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消化管がん薬物療法

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別　　刷

ヴァンメディカル

Close Up　胃がんに対する薬物療法のすべて

2．胃癌治療ガイドライン改訂と薬物療法，そしてその評価

1）術前化学療法へのアプローチ

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Summary

胃がん薬物療法は新規抗がん剤の登場により大きく発展した。単に抗腫瘍効果が上がっただけではなく，薬物療法により治癒までは望めないことから治癒を求めた化学療法後の手術が選択肢として浮上した。また，術前化学療法は手術が予定された切除可能進行胃癌に対するものだけではなく，当初手術が予定されなかった切除不能進行胃癌に対する治療戦略となる可能性は高いと思われる。術前化学療法に関する当科での取り組みを紹介するとともに，臨床試験の結果を踏まえて今後候補になりうるレジメンについて述べた。

術前化学療法の概念と適応

2010年３月に胃癌取扱い規約が改訂され第14版が出版された[1]。それに伴い，日本胃癌学会の胃癌治療ガイドラインも同年10月に第３版が出版され，ともに大幅な変更が行われた[2]。主たる改訂点が胃癌治療ガイドラインには８項目列記されているが，化学療法に関しては６．７．に記載されている。主な内容は切除不能進行・再発胃癌に対する化学療法と術後補助化学療法に関するものであり，まだ標準治療ではない術前化学療法については，「Ⅲ章　資料の臨床研究としての治療法の解説」のなかに，術前補助化学療法として記載されているのみである。「再発の一要因となる微小転移の消滅を図り，その後遺残した原発巣や転移巣を切除する集学的治療である。」と定義され，「奏効例の生存率向上が指摘されているが，明らかな全生存率の改善効果を認めたというエビデンスがないため，日常診療としては未だ奨励されていない。」と記されている。

術前化学療法の適応は，大きく２種類に分けられる。１つはＲ０手術が可能と判断されているが再発リスクが高いと考えられる場合（狭義の術前化学療法），もう１つは，Stage Ⅳと診断され化学療法が行われた後，その結果として手術が可能と判断された場合（広義の術前化学療法）である。前者は真の術前化学療法といえ，予定された期間・コース数が設定されていることが多く，後者は化学療法が奏効した場合で当初手術は予定されていないのが通常である。

Stage Ⅳ胃がんに対する術前化学療法

近年注目されているのが，Stage Ⅳ胃がんに対する治療戦略である。その理由として，抗がん剤治療は遅かれ早かれ耐性の獲得や長期投与による有害事象が不可避であり，大腸がんのように２年以上の median survival

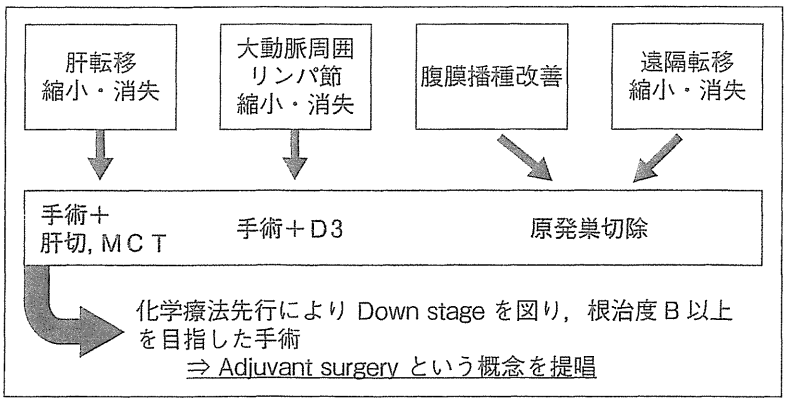

図 1　Stage Ⅳ 胃がんの治療方針
根治不能胃がんの治療は化学療法である。
新規抗がん剤の登場により奏効率など治療成績が大きく改善した。
（吉田和弘ほか：術前化学療法．消化器外科 5(383)：820-826(2008) より）

time（MST）が得られることもなく，薬物治療のみの予後に限界がみえてきたことである。意見の分かれるところではあるが，新たな治療戦略として挙げられるのが，奏効例に対する二次治療としての手術療法である。このような手術を当科では，adjuvant surgery と呼んでいる（**図 1**）。この場合，一次治療奏効中の手術療法であり，手術を行うタイミングを図ることは非常に困難であるが，増悪する前に切除することが肝要である。

Progression free survival（PFS）の概念に基づいて検討すると，一次治療―Adjuvant surgery―術後治療（一次治療あるいはティーエスワン®（S-1）単剤）といった一連の治療全体が，薬物療法的にはいわゆる一次治療であり，PFS を大きく延長させることが期待できる（**図 2**）。しかし，この治療戦略については，Stage Ⅳ 胃がんの中でその適応となる症例が限られることは言うまでもない。

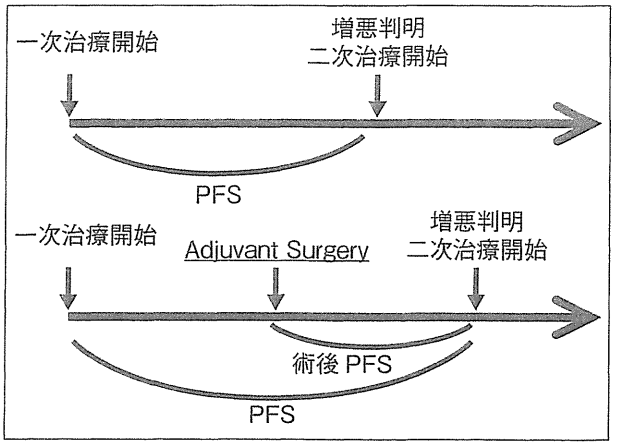

図 2　Progression free survival のとらえ方

術前化学療法の利点と欠点[3,4]

1．利　点

①経口摂取可能症例であれば術後より栄養状態が良好なため，薬剤強度の高い化学療法が可能になる。

②手術による腫瘍局所の血管構築の破壊がないため，薬剤の腫瘍への到達性が良好である。

③ Down staging による切除率の向上が期待できる。

④早期に遠隔転移が出現する症例の見極めが可能となり，不必要な手術を回避できる。

⑤切除標本による化学療法の効果を組織学的に評価できる。

2．欠　点

①化学療法の有害事象により手術の安全性が損なわれる可能性がある。

②化学療法の効果が得られず，根治手術のタイミングを失う可能性がある。

術前化学療法のレジメン

術前化学療法のレジメンについては，使用薬剤の種類・併用する組合せが問題となるが，現時点で進行・再発胃癌に対する効果・安全性が証明されているものの中から選択されるべきである。求められる条件を列記すると，以下のものが考えられる。

①高い奏効率
②高い disease control rate
③手術に影響を及ぼさない有害事象
④その時点での標準治療であること

①については当然であるが，局所浸潤が強い症例における他臓器合併切除の回避や，転移巣の消失の可能性があることにより，狭義・広義ともに術前化学療法として必要な条件であると思われる。②は狭義の術前化学療法の場合，PD 率が高い，すなわち disease control rate が低いと化学療法により手術のタイミングを逸したことになるため，non-PD の確率が高いことが要求される（術前化学療法の欠点）。③については，化学療法後の手術の安全性が担保されることが最低条件であり，臨床試験により手術先行の場合と比較して合併症の頻度が同等以下であることが証明されるべきである。④については，現時点では SPIRITS 試験[5]の結果から S-1＋シスプラチン（CDDP）併用療法が選択されるべきであるが，2011年 ASCO-GI で発表された START 試験[6]における S-1+ ドセタキセル（DOC）併用療法や，第Ⅰ・Ⅱ相試験が行われている DCS 併用療法（DOC+CDDP+S-1 の３剤併用療法）も術前化学療法の有力な候補になると思われる。

本邦で進行・再発胃癌に対して行われた主な第Ⅲ相試験は，結果が報告されたものでは JCOG 9912, SPIRITS 試験, IRIS 試験, START 試験がある。

JCOG 9912[7]は，進行再発胃癌に対する国内34施設での第Ⅲ相試験であり，①フルオロウラシル（５-FU）療法（１日800mg/㎡，D１-D５，４週間，234例），②イリノテカン（CPT-11）+CDDP 療法（CPT-11：70mg/㎡，D1，D15，CDDP：80mg/㎡，D１，236例），③ S-1療法（40mg/㎡，１日２回内服，D１-D28，６週間，234例）の３群での比較試験である。MST は５-FU 群で10.8ヵ月，CPT-11+CDDP 群で12.3ヵ月，S-1群で11.4ヵ月であり，CPT-11+CDDP 群の５-FU 群に対する優越性は認めなかったが，S-1群の５-FU 群に対する非劣性は証明された。奏効率はそれぞれ９％，38％，28％であり，併用療法である CPT-11+CDDP 療法が３群間では良好であった。

SPIRITS 試験は，進行再発胃癌に対する S-1療法（40mg/㎡，１日２回内服，D１-D28，６週間，150例）と S-1+CDDP 療法（S-1：40mg/㎡，１日２回内服，D１-D21，CDDP：60mg/㎡，D８，１コース５週間，148例）との第Ⅲ相比較試験であり，MST においてそれぞれ11ヵ月，13ヵ月で S-1+CDDP 療法が有意に予後を延長していた。PFS においても同様にそれぞれ４ヵ月，６ヵ月で，S-1+CDDP 療法が優れていた。S-1+CDDP 療法の奏効率は，第Ⅱ相試験で76％と驚異的な成績であったが，この第Ⅲ相試験でも54％であり，現時点での標準治療と位置付けられている。術前化学療法に採用するにあたり，ふさわしいレジメンと言える。

また，MST では併用療法の有意性を証明できなかった IRIS 試験[8]は，進行再発胃癌に対する S-1療法と S-1+CPT-11療法（S-1：40mg/㎡，１日２回内服，D１-D21，CPT-11：80mg/㎡，D１，D15，２週間休薬）を

比較した第Ⅲ相試験である。奏効率では有意にS-1+CPT-11療法が41.5%と高く，術前化学療法のレジメンに加わる可能性はある。日本がん臨床試験推進機構（JACCRO）からは，S-1療法とS-1+DOC療法（S-1：40mg/㎡，1日2回内服，D1-D14，DOC：40mg/㎡，D1，1週間休薬）の第Ⅲ相比較試験が韓国との共同研究で行われ，2011年1月のASCO-GIでその結果が報告された。抗腫瘍効果としては十分であり，S-1+CDDP療法と同様に術前化学療法としては有力な候補になると考えられる。

海外では，米国のCF療法（CDDP+5-FU），欧州のECF療法（エピルビシン+CDDP+5-FU）が標準治療であったが，1,002例のtwo-by-two designで行われたReal 2試験[9]にて，オキサリプラチンのCDDPに対する非劣性とカペシタビンの5-FUに対する非劣性がそれぞれ証明され，これらの薬剤を用いたEOX療法は従来のECF療法との比較で有意にOSを延長した。一方，韓国ではCF療法とXP療法（カペシタビン+CDDP）の優越性を比較検討した第Ⅲ相試験が行われ，MST（9.3ヵ月 vs. 10.5ヵ月），奏効率（29% vs. 41%）ともにXP療法が優れていることが証明された。

3剤併用療法としては，欧米ではV325試験[10]としてFP療法とDCF療法（DOC+CDDP+5-FU）の第Ⅲ相試験の結果が報告され，奏効率37% vs. 25%，PFS 5.6ヵ月 vs. 3.7ヵ月，MST 9.2ヵ月 vs. 8.6ヵ月の成績で，DOCの上乗せ効果が証明され，切除不能胃がんの標準治療のひとつであるとしている。本邦ではDCS併用療法（DOC+CDDP+S-1）があるが，いわゆる札幌医大レジメン[11]，金沢大学レジメン[12]，北里大学レジメン[13]の投与スケジュールが発表されており，いずれも期待通り高い奏効率でそれぞれ87.1%，77.8%，82.5%と報告されている。しかし，grade3/4の好中球減少，発熱性好中球減少の頻度が高く，術前化学療法のレジメンとしては慎重にならざるを得ず，第Ⅱ相試験にて手術へ向けての安全性が証明されなければならない。

また，分子標的治療薬を加えた併用療法のglobalな第Ⅲ相試験については，ToGA試験[14]，AVAGAST試験[15]の成績がすでに報告されている。ToGA試験は，5-FU or カペシタビン+CDDPに対するHER family inhibitorのひとつであるトラスツズマブの上乗せ効果をHER2陽性進行胃癌においてみたものである。奏効率47.3% vs. 34.5%，PFS 6.7ヵ月 vs. 5.5ヵ月，MST 13.8ヵ月 vs. 11.1ヵ月で，いずれも有意差をもってトラスツズマブ群が良好であった。AVAGAST試験は，カペシタビン+CDDPに対する血管新生阻害剤のひとつであるベバシズマブの上乗せ効果をみたもので，OSでは優越性を証明できなかったものの（12.1ヵ月 vs. 10.1ヵ月），PFS（6.7ヵ月 vs. 5.3ヵ月），奏効率（46% vs. 37%）では有意に良好であると報告された。

術前化学療法に関する臨床試験には，術前術後ECF療法をセットにしたperi-operative chemotherapyとしてMAGIC試験[16]が欧州で行われ，切除可能進行胃癌に対する治療として優越性（5年生存率：36%）が証明された。しかし，本邦における同等の病期の手術単独治療の5年生存率が71.4%であり，手術による治療成績の差が大きく，本邦独自の術前化学療法確立の必要性が示された[17]。国内では術前化学療法に関する主な臨床試験にJCOG0001[18]，JCOG0405[19]がある。CPT-11+CDDP療法を術前化学療法としたJCOG0001は，Primary endpointである治療関連死（TRD）が55例登録した段階で3例（5.5%）となり，試験は中止された。JCOG0405「高度リンパ節転移を伴う進行胃癌に対

表1　術前化学療法レジメン候補

・2剤併用療法
　S-1+α……S-1+CDDP，S-1+DOC

・3剤併用療法
　DCS 療法……DOC+CDDP+S-1
　　（札幌医大，金沢大学，北里大学）

・併用療法＋分子標的治療薬
　トラスツズマブ…カペシタビン（or S-1）+ CDDP + トラスツズマブ
　　2剤併用療法 + トラスツズマブ
　　3剤併用療法 + トラスツズマブ

表2　治療効果

	全症例	S1+CDDP	S1+Taxane	切除例
CR	2	1	1	2
PR	21	15	6	12
SD	39	12	27	17
PD	12	8	4	0
腫瘍制御率（%）	83.8	77.8	89.5	100

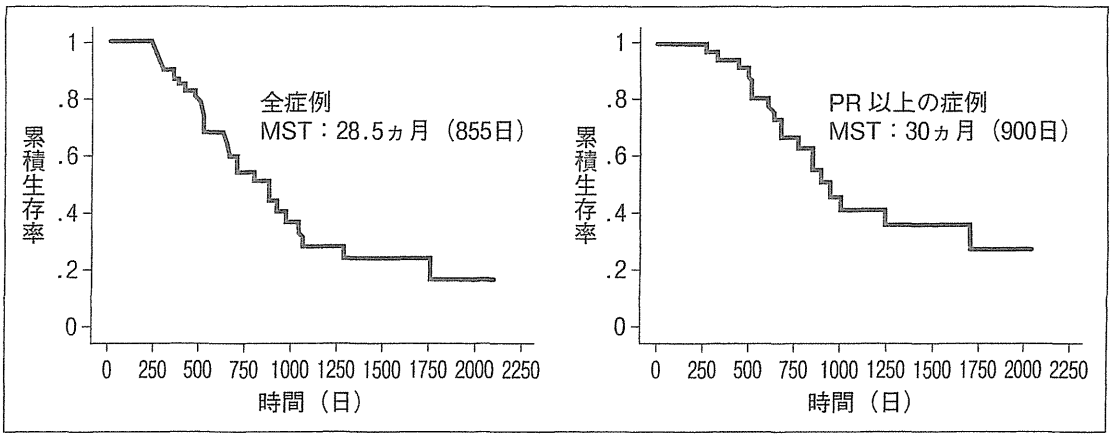

図3　Stage Ⅳ切除症例の生存曲線（抗腫瘍効果別）

する，術前 S-1+CDDP 併用療法＋外科切除の第Ⅱ相臨床試験」は，Primary endpoint とされた根治切除割合は82.4%であり，奏効率64.7%で TRD もなく安全に手術が行われたと評価された。

以上をまとめると，本邦で候補にあがる術前化学療法のレジメンは，2剤併用療法として S-1+CDDP，S-1+DOC，3剤併用療法として DCS 療法，個別化治療も考慮した分子標的治療薬を加えた治療が考えられる（表1）。術前化学療法に必要な条件は前述したが，奏効率と手術の安全性がとくに重要であり，今後，Inter-group study も考慮した登録スピードの速い臨床試験が進められることを期待したい。切除可能進行胃癌においては，手術＋術後補助化学療法に対する術前化学療法の上乗せ効果を，切除不能進行胃癌においては化学療法に対する手術の上乗せ効果を証明する必要がある。

当科での取り組み

当科では，切除不能進行胃癌に対する治療の第1選択として S-1+DOC 併用療法を採用している。当院消化器内科で治療が行われた症例も含めると，S-1+α 治療が一次治療で選択された症例は74例であり，31例に胃切除

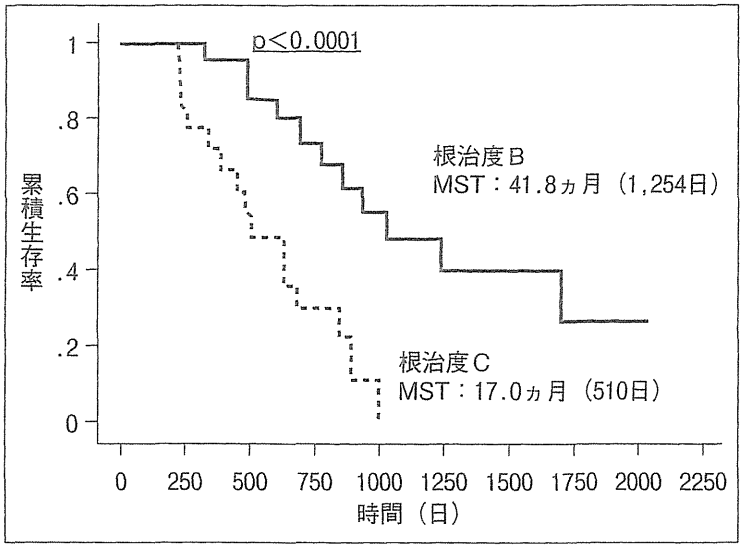

図4　Stage Ⅳ切除症例の生存曲線（根治度別）

術が行われていた。全症例のMSTは14.3ヵ月，disease control rateは83.8%，奏効率は31.1%であった（表2）。切除症例について検討すると，PD症例はなくMSTは28.5ヵ月であり，PR以上の症例では30ヵ月のMSTが得られた（図3）。さらに手術の結果として根治度Bと根治度Cに分けて検討すると，有意に根治度B症例の予後が延長されていた（図4）。Retrospectiveな検討であるが，Stage Ⅳ胃がんに対するadjuvant surgeryの効果として，症例を選択すれば長期生存が得られる可能性が期待できる。Adjuvant surgeryの有効性を証明するには臨床試験が必要であり，ある一定の効果が得られたStage Ⅳ症例を，標準治療である抗がん剤治療を可能な限り行う群と手術を加える群に分け，OSをprimary endpointとしたrandomized control trialが早急に望まれる。当科では，第Ⅲ相試験に向けての手術の安全性を評価するため，第Ⅱ相試験を計画し，現在進行中である。

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Placental Growth Factor and Soluble c-Kit Receptor Dynamics Characterize the Cytokine Signature of Imatinib in Prostate Cancer and Bone Metastases

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To assess the hypothesis that the dynamics of plasma angiogenic and inflammatory cytokines after docetaxel chemotherapy with or without the c-kit/abl/platelet-derived growth factor receptor (PDGFR) inhibitor imatinib mesylate for prostate cancer are associated with outcome, the kinetics of 17 plasma cytokines before versus after chemotherapy were assessed and associations with progression-free survival (PFS) examined. After adjusting for multiple tests, significantly different declines in placental growth factor (PIGF), soluble vascular endothelial growth factor receptor-1 (VEGFR1), VEGF, and soluble c-kit were observed with docetaxel plus imatinib ($n = 41$) compared to docetaxel alone ($n = 47$). Based on a piecewise linear regression model for change in concentration of each cytokine as a function of the probability of change in p-PDGFR *in vivo*, only the dynamics of PIGF ($P < 0.0001$) and soluble c-kit ($P < 0.0001$) differed with imatinib therapy. In a Bayesian log-normal regression model for PFS, a rise in human matrix metalloproteinase 9 after docetaxel alone associated with a longer PFS. Distinct plasma angiogenic cytokines are modified by imatinib and partitioned by *in vivo* p-PDGFR dynamics after docetaxel chemotherapy for metastatic prostate cancer. Plasma PIGF and soluble c-kit kinetics are candidate biomarkers of imatinib effect. The predictive value of human matrix metalloproteinase 9 kinetics for docetaxel efficacy requires prospective validation.

Introduction

Improved outcomes with docetaxel chemotherapy for advanced castration-resistant prostate cancer are being sought with novel combinations that target putative mechanisms of disease progression and drug resistance. Preclinical modeling indicated that the platelet-derived growth factor and its receptor (PDGFR) were upregulated in prostate cancer cells proliferating within the bone microenvironment (Uehara and others 2003). The PDGFR was observed to be upregulated in endothelial cells of vasculature specifically associated with PDGF-expressing tumor, and the PDGFR inhibitor imatinib potentiated taxane efficacy via enhanced endothelial apoptosis, an antivascular effect (Uehara and others 2003; Kim and others 2006).

Contrary to preclinical estimates, a randomized controlled study that compared the efficacy of imatinib in combination with docetaxel versus docetaxel alone in men with castration-resistant prostate cancer and bone metastases showed no added benefit with imatinib (Mathew and others 2007). Unexpectedly, *in vivo* pharmacodynamic monitoring of PDGFR inhibition showed that, within the docetaxel arm, an increased probability of PDGFR activation in peripheral blood leucocytes correlated with improved progression-free survival (PFS) and overall survival (OS) (Mathew and others 2008). Rising plasma PDGF levels were associated with a decreased probability of PDGFR activation and inferior PFS (Mathew and others 2008). While the fundamental biological implications of these observations are yet to be determined, these partitioned outcomes were not equally detected in the docetaxel–imatinib combination arm.

To further explore the dynamic signature of plasma cytokines and their prognostic impact after docetaxel chemotherapy, a panel of 17 additional angiogenic and inflammatory cytokines was constructed. Individual cytokine kinetics between baseline (BL) and after docetaxel exposure, modulation by concurrent PDGF inhibitor therapy, and association with PFS outcomes were studied.

Methods

Patients

One hundred sixteen men were enrolled to a randomized study of docetaxel with placebo or imatinib for metastatic castration-resistant prostate cancer and bone metastases (Mathew and others 2007). Of these, 88 paired plasma samples

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at BL and 6 weeks later after one cycle of weekly docetaxel-based therapy at cycle 2 day 1 (C2D1) were available.

Multiplex cytokine assay

Plasma levels of all analytes described here were subsequently analyzed in duplicates using a multiplex platform, Meso Scale Discovery (MSD) (Gaithersburg, MD). The analytes were soluble c-kit receptor (c-kit), soluble vascular endothelial growth factor receptor-2 (sVEGFR2, KDR), fibroblast growth factor, VEGF, sVEGFR1, placental growth factor (PlGF), interleukin (IL)2, IL8, IL12p70, IL10, granulocyte macrophage-colony stimulating factor, interferon-γ, IL6, IL10, tumor necrosis factor-α, transforming growth factor-β, and matrix metalloproteinase-(MMP)-9. All reagents were provided with the MSD kits and tests conducted according to the manufacturer's instructions.

Statistical methods

Numerical variables were summarized using means and standard deviations, with association between pairs of variables estimated by Pearson's correlation coefficient (Snedecor and Cochran 1980). The Wilcoxon signed rank test was used for 2 sample comparisons of numerical variables (Hollander and Wolfe 1979), applying the Bonferroni P value correction for multiple tests (Snedecor and Cochran 1980). For each cytokine, the Bayesian regression model and method of Morita and others (2010) were employed to evaluate the effects of change in the cytokine level from BL to C2D1 on PFS time while accounting for the effects of hemoglobin, change in prostate-specific antigen (PSA), and change in p-PDGFR. For each patient, because p-PDGFR was measured in ~2,000 cells both at BL and at C2D1, the within-patient BL and C2D1 distributions of p-PDGFR could be estimated very reliably. Because both the BL and C2D1 distributions of p-PDGFR were clearly bimodal for all patients, the within-patient change in p-PDGFR could not be summarized usefully as the difference between the C2D1 and BL sample means. Rather, a mixture model accounting for the observed bimodality first was fit and used to estimate the differences between the right modes, denoted by δ_{Ri}, and the differences between the left modes, denoted by δ_{Li}, for the within-patient C2D1-versus-BL distributions of p-PDGFR, for each patient, $i = 1, \ldots, 88$.

In the Bayesian regression model for PFS (Morita and others 2010), δ_{Ri} was used as a covariate representing change in p-PDGFR from BL to C2D1. This was done because the values of δ_{Ri} were much larger than δ_{Li}, and moreover δ_{Ri} was strongly associated with longer PFS. Based on preliminary goodness-of-fit analyses, it was assumed that the logarithm of PFS time was normally distributed, equivalently, that PFS was lognormal. The linear component of the lognormal regression model is the mean of log(PFS time), defined as follows. For patient i and cytokine $j = 1, \ldots, 17$, denote the (BL, C2D1) cytokine values by (X_{ij}, Y_{ij}), the difference between the log-transformed cytokine values by $W_{ij} = \log(Y_{ij}) - \log(X_{ij})$, $Z_{1i} = 1$ if treatment was docetaxel+imatinib (DI) and 0 if docetaxel+placebo (DP), Z_{2i} = Hb at BL, and Z_{3i} = change in PSA from BL to C2D1. For cytokine j and patient i, the linear component was assumed to be

$$\begin{aligned}\eta_j = {} & \beta_0 + \beta_1 Z_{1i} + \{\beta_2 Z_{1i} + \beta_3(1 - Z_{1i})\} Z_{2i} \\ & + \{\beta_4 Z_{1i} + \beta_5(1 - Z_{1i})\} Z_{3i} \\ & + \{\beta_6 Z_{1i} + \beta_7(1 - Z_{1i})\} \delta_{Ri} \\ & + \{\beta_8 Z_{1i} + \beta_9(1 - Z_{1i})\} W_{ij}\end{aligned}$$

In terms of their effects on PFS time, the parameters in the linear term may be interpreted as follows:

β_1 = main DI-vs-DP treatment effect
β_2 = effect of baseline Hb in the DI arm
β_3 = effect of baseline Hb in the DP arm
β_4 = effect of change in PSA in the DI arm
β_5 = effect of change in PSA in the DP arm
β_6 = effect of change in p-PDGFR in the DI arm
β_7 = effect of change in p-PDGFR in the DP arm
β_8 = effect of change in cytokine value in the DI arm
β_9 = effect of change in cytokine value in the DP arm

Using the large (n = ~2,000 cells) within-patient p-PDGFR samples taken at BL and at C2D1, the probability of decrease in p-PDGFR after treatment, denoted by Pr(Decr), was estimated very reliably for each patient as a standardized Wilcoxon statistic. Specifically, each patient's Pr(Decr) was computed as the mean over all 0/1 indictors that each BL value of p-PDGFR was larger than each C2D1 value. For each cytokine, the following piecewise linear regression model for the BL to C2D1 change in cytokine value, W_{ij}, as a function of the estimated Pr(Decr) was fit.

$$\begin{aligned}W_{ij} &= b_{0,t} + e_{ij} \text{ if } \Pr(\text{Decr}) \le 0.5 \\ &= b_{0,t} + b_{1,t} * \{\Pr(\text{Decr}) - 0.5\} \\ &\quad + e_{ij} \text{ if } \Pr(\text{Decr}) > 0.5,\end{aligned}$$

for treatment arm t = DI or DP, where e_{ij} denotes normally distributed random measurement error. Under this model, in treatment arm t, on average the BL to C2D1 change in the cytokine value equals the constant $b_{0,t}$ if Pr(Decr) $\le$0.5 and equals the straight line $b_{0,t} + b_{1,t}$ *{Pr(Decr) – 0.5} if Pr(Decr) > 0.5. The cut-off 0.5 was used because Pr(Decr) = 0.5 corresponds to no change in the cytokine from BL to C2D1, whereas Pr(Decr) $\ge$ 0.5 and Pr(Decr) < 0.5 correspond, respectively, to the cytokine going down or up, on average. The piecewise linear form was chosen based on preliminary goodness-of-fit plots of each cytokine change as a function of Pr(Decr). Under the null hypothesis $(b_{0,DP}, b_{1,DP}) = (b_{0,DI}, b_{1,DI})$, the piecewise linear model is the same for the 2 treatment arms. This null hypothesis corresponds to the kinetics of the cytokine, as a function of Pr(Decr), not changing with the addition of imatinib to docetaxel.

Results

The distributions of the 17 plasma angiogenic and inflammatory cytokines at BL and at C2D1 within each treatment arm are summarized in Table 1. These results indicate a significant decline in IL6 and significant increases in PlGF and soluble VEGFR1 in the docetaxel-placebo arm, and a significant decline in soluble c-kit and increase in IL10 in the docetaxel-imatinib arm. Table 2 summarizes changes in cytokine values from BL to C2D1, compared between treatment arms using the Wilcoxon rank sum test. These tests indicate significantly larger declines in PlGF, soluble c-kit,

TABLE 1. MEANS AND STANDARD DEVIATIONS (IN PARENTHESES) OF CYTOKINE VALUES AT BASELINE AND AT COURSE 2 DAY 1 OF CHEMOTHERAPY

	Docetaxel + placebo			*Docetaxel + imatinib*		
Cytokines	*BL*	*C2D1*	*P*	*BL*	*C2D1*	*P*
TGFβ	0.84 (0.22)	0.90 (0.19)	0.009	0.82 (0.22)	0.79 (0.18)	0.586
bFGF	−1.67 (0.24)	−1.67 (0.24)	0.439	−1.65 (0.22)	−1.64 (0.21)	0.881
PIGF	−1.30 (0.09)	−1.20 (0.12)	<0.001[a]	−1.28 (0.09)	−1.35 (0.11)	0.002
sVEGFR1	−0.68 (0.08)	−0.60 (0.10)	<0.001[a]	−0.65 (0.14)	−0.61 (0.26)	0.166
VEGF	−0.77 (0.14)	−0.73 (0.17)	0.05	−0.80 (0.17)	−0.86 (0.16)	0.004
c-kit	0.85 (0.16)	0.86 (0.15)	0.508	0.83 (0.13)	0.70 (0.15)	<0.001[a]
sVEGFR2	1.23 (0.13)	1.24 (0.14)	0.317	1.21 (0.15)	1.19 (0.15)	0.021
hMMP9	1.95 (0.22)	1.99 (0.29)	0.354	1.91 (0.25)	1.83 (0.23)	0.074
GM-CSF	−0.64 (1.14)	−0.68 (1.10)	0.529	−0.47 (0.71)	−0.58 (0.80)	0.05
IFNγ	−0.02 (0.74)	−0.20 (0.77)	0.071	0.13 (0.67)	0.09 (0.89)	0.834
IL10	0.39 (0.92)	0.56 (0.79)	0.019	0.64 (0.67)	0.91 (0.75)	<0.001[a]
IL12p70	0.46 (0.72)	0.50 (0.70)	0.184	0.40 (0.52)	0.39 (0.55)	0.167
IL1β	−0.77 (0.75)	−0.84 (0.73)	0.253	−0.49 (0.64)	−0.58 (0.72)	0.265
IL2	−0.15 (0.55)	−0.27 (0.59)	0.013	0.02 (50)	−0.03 (0.57)	0.677
IL6	0.43 (0.45)	0.06 (0.59)	<0.001[a]	0.57 (0.52)	0.30 (0.54)	0.002
IL8	0.76 (0.20)	0.72 (0.24)	0.068	0.76 (0.18)	0.81 (0.27)	0.178
TNFα	0.90 (0.18)	0.84 (0.19)	0.012	0.97 (0.37)	0.97 (0.32)	0.752

Comparisons of C2D1-versus-BL for each cytokine within each treatment arm were done using the Wilcoxon rank sum test. Using testwise *P* value 0.05 and a Bonferroni adjustment for multiple testing, with 34 tests, a *P* value <0.00147 implies significant change for that cytokine in that treatment arm.

[a]Significant *P* values.

bFGF, basic fibroblast growth factor; BL, baseline; C2D1, cycle 2 day 1; GM-CSF, granulocyte macrophage-colony stimulating factor; hMMP9, human matrix metalloproteinase; IFNγ, interferon gamma; IL, interleukin; PIGF, placental growth factor; sVEGFR, soluble vascular endothelial growth factor receptor-2; TGFβ, transforming growth factor beta; TNFα, tumor necrosis factor alpha.

VEGF, and sVEGFR1 in the docetaxel-imatinib arm compared to the docetaxel-placebo arm, on average. The largest individual quantitative difference in cytokines between the arms was the decline in soluble c-kit in the docetaxel-imatinib arm.

TABLE 2. MEANS AND STANDARD DEVIATIONS (IN PARENTHESES) OF CHANGE FROM BASELINE TO COURSE 2 DAY 1 OF CHEMOTHERAPY FOR EACH CYTOKINE VARIABLE, WITHIN EACH TREATMENT ARM, COMPARED BETWEEN ARMS USING THE WILCOXON RANK SUM TEST

Cytokines	*Docetaxel + placebo*	*Docetaxel + imatinib*	*P*
TGFβ	0.07 (0.23)	−0.03 (0.22)	0.020
bFGF	0.01 (0.28)	0.03 (0.28)	0.847
PIGF	0.12 (0.14)	−0.08 (0.14)	<0.0001[a]
sVEGFR1	0.07 (0.12)	0.04 (0.24)	0.001[a]
VEGF	0.04 (0.13)	−0.06 (0.14)	<0.0001[a]
c-kit	<0.01 (0.08)	−0.14 (0.12)	<0.0001[a]
sVEGFR2	0.01 (0.07)	−0.03 (0.08)	0.017
hMMP9	0.04 (0.25)	−0.08 (0.26)	0.049
GM-CSF	−0.04 (0.99)	−0.08 (0.99)	0.509
IFNγ	−0.20 (0.94)	0.11 (1.24)	0.099
IL10	0.19 (0.51)	0.32 (0.52)	0.137
IL12p70	0.04 (0.22)	−0.01 (0.70)	0.075
IL1β	−0.09 (0.94)	−0.06 (1.07)	0.913
IL2	−0.14 (0.66)	0.01 (0.50)	0.095
IL6	−0.39 (0.49)	−0.27 (0.48)	0.278
IL8	−0.05 (0.20)	0.09 (0.46)	0.053
TNFα	−0.06 (0.18)	0.02 (0.23)	0.042

Using testwise *P* value 0.05 and a Bonferroni adjustment for multiple testing, with 17 tests, a *P* value <0.00294 implies significant change for that cytokine in that treatment arm.

[a]Significant *P* values.

The fitted piecewise linear regression models are summarized in Table 3. For each cytokine, the test of $(b_{0,DP}, b_{1,DP})$ $(b_{0,DI}, b_{1,DI})$ between the 2 treatment groups was performed using an *F* statistic with (2, 84) degrees of freedom. The results indicate that, among the 17 cytokines, the kinetics of 2 specific angiogenic cytokines, PIGF and soluble c-kit, differed significantly between the 2 treatment arms in terms of relationship to *in vivo* p-PDGFR dynamics, as summarized by Pr(Decr). These 2 cytokines were previously identified as among the 4 cytokines decreasing in the docetaxel–imatinib arm compared to the docetaxel–placebo arm (Table 2).

A total of 17 Bayesian log-normal regression models for PFS were fit, one for each cytokine. Because it would be far too cumbersome to tabulate all 17 fitted models, we present only the estimated effects of the C2D1-versus-BL cytokine changes, within each treatment arm, on PFS time. These are the parameters denoted above by β_8 and β_9 in the model linear component. Because parameters are random quantities under a Bayesian model, each parameter has a posterior distribution under the fitted model. For each combination of cytokine and treatment arm, Fig. 1 summarizes the posterior distribution of the parameter in terms of a 95% credible interval. This interval is represented by a vertical line running from the 2.5th percentile up to the 97.5th percentile of the effect's posterior distribution, with the posterior mean represented by an open circle for the DI arm and by a filled circle for the DP arm. Thus, each vertical line summarizes the middle 95% of the effect's posterior distribution. Under the Bayesian model, a line having lower limit near or above the horizontal line at 0 corresponds to a significant increase in PFS as a function of the C2D1-versus-BL cytokine change. For example, a line for β_8 having lower limit 0 would correspond to posterior probability $\Pr(\beta_8 > 0 \mid \text{data}) = 0.975$.

TABLE 3. SUMMARIES OF 17 FITTED REGRESSION MODELS, ONE FOR EACH CYTOKINE

Cytokine	Parameter	Docetaxel + placebo		Docetaxel + imatinib		Test for homogeneity between treatment groups P value
		Estimate	SE	Estimate	SE	
TGFβ						0.013
	Intercept	0.024	0.034	−0.061	0.041	
	Slope	1.825	0.661	0.555	0.379	
bFGF						0.431
	Intercept	−0.038	0.044	−0.008	0.053	
	Slope	1.826	0.858	0.504	0.492	
PlGF						<0.001[a]
	Intercept	0.131	0.023	−0.084	0.027	
	Slope	−0.336	0.442	0.037	0.253	
sVEGFR1						0.772
	Intercept	0.070	0.030	0.052	0.036	
	Slope	0.036	0.585	−0.228	0.335	
VEGF						0.004
	Intercept	0.032	0.022	−0.067	0.026	
	Slope	0.321	0.421	0.114	0.241	
c-kit						<0.001[a]
	Intercept	0.005	0.017	−0.139	0.020	
	Slope	−0.046	0.321	−0.005	0.184	
sVEGFR2						0.157
	Intercept	0.01	0.012	−0.018	0.015	
	Slope	−0.01	0.235	−0.16	0.135	
hMMP9						0.111
	Intercept	0.041	0.041	−0.095	0.05	
	Slope	−0.097	0.797	0.255	0.457	
GM-CSF						0.122
	Intercept	−0.160	0.159	0.073	0.190	
	Slope	5.201	3.057	−2.396	1.752	
IFNγ						0.630
	Intercept	−0.265	0.178	0.010	0.212	
	Slope	2.894	3.422	1.531	1.962	
IL10						0.246
	Intercept	0.245	0.083	0.358	0.100	
	Slope	−2.28	1.606	−0.552	0.921	
IL12p70						0.474
	Intercept	0.031	0.081	0.111	0.097	
	Slope	0.505	1.558	−1.782	0.893	
IL1β						0.922
	Intercept	−0.112	0.164	−0.034	0.195	
	Slope	0.986	3.148	−0.463	1.805	
IL2						0.475
	Intercept	−0.117	0.097	0.020	0.116	
	Slope	−0.865	1.865	−0.097	1.069	
IL6						0.169
	Intercept	−0.447	0.078	−0.236	0.093	
	Slope	2.393	1.499	−0.464	0.860	
IL8						0.156
	Intercept	−0.062	0.056	0.114	0.067	
	Slope	0.638	1.077	−0.36	0.618	
TNFα						0.129
	Intercept	−0.071	0.033	0.037	0.040	
	Slope	0.348	0.632	−0.227	0.362	

In each model, the change in cytokine value from BL to C2D1 is a piecewise linear function of the estimated Pr(Decr) for p-PDGFR, with different parameters for the 2 treatment groups, where Pr(Decr) is the estimated probability that p-PDGFR decreased from BL to C2D1. For each fitted model, the test for identical intercept and slope parameters in the treatment groups, "homogeneity," is based on an *F*-statistic with (2, 84) degrees of freedom. Using testwise *P* value 0.05 and a Bonferroni adjustment for multiple testing, with 17 tests, a *P* value <0.00294 implies significant heterogeneity between treatment groups, implying different p-PDGFR dynamics with versus without imatinib for that cytokine.

[a]Significant *P* values.

PDGFR, platelet-derived growth factor and its receptor; SE, standard error.

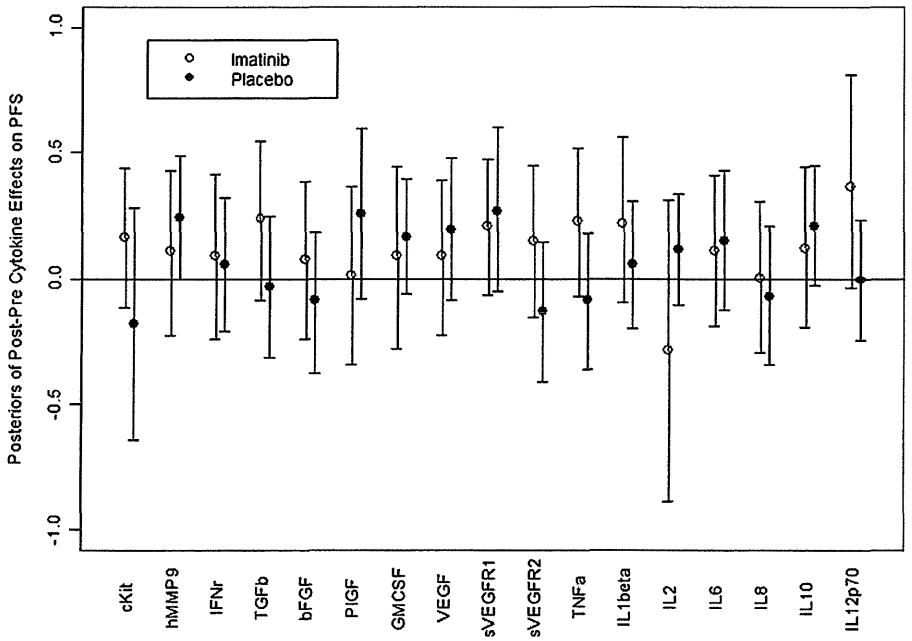

FIG. 1. Estimated posterior effect of each cycle 2 day 1-to-baseline cytokine change on progression-free survival (PFS) the baseline to cycle 2 day 1 change on PFS time for each cytokine within each treatment arm. Each effect was estimated under a Bayesian log-normal regression model, also accounting for the effects of Hb, change in prostate-specific antigen, and change in p-platelet-derived growth factor and its receptor. The posterior distribution of the parameter quantifying the effect of the in terms of a 95% credible interval. This interval is represented by a vertical line running from the 2.5th percentile to the 97.5th percentile of the effect's posterior distribution, with the posterior mean represented by an *open circle* for the docetaxel+ imatinib arm and a *filled circle* for the docetaxel+placebo arm.

This would say that, given the observed data, the posterior probability that the effect of the cytokine's change on PFS is positive equals 0.975, a nominally significant effect. A vertical line with mean at 0 would correspond approximately to posterior probability $\Pr(\beta_8 > 0 \mid \text{data}) = 0.50$, interpreted as the cytokine change having no effect on PFS. Figure 1 shows that, in the DP arm, human MMP9 (hMMP9) had a significant effect, whereas nearly significant effects on PFS were seen for soluble VEGFR1 and IL-10. In the DI arm, a nearly significant effect on PFS was seen for IL-12p70.

Discussion

In this study, the kinetics of 17 angiogenic and inflammatory cytokines in men with metastatic castration-resistant prostate cancer receiving docetaxel with or without the c-kit/abl/PDGFR inhibitor imatinib mesylate were examined. Post-treatment cytokines are significantly modified compared to BL in both treatment arms (Table 1), and several differences vary significantly between both treatment arms (Table 2). Our prior observations had indicated that the status of p-PDGFR activation in peripheral blood leucocytes after docetaxel chemotherapy for castration-resistant prostate cancer associated with PFS and OS (Mathew and others 2008). We then studied the differences in cytokine kinetics between the 2 treatment arms when specifically partitioned by post-treatment *in vivo* p-PDGFR dynamics in peripheral blood leucocytes (Table 3). We find that among these 17 cytokines, PIGF and soluble c-kit dynamics specifically comprise the cytokine signature of imatinib effect after docetaxel chemotherapy.

Decline in soluble c-kit after imatinib therapy has been previously reported in gastrointestinal stromal tumors and has been proposed as a predictive factor for favorable outcome in that disease state (Bono and others 2004, DePrimo and others 2009). In this study, soluble c-kit decline in the imatinib-containing arm was the largest quantitative cytokine difference between the 2 arms. Along with PIGF kinetics, soluble c-kit post-treatment differences retained strong statistical significance when partitioned by p-PDGFR dynamics in peripheral blood leucocytes. These observations may be concordant with the mechanism of action of imatinib as a PDGFR and c-kit inhibitor.

Surprisingly however, in the imatinib arm, increases in soluble c-kit rather than decreases trended toward a favorable PFS profile (Fig. 1) and similarly larger post-treatment values of PIGF and VEGF after docetaxel-alone therapy trended toward an improved PFS. Together, these trends suggest that the cytokine profiles associated with imatinib (c-kit, PIGF, and, to a lesser extent, VEGF declines) compare unfavorably when compared to those generated by docetaxel alone. These findings are also compatible with our previous observations that decreased activation of p-PDGFR in peripheral blood leucocytes after imatinib exposure associated with shorter PFS times (Mathew and others 2008). With the exception of hMMP9 kinetics after docetaxel therapy alone, multivariate analysis of individual cytokine profiles did not yield an independent predictor of outcome. It is conceivable that, with larger numbers of patients, a composite picture of a favorable cytokine signature potentially linked to an *in vivo* mechanism of action of docetaxel may emerge through such cytokine profiling studies.

Declines in the angiogenic cytokines, PIGF, and VEGF after imatinib therapy have not been reported previously. The altered dynamics of these cytokines together with those previously reported with PDGF (Mathew and others 2008) comprise a candidate cytokine signature of imatinib effect in prostate cancer and bone metastases after docetaxel chemotherapy. Formal mechanistic studies will be required to identify the putative link between the regulation of plasma PIGF and VEGF levels and imatinib therapy. It is conceivable that kinetics of these markers may have predictive value in other disease states, hematological and solid neoplasia, in which imatinib has been established as standard therapy, as these circulating cytokines may not be tumor specific.

Before this report, there have been few studies that demonstrate the profile of changes and/or the predictive value of inflammatory and angiogenic cytokine dynamics after docetaxel therapy in prostate cancer. The wide range of

nonhematological toxicities observed with docetaxel, such as peripheral edema or pleural effusions that reflect vascular effects, or fatigue and pneumonitis that reflect proinflammatory effects, are likely to be reflected in plasma cytokine dynamics after treatment. In 2 prior studies, declines in plasma IL6 associated with PSA-declines after docetaxel were reported; however, associations with PFS or OS were not assessed (Domingo-Domenech and others 2006; Ignatoski and others 2009). Our observations do not support a significant association of IL6 decline after docetaxel with PFS (Fig. 1). While significant increases in PIGF and sVEGFR1 and significant decreases in IL6 were observed after docetaxel therapy (Table 1), only an increase in hMMP9 associated with improved PFS (Fig. 1). Elevated hMMP9 expression in prostate cancer has been associated with improved disease-free and OS after prostatectomy for localized prostate cancer (Boxler and others 2010), but a link of plasma MMP9 dynamics with docetaxel efficacy has not been described to our knowledge. These findings suggest the potential predictive value of a cytokine dynamic signature after chemotherapy for prostate cancer, for which larger prospective studies will be required for validation.

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Application of the continual reassessment method to a phase I dose-finding trial in Japanese patients: East meets West

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After cancer-related phase I dose-finding trials are completed in Western countries, further phase I trials are often conducted to determine recommended doses (RDS) for Japanese patients. This may be due to concerns about possible differences in treatment tolerability between Caucasians and Japanese. In most of these, a conventional '3+3' cohort study design is used in making dose escalation decisions, possibly due to its relatively easy implementation. Since its proposal by O'Quigley *et al.* (1990; *Biometrics*, 46:33–48), the continual reassessment method (CRM) has been used increasingly in cancer-related phase I dose-finding studies as an alternative to '3+3' designs. One of the principal advantages of applying a Bayesian CRM may be the utilization of all available prior information to estimate RDS through prior distributions that are assumed for model parameters representing the dose–toxicity relationship. In this paper, we present an application of the Bayesian CRM to a phase I dose-finding study in Japanese patients with advanced breast cancer using an informative prior elicited from clinical investigators. In some settings, it may be appropriate to use an informative prior that reflects the accurate and comprehensive previous knowledge of clinical investigators. On the other hand, for a model-based Bayesian outcome-adaptive clinical trial, it is necessary to establish sufficiently vague priors so that accumulating data dominate decisions as the amount of observed data increases. Thus, we retrospectively investigated the relative strength of the prior using a recently proposed method to compute a prior effective sample size. Copyright © 2011 John Wiley & Sons, Ltd.

Keywords: continual reassessment method; dose-finding; phase I trial; prior distribution; prior effective sample size

1. Introduction

After cancer-related phase I dose-finding trials are completed in Western countries, Japanese investigators often conduct trials using the same regimens in Japan to find the optimal doses for Japanese patients. This may be because of concerns about possible differences in treatment tolerability between Caucasians and Japanese. In many cases, recommended doses (RDs) of treatments have been set at higher levels in Caucasians than in Japanese. For example, a phase I study of Taxotere (docetaxel) monotherapy was undertaken in Caucasians to test dose levels from 5 to 115 mg/m^2 [1]. This study identified 100 mg/m^2 as the RD. A subsequent phase I study in Japan tested dose levels from 20 to 90 mg/m^2, and determined that 60 mg/m^2 was the RD for Japanese patients [2].

Japanese clinical investigators develop phase I trial study designs using observed toxicity data and RD levels identified in Western trials as pre-study information. For example, they test a smaller number of dose levels than the original study at doses that account for the RDs in Caucasian patients. In most of these Japanese phase I trials, a conventional '3+3' cohort design is used for making dose escalation decisions, possibly due to its relatively easy implementation and statistical simplicity and the fact that clinical investigators are in general quite familiar with it.

Since its proposal by O'Quigley *et al.* [3], the continual reassessment method (CRM) has been increasingly used in phase I dose-finding studies in cancer patients as an alternative to the '3+3'

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design. The CRM, based on a Bayesian parametric model that includes a logistic and a power model [3, 4] is characterized by one or more model parameters representing the dose–toxicity relationship. Although two-parameter models are flexible, they generally require a larger number of patients to estimate two model parameters, e.g. intercept and slope. One-parameter models that analyze one aspect of the dose–toxicity curve (in many cases, the slope) may not be flexible enough to accurately estimate the entire dose–toxicity curve. However, because a one-parameter model in the CRM has proven to be robust in determining a RD [3], it may be reasonable to use a one-parameter model for dose-finding in a cancer phase I trial.

The prior distributions assumed for model parameters are derived from pre-study information and are updated based on accumulated toxicity data observed in consecutive patient cohorts. The prior distribution of the model parameter should reasonably represent clinical investigators' uncertainty about the dose–toxicity relationship before starting the study, sometimes based on historical data from previous clinical studies. A Bayesian approach that formally uses historical/external data to establish such a prior distribution has not yet been fully developed. However, the integration of any available prior information into the estimation of RD levels for Japanese patients may be one of the major advantages of applying Bayesian CRM.

In some settings, it may be appropriate to use an informative prior that reflects the accurate and comprehensive knowledge that clinical investigators already possess. On the other hand, in other cases one may need to avoid excessively informative priors that may unduly influence posterior inferences. In particular, for clinical trials with a model-based Bayesian outcome-adaptive design, it is necessary to establish sufficiently vague priors so that accumulating data dominate decisions as the amount of observed data increases. After completing a Japanese phase I trial, we were concerned about the strength of the established prior distribution relative to the observed data in the trial in which 16 patients were enrolled in total. Thus, we retrospectively investigated the relative strength of the prior using a recently proposed method to compute a prior effective sample size (ESS) [5]. In this paper, we present an application of the CRM to a phase I dose-finding study in Japanese patients with advanced breast cancer using an informative prior elicited from Japanese clinical investigators.

Section 2 provides a motivating example. In Section 3, we describe the application of the CRM to a Japanese phase I study. We discuss establishment of a prior assumed for a dose–toxicity relationship in Section 4. We close with a discussion in Section 5.

2. A motivating example

Although chemotherapy regimens utilizing infusional 5-FU, e.g. the CEF-infu regimen (cyclophosphamide, epirubicin, and infusional 5-FU) [6], have been shown to have high antitumor activity, such regimens require central venous access and pumps. To avoid these inconveniences, a research team from the European Organization for Research and Treatment of Cancer (EORTC) conducted a phase I dose-finding study to develop a new combination regimen substituting the infusional 5-FU in CEF-infu with capecitabine [7]. Capecitabine (Xeloda®) is a novel oral 5-FU prodrug with high single-agent antitumor activity in metastatic breast cancer [8, 9], and also represents an attractive combination partner for the other CEF-infu chemotherapeutic agents [10–12]. The primary objective of the EORTC study was to determine the RD of capecitabine in combination with epirubicin and cyclophosphamide (CEX) in patients with advanced breast cancer. In the EORTC CEX study, four dose levels were planned for capecitabine in combination with fixed doses of epirubicin and CEX (100 and 600 mg/m^2, day 1, every 3 weeks), as summarized in Table I. Capecitabine was escalated from 750 to 1250 mg/m^2 twice daily for three weeks in four dose levels. A conventional '3+3' cohort design was used when making dose escalation decisions. That is, escalation to the next dose level was permitted if zero out of three (0/3) or one out of six (1/6) patients experienced dose-limiting toxicity (DLT). DLT is usually defined as the occurrence of grade 4 hematologic toxicity and grade 3 or 4 non-hematologic toxicity. If more than one patient developed a DLT, the maximum toxic dose (MTD) was reached, and the previous dose level was defined as the RD for phase II studies. In this study, 11 patients received CEX at four dose levels. While defining the MTD, three, three, three, and two patients were entered at dose levels 1, 2, 3, and 4, respectively, as shown in Table I. No DLTs occurred at dose levels 1, 2, and 3. At dose level 4, two out of two patients experienced DLTs. In addition, a high rate of capecitabine treatment modification (interruption and/or reduction) was required at dose level 3. Thus, the EORTC CEX study concluded

Table I. Dose levels of epirubicin and capecitabine studied in the Japanese and EORTC CEX studies and incidence of dose-limiting toxicities (DLTs) observed in the EORTC CEX study. The dose level of cyclophosphamide was fixed at 600 mg/m^2 on day 1 in both studies.

	Dose level	Epirubicin (mg/m^2, day 1 q21d)	Capecitabine (mg/m^2 twice daily, days 1–14 q21d)	Incidence of DLTs*
Japanese CEX	4	100	900	—
	3	90	900	$\frac{2}{6}$
	2	90	829	$\frac{0}{3}$
	1	75	829	$\frac{1}{4}$
	0	75	628	$\frac{0}{3}$
EORTC CEX	4	100	1250	$\frac{2}{2}$
	3		1050	$\frac{0}{3}$
	2		900	$\frac{0}{3}$
	1		750	$\frac{0}{3}$

*The number of patients experiencing any DLT/the number of evaluable patients.

that the recommended CEX regimen be limited to dose level 2 and consist of capecitabine 900 mg/m^2 twice daily, epirubicin 100 mg/m^2, and CEX 600 mg/m^2.

Although the EORTC study identified a recommended CEX regimen in this way, concern was raised over possible differences in CEX tolerability between Caucasians and Japanese [6, 13]. To answer this question, we conducted a phase I dose-finding trial using the CRM to determine the RDs of the CEX combination in Japanese patients with advanced breast cancer [14, 15]. Based on data from the EORTC CEX study and assuming that the RD of CEX in Japanese patients should not be higher than that in Caucasians, five dose levels (0–4) were planned in the Japanese CEX study, as summarized in Table I. Treatment consisted of a fixed dose of CEX (600 mg/m^2 on day 1) in combination with three doses of epirubicin and three doses of capecitabine. Dose level 4, the highest in our study, corresponded to the CEX RD as determined in the EORTC CEX analysis. The European and Japanese CEX studies employed the same DLT definitions.

3. The CRM in the Japanese cex trial

3.1. Study design using the CRM

3.1.1. Dose–toxicity model. In the CRM we used numerical dose levels X_j for $j=0,\ldots,4$, to reduce the dimension of the dose levels for the CEX treatment consisting of the three anti-cancer agents. The numerical values of X_j were specified using 'backward fitting' [16] as described below, instead of the actual dose levels for the CEX treatment in Table I. This dimension reduction allows a dose–toxicity model to suitably fit the pre-study estimates of the proportion of patients who would experience a DLT at the dose levels. The outcome variable is the indicator $Y_i=1$ if a patient i suffers a DLT, 0 if not. A one-parameter logistic regression model,

$$\pi(X_i,\beta)=\Pr(Y_i=1|X_i,\beta)=\frac{\exp(\beta_0+\beta_1 X_i)}{1+\exp(\beta_0+\beta_1 X_i)} \tag{1}$$

with the intercept b_0 fixed at 3 and a slope parameter b_1, is assumed. The likelihood for n patients is

$$f(\mathbf{Y}_n|\mathbf{X}_n,\beta)=\prod_{i=1}^{n}\pi(X_i,\beta)^{Y_i}\{1-\pi(X_i,\beta)\}^{1-Y_i}. \tag{2}$$

3.1.2. Setting up the CRM. Before starting the study, we conducted a preliminary study among participating clinical oncologists to obtain necessary reference information for implementing the CRM. We set up the CRM design using the following five steps:

(i) In step 1, we identified the target DLT probability as 0.33 and obtained the prior estimates of the proportion of patients who would experience a DLT at each dose level from 0 to 4 as 0.05, 0.10, 0.25, 0.40, and 0.60, respectively.

(ii) In step 2, we predetermined the model's intercept b_0 at 3, as discussed in Section 3.1.3.
(iii) In step 3, we specified a prior distribution function of the slope b_1. Letting $Ga(a,b)$ denote the gamma distribution with mean a/b and variance a/b^2, we assumed $Ga(a,b)$ for b_1 in order to constrain the slope b_1 to be positive and for computational convenience. This constraint implies an assumption that a higher dose level increases the probability of DLT.
(iv) In step 4, we specified numerical values of X_j for $j=0,\ldots,4$ using backward fitting as follows. We added a constraint $E(b_1)=1$ that corresponds to an equation $a=b$ in the gamma prior distribution to make the *a priori* dose–toxicity curve exactly reflect the prior estimate of DLT occurrence probabilities regardless of the degree of clinical uncertainty [17]. Under the dose–toxicity model with the slope b_1 fixed at 1, we computed each X_j to match $\Pr(Y=1|X_j,\beta_0=3,\beta_1=1)$ with the prior probability estimate of DLT occurrence at dose level j for $j=0,\ldots,4$. As a result, $\{X_0,X_1,X_2,X_3,X_4\}=\{-5.94,-5.20,-4.10,-3.41,-2.60\}$.
(v) In step 5, we specified the hyperparameters of the prior $p(b_1|a,b)$ as $a=b=5$. Details of this step are described in Section 4.

3.1.3. Specification of the intercept b_0. Under $a=b=5$ and $b_0=3$, the prior dose-toxicity curve with a 90 per cent credible interval is given in Figure 1(a). This prior dose-toxicity curve may reflect the oncologist's greater confidence in higher rather than lower dose levels. That is, taking into account that dose level 4 in the Japanese CEX study corresponds to the RD identified in the EORTC CEX study, $b_0=3$ may be a reasonable choice. In contrast, if we use a negative value for the intercept, i.e. $b_0=-5$, $\{X_0,X_1,X_2,X_3,X_4\}$ is computed as $\{2.06, 2.80, 3.90, 4.59, 5.41\}$ using backward fitting. In this setting, the prior dose–toxicity curve represents greater uncertainty in higher rather than lower dose levels (Figure 1(b)) and therefore should be considered that the specification $b_0=-5$ contradicts the pre-study information.

3.1.4. Dose escalation/de-escalation rule. Our study plan involved treating up to 22 patients. The starting dose was level 1, which was given to the first enrolled patient. The CRM then ran sequentially with three patients per cohort. Each cohort was treated at the dose level X_j with an estimated probability of DLT $\pi\{X_j, E(\beta_1|\text{data})\}$ closest to 0.33 and not exceeding 0.40. If the computed probability of the suggested dose level was greater than 0.40, the cohort was treated at the preceding dose level. Untried doses were not skipped when escalating dose level. The trial was stopped if level 0 was considered too toxic to be administered, e.g. $\pi\{X_0, E(\beta_1|\text{data})\}>0.40$. The posterior distribution of the slope parameter b_1 and each posterior estimate $\pi\{X_j, E(\beta_1|\text{data})\}$ along with its 90 per cent credible

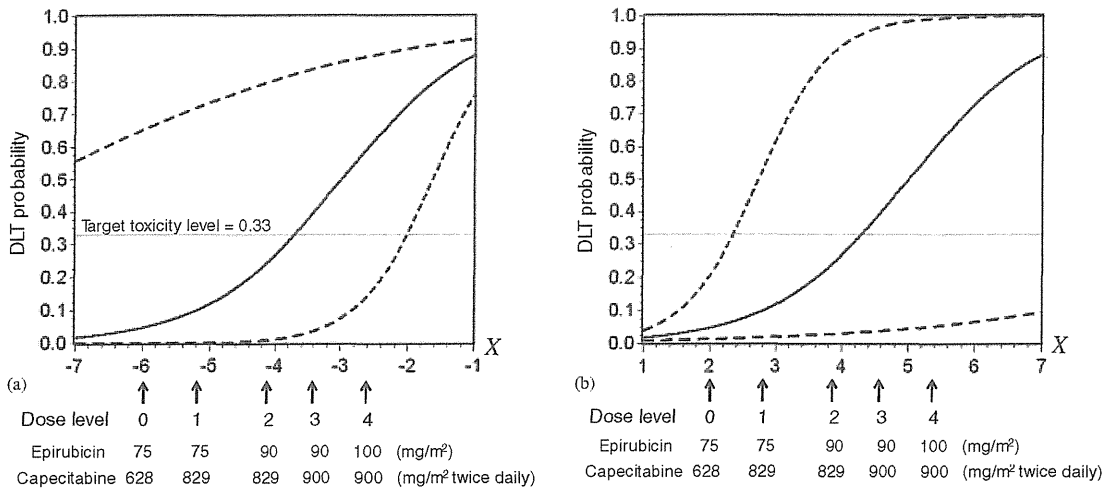

Figure 1. (a) Prior dose–toxicity curve (solid line) and its 90 per cent credible intervals (dashed lines) with the intercept $b_0=3$ under the gamma prior distribution, Ga (5,5). The horizontal axis X denotes the dose levels. The five values of $\{X1, X2, X3, X4, X5\}=\{-5.94, -5.20, -4.10, -3.41, -2.60\}$ used in the CRM computation are indicated by arrows. *The actual dose levels of epirubicin and capecitabine are also shown.* The horizontal straight line indicates the target DLT level (0.33) and (b) Prior dose–toxicity curve and its 90 per cent credible intervals with the intercept $b_0=-3$.

Table II. Incidence of dose-limiting toxicities (DLTs).

	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 5	Cohort 6
No. of evaluable patients	1	3	3	3	3	3
Doselevel*	1	0	1	2	3	3
Epirubicin (mg/m^2, day 1 q21d)	75	75	75	90	90	90
Capecitabine (mg/m^2 twice daily, days 1–14 q21d)	829	628	829	829	900	900
No. of patients experiencing any DLT	1	0	0	0	1	1
Grade 3 HFS†	1	—	—	—	—	—
Grade 3 anorexia	—	—	—	—	1	—
Grade 3 mucositis	—	—	—	—	—	1

*The dose level of CEX was fixed at 600 mg/m^2 on day 1 every 3 weeks.
†HFS, hand-foot syndrome.

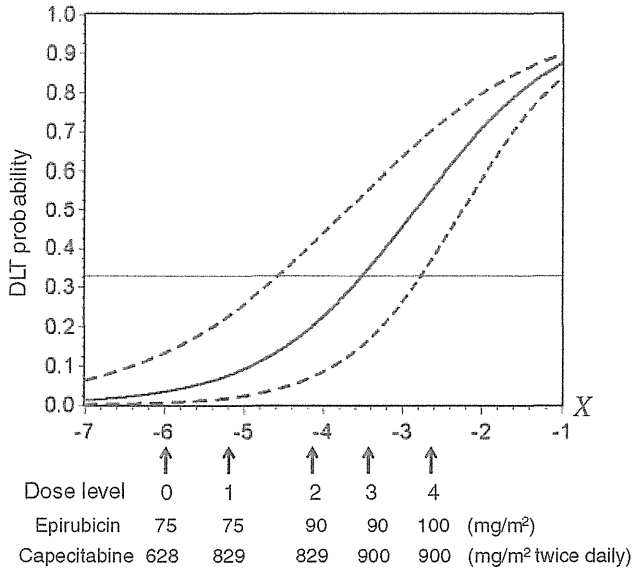

Figure 2. The posterior mean dose–toxicity curve (solid line) and its 90 per cent credible intervals (dashed lines) after updating with the toxicity data from all 16 patients.

interval were computed using numerical integration. An Independent Data and Safety Monitoring Committee (IDSMC) reviewed the interim analyses and was assigned the responsibility of making any recommendations to stop the trial on both clinical and statistical perspectives.

3.2. Implementation of the CRM

Because the results of the Japanese CEX trial were reported in detail in Saji *et al.* [14] and Morita *et al.* [15], we report here in brief. DLTs observed at each dose level and the dose escalation/de-escalation history throughout the study are shown in Tables I and II, respectively. The first patient treated at level 1 experienced a DLT (grade 3 hand-foot syndrome). The dose level was then de-escalated to level 0 for the second cohort. No DLTs were identified in the second, third (level 1), and fourth (level 2) cohorts. One of three patients in cohort 5 treated at level 3 experienced DLT (grade 3 anorexia). In the next cohort treated at level 3, one patient experienced DLT (grade 3 mucositis). Figure 2 shows the updated dose–toxicity curve including toxicity data from these 16 patients. The estimated DLT occurrence probability at level 3 was 0.354 (90 per cent credible interval: 0.174–0.560). With respect to efficacy data, one complete response and three partial responses were observed in six patients at level 3. Taking these CRM computations and the encouraging efficacy data into account, the DSMC recommended that the study be stopped. Therefore, we terminated the study and recommended that dose level 3 be further evaluated in a phase II trial.