKI258, FMI capsule (supplied in 100 mg strength) and FMI tablet (supplied in 250 mg strength), in patients with advanced solid tumors, excluding breast cancer.

Secondary objectives
To characterize the safety and tolerability of TKI258 following a 5 days on/2 days off dosing schedule in patients with advanced solid tumors, excluding breast cancer.
To evaluate preliminary evidence of anti-tumor activity of TKI258 in patients with advanced solid tumors, excluding breast cancer.

Exploratory objectives
・ To investigate, in archival tumor samples, mutations as well as expression of biomarkers related to TKI258 mechanism of action

Study population:
Adult patients with a cytopathologically or histopathologically-confirmed diagnosis of an advanced solid tumor, excluding breast cancer, which has progressed despite standard therapy, or for which no standard therapy exists, will be enrolled into the study. At least 48 evaluable patients will be required for the bioequivalence (BE) test. However, due to the potential need to replace patients not meeting evaluability criteria, up to a maximum of approximately 80 patients may be enrolled assuming a 40% non-evaluable rate.

Overview of study design:

This is a phase I, open-label, multi-center, randomized, two way crossover study to assess the bioequivalence of FMI capsule and FMI tablet in patients with advanced solid tumors, excluding breast cancer. The bioequivalence phase will be performed in the first 4 weeks of the trial.

Bioequivalence phase				
	Period 1		Period 2	
Sequence	**Days 1 – 18**	**Days 19 - 21**	**Days 22 - 25**	**Days 26 - 28**
1	500 mg (FMI capsule) 5 days on/2 days off	Day 19 only: 500 mg (FMI capsule) PK samples 0 – 72 hours post dose	500 mg (FMI tablet) 5 days on/2 days off	Day 26 only: 500 mg (FMI tablet) PK samples 0 – 72 hours post dose
2	500 mg (FMI tablet) 5 days on/2 days off	Day 19 only: 500 mg (FMI tablet) PK samples 0 – 72 hours post dose	500 mg (FMI capsule) 5 days on/2 days off	Day 26 only: 500 mg (FMI capsule) PK samples 0 – 72 hours post dose

Topic: A phase I study of FOLFIRINOX plus IPI-926 for advanced pancreatic adenocarcinoma (這是一個針對胰臟癌病患標準化療處方 FOLFIRINOX 合併 IPI-926 的一期試驗)

The Hedgehog signaling pathway is important for normal mammalian embryonic development and for adult tissue remodeling. Recent reports have demonstrated that aberrant activation of the Hh pathway is associated with many types of cancer, including basal cell carcinoma (BCC), medulloblastoma, pancreatic adenocarcinomas, small-cell lung cancer (SCLC), metastatic prostate cancer, glioma, breast cancer, hepatocellular cancer, and hematologic malignancies. High levels of Hh pathway activation, either through mutation of pathway components or through constitutive expression of Hh pathway genes, appear to be involved in both the initiation of cancer and tumor cell survival, as well as tumor growth and metastasis. Given the therapeutic potential of Hh pathway inhibition in cancer, Infinity has developed **IPI-926**, a potent and specific antagonist of the Hh pathway that binds Smoothened (Smo), a key signaling transmembrane protein in this pathway, thereby diminishing downstream promoters of cellular proliferation.

Primary Objective

The primary objective is to determine the maximum tolerated dose (MTD) for FOLFIRINOX plus IPI-926 in patients with advanced pancreatic cancer. This will include

Secondary Objectives

The secondary objectives include the following:

- To establish the safety profile of FOLFIRINOX plus IPI-926
- To gain preliminary data on the efficacy of this combination
- To evaluate the pharmacokinetics of IPI-926 and its relevant metabolites when administered in combination with FOLFIRINOX

Exploratory Objectives

The exploratory objectives include the following:

1)To analyze pre-treatment tumor samples, where available, for expression of potential predictive markers of IPI-926 activity, including (but not limited to) Hedgehog signaling molecules

2)To evaluate potential pharmacogenomic markers of IPI-926 activity

3)To explore potential serum or plasma pharmacodynamic markers of IPI-926 activity

Dose level	5-FU bolus (mg/m2)	5-FU infusion (mg/m2 x 44-46 hrs)	LV (mg/m2)	Oxaliplatin (mg/m2)	Irinotecan (mg/m2)	IPI-926 (mg/day)
-1	----	1600	400	50	120	130
1*	----	1920	400	65	150	130
2	----	2400	400	85	180	130
3	----	2400	400	85	180	160

*Starting dose level.

2. 藥物開發與藥理的研究：

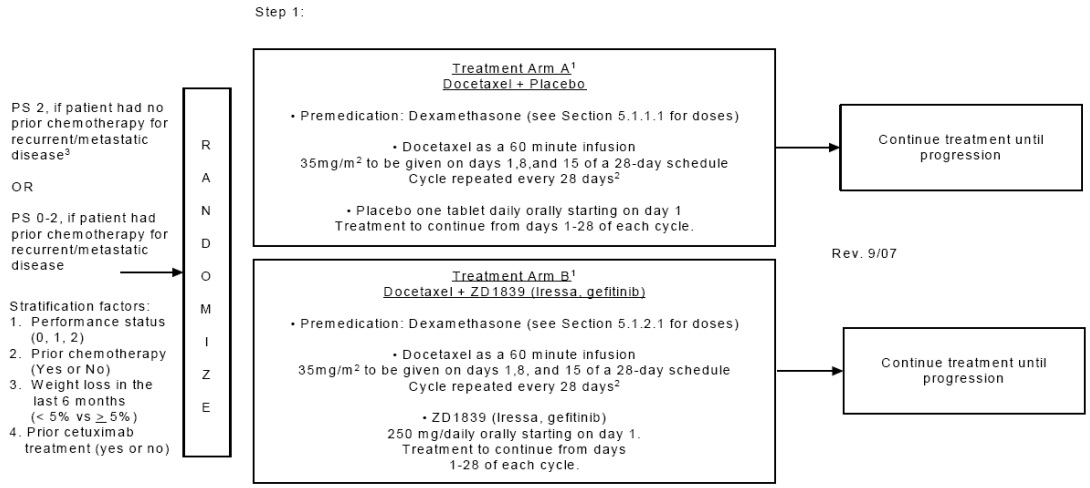
Topic: Pharmacokinetic study of ^{125}I-NM404 in mice by small animal imaging.(小動物影像的藥物動力學實驗)

說明：NM-404 是一個磷酸脂架構的藥物，跟惡性腫瘤有很強的結合性，跟放射線碘

同位素結合（^{124}I, ^{125}I, ^{131}I）可以應用在腫瘤顯影和放射線藥物治療上。目前這個藥物的第一期臨床試驗正在進行中。這個實驗是把藥物注射在有接種腫瘤的小老鼠，然後利用密集的正子斷層掃描，測量藥物在老鼠體內藥物動力學的情況。

Topic: Evaluation of Polymorphisms and Mutations in Genes Postulated to Alter the Efficacy of Gefitinib in Samples from E1302(附屬於臨床試驗內藥物動力學，藥物基因學的研究)：

Schema



In the recently completed E1302 phase III study, the efficacy of docetaxel alone or in combination with ZD1839 (Iressa, gefitinib) was evaluated in patients with recurrent or metastatic head and neck cancer. Gefitinib is a tyrosine kinase inhibitor that targets the epidermal growth factor receptor (EGFR). No statistically significant difference in survival between placebo and gefitinib when combined with docetaxel were observed in the parent protocol. The study included a total of 270 patients of which samples are expected from 183. Of the currently evaluable 146 patients, 80 tissue blocks have been provided which are available for analysis.

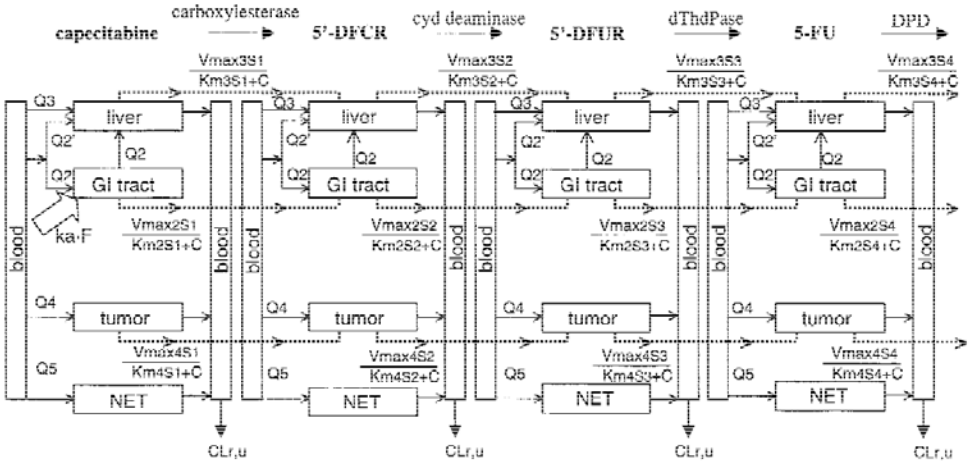
Since the development of this clinical trial, substantial evidence supporting the efficacy of EGFR inhibitors in only Kras wild-type individuals as well as the role of c-MET in Kras regulation have emerged. Utilizing the samples from the study, we propose to evaluate mutations in Kras and c-MET to identify those that may be predictive of gefitinib efficacy. Polymorphisms included in the initial protocol targeted for analysis in the study include those within EGFR, CYP3A and ABCB1 (P-gp). Additional genes have been postulated to also be relevant in modulating the efficacy of gefitinib in this patient population and thus we propose to investigate polymorphisms and mutations in c-MET, ABCG2, and K-ras.

說明：這是一個第三期頭頸癌的臨床試驗，一組病人接受 docetaxel 治療，一組病人接受 gefitinib 治療。取病人腫瘤的檢體進行癌細胞基因（EGFR, CYP3A, ABCB1,

c-MET,K-ras, 和 ABCG2）的突變和 polymorphism 的判定，進而分析療效預測與預後的關聯性。

Topic: Physiology-based pharmacokinetic model of capecitabine (capecitabine 的生理藥物動力學模型):

This PK model is based on some *in vivo* and *in vitro* human data. The parameters in each enzyme system, such as K_m and V_{max}, were obtained from *in vitro* experiment with enzymes extracted from commercialized human cells.



The picture above illustrates the 4 steps of enzyme metabolism to transform capecitabine to 5'-DFCR, 5'-DFUR, and 5-FU serially. There are some problems for the model. First of all, we do not know the real K_a, which is not equal to the K_a we gained from the previous PK model. Secondly, the enzyme parameters, such as K_m and V_{max}, are obtained from *in vitro* studies and needs to multiply scaling factors to be applicable in *in vivo* scales. These scaling factors, K_a and K_p (partition coefficient) can be obtained by fitting to blood concentrations of capecitabine and all its metabolites. However, this sophisticated model is developed under many assumptions and could be used with some uncertainty.

However, if we can prove the physiology-based model is reliable, it can be very useful. As we see from the graphs above, we can estimate the drug concentration in all kinds of tissue and tumor, which is difficult to measure directly. The concentrations of active drugs in these specific compartments are responsible for the treatment effects and side effects.

Here, we tried to estimate the drug distribution of 4 different dosing schedules by this model in a human with height 175cm, weight 70kg, and BSA 1.84m^2.

a.Capecitabine 1000mg bid daily

b.Capecitabine 2300mg (1250mg/m^2) bid 14 days on and 7 days off in a 21-day cycle.

c.Capecitabine 3220mg (1750mg/m^2) bid 7 days on and 7 days off in a 14-day cycle.
d.Capecitabine 4140mg (2250mg/m^2) q8h for 2 days in a 14-day cycle.
The concentration in tumor is related to treatment effects. The concentration in GI mucosa is related to side effects of diarrhea. The concentration in soft tissue is related to side effects of hand foot syndrome. The concentration in blood is supposed to be related to metronomic chemotherapy-associated anti-angiogenesis (effects on vascular endothelial cells). The concentration in liver is related to side effects of hepatotoxicity (elevated liver enzymes, hyperbilirubinemia).

AUC(umol*hr/L)	tumor	blood	GI mucosa	liver	Soft tissue
Schedule a	0.35	0.5 (1.43)	1.43 (4.09)	1.7 (4.86)	0.28 (0.8)
Schedule b	0.97	1.25 (1.29)	4.08 (4.21)	4.24 (4.37)	0.7 (0.72)
Schedule c	1.63	1.88 (1.15)	6.96 (4.27)	6.34 (3.89)	1.05 (0.64)
Schedule d	2.67	2.63 (0.99)	11.41 (4.27)	8.78 (3.29)	1.47 (0.55)

The numbers in parentheses are the relative AUC in each compartment to in tumor in each dosing schedule.
From this table, we have some observations:
1.Lower dose schedules have more 5-FU distributed in blood than in tumor, which means more anti-angiogenesis than direct anti-tumor.
2.Lower dose schedules have more 5-FU distributed in soft tissue and liver than in tumor, which might be responsible for the different toxicity profiles for different schedules.
A randomized phase II clinical trial comparing schedule a and b showed the risks of grade 3/4 diarrhea were 5% and 9%, respectively, and the risks of grade 3/4 hand-foot syndrome were 10% and 15%, respectively. Another randomized phase II clinical trial comparing schedule b and c showed the risks of grade 3/4 diarrhea were 9% and 12%, respectively, and the risks of grade 3/4 hand-foot syndrome were 0 and 2%, respectively.

4. 生物統計學的應用：

Tpoic: Comparison of Weekly versus Every 3 Weeks Paclitaxel in the Treatment of Advanced Solid Tumors, A Meta-analysis

說明：除了參與臨床試驗統計方法的討論，研習整合分析(meta-analysis)的原理並提出一個計畫，目前此計畫已經完成分析，已經投稿於 Cancer Treatment Reviews。

ABSTRACT

Background: Paclitaxel is commonly given as a 3-hour infusion every 3 weeks for a variety of malignancies. Several randomized clinical trials comparing weekly paclitaxel with Q3-week (Q3W) have produced mixed results in terms of efficacy and toxicity

creating controversy about the ideal dose and schedule.

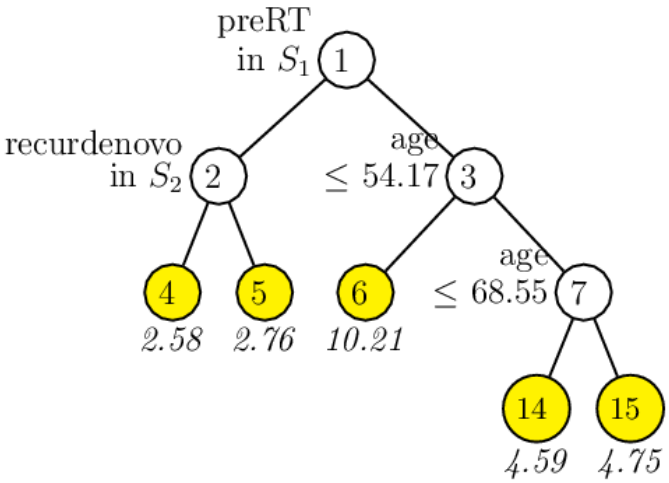
Methods: A literature search using PubMed, Cochrane Library, and *Proceedings of the American Society of Clinical oncology* from 1995 to 2011 was performed. We included all published and registered RTCs for advanced solid tumors which compared weekly paclitaxel with Q3W. Primary dependent variables—grade 3, 4 neutropenia rates and grade 3 sensory neuropathy rates—were analyzed for all cancer types. Secondary dependent variables—hazard ratios for survival and response rates—were analyzed for each cancer type. Moderators of cancer types, ethnicity, and paclitaxel dose ratio were analyzed for primary dependent variables.

Results: Ten trials were included. The summary effects of the meta-analysis revealed less grade 3, 4 neutropenia (odds ratio: 0.49, p=0.0023) and a trend towards less grade 3 sensory neuropathy (odds ratio:0.54, p=0.092) with weekly paclitaxel compared with Q3W. Moderator analysis by meta-regression revealed that paclitaxel dose ratios have a significantly positive correlation with rates of G3/4 neutropenia and sensory neuropathy. In the five NSCLC (non small cell lung cancer) trials, the summary effect revealed a better response rate with weekly paclitaxel (odds ratio: 1.24, p=0.042).

Conclusion: Weekly paclitaxel has a favorable toxicity profile compared to the current standard of Q3W paclitaxel.

Topic: Decision-Tree-based multi-variate Analysis for metastatic or recurrent esophageal cancer patients treated with regimens with and without taxanes.

The data of esophageal cancer patients are a combination of 2 clinical trials and a prospective cohort in National Taiwan University Hospital. One clinical trial is MP-HDFL (methotrexate, cisplatin, and 24-hour infusion of 5-FU) with 26 patients in 1997. The other clinical trial is TP-HDFL (paclitaxel, cisplatin, and 24-hour infusion of 5-FU) with 41 patients in 2001. The prospective cohort includes 46 patients treated with P-HDFL (cisplatin and 24-hour infusion of 5-FU), TP-HDFL, and DP-HDFL (docetaxel, cisplatin, and 24-hour infusion of 5-FU) from 2004 to 2009.



Node No.	Case number	Hazard (paclitaxel : non-taxane : docetaxel)
4	59	2.23 (p=0.045): 8.25 (p=6*10^{-6}): 1
5	14	Non-significance
6	18	0.36 (p=0.34): 11.82 (p=0.048): 1
14	15	Non-significance
15	7	0.027 (p=0.0258): 0.040 (p=0.039): 1

<table>
<tr><td rowspan="2">recur</td><td rowspan="2">N=14
D:P:N=ns</td><td>N=10
D:P:N=1:0.027:0.039
In elderly patients with previous RT, docetxel could be detrimental.</td><td>81
|
|
68.55</td></tr>
<tr><td>N=10
D:P:N=ns</td><td>68.55
|
|
|
54.17</td></tr>
<tr><td>De novo</td><td>N=59
D:P:N=1:2.23:8.25
For patients with advance disease at initial diagnosis, docetaxel-contained regimen is the best choice.</td><td>N=20
D:P:N=1:0.36(ns):11.82
In young patients with previous RT, taxanes combination could still be beneficial.</td><td>54.17
|
|
|
|
37</td></tr>
<tr><td></td><td>Pre-RT(-)</td><td>Pre-RT(+)</td><td>Age</td></tr>
</table>

Conclusion

From Guide analysis, we got very useful information. It told us that for fresh advanced stage esophageal cancer, we should treat with docetaxel, but for patients recurrent or refractory after radiotherapy, it is still beneficial to treat younger patients with taxanes but becomes detrimental to treat older patients with docetaxel.

5. 建立與威斯康辛州卡本癌症中心的接續合作:

Topic: Population Pharmacokinetics of Paclitaxel with Platinum in Patients with Non-Small Cell Lung Cancer, Ovarian Cancer, and Breast Cancer (這是一個與卡本癌症中心的合作研究，是雙方合作的一個開端，目前正在本院 IRB 送審中)

簡介:

太平洋紫杉醇廣泛使用於多種癌症的化學治療，目前健保局給付於非小細胞肺癌、乳癌與卵巢癌的術後輔助性化療和晚期緩解性化療。太平洋紫杉醇常常和鉑金合併使用，是一個常見的合併處方。雖然已經上市約二十年，相關研究仍持續進行。有關個人化治療的臨床研究是目前醫學研究的一個熱門主題。這個研究能夠提供太平洋紫杉醇個人化治療知識上的進展。

研究目的:

1.ABCB1 的基因多態性(polymorphisms)和太平洋紫杉醇藥物動力學的相關性。
2.CYP3A4, CYP3A5, CYP2C8 的基因多態性(polymorphisms)和太平洋紫杉醇藥物動力學的相關性。
3.ABCB1, CYP3A4, CYP3A5, CYP2C8, ERCC1 的基因多態性(polymorphisms)和太平洋紫杉醇與鉑金併用時治療效果與毒性的相關性。

研究群體:

非小細胞肺癌、乳癌與卵巢癌接受太平洋紫杉醇與鉑金併用輔助性或緩解性化療的病患。

納入與排除條件:

1.病理確診為非小細胞肺癌、卵巢癌或者乳癌。

2.年齡大於 20 歲。

3.肝、腎與骨隨造血功能必須在容許範圍之內。

4.除了根除性手術後的輔助性化療之外，非小細胞肺癌與乳癌受試者的腫瘤必須是可以測量大小以評估腫瘤治療反應。

5.女性受試者不可以是正在懷孕或正在哺乳。

6.尚未停經的婦女必須同意在試驗的期間使用適當的避孕方式。

7.受試者不能有急性感染、其他無法控制或不穩定的病症。

8.受試者不能曾經對太平洋紫杉醇或其溶劑(cremaphor)過敏。

心得:

本人覺得在威斯康辛兩年的時光收穫頗多。除了學術上的收穫以外，在整體的醫療環境以及醫病關係上都得以和台灣做個對照。在那裡，我發現癌症病人想的事情、問的問題，原來都和台灣的病人一樣。而醫師看病人的觀點和方法也沒有和台灣的醫師有太大的差別。我們所不足的地方，一個是歷史，一個是資源。相對於卡本癌症中心悠久的歷史而言，台大腫瘤部成立十幾年來，雖然已經小有規模，還需要更多的時間來累積資歷。在資源上，卡本癌症中心旁邊有一所全美排名前十的大學，上面有資源豐富的美國國家癌症機構。台大醫院雖然也有台灣最好的台灣大學，但是上面的教育部和衛生署所能提供的資源當然不若美國癌症機構。這兩年當中，隨者國際經濟情勢的變化，卡本癌症中心的研究資源也在轉變。兩年前，大約八成的第一期臨床試驗是由美國癌症機構贊助的；兩年後，這個比例已經降到五成，而且還有下降的趨勢。國際大藥廠所贊助的研究比例，即使在這個公立的核心研究機構裡，也是逐年攀升。我在這當中，看得出來上層領導者所做出的努力，他們努力和業界溝通培養關係和建立互信。這件事對他們來說是新的，他們在這方面不斷的學習。我們希望成為亞洲主要的早期臨床試驗中心，需要和國際大藥廠建立穩定的合作關係，這點可以從他們的經驗來學習。

建議事項:

威斯康辛卡本癌症中心是一個歷史悠久，地位崇高的癌症醫學的發展重鎮。那裡的人對亞洲癌症醫學的發展一直都很關注，對我們也相當和善。我建議我們應該而且需要和卡本癌症中心建立穩定的合作關係。希望可以從幾個比較小型的學術案的合作開始，培養彼此的默契後，可以有較高層級，甚至官方的溝通合作。這對於台大在亞洲癌症醫學發展上應該會有相當大的助益。