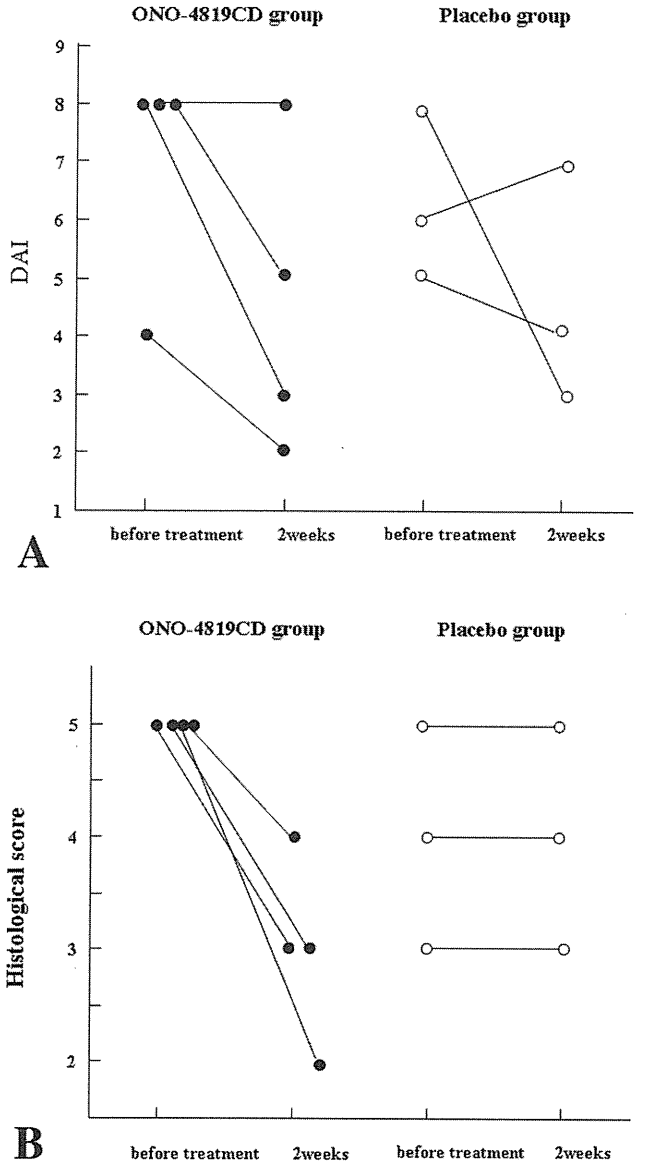


FIGURE 1. (A) Changes in DAI score in patients who received ONO-4819CD or placebo for 14 days. (B) Changes in histological score in patients who received ONO-4819CD or placebo for 14 days.

sided colitis and 2 patients had pancolitis. One patient had proctitis.

Changes of DAI score are shown in Figure 1A. Three of 4 patients treated with ONO-4819CD showed a decrease of DAI score at 2 weeks. One of 3 responders to ONO-4819CD achieved clinical remission. On the other hand, 2 patients in the placebo group showed a decrease of DAI score but did not achieve clinical remission. Therefore, 1 of the patients treated with ONO-4819CD achieved clinical remission, whereas no patient in the placebo group showed remission. There was no statistically significant difference in changes of DAI score between the placebo and treatment groups. Histological score of biopsy specimen was decreased in all the patients treated with ONO-4819CD, while it did not change in patients receiving placebo (Fig. 1B).

Percentage of IL-10-producing cells of peripheral CD4 T cells was increased in 3 patients showing improvement of DAI score in ONO-4819CD group, while no increase was observed in patients treated with placebo. The Th1/Th2 ratio of peripheral CD4 T cells (as assessed by ratio of IFN-$\gamma$ and IL-4-producing CD4 T cells) increased in 3 of 4 patients with ONO-4819CD, while this ratio decreased in patients treated with placebo.

No serious adverse events were observed during this clinical study. The incidence of adverse events was similar among the groups (3 of 4 in ONO-4819CD group and 2 of 3 in placebo group). The adverse drug reaction observed in the ONO-4819CD group were neutropenia, elevated blood eosinophilis, headache, hot flashes, constipation, diarrhea, fever, and hypotension. All of these reactions were mild and transient.

Here we report the first phase II, randomized, double-blind, placebo-controlled trial on the therapeutic effects of an EP4 agonist, ONO-4819CD, on patients with mild to moderate UC refractory to 5-ASA. In this study the decrease in DAI was observed in 3 of 4 patients treated with ONO-4819CD. One patient treated with ONO-4819CD achieved remission, while no patients on placebo achieved remission. Remarkably, although the number of patients is small, the improvement of histological scores was observed in all patients treated with ONO-4819CD.

EP4 activation was shown to have both antiapoptotic action on intestinal epithelial cells and a stimulating effect on mucus secretion from Goblet cells.[5] Thus, it appears reasonable to speculate that the histological improvement obtained by ONO-4819CD administration in our UC patients could be attributed to the enhanced mucosal defense through both antiapoptotic action on colonocytes and mucous secreting activity on Goblet cells of the EP4 agonist.

Another possible mechanism for improvement of histological score may

be modulation of cytokine balance by the EP4 agonist. Indeed, we previously reported that an EP4 agonist inhibited immune response in a mouse IBD model.[2,3] Moreover, in vitro study showed that PGE2 induces the production of IL-10 in bone marrow-derived dendritic cells.[6] The present results showing that the percentage of IL-10-producing peripheral CD4 T cells was increased in all the patients treated by the EP4 agonist is well in accord with the previous studies.

The pathophysiology of UC is associated with a Th2 cytokine phenotype. We reported that alteration of the Th1/Th2 ratio of peripheral CD4 T cells could be a biomarker of effectiveness of therapy for patients with UC and shifting toward a Th1-dominant cytokine profile reflected improvement of patients with UC.[7] We found here that the increase of the Th1/Th2 ratio of peripheral CD4 T cells was observed in 3 of 4 patients treated with ONO-4819CD, while it was not observed in patients with placebo. Consistent with the elevation of the Th1/Th2 ratio observed in this trial, we recently found that EP4 stimulation can promote Th1 differentiation without an effect on Th2 cells.[8] Thus, ONO-4819CD may improve colonic inflammation by not only an increase of IL-10-producing cells but also shifting toward a Th1 cytokine profile.

In conclusion, although we could not obtain statistically significant therapeutic effects of an EP4 agonist, ONO-4819CD, in our UC patients, all the treated patients showed improvement of histological scores. This might suggest a clinical benefit of ONO-4819CD therapy for patients with mild to moderate UC. Because the number of patients was small in our study, further studies with a larger number of patients with UC would be required.

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〈抄録〉第30回 日本臨床薬理学会年会 2009年12月3～5日 横浜
シンポジウム9：わが国における臨床研究スタッフのあり方を考える
—SCRP（Senior Clinical Research Professional）をめぐって

# 2．研究職・教職として今できること，目指すこと

新 美 三由紀*

## 1．はじめに

近年，わが国でも研究者主導臨床試験や観察研究を含めた臨床研究の重要性とその環境整備の必要性が叫ばれている．医薬品や医療機器の販売承認のために行われる治験と異なり，診断法や治療法の開発とともに医学および薬理学の発展の基礎となる臨床研究は，医療機関および大学が活動の主体となる．そのため，治験とは異なり病院・大学のスタッフが多く関わることになる．

この度，日本臨床薬理学会より新たにSCRP（Senior Clinical Research Professional）が制定された．臨床薬理学会の規則では，SCRPは「臨床研究の領域において造詣が深く，将来，認定CRC（Clinical Research Coordinator）制度の発展に寄与すると思われる者」とあり，筆者も2009年に同学会理事長よりSCRPの委嘱を受けた．今後このSCRPという役割を果たすため，現在の研究職・教職という立場から何ができるか，どう活動していくか，考えを述べたい．

## 2．研究職・教職として臨床研究にかかわること

中野[1]は，創薬育薬医療スタッフを治験だけに限らず，広く臨床研究を対象としたスタッフと位置づけ，臨床薬理の立場から，「創薬と育薬に関わる人たちが実践している領域を創薬育薬医療として1つにくくり，同じ目標を目指してこの領域で働いているチームのプレイヤー」と定義している．その際，医師，CRC，看護師，薬剤師といった医療従事者以外にも，「研究者」をその中に明示している．この研究者は，治験では製薬企業側のスタッフという位置づけになっているが，研究者主導の臨床研究においては，同じ大学・病院内のスタッフになる．

筆者は，病院所属ではあるが直接的に診療には従事しない，いわゆる研究職・教職として雇用されており，臨床研究支援あるいは共同研究者として試験実施計画書の作成やモニタリング，データマネジメント等を行っており，上記の「研究者」に該当すると思われる．近年，わが国でも臨床研究・臨床試験の活性化により，さまざまな雇用形態ができあがり，このような医師ではなく，医療職でもない，臨床研究スタッフが雇用される機会も増えてきた．しかし，研究職として雇用された場合，臨床研究の支援という業務を遂行することに加え，自分自身の研究課題を持ち，その研究成果を出さなければならないという義務も生じる．その業績はどのくらい働いたかではなく，自分自身が研究者として，評価の高い学術雑誌へ研究成果をいくつ発表したかという形で評価されることが一般的である．

しかし，臨床研究は通常，多くの研究者および支援者による共同研究であるため，臨床研究支援スタッフとしていくら質の高い臨床研究の業務支援を行ったとしても，なかなか自分自身の研究業績に直接反映されることは少ない．研究支援そのものが主業務であり評価につながる医療職のCRCとは異なる点である．しかし，研究者がSCRPとなり，CRCのキャリアパスのひとつとして位置づけられるのなら，何らかの形でキャリアアップにつながる業績を残し，仕事が続けられることが必要となる．

そのためには，支援する研究を「Extramural Research」とし，自分自身の研究を「Intramural Research」として進めることが重要となる．

## 3．Extramural ResearchとIntramural Research

統計解析方法や臨床試験方法論を研究する研究者は，実際の臨床試験・臨床研究の共同研究者または支援者として関わるが，これをExtramural Researchと位置づける．National Institutes of Health（NIH）やNational Human Genome Research Instituteなど，欧米の研究組織ではこのExtramural Researchを専門とする部署（Division of Extramural Research：DER）

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を持ち，Extramural Research のみを専門で行うスタッフが公式に認められている．

一方，支援する研究を基に自分自身の研究課題，すなわち，新しい臨床試験・研究手法や統計解析手法，デザインを開発し，シミュレーションを行い，実際の臨床試験・臨床研究に当てはめ，そこで得られたデータの二次的な解析や，計画・実施過程で得られたメタデータを用いて，その手法やデザインを評価するという Intramural Research も行う．ここでいうメタデータとは，「データに関する情報を記述したデータであり，data about data と英語で表現される」[2]と説明されるように，いわゆるデータ処理過程で発生する作業・管理ログ等である．

筆者は，データマネジメントやモニタリング，監査といった臨床試験支援業務を行いながら，Intramural Research として品質マネジメントに関する方法論の研究を進めてきた．この研究課題は，実際の臨床試験の業務を行うことなしに進められるものではなく，自分自身の手でデータ入力やデータバリデーション作業を行い，モニタリングを行い，プロトコルを書くことが基盤となる実践的科学である．そして，その研究結果を次の臨床試験・臨床研究に当てはめることで，臨床試験の現場の改善にもつなげることができるのである．そういう意味で，CRC のキャリアパスの１つになり，SCRP にもなり得るのではないかと考える．

## 4．ま と め

SCRP とは，形態・目的によらず臨床研究までも含めた臨床現場で行われるあらゆる研究に対して，社会的にも積極的に関わり，臨床試験・研究に対する自らの確固たる考えを示すことのできるプロフェッショナルを指すのではないかと筆者は考えており，そうありたいと思っている．

ある米国のリサーチナースが，自分の将来が見えないと嘆いた日本の CRC に聞いたことがある．

「あなたの今やっていることは Job なの？　それとも Career なの？」

「Job」とは，職務，与えられる賃金に対して提供すべき仕事である．これに対し，「Career」とは，直接賃金には結びつかず，職務ではなく，むしろより高い資格・能力を得ようとして自ら行う経歴や一生の仕事といえる．

この言葉は，SCRP が業務範囲も役割もポジションも，すべて自らが切り拓くことができる厳しさと可能性を我々に示しているのかもしれない．

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第１回 日本臨床試験研究会学術集会

シンポジウム２ ● 研究者主導臨床試験の支援をどうするか

# 試験実施計画書の作成支援

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## はじめに

治験によってわが国の臨床試験実施体制は整備が進んだが，研究者主導臨床試験（臨床研究）は，相変わらず資金不足や慢性的な人員不足に悩まされている。「臨床研究に関する倫理指針」の全部改正によって一見整備が進んだように見えるが，臨床スタッフの減少もあり，臨床試験を適切に計画・実施しようとすればするほど，研究者（医師）の負担はさらに増えている。

当院では，未承認または適応外の医薬品・医療機器を用いた医師主導治験や高度医療評価制度下での臨床試験，承認薬を用いた研究者主導臨床試験等，多くの試験が行われている。われわれ臨床試験専門職は支援業務として，またみずからが共同研究者として試験実施計画書の作成に関わっているが，実際に関与できる試験数には限界がある。このため，ある一定以上の質を担保しつつ，効率的に，スピーディーに試験実施計画書を作成できるかが重要となる。とくに，トランスレーショナルリサーチが多く行われている当院の特徴から，早期開発フェーズの試験をより早く開始して結果を出す必要があり，試験実施計画書作成に費やせる時間は多くない。

今回，演者が所属する探索医療センターが試験実施計画書を作成する医師を支援する実際の方法を紹介し，そのなかで用いているツールや仕組みの利点・欠点について述べる。また，今後臨床研究コーディネーター（CRC）やコメディカルらが試験実施計画書を作成できるようになるためのトレーニングについても触れる。

## 1 プロトコル委員会からプロトコル作成ワーキンググループへ

通常，臨床試験実施計画書の要件としてあげられる事項は，以下の４点である。

１）臨床的に意味がある（科学性）
２）倫理的である（倫理性）
３）法規・ガイドラインに従っている（遵守性）
４）実行できる・守ることができる(実施可能性)

しかし，日本の臨床試験・臨床研究が抱える，遅い，高いという問題を考慮すると，さらに以下の２つの要件を加える必要があると考えられる。

５）早く・タイムリーに研究が始められる(時機性)
６）コスト（人・費用・時間）がかからない（効率性）

これらの要件のウェイトや優先順位のつけかたが，実際に試験実施計画書を作成しようとする場合に，原則として１人で書くか，複数人の共同作業とするかを決定する要因にもなるだろう。１人で書くとした場合，研究者主導臨床試験（臨床研究）では専門のプロトコルライターの雇用はほとんど望めない。したがって，必然的に研究者（医師）が書くことになる。医師が１人で書けば，研究の背景や研究仮説，目的といった研究の根本はその医師自身の中にあるため，複数人で書くより論旨も首尾一貫し，用語も統一された計画が書けるはずである。

しかし，医師は臨床試験が主業務ではないため，

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通常は診療の終わった夜や休日といった勤務時間外にその活動を行うこととなり，当然のことながら時間がかかることとなる。また，1人の医師が一生の間に最初から最後まで臨床試験計画書を書く数は多くても数試験，たった1つという場合も多いことを考慮すると，経験やノウハウの蓄積という点では非効率となり，支援スタッフを含めた複数人のチームで書くほうがより現実的である。

試験実施計画書を複数人で分担作成した場合の一番のメリットは，早く書けること，得意な人（その領域の専門家）が得意なところを書けることがあげられるが，反面，統一性や整合性に欠けるかもしれない。この欠点を補うための仕組みとして，ワーキンググループとプロトコルコーディネーター制があげられる。

当院の探索医療センターでは，今までは管理職と実務者からなるプロトコル委員会という会議体で試験実施計画書を作成していたが，2009年度より体制を変更した。プロトコル委員会は管理職と主任研究者，プロジェクトマネージャーだけから構成され，ワーキンググループのメンバーの選定と，できあがった試験実施計画書を承認するという管理的な役割となった。一方，実際の試験実施計画書の作成作業は，主任研究者に加え，統計解析，データマネジメント，モニタリング，CRC等の実務者からなるワーキンググループに移行された。ここではプロジェクトマネージャーが業務全般のマネジメントを行うが，マネジメントと調整作業を分離するため，プロトコルコーディネーターを新たに設けることとなった。また，このプロトコルコーディネーターは恒常的な役割とするのではなく，試験によってモニタリング責任者や，データマネジメント責任者，医師等がケースバイケースで担当することで，業務量の分散化を図ることができた。

これらの体制変更のほか，これまでの作成要領（作成ガイドライン）に加え，テンプレートを利用することで，試験実施計画書の漏れが減るだけでなく，作成作業が格段に早くなった。こうした仕組みやテンプレート利用は，当院のようなセンターだけでなく，医療機関内の臨床試験支援室のような比較的小規模な組織でも活用できるものであると考える。

## 2　プロトコルコーディネーターとしてのトレーニングと活動

当院が導入したプロトコルコーディネーターは，固定のプロトコルライターではない。あくまで，それぞれの専門家が分担して書いたものを集め，不足点を補い，統一性・整合性を確保するための記述を行う。また，作成過程のログ管理を行う。まさに調整業務をする「コーディネーター」である。

こうした特徴から，プロトコルコーディネーターという役割を果たすためには，試験全体を横断的に，かつ縦断的に理解することが必要となる。それには，多くの業務を経験することや，自分自身が研究者となって，主体的に研究を計画・運営することもプラスになるだろう。また，とかく批評家的になりがちなプロトコルレビューを，いかに建設的に行えるかが重要であり，代替案を必ず提示するという姿勢が求められる。作成過程の試験実施計画書を1人で長く保持しないことも重要である。

これらプロトコルコーディネーターとしてのトレーニングは，必ずしもライターとしてのトレーニングとは一致しない。むしろ，いかにチームメンバーの力を上手く統合して，効率的に短時間で試験実施計画書という成果物を作り上げられるかという，コーディネート力が求められるだろう。そういった点から，CRCの新たなチャレンジとしても魅力ある役割と考えられる。

## ま と め

日本臨床試験研究会のミッションは，「臨床試験・臨床研究に携わる専門職全体の知識と技術の向上を図り，職種の枠を超えた情報交換と研究活動を推進すること」とされており，まさにプロトコルコーディネーターのような，複数の専門職が担う可能性のある役割のトレーニング機会を提供できる組織として期待される。プロトコルコーディネートには，試験実施計画書を，1）読む（読解），2）レビューする（批判的吟味と代替案提示），3）自分で手を入れる（具体的な修正），4）ゼロから書く（記述），5）リサーチクエスチョンの設定から試験実施計画書完成までを統括する，という段階的なトレーニングが必要であろう。これらを網羅した教育コースの立ち上げが望まれる。

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ORIGINAL ARTICLE

# Phase II study of S-1 and docetaxel for previously treated patients with locally advanced or metastatic non-small cell lung cancer

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## Abstract

*Purpose* The purpose of the present phase II study was to evaluate both the efficacy and toxicity of the combination of S-1 and docetaxel in previously treated patients with locally advanced or metastatic non-small cell lung cancer.

*Methods* Thirty-eight previously treated patients with non-small cell lung cancer were treated with S-1 (80 mg/m$^2$, days 1–14, oral) and docetaxel (40 mg/m$^2$, day 1, intravenous) every 3 weeks.

*Results* No complete response was observed, and seven patients had a partial response, yielding an overall response rate of 18.4% (95% CI, 7.7–34.3%). The median overall survival time and 1-year overall survival rate were 16.1 months and 60%, respectively. The median progression-free survival time was 4.4 months. Myelosuppression was the main toxicity with grade 3 or 4 neutropenia and leukopenia in 50 and 21%, respectively. There was no irreversible toxicity in this study.

*Conclusions* The combination of S-1 and docetaxel is well tolerable and has substantial activity for patients with locally advanced or metastatic non-small cell lung cancer. A phase III trial comparing docetaxel with or without S-1 would warrant further investigation.

**Keywords** Non-small cell lung cancer · Phase II study · Docetaxel · S-1 · Second-line chemotherapy · Third-line chemotherapy

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## Introduction

Non-small cell lung cancer (NSCLC) is a leading cause of cancer deaths worldwide, but only a minority of patients is amenable to surgical or definitive chemoradiotherapy. The overall prognosis of NSCLC patients remains poor; only 15.2% patients are alive after 5 years [1]. Almost all patients eventually experience progression during or after treatment. Second-line chemotherapy with docetaxel showed modest antitumor activity, with overall response rate (ORR) of 6.7–7.1%, and can prolong survival after failure of platinum-based regimens for NSCLC, with a 1-year overall survival (OS) rate of 21–31% [2, 3]. However, despite current evidences supporting the use of second-line chemotherapy, the modest survival benefits, the negligible low response rate and relevant toxicity may reduce the role of second-line chemotherapy in clinical settings.

S-1 (Taiho Pharmaceutical Co., Ltd., Tokyo, Japan) is an oral fluoropyrimidine agent comprising the 5-fluorouracil (5-FU) prodrug tegafur and two enzyme inhibitors, 5-chloro-2,4-dihydroxypyrimidine (CDHP) and potassium oxonate (OXO), in a molar ratio of 1:0.4:1. CDHP enhances the serum 5-FU concentration by competitive inhibition of dihydropyrimidine dehydrogenase (DPD), an enzyme responsible for 5-FU catabolism. OXO is a reversible competitive inhibitor of orotate phosphoribosyl transferase (OPRT), a phosphoenzyme for 5-FU and reduces the gastrointestinal toxicity of 5-FU [4]. These mechanisms mean that oral S-1 administration can generate a higher concentration of 5-FU than protracted intravenous injection of 5-FU alone, while the incidence of toxicity in the gastrointestinal tract does not increase.

The combination of S-1 and docetaxel holds particularly great promise because both drugs have substantial antitumor activity as single agents, and they have different mechanisms of action and different toxicity profiles [2, 3, 5–7]. Recent preclinical studies have shown that S-1 has synergistic effects in human cancer xenografts [8–10]. The low level of DPD, thymidylate synthase activities, and a high level of OPRT activity enhance the antitumor effect of 5-FU and S-1. Docetaxel is one of the agents that modulate these enzyme expressions and activities. A phase I/II study has shown that this combination was well tolerated with moderate toxicities and promising activity in patients with gastric cancer [11]. Therefore, we conducted a phase II study to evaluate both the efficacy and toxicity of S-1 combined with docetaxel in previously treated patients with locally advanced or metastatic NSCLC.

## Materials and methods

### Eligibility criteria

Eligible patients were aged 20–74 years and had histologically or cytologically confirmed locally advanced or metastatic NSCLC (stages IIIB–IV or relapse after surgery) that progressed after first- or second-line chemotherapy or chemoradiotherapy. The patients were required to have measurable disease by the response evaluation criteria in solid tumors (RECIST), an Eastern cooperative oncology group (ECOG) performance status (PS) of 0 or 1, ability to take oral medication and normal ECG. Eligibility requirements also included a white blood cell count of $\leq$12,000 cells/mL, an absolute neutrophil count of $\geq$2,000 cells/mL, a platelet count of $\geq$100,000 cells/mL, a hemoglobin level of $\geq$9 g/dL, a serum total bilirubin level of $\leq$1.5 mg/dL, a serum aspartate aminotransferase (AST)/alanine aminotransferase (ALT) of less than or equal to twice the upper limit of normal, a serum creatinine level of $\leq$1.5 mg/dL and a normal electrocardiogram. Prior thoracic radiotherapy was allowed as long as it had been completed at least 12 weeks prior to inclusion and the patient had recovered from any toxicity. At least 4 weeks had to have elapsed from prior surgery and completion of prior chemotherapy or chemoradiotherapy. Patients who had exhibited evidence of severe heart or pulmonary disease or concomitant malignancy were excluded. The protocol was approved by the Ethics Committee of Kyoto University, and every patient gave written informed consent. This trial was registered at University hospital Medical Information Network, Japan (protocol ID number, UMIN000000501 at http://www. umin.ac.jp/).

### Treatment plan

S-1 was given orally twice daily for 2 weeks, followed by a drug-free interval of 1 week (one cycle). Dose of S-1 administered each time was calculated according to the patient's body surface area as follows: less than 1.25 $m^2$, 40 mg; 1.25–1.5 $m^2$, 50 mg; and greater than 1.5 $m^2$, 60 mg. Docetaxel intravenous infusion (40 mg/$m^2$) was administered on day 1. The treatment regimen was repeated every 3 weeks until disease progression or intolerable toxicity occurred. For patients who experienced febrile neutropenia, hemorrhage with grade 3 or 4 thrombocytopenia, or grade 3 or 4 non-hematologic toxicity, the dose of docetaxel was to be reduced to 35 mg/$m^2$ and the dose of S-1 was also to be reduced to 80% of the initial dose. For patients who still experienced the same toxicity after the dose reduction, S-1 was to be reduced to 80% of the reduced dose, and this could be done up to twice. If recovery from such toxicities at a reduced dose was confirmed, administration at the reduced dose was continued. Patients who still experienced the same toxicity after the dose reduction were to be withdrawn from the study treatment.

### Evaluation of response and toxicity

Patients underwent tumor assessments at baseline and every 6 weeks by investigators using RECIST. Patient survival was observed until death, loss to follow up, or study closure. Adverse events were recorded using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3).

### Statistical analysis

The primary end point was the ORR as assessed in all eligible and treated patients, with success being defined as a complete response (CR) or partial response (PR) according to RECIST. The secondary endpoints were OS, progression-free survival (PFS) and adverse events. The design of

this study was based on a binomial distribution with no planned interim analysis. Assuming a null hypothesis of a 9% ORR and an alternative hypothesis of a 25% ORR, with one-sided type I error = 0.1 and type II error = 0.1, it was necessary to enroll a minimum of 35 patients. According to this, we aimed for 40 patients to take non-evaluable patients into consideration.

Exact confidence interval (CI) and exact *P*-value for ORR were based on the binomial distribution. OS was calculated from the date of registration until death from any cause, whereas PFS until disease progression or death from any cause. OS and PFS were analyzed using the Kaplan–Meier method. All statistical tests were one sided, and a *P*-value of less than 0.05 was considered statistically significant. All analyses were performed using SAS version 9.1.3 (SAS Institute, Cary, NC, USA).

## Results

### Patient characteristics

Between August 2006 and December 2007, 42 patients were enrolled in this study according to the eligibility criteria. Thirty-nine of these 42 patients were eligible, of the remainder one patient had stage IIIA NSCLC and two patients were without adequate liver function. Following the study protocol, one eligible but untreated patient was excluded from the analysis because of the incidence of a compression fracture caused by osteoporosis before treatment. Baseline characteristics of the 38 patients are summarized in Table 1. The median age was 65 years (range, 44–74 years). The majority of patients had an ECOG PS of 0 (95%), had been histologically or cytologically diagnosed as having adenocarcinoma (79%) and had progressed after at least one previous platinum-based chemotherapy regimen (92%). The median number of courses administered per patient was five (range, 1–8). The median follow-up time was 17.2 months.

### Efficacy

Tumor response results are shown in Table 2. Among all treated patients, no CR was observed and seven patients had a PR, yielding an ORR of 18.4% (95% CI, 7.7–34.3%; $P = 0.05$ under the null hypothesis of a 9% ORR). Among the patients with adenocarcinoma, PR was observed in 4/30 (13.3%). As shown in Fig. 1, the median OS time was 16.1 months and the 1-year OS rate was 60% (95% CI, 42.5–73.6%). The 1-year OS rates in stage-IIIB patients, stage-IV patients and patients with relapse after surgery were 70, 42 and 80%, respectively. The median PFS time was 4.4 months, and the 1-year PFS rate was 37% (Fig. 1).

**Table 1** Patient characteristics ($n = 38$)

| | No. of patients (%) |
|---|---|
| Median age | 65 years; range, 44–74 years |
| Gender | |
| Male | 23 (61%) |
| Female | 15 (40%) |
| Histology | |
| Adenocarcinoma | 30 (79%) |
| Squamous cell carcinoma | 4 (11%) |
| Others | 4 (11%) |
| Stage | |
| IIIB | 10 (26%) |
| IV | 18 (47%) |
| Relapse after surgery | 10 (26%) |
| IIIB[a] | 3 (8%) |
| IV[a] | 7 (18%) |
| ECOG PS | |
| 0 | 36 (95%) |
| 1 | 2 (5%) |
| Smoking history | |
| Current/former | 24 (63%) |
| Never | 14 (37%) |
| Number of previous chemotherapy regimens | |
| 1 | 23 (61%) |
| 2 | 15 (39%) |
| Previous chemotherapy | |
| Platinum-containing | 35 (92%) |
| Gefitinib | 7 (18%) |

*ECOG PS* Eastern Cooperative Oncology Group performance status

[a] Restaging after relapse

**Table 2** Overall response rates according to RECIST ($n = 38$)

| CR | PR | SD | PD | NE | ORR |
|---|---|---|---|---|---|
| 0 | 7 | 25 | 6 | 0 | 18.4% (95% CI, 7.7–34.3%) |

*RECIST* response evaluation criteria in solid tumors, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *NE* not evaluable, *ORR* overall response rate, *CI* confidence interval

### Safety

The major adverse events are shown in Table 3. The most frequent hematological toxicity was neutropenia with grade 3 or 4 neutropenia observed in 50% of patients. Of these events, grade 4 neutropenia was observed in seven patients (18%) and febrile neutropenia in one patient (3%). Grade 3 or 4 leukopenia was reported in 21% of patients. The non-hematological grade 3 toxicities were anorexia in five

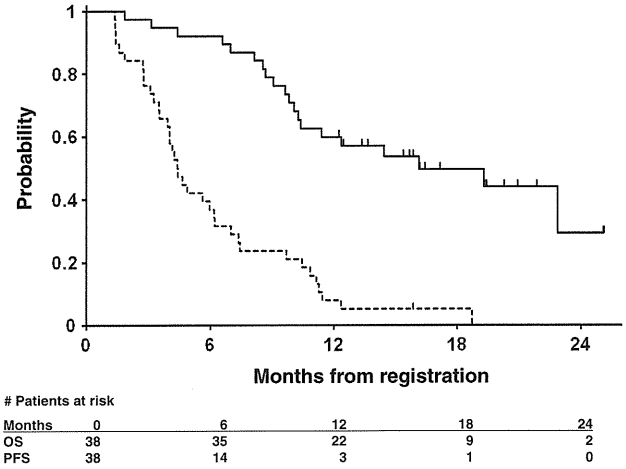


**Fig. 1** Kaplan–Meier survival curves demonstrating overall (*solid line*) and progression-free (*dashed line*) survival. *OS* overall survival, *PFS* progression-free survival

**Table 3** Adverse effects according to National Cancer Institute Common Terminology Criteria for Adverse Events (version 3) ($n = 38$)

| Toxicity | All grades | | Grade 3 or 4 | |
|---|---|---|---|---|
| | No. | (%) | No. | (%) |
| Hematological toxicity | | | | |
| Neutropenia | 31 | (82%) | 19 | (50%) |
| Leukopenia | 22 | (58%) | 8 | (21%) |
| Anemia | 18 | (47%) | 1 | (3%) |
| Thrombocytopenia | 3 | (8%) | 0 | |
| Febrile neutropenia[a] | 1 | (3%) | 1 | (3%) |
| Gastrointestinal toxicity | | | | |
| Stomatitis | 33 | (87%) | 4 | (11%) |
| Nausea | 17 | (45%) | 0 | |
| Vomiting | 7 | (18%) | 1 | (3%) |
| Diarrhea | 2 | (5%) | 2 | (5%) |
| Metabolic/laboratory | | | | |
| AST | 15 | (39%) | 0 | |
| Hyperbilirubinemia | 10 | (26%) | 1 | (3%) |
| ALT | 10 | (26%) | 0 | |
| Hypercreatinemia | 3 | (8%) | 0 | |
| Other toxicity | | | | |
| Anorexia | 25 | (66%) | 5 | (13%) |
| Hand-foot skin reaction | 25 | (66%) | 2 | (5%) |
| Fatigue | 24 | (63%) | 0 | |
| Hyperpigmentation | 8 | (21%) | – | |
| Weight loss | 4 | (11%) | 0 | |
| Pneumonitis | 2 | (5%) | 0 | |

*AST* aspartate aminotransferase, *ALT* alanine aminotransferase

[a] Fever with concomitant grade 3 or 4 neutropenia

patients (13%), stomatitis in four patients (11%), hand-foot skin syndrome in two patients (5%), diarrhea in two patients (5%) and vomiting in one patient (3%). There was no death or irreversible toxicity in this study that was considered to be related to treatment.

## Discussion

Almost all patients with advanced NSCLC treated with first-line chemotherapy experience progression, and current options for the second-line treatment of NSCLC include single-agent chemotherapy with docetaxel, pemetrexed or erlotinib [12], which large-scale randomized clinical trials indicate as the standard regimen. However, the clinical responses to these agents are of short duration, and the survival benefit is limited.

Many reports have been published investigating combination chemotherapy using two non-platinum agents for recurrent NSCLC in randomized clinical trials, with the objective of improving outcomes further. However, none of these studies have demonstrated improved survival with combination chemotherapy, whereas there have been relatively higher or intolerable toxicities [13–16]. Therefore, more active regimens for the second-line chemotherapy are much needed.

In the present study, we evaluated the efficacy and safety of the combination of S-1 and docetaxel, two agents that separately have shown promise in the treatment of advanced or metastatic NSCLC. This combination chemotherapy conferred efficacy with an ORR of 18%, a median OS time of 16 months and a 1-year OS rate of 60%. The 18% ORR observed in this study was slightly lower than expected. However, the survival benefits as second- or third-line therapy observed compare favorably with other chemotherapy regimens, such as monotherapy with docetaxel (6–14 months) [2, 3, 7], pemetrexed (8 months) [17], erlotinib (6–15 months) [18–20] or oral topotecan (6–8 months) [21, 22], or combination chemotherapy of irinotecan and cisplatin (11 months) [23], or oral fluoropyrimidine UFUR and gemcitabine (13 months) [24], although between-study comparisons should be made with caution.

Prolonged survival may be due to substantial post-study treatment, especially epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs). Although EGFR mutation status was not analyzed in this study, 17 patients received EGFR-TKIs and 9 of those patients for over a month.

The hematological toxicity observed here was minimal and tolerable, despite the fact that grade 3 or 4 neutropenia occurred in 50%, which is comparable with the toxicity caused by docetaxel monotherapy. The majority of non-hematologic toxicities were mild and tolerable without grade 4 non-hematologic toxicity. These toxicity results are consistent with those observed in a phase I/II study in patients with gastric cancer [11].

During the preparation of this manuscript, Atagi et al. [25] reported the results of a phase I/II study, in which the combination of S-1 and docetaxel was evaluated for patients who had failed one or more prior chemotherapy regimens. In the phase II part of their study, seven of 29 eligible patients achieved a PR, yielding an ORR of 24%, with a median OS time and the 1-year OS rate of 12 months and 42%, respectively. Patient characteristics were similar except for stage and ECOG PS: fewer patients who had experienced relapse after surgery were included, and 31 and 69% patients had ECOG PS of 0 and 1, respectively, in the study by Atagi et al. [25]. Although these differences in patient characteristics may lead to more favorable survival results in our study, the combination of S-1 and docetaxel still seems to be consistently promising as a chemotherapy option after the failure of prior chemotherapy for advanced NSCLC.

In this study, the dose of docetaxel was lower than that commonly used in docetaxel monotherapy. As a second-line docetaxel monotherapy, a dose of 75 mg/m$^2$ every 3 weeks is used in the United States and Europe, and the dose is 60 mg/m$^2$ every 3 weeks in Japan. However, our regimen is widely recognized as a tolerable and optimized combination of S-1 and docetaxel in gastric cancer [11], and thus, also in lung cancer, it is considered promising in terms of toxicity and efficacy. Furthermore, it was the recommended dose in the phase I part of study reported by Atagi et al. [25].

There are many report of ethnic differences in the safety and efficacy profile of S-1 and docetaxel [25–28], and it is shown that CYP2A6*9 genetic polymorphism is a potential predictive marker, for efficacy and toxicity, for the patients received the combination of S-1 and docetaxel for metastatic gastric carcinoma [29]. In the development of a S-1/docetaxel combination therapy in the United States and Europe, further optimization of the dose of each agent may be required to account for these differences.

In conclusion, the combination of S-1 and docetaxel is well tolerable and promisingly effective for patients with locally advanced or metastatic NSCLC. A phase III trial comparing docetaxel with or without S-1 would warrant further investigation.

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ORIGINAL ARTICLE

# A multi-institution phase II study of gemcitabine/S-1 combination chemotherapy for patients with advanced biliary tract cancer

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**Abstract**
*Purpose* We aimed to evaluate the efficacy and safety of gemcitabine/S-1 combination chemotherapy for the treatment of patients with advanced biliary tract cancer.
*Methods* Patients with histologically or cytologically confirmed unresectable or recurrent biliary tract cancer were eligible for inclusion. The primary endpoint was overall survival. Gemcitabine was administered intravenously at a dose of 1,000 mg/m$^2$ over 30 min on days 1 and 8, and oral S-1 was administered daily at a dose of 60 mg/m$^2$ on days 1–14. This schedule was repeated every 3 weeks until disease progression or patient refusal.
*Results* Twenty-five patients were enrolled between October 2007 and January 2009. Eleven patients (44%) had extrahepatic bile duct cancer, 5 (20%) had intrahepatic bile duct cancer, 8 had gallbladder cancer (32%), and 1 (4%) had ampulla of Vater cancer. The median overall survival time was 12.7 months (95% CI, 8.4–23.5 months), and the 1-year survival rate was 52.0% (95% CI, 31.2–69.2%). Of the 23 patients with evaluable target regions, seven patients experienced a partial response, and an overall response rate was 30.4%. The following grade 3–4 hematological toxicities occurred: neutropenia (56%), leukopenia (24%), anemia (8%) and thrombocytopenia (4%). In spite of the high incidence of grade 3–4 neutropenia, no patients developed febrile neutropenia in the present study. The major grade 3–4 non-hematological toxicities were fatigue (8%), anorexia (8%) and diarrhea (4%).
*Conclusions* Gemcitabine/S-1 combination chemotherapy offered a promising survival benefit with acceptable toxicity in patients with advanced biliary tract cancer.

**Keywords** Biliary tract cancer · Gemcitabine · S-1 · Chemotherapy

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## Introduction

Biliary tract cancer is one of the most lethal malignancies worldwide, with surgery representing the only potentially curative treatment for this disease. However, many patients are diagnosed too late for curative resection, and even if surgery can be performed, the likelihood of relapse is very high [7, 13]. Over the past decade, gemcitabine has been widely used to treat unresectable or recurrent biliary tract

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cancer [3, 4, 9, 17, 18, 23, 27], although no phase III trials have established this drug as a standard treatment for advanced biliary tract cancer. We have previously evaluated the outcome of consecutive 22 patients with advanced biliary tract cancer who received gemcitabine monotherapy as first line and reported that median survival time (MST) was 8.3 months (95% CI 6.4–11.2 months) [9].

In the ABC-02 study, the first prospective multicenter phase III study in this field, gemcitabine/cisplatin combination chemotherapy was compared with gemcitabine monotherapy. The study found that the combination regimen significantly prolonged MST (from 8.1 to 11.7 months; $P < 0.001$) [26]. The superiority of gemcitabine/cisplatin combination chemotherapy over gemcitabine monotherapy was also demonstrated in a randomized phase II study conducted in Japan (the BT-22 study) [6]. Given these findings, gemcitabine/cisplatin combination chemotherapy is now becoming accepted as a new standard regimen for advanced biliary tract cancer.

S-1 is an oral fluoropyrimidine prodrug that has confirmed efficacy against various solid tumors, both alone and in combination with other cytotoxic drugs [1, 12, 14, 19, 29]. S-1 monotherapy has yielded good results against advanced biliary tract cancer [5, 24], and gemcitabine/S-1 combination therapy has yielded promising results with acceptable toxicity levels for patients with advanced pancreatic cancer [15, 16, 28]. At the time of planning this clinical trial in 2007, there had been no reports on gemcitabine/S-1 combination chemotherapy for patients with advanced biliary tract cancer, so we designed this clinical trial to determine its efficacy and safety in this context.

## Patients and methods

### Eligibility criteria

Patients with advanced biliary tract cancer that was not amenable to potentially curative surgery or that had recurred after surgery were eligible for inclusion if they met the following criteria: histologically or cytologically confirmed biliary tract cancer; Eastern Cooperative Oncology Group performance status of 0–2; age $\geq$20 years; adequate bone marrow function (neutrophil count $\geq$1,500/mm$^3$, and platelet count $\geq$100,000/mm$^3$), liver function (total bilirubin $\leq$3 times the upper limit of normal (ULN) and aspartate aminotransferase [AST]/alanine aminotransferase [ALT] $\leq$5 times ULN) and renal function (creatinine $\leq$ 1.5 mg/dL); adequate oral intake; life expectancy $\geq$3 months. All patients provided written informed consent. Exclusion criteria included a history of chemotherapy or radiotherapy (patients who had undergone adjuvant chemotherapy were not excluded if at least 6 months had passed since the last administration), pregnancy or lactation, a history of severe drug allergy and other severe comorbid diseases. This phase II study (UMIN ID 000000792) was conducted in five institutions in Japan. The protocol was approved by the institutional review board at each institution, and patient registration and data management were conducted at an independent data center at Translational Research Center, Kyoto University Hospital. All procedures were performed in accordance with the 1964 Declaration of Helsinki.

### Treatment

Gemcitabine was infused at a dose of 1,000 mg/m$^2$ over 30 min on days 1 and 8. S-1 was given orally twice a day for 14 consecutive days. Doses of S-1 were calculated according to body surface area (BSA) as follows: BSA $<$ 1.25 m$^2$, 60 mg/day; 1.25 m$^2$ $\leq$ BSA $<$ 1.5 m$^2$, 80 mg/day; BSA $\geq$ 1.5 m$^2$, 100 mg/day. The gemcitabine and S-1 treatment regimen was repeated every 3 weeks. Doses were reduced in response to adverse effects (graded according to the Common Terminology criteria for Adverse Events v 3.0) [22].

Chemotherapy was started if on day 1 the neutrophil count was $\geq$1,500/mm$^3$, platelet count was $\geq$100,000/mm$^3$, total bilirubin was $\leq$3 times the ULN, AST/ALT was $\leq$5 times ULN, and there were no non-hematological toxicities of grade 3 or higher (except for abnormal blood test results not relevant to the chemotherapy regimen). Chemotherapy was continued if on day 8 the neutrophil count was $\geq$1,000/mm$^3$, platelet count was $\geq$75,000/mm$^3$, total bilirubin was $\leq$3 times the ULN, AST/ALT was $\leq$5 times the ULN, and there were no non-hematological toxicities of grade 3 or higher. If the patient did not meet the above criteria, chemotherapy was delayed by 1 week. If neutropenia (grade 3–4), thrombocytopenia (grade 3–4), febrile neutropenia or non-hematological toxicity associated with gemcitabine (grade 3) occurred, the subsequent gemcitabine dose was reduced to 800 mg/m$^2$. If further toxicity occurred with the reduced dose, it was further reduced to 600 mg/m$^2$. If a further dose reduction was necessary, the subsequent gemcitabine dose was reduced by 20%. If diarrhea or stomatitis (grade 3–4) associated with S-1 occurred, S-1 was discontinued, and patients were withdrawn from the study. No dose reescalation was allowed. The treatment regimen was continued until disease progression, unacceptable toxicity including non-hematological toxicity of grade 4 or patient refusal occurred.

### Pretreatment and follow-up evaluation

Pretreatment evaluation included obtaining the patient's medical history and performing a physical examination, imaging using contrast-enhanced computed tomography

(CT) or magnetic resonance imaging (MRI), a complete blood cell count, serum biochemical tests, an electrocardiogram and chest X-rays. During the treatment cycles, physical examinations and blood tests were scheduled on days 1 and 8. Carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) were measured at the time patients were enrolled in the study and every month thereafter. Toxicity was evaluated using the Common Terminology criteria for Adverse Events v3.0.

### Statistical analysis

The primary endpoint was overall survival. The secondary endpoints were toxicity and response rate. Twenty-five patients were enrolled, a sample size that would allow rejection of a null hypothesis of a 30% 1-year survival rate and acceptance of an alternative hypothesis of a 50% 1-year survival rate, with a significance level of 0.05 and a power of 80%. Overall survival was calculated using the Kaplan–Meier method and was defined as the time from initiation of therapy to death from any cause or the final follow-up. Among patients with measurable target lesions, the objective response rate was evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 [21]. Patients were enrolled between October 2007 and January 2009, and the final analysis was conducted in January 2010 after a 1-year follow-up period. All analyses were conducted on an intention-to-treat basis and were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA).

## Results

### Patient characteristics

Twenty-five patients were enrolled between October 2007 and January 2009. The patient characteristics are shown in Table 1. The median age was 63 years (range 32–78 years), and 18 patients (72%) were men. Four of the 25 patients (16%) experienced recurrent disease after undergoing curative surgery. Out of the 21 patients with unresectable disease, distant metastasis was reported in 13 patients at the time of enrollment. Eleven patients (44%) had extrahepatic bile duct cancer, 8 had gallbladder cancer (32%), 5 (20%) had intrahepatic bile duct cancer, and 1 (4%) had ampulla of Vater cancer.

**Table 1** Characteristics of patients with advanced biliary tract cancer ($n = 25$)

| | |
|---|---|
| Sex | |
| Male | 18 (72.0%) |
| Female | 7 (28.0%) |
| Median age (years) | 63 (range 32–78) |
| Primary lesion | |
| Intrahepatic | 5 (20.0%) |
| Extrahepatic | 11 (44.0%) |
| Gallbladder | 8 (32.0%) |
| Ampulla of Vater | 1 (4.0%) |
| Disease status | |
| Unresectable | 21 (84.0%) |
| Recurrent* | 4 (16.0%) |
| Target lesion | |
| Primary | 18 |
| Liver | 7 |
| Lymph node | 3 |
| Peritoneum | 2 |
| Local recurrence | 2 |
| Lung | 1 |
| None | 2 |
| Median no. treatment cycles | 7 (range 1–20) |
| Median CEA (ng/mL) | 4.5 (range 0.3–468) |
| Median CA19-9 (U/mL) | 167 (range 1–6,373) |

*CEA* carcinoembryonic antigen, *CA 19-9* carbohydrate antigen

* One patient had a history of adjuvant chemotherapy using gemcitabine

### Efficacy

Seventeen patients (68%) died during the study period. The median overall survival time was 12.7 months (95% CI, 8.4–23.5 months), and the 1-year overall survival rate was 52% (95% CI, 31.2–69.2%, $P = 0.02$ under a null hypothesis of 30%). Of the 23 patients with target regions that were evaluable according to RECIST, 7 (30.4%) experienced a partial response, and 13 (56.5%) had stable disease, with an overall disease control rate of 87.0%.

### Toxicity

In total, 229 cycles of gemcitabine/S-1 combination chemotherapy were delivered, with a median of 7 cycles per patient (range 1–20 cycles; Table 1). The mean relative dose intensities of gemcitabine and S-1 were 75% and 84%, respectively. The incidence rates of hematological and non-hematological adverse events are summarized in Tables 2 and 3, respectively. The most common grade 3–4 hematological toxicity was neutropenia (56%); however, no instances of febrile neutropenia were observed in this study. The incidence rates of grade 3–4 anemia and thrombocytopenia were 8% and 4%, respectively. Grade 3–4 hyperbilirubinemia and ALT were observed in 16% and 8% of patients, respectively, mostly associated with obstructive jaundice caused by the primary disease. Other grade 3–4

**Table 2** Hematological adverse events among patients with advanced biliary tract cancer treated with gemcitabine/S-1 combination chemotherapy ($n = 25$)

| | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Incidence of grade 3–4 events (%) |
|---|---|---|---|---|---|
| Neutropenia | 0 | 5 | 12 | 2 | 56 |
| Leukopenia | 1 | 9 | 6 | 0 | 24 |
| Anemia | 5 | 7 | 1 | 1 | 8 |
| Thrombocytopenia | 1 | 4 | 1 | 0 | 4 |
| Febrile neutropenia | – | – | 0 | 0 | 0 |

**Table 3** Non-hematological adverse events among patients with advanced biliary tract cancer treated with gemcitabine/S-1 combination chemotherapy ($n = 25$)

| | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Incidence of grade 3–4 events (%) | Incidence of grade 1–4 events (%) |
|---|---|---|---|---|---|---|
| Fatigue | 8 | 3 | 2 | 0 | 8 | 52 |
| Anorexia | 3 | 2 | 2 | 0 | 8 | 28 |
| Diarrhea | 1 | 4 | 1 | 0 | 4 | 24 |
| Constipation | 1 | 6 | 0 | 0 | 0 | 28 |
| Rash | 9 | 3 | 0 | 0 | 0 | 48 |
| Fever | 8 | 3 | 0 | 0 | 0 | 44 |
| Hand-foot rash | 7 | 3 | 0 | – | 0 | 40 |
| Infection-other | 8 | 2 | 0 | 0 | 0 | 40 |
| Nausea | 3 | 2 | 0 | 0 | 0 | 20 |
| Stomatitis | 5 | 1 | 0 | 0 | 0 | 24 |
| Allergic reaction | 4 | 1 | 0 | 0 | 0 | 20 |
| Hyperpigmentation | 8 | 0 | – | – | 0 | 32 |
| Alopecia | 3 | 0 | – | – | 0 | 12 |
| Injection site reaction | 2 | 0 | 0 | – | 0 | 8 |
| Vomiting | 1 | 0 | 0 | 0 | 0 | 4 |
| Hyperbilirubinemia | 3 | 1 | 4 | 0 | 16 | 32 |
| AST | 11 | 5 | 0 | 0 | 0 | 64 |
| ALT | 8 | 4 | 2 | 0 | 8 | 56 |
| Creatinine | 3 | 0 | 0 | 0 | 0 | 12 |

*AST* aspartate aminotransferase, *ALT* alanine aminotransferase

non-hematological adverse events were fatigue (8%), anorexia (8%) and diarrhea (4%).

## Discussion

In our population of patients with advanced biliary tract cancer, gemcitabine/S-1 combination chemotherapy achieved an MST of 12.7 months and a 1-year survival rate of 52%. The MST for patients with gall bladder cancer ($n = 8$) was shorter (7.6 months) than that for patients with other cancer types (16.0 months), which is consistent with the findings of previous studies and possibly reflects the more aggressive nature of gall bladder cancer [8, 10, 20]. The proportion of patients with gall bladder cancer in our study (32%) was comparable with the proportions in previous randomized trials (26–39%) [6, 25, 26], so the good MST observed in the current study was unlikely to be simply due to tumor-type selection bias. Furthermore, this was a multi-institution trial, and the eligibility criteria were almost identical to the indications used for administering chemotherapy in daily clinical practice; both these factors are likely to have contributed to reducing selection bias. Although comparing single-arm phase II studies can be problematic, our current results are comparable to those of Sasaki et al., who observed an MST of 11.6 months and a 1-year survival rate of 44% among patients with advanced biliary tract cancer treated with gemcitabine/S-1 combination chemotherapy [20] (Table 4). Their treatment schedule differed slightly from ours: it consisted of 1,000 mg/m$^2$ gemcitabine on days 1 and 15 and 80 mg/m$^2$ S-1 daily for 14 consecutive days every 4 weeks. In this study, grade 3–4 neutropenia was observed in 56% of patients, and this often caused suspension of chemotherapy on day 8. In fact, planned chemotherapy administration on day 8 needed to be suspended in 28.5% of cycles. Meanwhile, Sasaki et al.

**Table 4** Results of clinical trials of gemcitabine and oral fluoropyrimidine combination chemotherapy for the treatment of advanced biliary tract cancer

| | Present study | Sasaki et al. [20] | Knox et al. [10] | Cho et al. [2] | Koeberle et al. [11] |
|---|---|---|---|---|---|
| Oral fluoropyrimidine | S-1 | S-1 | Capecitabine | Capecitabine | Capecitabine |
| MST (months) | 12.7 | 11.6 | 14 | 14 | 13.2 |
| 1-year survival rate (%) | 52 | 44 | 49 | 58 | N/A |
| Prevalence of gall bladder cancer (%) | 32 | 40 | 49 | 16 | 18 |
| Incidence of grade 3–4 neutropenia (%) | 56 | 34 | 34 | 11 | 11[a] |
| Incidence of grade 3–4 anorexia (%) | 8 | 3 | N/A | 2 | 7 |
| Incidence of grade 3–4 fatigue (%) | 8 | N/A | 4 | 0 | 11 |
| Sample size | 25 | 35 | 45 | 44 | 44 |

*MST* median survival time, *N/A* not available

[a] These subjects had leukopenia

reported grade 3–4 neutropenia was 34%, and their regimen might have an advantage of avoiding suspension of chemotherapy due to neutropenia because gemcitabine administration was scheduled on day 1 and 15, not on day 8 with 2-week interval. Interestingly, a previous study of gemcitabine/cisplatin combination therapy in Japanese patients (BT-22 study) yielded a 56.1% incidence rate of grade 3–4 neutropenia, whereas in ABC-02 study involving the same regimen, the rate was only 22.6% among Caucasian patients [6, 26]. Although we need to take into account the difference of treatment duration between 2 studies (up to 24 weeks in ABC-02 study versus up to 48 weeks in BT-22 study), it is tempting to speculate that ethnic differences exist between patients with biliary tract cancer in terms of susceptibility to gemcitabine-related neutropenia. In spite of the high incidence of grade 3–4 neutropenia in the present study, no patients developed febrile neutropenia, probably due to the short duration of neutropenia caused by this combination therapy. Aside from AST/ALT elevation, the most common non-hematological toxicity was fatigue (52%); however, the incidence rates of grade 3–4 toxicities were relatively low, showing that this regimen was generally well tolerated in an outpatient setting. The grade 3–4 hyperbilirubinemia observed in this study was associated with obstructive jaundice caused by the primary disease and so was unlikely to be relevant to the combination therapy regimen. In vitro study also demonstrated the advantage of gemcitabine/S-1 combination. Yoshizawa et al. tested the combination of S-1 with other anticancer drugs (gemcitabine, cisplatin, irinotecan, mitomycin C, adriamycin and paclitaxel) and reported that synergic effect was most evident in gemcitabine/S-1 combination [30]. The combination of gemcitabine and another oral fluoropyrimidine, capecitabine, was found to be similarly efficacious in previous single-arm phase II studies [2, 10, 11]. In their respective studies, Cho et al. [2] observed an MST of 14 months and a 1-year survival rate of 58%, and Knox et al. [10] also observed an MST of 14 months and a 1-year survival rate of 49%. Koeberle et al. [11] found similar results, with an MST of 13.2 months (Table 4). Koeberle et al. also highlighted the importance of maintaining a balance between treatment efficacy and quality of life in palliative chemotherapy for advanced biliary tract cancer. From the point of view of quality of life, combination therapy using oral fluoropyrimidines has the major advantage of being very convenient to administer. Clearly, we must be cautious about the interpretation of data from single-arm phase II studies; however, the combination of gemcitabine and oral fluoropyrimidines can be used for patients with advanced biliary tract cancer in situations that preclude the use of cisplatin (e.g., allergy to cisplatin). In summary, gemcitabine/S-1 combination chemotherapy yielded a promising survival benefit with acceptable toxicity in patients with advanced biliary tract cancer. We believe that this regimen would be a good candidate for the experimental arm of a future phase III trial of gemcitabine/cisplatin combination therapy.

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REVIEW

# Cardiovascular Side-Effects of Modern Cancer Therapy

Manabu Minami, MD, PhD; Shigemi Matsumoto, MD, PhD; Hisanori Horiuchi, MD, PhD

Recent advances in chemotherapy have substantially improved the prognosis of cancer patients. However, many anticancer drugs, especially newly developed 'molecular-target drugs', such as the anti-HER2 blocking antibody and the anti-vascular endothelial growth factor antibody, have serious cardiovascular side-effects such as heart failure, thromboembolism, severe hypertension and lethal arrhythmia, which interrupt cancer treatment and decrease the patient's quality of life. Despite the increasing clinical significance, cardiologists have not been focusing enough of their attention on this issue. The major cardiovascular complications associated with anticancer drugs, and current diagnosis, treatment and prevention strategies are reviewed. Close collaborations between oncologists and cardiologists is necessary to tackle cardiovascular complications and advance cancer treatment. (*Circ J* 2010; **74:** 1779–1786)

**Key Words:** Cancer; Cardioncology; Cardiotoxicity; Chemotherapy

Over the past few decades, cancer treatment has dramatically evolved. The development and implementation of intensive anticancer treatments have substantially improved the prognosis of cancer patients. Among the recently advanced cancer therapeutic modalities, the progress of chemotherapy is striking.

Significant efforts to explore the molecular mechanism of cancer development and progression have recently born fruit, in the so-called 'molecular-target drugs'. Most are either antibodies against cell surface proteins or small molecule protein kinase inhibitors. These drugs bring great promise, especially for advanced or recurrent cancers. Today their application is widening and producing excellent clinical outcomes. Furthermore, many new agents are currently under development for clinical use.

On the other hand, adverse side-effects of these cytotoxic drugs are inevitable, and some exhibit specific and potentially lethal side-effects on the cardiovascular system. Until recently, we have only needed to consider a few well-described examples of cardiotoxicity of anticancer drugs, such as those accompanying the anthracycline antibiotics. However, now we must also be mindful of the cardiovascular side-effects of these novel molecular-target drugs (**Tables 1,2**). Both the prevalence and impact of cardiovascular toxicity, including unexpected adverse effects, are expanding. The assessment of a patient's cardiovascular condition and risks throughout chemotherapy, even years after completion of treatment, has become quite important.

With only a few exceptions, most of the molecular mechanisms that lead to cardiovascular toxicity during cancer treatment remain unclear. Anticancer drugs influence or disrupt pathways that are centrally involved in cell survival, cell growth, inflammatory activation, and angiogenesis (**Figure 1**), which can spontaneously result in cardiovascular side-effects. Therefore, research on cancer treatment-associated cardiovascular side-effects may unveil novel molecular mechanisms that lead to heart failure, atherosclerosis, thrombogenesis, cardiomyocyte regeneration, and arrhythmia.

We review the major cardiovascular complications associated with cancer chemotherapeutic agents that current cardiologists should know about. Oncologists and cardiologists must collaborate closely to further improve the prognosis and quality of life of cancer patients. As was recently proposed, it is time that we explored the interdisciplinary field termed 'cardioncology'.[1]

## Cytotoxic Agents

### Anthracycline Antibiotics

The most notorious, but best studied, cardiovascular side-effects associated with cancer chemotherapies are those induced by the anthracyclines, including doxorubicin, daunorubicin, epirubicin, and idarubicin, which are approved and widely used to treat leukemia and many soft tissue tumors. Anthracyclines accomplish their antitumor activity by intercalating into nuclear DNA, impairing transcription and cell division, inhibiting topoisomerase II activity, producing reactive oxygen species (ROS), and further injuring DNA as well as cell membranes and mitochondria.[2]

Anthracycline-mediated cardiomyocyte damage is cumulative, dose-dependent, and thought to occur through several mechanisms,[3–5] but mainly through oxidative stress or free

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**Table 1. Antibody-Based Molecular-Target Drugs and Their Cardiovascular Complications**

| Drug | Type | Target | Major cardiovascular complications |
|---|---|---|---|
| Trastuzumab (Herceptin) | Humanized | HER2/neu | LV dysfunction, heart failure |
| Cetuximab (Erbitux) | Chimeric | HER1/EGFR | Thromboembolism, hypotension |
| Bevacizumab (Avastin) | Humanized | VEGF-A | Hypertension, thromboembolism, gastrointestinal perforation, LV dysfunction |
| Alemtuzumab (Campath) | Humanized | CD52 | Hypotension |
| Rituximab (Rituxan) | Chimeric | CD20 | Hypotension |

HER, human epidermal growth factor receptor; LV, left ventricular; EGFR, epidermal growth factor receptor; VEGF, vascular endothelial growth factor.

**Table 2. TKI and Their Cardiovascular Complications**

| Drug | Target | Major cardiovascular complications |
|---|---|---|
| Lapatinib (Tykerb) | HER1/EGFR, HER2 | LV dysfunction |
| Erlotinib (Tarceva) | HER1/EGFR | * |
| Gefitinib (Iressa) | HER1/EGFR | * |
| Sunitinib (Sutent) | VEGFR1/2/3, KIT, PDGFR, Flt-3, RET, CSF-1 receptor | LV dysfunction, hypertension |
| Sorafenib (Nexavar) | Raf, VEGFR2/3, KIT, PDGFR, RET | Hypertension |
| Imatinib (Glivec) | BCR-ABL, KIT, PDGFR | LV dysfunction |
| Dasatinib (Sprycel) | BCR-ABL, KIT, PDGFR | QT prolongation, edema |
| Nilotinib (Tasigna) | BCR-ABL, KIT, PDGFR | QT prolongation |

*Severe cardiac toxicity has not yet been reported.
TKI, tyrosine kinase inhibitors; VEGFR, VEGF receptors; KIT, stem cell factor receptor; PDGFR, platelet-derived growth-factor receptor; Flt-3, Fms-like tyrosine kinase 3; RET, receptor tyrosine kinase; CSF-1, colony stimulating factor-1. Other abbreviations see in Table 1.

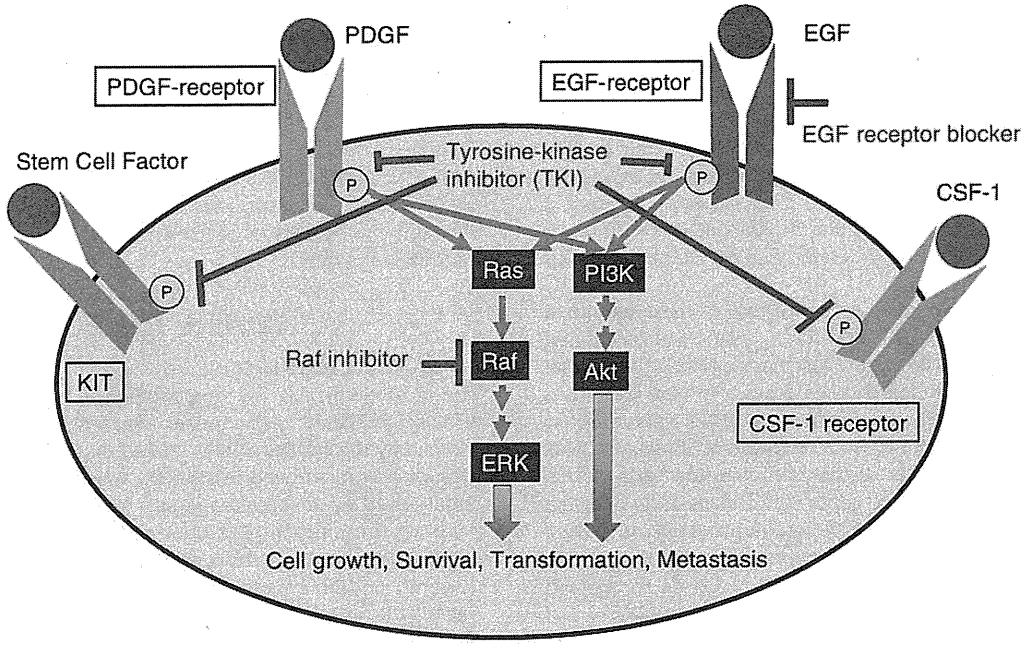


**Figure 1.** Targeted treatment of cancers. Molecular-target drugs block signaling pathways involved in tumor growth, apoptosis, and metastasis. CSF-1, colony stimulating factor-1; EGF, epidermal growth factor; KIT, stem cell factor receptor; PDGF, platelet-derived growth-factor.

radical formation induced by the electron redox cycling of anthracyclines after binding to DNA.[2,6,7]

Anthracycline-induced cardiotoxicity can be classified according to the time of onset. Acute or subacute (shortly after intravenous infusion) cardiac side-effects include acute heart failure, myocarditis, myocardial infarction and arrhythmias, and were reported to occur in 3.2% of non-Hodgkin's lymphoma (NHL) patients who were administered doxorubicin.[8] Arrhythmias, caused by ROS-mediated cardiac ion channel dysfunction, range from atrial fibrillation to supra-