特集 高齢者のがん治療

JCOG高齢者研究小委員会の活動と高齢大腸癌を対象とした臨床研究について

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〔*Jpn J Cancer Chemother* 42(1): 16-20, *January*, 2015〕

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Summary

Japan Clinical Oncology Group (JCOG) is a largest cooperative group in Japan, funded by the ministry of health, labor and welfare of Japanese government. We just established the Geriatric Study Committee in December 2013. The goal of this committee is to make a policy to promote clinical trials for older patients with 3 major tasks: (1) Create a clear and operational definition of vulnerability/frailty applicable to oncology, (2) Develop, test and disseminate geriatric assessments, (3) Improve research in the field of geriatric oncology, in collaboration with SIOG. JCOG1018 is a randomized phase III study of mFOLFOX7 or CAPOX plus bevacizumab versus 5-fluorouracil/Leucovorin or capecitabine plus bevacizumab as first-line treatment in elderly patients with metastatic colorectal cancer. This study includes geriatric assessments (VES-13) before chemotherapy. Key words: Geriatric assessment, G8, Colorectal cancer, Corresponding author: Fumio Nagashima, Department of Medical Oncology, Kyorin University School of Medicine, 6-20-2 Shinkawa, Mitaka, Tokyo 181-8611, Japan

要旨 高齢がんの診療では，年齢・PS以外にも虚弱（フレイル）を評価することは重要とされ，ADLや認知機能，抑うつ，併存症，服薬状況，社会的支援などのgeriatric assessment（GA）を行うことが国際老年腫瘍学会（SIOG）において推奨されている。日本臨床腫瘍研究グループ（JCOG）は高齢者研究小委員会を設置し，GAを含む臨床研究ポリシーを策定すべく検討中である。エビデンスは少ないものの高齢の切除不能大腸癌の初回化学療法として，69歳以下と70～74歳でPS 0-1の患者に対しては標準治療の導入を考慮する。一方，70～74歳の脆弱患者（PS 2）および75歳以上（PS 0-2）においては，オキサリプラチンやイリノテカンの導入には慎重な判断が必要と考えられ，JCOGでは高齢の切除不能大腸癌を対象として，オキサリプラチンの上乗せ効果をみる第III相比較試験（JCOG1018）が進行中である。

I．高齢がんにおける特殊性

国際老年腫瘍学会（International Society of Geriatric Oncology: SIOG）学術総会が2014年10月23日からポルトガルにて開催された。今年のテーマは“Bringing two worlds together: Oncology and Geriatrics”であり，腫瘍学と老年医学の重なる領域に家族および介護者に囲まれた高齢がん患者がいるという考え方が提示された。

一般に，高齢（虚弱）のがん患者では，加齢に伴う生理的変化に加えて，併存疾患による内服薬の増加，認知機能低下などの精神心理的な問題，家族形態や経済的困窮などといった社会的問題などが存在する。各患者の多様性に応じて，提供し得る治療の個別化を考慮する。高齢であっても全身状態が良好であれば非高齢者で確立している標準治療を行うが，高齢（虚弱）者でも導入できるかどうかは，治療法の強度，さらにはがん腫によって異なると考えられる。日本人死因の第1位はがんであるが，高齢になると併存症も多くなり，がん以外の死因が増えてくる。また，医療提供者は各患者の虚弱の程度を正確に把握できているとは限らない。高齢（虚弱）がんにおいては，実地診療に有用なgeriatric assessment（GA）ツールの開発と高齢者を対象とした臨床研究の推

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進といった両側面から検討を進めていくことが重要である。

Ⅱ．老年腫瘍学（geriatric oncology）の現状

長寿科学総合研究CGAガイドライン研究班によると，高齢者総合的機能評価（comprehensive geriatric assessment: CGA）は，①日常生活活動度（activity of daily life: ADL），②手段的日常生活活動度（instrumental ADL: IADL），③認知能，④情緒・気分・幸福度，⑤コミュニケーション，⑥社会的環境（家庭環境，介護者，支援体制など）を基本的構成成分として，その活用を提言している［長寿科学総合研究CGAガイドライン研究班（鳥羽研二・監修）：高齢者総合的機能評価ガイドライン．厚生科学研究所，2003］。本邦における老年医学の考え方が，腫瘍学にどのように応用できるのかは今後の課題といえる。

NCCNガイドライン（senior adult oncology）によれば加齢は個人差が大きいため，がん治療が適切かの判断は余命の推定やリスクの評価が重要であるとされている。これまでにがん診療においてもGAの有用性が報告されており，SIOGはがん診療におけるGAの実施を推奨している。2013年のSIOG学術集会において，「高齢がん患者の高齢者機能評価に関するSIOGコンセンサス」がアップデートされた。GAを行う理由として，以下の三つがあげられている。①未確認の問題およびリスクの発見，②有害転帰の予測（たとえば有害事象，機能あるいは認知力の低下，術後合併症など），③余命予測および悪性腫瘍による死亡の予測の補助である。

European Organisation for Research and Treatment of Cancer（EORTC）は，高齢のがん患者が対象である臨床試験を先導することを目的に，Eldery Task Forceを2009年に設置している。臨床試験の方法論を確立する，高齢者を評価するための共有ツールを開発する，translational researchを実施することがミッションである。SIOGおよびEORTCコミュニティーで比較的よく用いられるGAスクリーニングツールとしては，G8，vulnerable elders survey-13（VES-13），flemish version of the Triage Risk Screening Tool（fTRST）などがあり，それぞれ特徴がある。EORTCでは2014年9月以降は，全試験で70歳以上の患者を対象にG8（表1）の収集を義務付けることになった。

本邦では，2014年3月に日本臨床腫瘍研究グループ（JCOG）が高齢者研究小委員会を設置した。本邦には高齢がんを対象としたsenior adult oncologyのプログラムなどが存在しなかったため，各臓器がんグループからだけでなく，放射線治療や消化器内視鏡といった治療モダリティーに特化したグループ，精神医学，老年医学，臨床薬理学など複数領域研究者間で意見調整を行えるように配慮した。本委員会では，①高齢（虚弱）者の定義をがん治療の視点から検討，②高齢（虚弱）者をスクリーニングする実際的な方法を検討，③高齢（虚弱）者を対象とした臨床研究のための高齢者研究ポリシーをまとめることを責務としている。現在，JCOG試験共通のGAスクリーニングツールを選定する作業などを進めている。

Ⅲ．切除不能高齢者大腸癌についての取り組み

本邦の大腸癌（結腸癌・直腸癌）に関するがん統計によると，年齢階級別罹患数における後期高齢者が占める割合は36.6%である。また，2009年の年齢階級別死亡数における後期高齢者が占める割合も55.4%と大腸癌死亡者の半数以上を後期高齢者が占めている[1]。また，がん患者が最も速やかに増加するコホートは65歳以上であり，20年以内に新規大腸癌患者の75%以上，大腸癌死亡者の85%以上を65歳以上の患者が占めると予想されている[2]。

本邦における大腸癌治療後の予後は，大腸癌全国登録（1991～1994年度）によると，累積5年生存割合がStage 0: 94.3%，Stage Ⅰ: 90.6%，Stage Ⅱ: 81.2%，Stage Ⅲa: 71.4%，Stage Ⅲb: 56.0%，Stage Ⅳ: 13.2%となっている[3]。このように大腸癌の予後は，Stage Ⅰ，Ⅱ，Ⅲに比してStage Ⅳ，すなわち遠隔転移が認められる場合には著しく不良である。

Stage Ⅳを含めた治癒切除不能の進行・再発大腸癌において，16の第Ⅱ，第Ⅲ相試験を集めて行った統合解析の結果から，化学療法施行前のperformance status（PS），白血球数，ALP，転移臓器数が予後因子であると報告されている[4]。新規薬剤の登場は過去10年間の全身化学療法の進歩により，予後は大幅に改善し，治癒切除不能の進行・再発大腸癌においても全生存期間中央値（median survival time: MST）は2年程度が期待できる。

1997～2000年に米国で施行された大腸癌の第Ⅱ相または第Ⅲ相臨床試験，495試験に登録された大腸癌患者59,300名の統合解析によれば，疾患登録のデータで同時期に進行大腸癌と新規に診断された患者のなかで高齢者の占める割合は73%であったにもかかわらず，臨床試験の登録患者に占める高齢者の割合は41%にすぎなかった[5]。これは高齢者で積極的に臨床試験へ参加しようとする患者が少数であることに加え，臨床試験では一般に合併症がほとんどなくPSが良好な高齢者のみを対象としていることが原因と考えられ，虚弱な前期高齢者あるいは後期高齢者を含む「一般的」な高齢者の予後を，臨

表 1 栄養（G8 geriatric assessment screening tool）

G8 screening tool		
質問項目	該当回答項目	点数
A 過去3か月間で食欲不振，消化器系の問題，そしゃく・嚥下困難などで食事量が減少しましたか	0：著しい食事量の減少 1：中等度の食事量の減少 2：食事量の減少なし	
B 過去3か月間で体重の減少はありましたか	0：3 kg 以上の減少 1：わからない 2：1～3 kg の減少 3：体重減少なし	
C 自力で歩けますか	0：寝たきりまたは車椅子を常時使用 1：ベッドや車いすを離れられるが，歩いて外出できない 2：自由に歩いて外出できる	
E 神経・精神的問題の有無	0：高度の認知症または鬱状態 1：中程度の認知障害 2：精神的問題なし	
F BMI 値	0：19 未満 1：19 以上 21 未満 2：21 以上 23 未満 3：23 以上	
H 1日に4種類以上の処方薬を飲んでいますか	0：はい 1：いいえ	
P 同年齢の人と比べて，自分の健康状態をどう思いますか	0：よくない 0.5：わからない 1：同じ 2：よい	
年齢	0：86 歳以上 1：80～85 歳 2：80 歳未満	
	合計点数（0～17）	

［本質問紙は G8 原版を元とし Mini Nutritional Assessment（MNA®）日本語版より該当する項目を引用］

床試験の結果が真に反映しているとはいい難い状況である。実年齢の他に，高齢者の治療の決定に影響を与えるその他の要因もいくつか存在する。すなわち，① 腎機能や肝機能の低下など，加齢に関連した生理学的変化が薬物代謝および毒性に影響する，② 実年齢は必ずしも生理的変化または臓器機能と相関しない，③ 高齢者では化学療法の毒性が軽度であっても QOL が容易に悪化する傾向にある，④ 高齢者における化学療法の忍容性および有効性に関する情報が少ない，といった問題である。こうした背景から，若年者を対象とした臨床試験の結果がそのまま高齢者に外挿できるとは限らないと考えられる。大腸癌薬物療法の選択肢が増えていて，多様な合併症を有する高齢者および脆弱患者に対する標準治療を確立することは重要である。

以下，切除不能大腸癌初回化学療法として 70～74 歳，75 歳以上の標準化学療法について説明する。

Ⅳ．70～74 歳で PS 良好な高齢者に対する標準化学療法

70～74 歳で PS 良好（PS 0-1）な高齢者に対する標準的な化学療法は，若年者と同じく FOLFOX 療法や FOLFIRI 療法のような intensive chemotherapy であり，同様にベバシズマブ（BEV）も併用されることが多い。

Goldberg らは，FOLFOX4 療法の安全性および有効性を比較する四つの臨床試験[6-9]（n＝3,742）の統合解析により，FOLFOX4 療法を受けた 69 歳以下の大腸癌患者 1,567 名に対する 70 歳以上の大腸癌患者 614 名の安全性および有効性を検討した[10]。当該試験の一つは Stage Ⅱ/Ⅲ大腸癌に補助療法として FOLFOX4 療法を行った MOSAIC 試験であり[6]，その他の試験では進行・再発大腸癌の初回治療[7,8]もしくは二次治療[9]として FOLFOX4 療法が行われていた。69 歳以下の大腸癌患者と比較して，70 歳以上の大腸癌患者では Grade 3 以上の末梢神経障害（14% vs 12%），下痢（11% vs 13%），悪心・嘔吐（9% vs 7%），感染（5% vs 4%）および

Grade 3以上のあらゆる有害事象の発現割合（63% vs 67%）で特に多い傾向は認めず，さらには60日以内死亡割合（1.1% vs 2.3%）においても70歳以上で若干多い傾向を認めたが，統計学的な有意差は認められなかった（p=0.15）。しかし，Grade 3以上の好中球減少症（43% vs 49%，p=0.04）および血小板減少症（2% vs 5%，p=0.04）の発現頻度は70歳以上の大腸癌患者で有意に高かった。

この統合解析のなかで，標準治療群［5-FU/LV療法（de Gramont法）2試験，IFL療法1試験］に対してFOLFOX4療法群を比較した場合の奏効率（RR）のオッズ比は1.65-7.22とFOLFOX4療法群が良好であった［転移性大腸癌（mCRC）を対象とした3試験のみの解析］。標準治療群に対するFOLFOX4療法群のPFS（Stage Ⅱ/Ⅲを対象とした1試験では無病生存期間）も，ハザード比（HR）にすると，69歳までで0.70，70歳以上で0.65（p=0.42）と年齢によらずFOLFOX4療法群が良好であった。また，OSにおけるHRも69歳までで0.77，70歳以上で0.82（p=0.79）と同様にFOLFOX4療法群で良好であった。全般に70歳以上の高齢大腸癌患者におけるFOLFOX4療法の安全性プロファイルおよび有効性についても，69歳以下の患者と同様であった。

Porschenらは，初回治療としての5-FU/LV＋オキサリプラチン（FUFOX）療法とCAPOX療法を比較した第Ⅲ相試験[11]の探索的解析を実施し，対象患者を69歳以下のmCRC患者336名と70歳以上のmCRC患者140名に分けて安全性および有効性を比較検討した[12]。69歳以下のmCRC患者および70歳以上の高齢mCRC患者のRRは，FUFOX療法とCAPOX療法でそれぞれ52%，49%，PFS中央値はそれぞれ7.5か月，7.7か月（p=0.54，HR: 1.07，95% CI: 0.86-1.34）とほぼ同等であった。しかし，69歳以下のmCRC患者におけるMSTが18.8か月であったのに対し，70歳以上のmCRC患者のMSTは14.4か月（p=0.013，HR: 1.37，95% CI: 1.07-1.76）と，高齢患者で不良な傾向を認めた。両療法ともに忍容性は良好で，Grade 3/4の有害事象の発現割合は69歳以下および70歳以上のコホートで同様であったが，69歳以下より70歳以上では消化管の有害事象が多く感音性難聴の副作用が少なかった。

以上より，Arkenauらが高齢者のMSTが若干不良と報告しているものの，他の報告[10,13]では69歳以下と70歳以上で有効性は同等であり，有害事象のなかには高齢者で多い傾向を示すものもあるが忍容可能であるとしており，PS良好な前期高齢者（69歳以下と70～74歳でPS 0-1の患者）は，若年者と同様にintensive chemotherapyを行ってよいと考える。

Ⅴ．70～74歳の脆弱高齢者および後期高齢者に対する標準化学療法

これまでの臨床試験は主にPSの良好な前期高齢者を対象に行われてきた。よって，70～74歳の脆弱高齢者もしくは後期高齢者におけるintensive chemotherapyの安全性および有効性は，極めて限定的なデータしか存在しない。フルオロピリミジン療法に比べてオキサリプラチン併用療法は，好中球減少，下痢，末梢神経障害などの有害事象が増強するために，70～74歳の脆弱高齢者または後期高齢者に対する安全性には懸念があり，有効性が低下する可能性も十分あり得る。

一方，オキサリプラチンに比べてBEVの有害事象は一般的に軽微であり，動脈性血栓塞栓症以外のBEV関連有害事象の発現割合は若年者とは変わらないと報告されており[14-16]，BEV併用による有害事象増強の懸念は少ない。また，動脈性血栓塞栓症はそのものの実際の頻度は少なく，動脈性疾患の既往がありながら抗凝固療法を行っていない患者を除くと，その頻度はさらに少なくなる。そのため，70～74歳の虚弱高齢者および後期高齢者においては，less toxicなフルオロピリミジン＋BEV併用療法をみなし標準治療と考えている。実際，米国の観察研究[17]やBRiTE試験[14-16]では，高齢になるにつれてフルオロピリミジン（＋BEV併用）療法を使用する頻度が増すにもかかわらず，PFSにおいてはFOLFOXの使用頻度が多い若年者と高齢者であまり変わらないという結果であった。

表2　年齢，PSごとの標準治療

年齢	PS	標準治療
69歳以下	0，1，2	FOLFOX＋BEV，FOLFIRI＋BEV，CAPOX＋BEV
70～74歳	0，1	
	2	5-FU/LV＋BEV，Cape＋BEV
75歳以上	0，1，2	

FOLFOX: 5-FU/LV（ロイコボリン）＋オキサリプラチン，BEV: ベバシズマブ，FOLFIRI: 5-FU/LV＋イリノテカン，CAPOX: カペシタビン＋オキサリプラチン

以上より，後期高齢者の標準治療としての十分なエビデンスがあるとはいえない状況ではあるが，みなし標準治療はフルオロピリミジン（5-FU/LV またはカペシタビン）＋BEV 併用療法と考えることは妥当であろう。なお，重篤な好中球減少などの頻度を少なくすることを期待して，フルオロピリミジン療法のレジメンは，5-FU 急速静注を伴わない 5-FU/LV 療法［modified simplified de Gramont（msDG 法）］と考える。

JCOG 大腸がんグループでのアンケートおよび班会議の議論で得られた，治癒切除不能の進行・再発大腸癌に対する標準的な化学療法は表 2 のとおりである。70～74 歳の虚弱患者（PS 2）および 75 歳以上の後期高齢者（PS 0-2）においては，イリノテカンやオキサリプラチンの導入は慎重に判断する。この考え方を受けて JCOG 大腸がんグループでは，この 70～74 歳の虚弱患者（PS 2）および 75 歳以上の後期高齢者（PS 0-2）を対象としたオキサリプラチン上乗せ治療の有効性を比較する第Ⅲ相試験（JCOG1018）を展開している。なお，本臨床試験では，治療前に GA として VES-13 を全登録例で採録している。

おわりに

高齢者を対象とした臨床研究のエビデンスは乏しく，様々な切り口でデータの蓄積が必要である。一方，各患者の治療方針の決定に際しては，限られた医療資源の有効活用のためにも包括的なリスク評価は重要である。これらを総合的に研究する geriatric oncology は，本邦独自の文化をも考慮する必要があり，医療・介護・コミュニティーを含めた研究体制の構築が急務である。

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Cancer Chemother Pharmacol (2014) 73:673–683
DOI 10.1007/s00280-014-2374-3

ORIGINAL ARTICLE

Phase 1 study of pazopanib alone or combined with lapatinib in Japanese patients with solid tumors

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Received: 27 November 2013 / Accepted: 31 December 2013 / Published online: 24 January 2014

Abstract
Purpose A phase 1 study of pazopanib alone or in combination with lapatinib was conducted to assess the safety, tolerability, and pharmacokinetics of these oral tyrosine kinase inhibitors in Japanese patients with solid tumors.
Methods In part A (monotherapy), 7 patients initially received pazopanib 800 mg/day, the recommended dose for non-Japanese patients. Then, 3 patients received pazopanib 400 mg/day on day 1 followed by 800 mg/day from day 2 onward. Three other patients received pazopanib 1,000 mg/day. In part B (combination therapy), 17 patients received pazopanib plus lapatinib (pazopanib/lapatinib) at once-daily doses of 400/1,000 mg (4 patients), 800/1,000 mg (3 patients), 400/1,500 mg (3 patients), and then 600/1,250 mg (7 patients).
Results There was no dose-limiting toxicity during the study. In part A, most drug-related adverse events were grade 2 or lower, including neutropenia/neutrophil count decreased, thrombocytopenia/platelet count decreased, diarrhea, hypertension, aspartate aminotransferase increased, and lipase increased. In part B, rash, decreased appetite, and serum thyroid-stimulating hormone increased also occurred. In all dose groups, the plasma concentrations after multiple doses of pazopanib exceeded the target trough concentration for inhibition of vascular endothelial growth factor receptor-2 activity (20 μg/mL).

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Conclusions The pharmacokinetic profiles of pazopanib and lapatinib in Japanese patients were not apparently different from those reported in non-Japanese patients. There were no consistent trends in pharmacokinetic drug interactions between pazopanib and lapatinib. Pazopanib monotherapy at 800 and 1,000 mg once daily and pazopanib plus lapatinib once daily at any doses studied were well tolerated in Japanese patients.

Keywords Pazopanib · Lapatinib · Japanese patients · Phase 1 · Pharmacokinetics

Introduction

Pazopanib (GW786034, Votrient®, GlaxoSmithKline) is a potent, oral, small-molecule inhibitor of vascular endothelial growth factor receptors (VEGFR)-1, -2, and -3, platelet-derived growth factor receptors (PDGFR)-alpha and -beta, and c-kit [1]. Clinical studies of pazopanib have demonstrated single-agent activity in patients with renal cell carcinoma and soft tissue sarcoma [2–4]. A previous phase 1 study of pazopanib in non-Japanese patients with solid tumors (VEG10003) showed that the drug was well tolerated up to 2,000 mg once daily, but the maximum tolerated dose (MTD) was not determined [5]. However, maximum plasma concentrations (C_{max}) and areas under the plasma drug concentration–time curves (AUC) were similar after treatment with pazopanib 800–2,000 mg daily, suggesting that drug absorption is saturated at daily doses of 800 mg or higher. Moreover, the daily dose of pazopanib 800 mg achieved the target trough concentration of ≥17.5 μg/mL (40 μmol/L) required for optimal inhibition of tumor angiogenesis [6]. Based on the tolerable safety profile and plateau in steady-state systemic exposure at this dose level and achievement of the target trough concentration of pazopanib, the recommended dose for pazopanib monotherapy was determined to be 800 mg once daily for future studies. Pazopanib has been approved for the indications of soft tissue sarcoma and renal cell carcinoma in the United States, European Union, and other countries, and for the indication of soft tissue sarcoma in Japan. In phase 3 studies, pazopanib showed a statistically significant and clinically meaningful improvement in the primary end point of progression-free survival as compared with placebo in patients with ovarian cancer who did not have disease progression after first-line chemotherapy [7].

Lapatinib (Tykerb®, GlaxoSmithKline) is a potent, oral, small-molecule, dual tyrosine kinase inhibitor of epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor-2 (HER2) [8]. This drug is used at a dose of 1,250 mg once daily for the treatment of HER2-positive advanced or metastatic breast cancer resistant to prior trastuzumab-based chemotherapy [9]. Lapatinib has been approved for the indication of breast cancer in Japan, the United States, European Union, and other countries.

Several lines of evidence support the combined inhibition of VEGFR and EGFR in the management of some malignancies [10, 11]. A preclinical study showed that pazopanib and lapatinib act synergistically to induce apoptosis of non-small-cell lung cancer cells in vitro [12]. A previous phase 1 study of combination therapy with pazopanib and lapatinib in non-Japanese patients (VEG10006) showed that pazopanib and lapatinib could be administered concurrently at their respective single-agent doses with an acceptable safety profile [13].

Accordingly, the current phase 1 study evaluated the safety, tolerability, and pharmacokinetic (PK) profile of pazopanib alone and combining pazopanib and lapatinib in Japanese patients with solid tumors, as a first step to exploring the potential benefit of this combination regimen for the treatment of various cancer classes.

Patients and methods

Eligibility criteria

Eligible patients were at least 20 years of age with a histologic or cytologic diagnosis of solid tumor and an Eastern Cooperative Oncology Group performance status of 0 or 1. While the study was in progress, the protocol was amended to exclude patients with uterine cervical carcinoma from part B because a clinical trial in non-Japanese patients with uterine cervical carcinoma (VEG105281) showed that the potential benefits of combination therapy with pazopanib and lapatinib were outweighed by the risk of severe toxicity [14]. Eligible patients also had to have adequate hematologic and organ functions, including: absolute neutrophil count ≥1,500/mm^3; platelet count ≥100,000/mm^3; hemoglobin level ≥9.0 g/dL; prothrombin time or prothrombin time–international normalized ratio ≤1.2 × the upper limit of normal (ULN); creatinine clearance calculated by the Cockcroft–Gault formula ≥50 mL/min; urine protein:creatinine ratio <1; total bilirubin level ≤1.5 × ULN; and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels ≤2.5 × ULN. In part B, patients additionally had to have a left ventricular ejection fraction of >50 %. Patients were excluded if they had central nervous system metastases, carcinomatous meningitis, clinically meaningful gastrointestinal abnormalities, uncontrolled infection, a corrected QT interval of >480 ms, a history of cardiovascular disease requiring cardiac angioplasty or stenting, or poorly controlled hypertension (≥140/90 mmHg). All patients provided written

informed consent in accordance with the requirements of the review board of each participating institution.

Study design and treatment

This was a 2-center, open-label, non-randomized, dose-finding phase 1 study (VEG109693; NCT00516672) in Japanese patients with solid tumors who received pazopanib alone or in combination with lapatinib. The main objective was to assess the safety and tolerability of these oral tyrosine kinase inhibitors.

The study consisted of two parts: part A, in which patients received pazopanib monotherapy and part B, in which patients received combination therapy with pazopanib and lapatinib. Both parts were designed to evaluate safety, tolerability, and PK. Part A comprised an original cohort and an additional cohort, while part B comprised a dose-escalation cohort and a PK cohort (Fig. 1).

In the original cohort of part A, a minimum of 6 patients were assigned to receive pazopanib 800 mg once daily (P800), the recommended dose for non-Japanese patients, for assessing safety, tolerability, and PK in Japanese patients. Blood samples for PK analysis were taken during the 96 h after the first dose. From day 2 onward, the patients received additional doses of pazopanib 800 mg once daily. On day 22, blood samples for PK analysis were taken during the 24 h after dosing. If 2 or more of the 6 patients in the original cohort had dose-limiting toxicity (DLT), a lower dose of 600 mg/day was to be evaluated in 6 additional patients.

In the additional cohort of part A, a minimum of 3 patients received pazopanib 400 mg once daily on day 1 for assessing safety and PK, followed by pazopanib 800 mg once daily from day 2 (P400/800). A minimum of 3 other patients received pazopanib 1,000 mg once daily from day 1 onward (P1000) for assessing safety, tolerability, and PK. In both groups, blood samples for PK analysis were taken during the 96 h after the first dose of pazopanib. On day 22, blood samples for PK analysis were taken during the 24 h after dosing. If 1 of the 3 patients assigned to P1000 had DLT, 3 additional patients were enrolled, and if 2 of the first 3 patients or 2 or more of the 6 patients had DLT, the dose was considered to exceed the MTD.

In the dose-escalation cohort of part B, 3 patients were initially assigned to receive pazopanib 400 mg plus lapatinib 1,000 mg once daily (P400/L1000) for assessing safety, tolerability, and PK in Japanese patients. On day 1 and day 22, blood samples for PK analysis were taken during the 24 h after dosing. Then, 3 patients each received pazopanib 800 mg plus lapatinib 1,000 mg (P800/L1000) or pazopanib 400 mg plus lapatinib 1,500 mg (P400/L1500) once daily. If no DLT occurred among the first 3

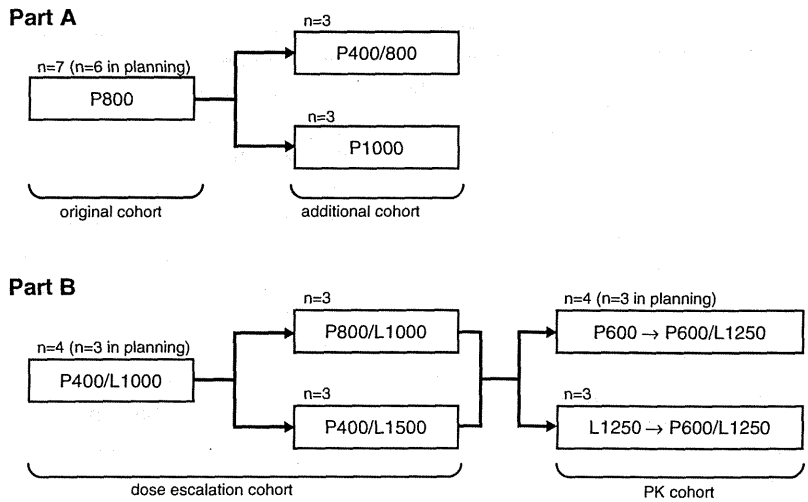

Fig. 1 Schematic diagram of the study. In part A, pazopanib monotherapy was evaluated at a dose of 800 mg once daily (P800) in the original cohort. In the additional cohort, one group of patients received pazopanib 400 mg once daily on day 1, followed by pazopanib 800 mg from day 2 onward (P400/800), and another group of patients received pazopanib 1,000 mg once daily from day 1 onward (P1000). In part B, combination therapy with pazopanib and lapatinib was evaluated for pazopanib 400 mg plus lapatinib 1,000 mg once daily (P400/L1000), pazopanib 800 mg plus lapatinib 1,000 mg once daily (P800/L1000), and pazopanib 400 mg plus lapatinib 1,500 mg once daily (P400/L1500) in the dose-escalation cohort. Patients in the pharmacokinetic (PK) cohort received pazopanib 600 mg (P600) or lapatinib 1,250 mg (L1250) once daily for 15 days, followed by combination therapy with pazopanib 600 mg and lapatinib 1,250 mg once daily (P600/L1250) from day 16 onward. Dose-limiting toxicity was evaluated between day 1 and day 21 in the original (P800) and additional (P1000) cohorts of part A and the dose-escalation cohort of part B (P400/L1000, P800/L1000, and P400/L1500) or between day 16 and day 36 in the PK cohort of part B (P600/L1250)

patients who received P400/L1000, dose escalation proceeded to P800/L1000 and P400/L1500 in parallel, and patients were simultaneously enrolled. If 1 of the 3 patients had DLT, 3 additional patients were enrolled, and if 1 of the 6 patients had DLT, the dose was escalated. The dose at which 2 of the first 3 patients or 2 or more of 6 patients had DLT was considered to exceed the MTD. At the dose level of P800/L1000 and P400/L1500, MTD was considered by the same procedures as P400/L1000. If the MTD was not reached in the dose-escalation cohorts of part B (P400/L1000, P800/L1000, and P400/L1500), a minimum of 6 patients were assigned to the PK cohort of part B, designed to investigate potential PK interactions between pazopanib and lapatinib, for assessing safety, tolerability, and PK in Japanese patients. The originally planned doses for combination therapy in the PK cohort in part B were pazopanib 800 mg plus lapatinib 1,500 mg, based on the results of a phase 1 study (VEG10006) [13]. However, the doses were reduced during the study to pazopanib 600 mg (P600) and lapatinib 1,250 mg (L1250) because the interim analysis of a phase 2 study (VEG20007) in non-Japanese patients reported that intolerable toxicity occurred at doses of pazopanib 800 mg and lapatinib 1,500 mg [15].

A minimum of 3 patients in the PK cohort were assigned in each of the two groups receiving P600 once daily or L1250 once daily for 15 days. Patients in both groups then received pazopanib 600 mg plus lapatinib 1,250 mg once daily (P600/L1250) from day 16 onward. On day 15 and day 37, blood samples for PK analysis were taken during the 24 h after dosing. If 2 or more of the 6 patients had DLT, the dose was considered to exceed the MTD.

Patients in both part A and part B orally received pazopanib once daily, at least 1 h before or at least 2 h after breakfast. In part B, patients received lapatinib first, followed by pazopanib within a 15-min interval, at least 1 h before, or at least 2 h after breakfast.

Study assessments

Baseline assessments on day 1 or within 72 h before treatment included medical history, physical examination, complete blood counts, serum chemical analysis, coagulation tests, urinalysis, pregnancy tests (for all women of childbearing potential), thyroid-stimulating hormone (TSH) levels, electrocardiography, left ventricular ejection fraction (LVEF; part B only), ErbB2 expression (part B only), and chest radiography. Assessments conducted on days 8, 15, and 22 (days 8, 15, 22, 29, and 37 in the PK cohort) and every 3 weeks thereafter included physical examination, complete blood counts, serum chemical analysis, and urinalysis. TSH levels were measured on day 22 (day 37 in the PK cohort) and every 3 weeks thereafter. Coagulation tests were performed every 9 weeks. Electrocardiography and LVEF measurements (part B only) were performed on day 22 (day 37 in the PK cohort) and every 9 weeks thereafter. Chest radiography (part B only) was performed on day 22 (day 29 in the PK cohort) and every 9 weeks thereafter. Toxicity was monitored continuously and graded according to the Common Terminology Criteria for Adverse Events, version 3.0 [16]. Disease assessments by investigator according to the Response Evaluation Criteria in Solid Tumors [17] were performed at baseline and every 9 weeks after starting the study medications until withdrawal from the study.

Dose-limiting toxicity was defined as at least 1 of the following events occurring between day 1 and day 21 in the original (P800) and additional (P1000) cohorts of part A and the dose-escalation cohort of part B (P400/L1000, P800/L1000, and P400/L1500) or between day 16 and day 36 in the PK cohort of part B (P600/L1250): grade 3 neutropenia persisting for at least 5 days, grade 4 neutropenia, febrile neutropenia, grade 3 or 4 thrombocytopenia, inability to resume treatment within 14 days of the scheduled date because of unresolved toxicity, inability to receive at least 75 % of the scheduled doses in a treatment period due to toxicity, any grade 3 or 4 clinically significant nonhematologic toxicity, and any grade 2 toxicity evaluated to be DLT by the investigator and medical monitor. However, grade 3 nausea, vomiting, or diarrhea in the absence of appropriate supportive therapy, grade 3 hypertension adequately controlled by antihypertensive therapy, and increased amylase/lipase levels unaccompanied by clinical symptoms were not considered DLT.

Pharmacokinetic assessments

Blood samples (3 mL) were collected for measurement of plasma pazopanib and lapatinib concentrations. In part A, blood samples were collected before treatment and 0.5, 1, 2, 3, 4, 6, 8, 24, 48, 72, and 96 h after treatment on day 1, and before treatment and 0.5, 1, 2, 3, 4, 6, 8, and 24 h after treatment on day 22. The blood sample 24 h after treatment was collected within 1 h before the next treatment, to confirm that the trough plasma concentrations of pazopanib were above 20 μg/mL (i.e., high enough to inhibit VEGFR-2 activity). In the dose-escalation cohort of part B, blood samples were collected before treatment and 0.5, 1, 2, 3, 4, 6, 8, and 24 h after treatment on days 1 and 22. In the PK cohort of part B, blood samples were collected before treatment and 0.5, 1, 2, 3, 4, 6, 8, and 24 h after treatment on days 15 (monotherapy, steady state) and 37 (combination therapy). Concentrations of pazopanib and lapatinib were determined by protein precipitation of human plasma, followed by high-performance liquid chromatography–tandem mass spectrometry analysis. Quantification was performed by multiple reaction monitoring with

TurboIonSpray® interface (AB Sciex, Concord, Ontario, Canada) in positive-ion mode. The calibration range was 100–50,000 ng/mL for pazopanib and 5–5,000 ng/mL for lapatinib in 20 and 25 μL of human plasma, respectively. The coefficient of variation (CV %) and accuracy bias (%) obtained with this method were both less than 15 %. WinNonlin Professional® software (Pharsight Corporation, Mountain View, California, USA) and standard non-compartmental methods were used to calculate the AUC, C_{max}, time to maximum plasma concentration (t_{max}), and elimination half-life ($t_{1/2}$).

Results

Patient characteristics

A total of 30 patients were enrolled between September 2007 and May 2010: 7 in the original cohort and 6 in the additional cohort of part A; 10 in the dose-escalation cohort and 7 in the PK cohort of part B. In addition to the initially planned numbers of patients (12 patients in part A and 15 patients in part B), 3 patients were additionally enrolled (1 each was assigned to P800 in part A and to P400/L1000 and P600/L1250 in part B) to compensate for patients who were ineligible for the evaluation of DLT. The most common tumor types were soft tissue sarcoma and colorectal cancer in part A and head and neck cancer in part B (Table 1). One patient in part A and 3 in part B were receiving the study treatment at the time of data cutoff (August 2010).

Safety and tolerability

In part A, none of the 9 eligible patients (6 patients assigned to P800 and 3 assigned to P1000) had DLT. In part B, none of the 15 eligible patients (3 patients each assigned to P400/L1000, P800/L1000, and P400/L1500, and 6 patients assigned to P600/L1250) had DLT.

In part A, 12 (92 %) of the 13 patients had adverse events (AEs) associated with pazopanib, including leukopenia/white cell count decreased (62 %), neutropenia/neutrophil count decreased (62 %), thrombocytopenia/platelet count decreased (62 %), diarrhea (46 %), AST increased (38 %), hypertension (38 %), and lipase increased (38 %) (Table 2). Most AEs were manageable by dose reduction or treatment interruption. Five (42 %) of the 12 patients with AEs had drug-related AEs of grade 3 or worse, including neutropenia, hepatic function abnormal, hypertension, leukopenia, lymphopenia, hyperbilirubinemia, and lipase increased. The study treatment was discontinued because of AEs in 3 of these patients, 1 of whom had abnormal hepatic function (grade 4) related to pazopanib. The other 2 patients had AEs unrelated to pazopanib: 1 patient had abnormal hepatic function (grade 3) and lower respiratory tract infection (grade 2), and the other had ileus (grade 2). No patient died during the study.

In part B, all 17 patients had AEs related to the study drugs, including diarrhea (94 %), neutropenia/neutrophil count decreased (71 %), thrombocytopenia/platelet count decreased (71 %), leukopenia/white cell count decreased (65 %), rash (65 %), decreased appetite (65 %), and increased serum TSH level (59 %) (Table 2). Most of these AEs were manageable by dose reduction or treatment interruption. Nine (53 %) of the 17 patients had drug-related AEs of grade 3 or worse, including lipase increased, hypertension, diarrhea, weight decreased, stomatitis, blood amylase increased, vomiting, pyrexia, hepatic function abnormal, pneumonia, lymphopenia, and leukopenia. The study treatment was discontinued because of AEs in 3 patients, 2 of whom had AEs related to the study drugs: 1 had ALT increased (grade 2), AST increased (grade 2), and fatigue (grade 1), and the other had abnormal hepatic function (grade 3) and pneumonia (grade 3). The third patient had ileus (grade 2) unrelated to the study drugs. One patient with head and neck cancer who received P800/L1000 died of disease progression 47 days after the last dose of the

Table 1 Patient characteristics

	Part A ($n = 13$)	Part B ($n = 17$)
Age, median years (range)	49 (39–74)	56 (27–74)
Gender, *n*		
Male	9	5
Female	4	12
Prior chemotherapy regimens, *n* (%)	9 (69)	10 (59)
≥4 regimens	3 (23)	5 (29)
Tumor type	Soft tissue sarcoma, $n = 4$	Head and neck, $n = 4$
	Colorectal, $n = 4$	Breast, $n = 3$
	Head and neck, $n = 2$	Ovarian, $n = 2$
	Other[a], $n = 3$	Carcinoid, $n = 2$
		Other[b], $n = 6$

[a] Other tumor types included thyroid cancer, gastrointestinal stromal tumor, and malignant melanoma

[b] Other tumor types included renal cell carcinoma, thyroid cancer, soft tissue sarcoma, bone sarcoma, gastric cancer, and central nervous system tumor (hemangiopericytoma)

Table 2 Summary of drug-related adverse events (at least 30 % in any part)

Adverse event	Part A							
	Total ($n = 13$)		P400/800 ($n = 3$)		P800 ($n = 7$)		P1000 ($n = 3$)	
	All Gr, *n* (%)	Gr 3/4, *n* (%)	All Gr	Gr 3/4	All Gr	Gr 3/4	All Gr	Gr 3/4
Any event	12 (92)	5 (38)	3	3	6	1	3	1
Leukopenia/white cell count decreased	8 (62)	1 (8)	3	0	4	0	1	1
Neutropenia/neutrophil count decreased	8 (62)	3 (23)	3	2	4	0	1	1
Thrombocytopenia/platelet count decreased	8 (62)	0	3	0	4	0	1	0
Diarrhea	6 (46)	0	1	0	3	0	2	0
Hypertension	5 (38)	1 (8)	3	1	1	0	1	0
AST increased	5 (38)	0	2	0	3	0	0	0
Lipase increased	5 (38)	1 (8)	2	0	2	1	1	0
Nausea	4 (31)	0	1	0	0	0	3	0
Rash	4 (31)	0	1	0	3	0	0	0
ALT increased	4 (31)	0	2	0	2	0	0	0
Fatigue	3 (23)	0	0	0	1	0	2	0
Skin hypopigmentation	3 (23)	0	2	0	0	0	1	0
Lymphopenia	3 (23)	1 (8)	2	0	1	1	0	0
Serum TSH increased	3 (23)	0	2	0	1	0	0	0
Hair color changes	2 (15)	0	0	0	2	0	0	0
Proteinuria	2 (15)	0	1	0	1	0	0	0
Decreased appetite	1 (8)	0	1	0	0	0	0	0
Dysgeusia	1 (8)	0	1	0	0	0	0	0

Adverse event	Part B									
	Total ($n = 17$)		P400/L1000 ($n = 4$)		P800/L1000 ($n = 3$)		P400/L1500 ($n = 3$)		P600/L1250 ($n = 7$)	
	All Gr *n* (%)	Gr 3/4, *n* (%)	All Gr	Gr 3/4	All Gr	Gr 3/4	All Gr	Gr 3/4	All Gr	Gr 3/4
Any event	17 (100)	9 (53)	4	2	3	2	3	1	7	4
Leukopenia/white cell count decreased	11 (65)	1 (6)	2	0	3	1	1	0	5	0
Neutropenia/neutrophil count decreased	12 (71)	0	3	0	3	0	2	0	4	0
Thrombocytopenia/platelet count decreased	12 (71)	0	3	0	2	0	1	0	6	0
Diarrhea	16 (94)	1 (6)	3	0	3	0	3	0	7	1
Hypertension	8 (47)	2 (12)	1	1	1	0	2	0	4	1
AST increased	5 (29)	0	1	0	1	0	3	0	0	0
Lipase increased	4 (24)	4 (24)	2	2	0	0	1	1	1	1
Nausea	7 (41)	0	1	0	1	0	2	0	3	0
Rash	11 (65)	0	3	0	1	0	2	0	5	0
ALT increased	7 (41)	0	1	0	1	0	3	0	2	0
Fatigue	9 (53)	0	1	0	2	0	2	0	4	0
Skin hypopigmentation	7 (41)	0	2	0	2	0	1	0	2	0
Lymphopenia	7 (41)	1 (6)	2	0	1	0	1	0	3	1
Serum TSH increased	10 (59)	0	1	0	3	0	1	0	5	0
Hair color changes	6 (35)	0	1	0	1	0	0	0	4	0
Proteinuria	6 (35)	0	1	0	2	0	1	0	2	0
Decreased appetite	11 (65)	0	3	0	1	0	2	0	5	0
Dysgeusia	9 (53)	0	1	0	1	0	3	0	4	0
Weight decreased	7 (41)	1 (6)	3	1	1	0	1	0	2	0
Stomatitis	7 (41)	1 (6)	0	0	1	0	2	0	4	1

AST aspartate aminotransferase, *ALT* alanine aminotransferase, *Gr* grade, *L* lapatinib, *P* pazopanib, *TSH* thyroid-stimulating hormone

study drugs. This disease progression was not considered to be related to study treatment.

In part A, treatment-related AEs involving liver function, such as AST/ALT and bilirubin increased, occurred in 8 patients (62 %), most of which were grade 2 or lower. Grade 3 or higher AEs involving liver function were reported in 3 patients (23 %). In part B, 11 patients (65 %) had treatment-related AEs involving liver function, most of which were grade 2 or lower. Grade 3 AEs involving liver function occurred in 1 patient.

In part A, 5 patients (38 %) had drug-related hypertension. Treatment was not discontinued or interrupted or the dose reduced in any patient due to hypertension. In part B, drug-related hypertension occurred in 8 patients (47 %), none of whom underwent treatment discontinuation, interruption, or dose reduction due to hypertension.

In part A, there was no clinically important prolongation of QTc interval on electrocardiography. In part B, grade 2 prolongation of QTc interval occurred in 1 patient who had a grade 2 supraventricular arrhythmia 14 days after discontinuation of the study drug. In part B, the LVEF did not decrease by at least 20 % from the baseline value in any patient.

In Part A, 1 patient (8 %) had a grade 3 drug-related increase in serum lipase levels. No patient had increased amylase levels. In part B, 4 patients (24 %) had grade 3 or higher drug-related increases in serum lipase levels, and 1 patient (6 %) had a drug-related grade 3 increase in amylase levels. None of the patients had any signs or symptoms suggesting acute pancreatitis on physical examinations. Treatment discontinuation or interruption or dose reduction was not required.

Pharmacokinetics

In part A, the PK of pazopanib were evaluated in all 13 patients in the original and the additional cohorts after single-dose treatment on day 1 and in 11 patients after repeated treatment on day 22 (Table 3). There were considerable inter-patient variations in the PK parameters of pazopanib. Median t_{max} was approximately 2.5 and 4.0 h, and the geometric mean of $t_{1/2}$ was between 28.4 and 42.5 h. The AUC from 0 to 24 h (AUC_{0-24}) and C_{max} did not increase in proportion to the doses of pazopanib on day 1 (400, 800, and 1,000 mg). The geometric mean of plasma pazopanib concentration 24 h after treatment (C_{24}) on day 22 was higher than the target trough concentration of pazopanib for the inhibition of VEGFR-2 activity (>20 μg/mL in this study) after repeated doses of pazopanib 800 mg and 1,000 mg.

In part B, the PK of pazopanib and lapatinib were evaluated in all 10 patients on days 1 and 22 in the dose-escalation cohort, and in all 6 patients on days 15 and 37 in the PK cohort (Tables 4, 5). There were considerable inter-patient variations in the PK parameters of pazopanib and lapatinib in both the dose escalation and the PK cohorts. The PK parameters of AUC_{0-24} or C_{max} in the dose-escalation cohort apparently did not depend on the doses of pazopanib or lapatinib. The geometric mean of C_{24} of pazopanib after multiple doses of pazopanib plus lapatinib was higher than the target trough concentration of pazopanib for inhibition of VEGFR-2 activity (>20 μg/mL in this study) in all dose groups (P400/L1000, P800/L1000, P400/L1500, and P600/L1250) in part B. There were large variations in the ratio of combination therapy to monotherapy for C_{max}

Table 3 Pharmacokinetic parameters of pazopanib in part A

Parameter	Day	Cohort		
		P400/800 ($n = 3$)	P800 ($n = 7$)	P1000 ($n = 3$)
C_{max} (μg/mL), geometric mean (% CVb)	1	25.1 (34.0)	22.9 (69.5)	21.3 (118.1)
	22	55.8[a] (35.2)	40.6[b] (47.7)	53.9 (55.4)
t_{max} (h), median (min–max)	1	4.0 (3.0–23.7)	3.0 (2.0–6.0)	3.0 (3.0–3.0)
	22	2.5[a] (2.0–3.0)	2.5[b] (1.9–4.0)	4.0 (3.0–4.1)
AUC_{0-24} (h × μg/mL), geometric mean (% CVb)	1	402.3 (17.7)	324.6 (76.7)	305.0 (128.6)
	22	962.4[a] (46.3)	677.3[b] (45.5)	759.5 (63.8)
$t_{1/2}$ (h), geometric mean (% CVb)	1	28.4 (35.9)	42.5 (31.6)	33.0 (23.8)
C_{24} (μg/mL), geometric mean (% CVb)	1	14.8 (12.7)	9.1 (90.1)	8.5 (139.6)
	22	34.6 (47.2)	22.0[b] (48.4)	21.1 (80.5)

AUC_{0-24} the area under the plasma drug concentration–time curve from 0 to 24 h, *C_{max}* maximum plasma concentration, *C_{24}*, plasma concentration 24 h after treatment (trough), *$t_{1/2}$* elimination half-life, *t_{max}*, time to maximum plasma concentration, *% CVb*, between-subject coefficient of variation

[a] $n = 2$

[b] $n = 6$

Table 4 Pharmacokinetic parameters of pazopanib and lapatinib in the dose-escalation cohort of Part B

Pazopanib parameter	Day	Cohort P400/L1000 ($n = 4$)	P800/L1000 ($n = 3$)	P400/L1500 ($n = 3$)
C_{max} (μg/mL), geometric mean (% CVb)	1	46.4 (10.1)	48.9 (51.1)	31.7 (68.6)
	22	57.9 (18.6)	55.6 (7.3)	51.7 (69.8)
t_{max} (h), median (min–max)	1	5.0 (3.0–8.0)	6.0 (4.0–8.0)	4.0 (3.0–4.0)
	22	4.1 (4.0–8.0)	3.0 (0.5–6.2)	4.0 (3.0–8.0)
AUC_{0-24} (h × μg/mL), geometric mean (% CVb)	1	755.0 (15.0)	853.4 (53.8)	523.7 (66.6)
	22	988.1 (33.2)	1,140.6 (18.4)	1,003.8 (65.6)
$t_{1/2}$ (h), geometric mean (% CVb)	1	30.1 (21.5)	33.7 (48.3)	29.3 (24.8)
C_{24} (μg/mL), geometric mean (% CVb)	1	26.8 (17.9)	31.0 (37.5)	17.6 (61.2)
	22	34.8 (27.6)	41.9 (28.5)	35.2 (65.2)
Lapatinib parameter	Day	Cohort P400/L1000 ($n = 4$)	P800/L1000 ($n = 3$)	P400/L1500 ($n = 3$)
C_{max} (μg/mL), geometric mean (% CVb)	1	2.4 (21.4)	1.5 (50.5)	2.8 (36.9)
	22	1.6 (39.1)	1.6 (77.3)	2.0 (107.1)
t_{max} (h), median (min–max)	1	6.0 (3.0–8.0)	6.0 (6.0–8.0)	6.0 (4.1–6.1)
	22	4.1 (3.0–6.0)	4.0 (4.0–6.0)	6.0 (4.0–8.0)
AUC_{0-24} (h × μg/mL), geometric mean (% CVb)	1	33.8 (25.9)	18.0 (61.5)	32.6 (52.3)
	22	22.8 (44.2)	23.6 (36.1)	32.0 (92.1)
$t_{1/2}$ (h), geometric mean (% CVb)	1	11.6 (30.8)	7.8 (21.5)	9.8 (19.0)

AUC_{0-24} the area under the plasma drug concentration–time curve from 0 to 24 h, C_{max} maximum plasma concentration, C_{24} plasma concentration 24 h after treatment (trough), *L* lapatinib, *P* pazopanib, $t_{1/2}$ elimination half-life, t_{max} time to maximum plasma concentration, *% CVb* between-subject coefficient of variation

and AUC_{0-24} of pazopanib and lapatinib, with the 90 % confidence intervals including 1 (Table 5).

Clinical activity

In part A, none of the 13 patients had a complete response (CR) or partial response (PR). Three patients (2 patients who received P800; 1 patient who received P400/800) had stable disease (SD). In 2 of these patients (1 patient with gastrointestinal stromal tumor [GIST]; 1 patient with head and neck cancer), SD lasted for more than 6 months. The other 9 patients had progressive disease (PD). In 1 patient with colorectal cancer, clinical response was undetermined because the target lesion could not be evaluated because of cystic changes occurring during treatment.

In part B, clinical response was assessable in all 17 patients. None of the patients had a CR, and 3 patients had PR (1 patient with renal cell cancer; 1 patient with a mediastinal carcinoid tumor who received P400/L1000; 1 patient with HER2-positive breast cancer who received P400/L1500). Nine patients had SD, 5 of whom had prolonged SD lasting for more than 6 months (2 patients with head and neck cancer; 1 patient each with abdominal carcinoid tumor, central nervous system neoplasm, and thyroid cancer). The remaining 5 patients had PD.

Discussion

This phase 1 study of Japanese patients with solid tumors showed that pazopanib monotherapy was well tolerated and had a manageable toxicity profile up to a dose of 1,000 mg once daily and that combination therapy with pazopanib and lapatinib was well tolerated and had a manageable toxicity profile at all dose levels studied (P400/L1000, P800/L1000, P400/L1500, and P600/L1250). Because no patient had DLT, the MTD for monotherapy and combination therapy was not determined. The safety profiles and the PK of pazopanib and lapatinib in Japanese patients were similar to those reported in non-Japanese patients [5, 13]. There were no consistent trends in PK interactions between pazopanib and lapatinib.

Drug-related liver toxicity is one of the most clinically important AEs in pazopanib-treated patients. Adverse events of grade 3 or higher involving liver function developed in 4 patients in this study: 3 of 13 patients in part A (23 %; P400/800, P1000) and 1 of 17 patients in part B (6 %; P600/L1250). The frequencies and grades of AEs involving liver function in Japanese patients were similar to those in non-Japanese patients [2, 4, 18].

Two of the 17 patients in part B received the study treatment for more than 3 years with no evidence of PD. The first patient was a 56-year-old man with renal cell carcinoma in whom a PR was maintained while receiving P400/

Table 5 Pharmacokinetic parameters of pazopanib and lapatinib in the PK cohort of part B

Pazopanib parameter	P600 → P600/L1250		
	Day 15 Pazopanib monotherapy ($n = 3$)	Day 37 Combination therapy ($n = 6$)	Ratio[a] (90 % CI) ($n = 3$)
C_{max} (μg/mL), geometric mean (% CVb)	79.6 (10.3)	63.5 (40.6)	0.68 (0.27, 1.73)
t_{max} (h), median (min–max)	3.0 (3.0–4.0)	3.0 (3.0–5.9)	
AUC_{0-24} (h × μg/mL), geometric mean (% CVb)	1,331.4 (13.8)	1,188.8 (37.1)	0.77 (0.33, 1.79)
C_{24} (μg/mL), geometric mean (% CVb)	45.1 (4.2)	43.0 (38.4)	
Lapatinib parameter	L1250 → P600/L1250		
	Day 15 Lapatinib monotherapy ($n = 3$)	Day 37 Combination therapy ($n = 6$)	Ratio[a] (90 % CI) ($n = 3$)
C_{max} (μg/mL), geometric mean (% CVb)	2.09 (49.2)	2.07 (37.0)	0.89 (0.49, 1.62)
t_{max} (h), median (min–max)	4.0 (3.0–4.0)	4.0 (3.0–6.0)	
AUC_{0-24} (h × μg/mL), geometric mean (% CVb)	28.4 (45.4)	29.5 (41.6)	0.97 (0.45, 2.09)

AUC_{0-24} the area under the plasma drug concentration–time curve from 0 to 24 h, *CI* confidence interval, *C_{max}* maximum plasma concentration, *C_{24}* plasma concentration 24 h after treatment (trough), *L* lapatinib, *P* pazopanib, *t_{max}* time to maximum plasma concentration, *% CVb* between-subject coefficient of variation

[a] Ratio of combination therapy/monotherapy

L1000. Urinary protein became positive approximately 2 years after starting the study treatment, and proteinuria gradually progressed without serious clinical symptoms. Eventually, treatment was stopped because proteinuria exceeded 3 g/g creatinine per day 54 months after study entry. The results of liver function tests remained normal throughout the study. The other patient was a 56-year-old woman with thyroid medullary carcinoma who received P600/L1250. She has been receiving the study treatment for more than 40 months, with a best response of SD (as of June 2013). The patient has had several AEs, including liver toxicity, most of which were grade 1. Although the number of patients is small, these findings provide important information on the safety and efficacy of prolonged treatment with pazopanib and lapatinib.

There were no apparent differences in PK parameters of pazopanib and lapatinib between Japanese and non-Japanese patients. The plasma concentrations of pazopanib did not increase in proportion to doses exceeding 800 mg in a previous study of non-Japanese patients (VEG10003) [5] or exceeding 400 mg at single dosing and 800 mg at multiple dosing in our study. These findings suggested that the absorption of pazopanib is saturated at least after doses of 800 mg or higher, and this partially accounts for why the MTD of this oral drug could not be determined despite dose escalation. However, the trough concentrations of pazopanib were consistently above the threshold of >20 μg/mL after monotherapy at doses of 800 mg and 1,000 mg and combination therapy at doses of 400 mg, 600 mg, and 800 mg together with lapatinib. These doses were therefore considered adequate for antitumor efficacy. The large variations in the ratios of combination therapy to monotherapy for the concentrations of pazopanib and lapatinib indicated no consistent trends in drug interactions between pazopanib and lapatinib. However, because a phase 1 study of non-Japanese patients (VEG10006) reported that the AUC and C_{max} of pazopanib increased by approximately 50–60 % when pazopanib 800 mg was combined with lapatinib 1,500 mg [13], potential PK interactions between these drugs cannot be excluded.

In part B, 1 patient each with renal cell cancer, carcinoid tumor, and HER2-positive breast cancer achieved PR. Substantial antitumor activity with prolonged SD was obtained in 1 patient each with GIST and head and neck cancer in part A, and in 2 patients with head and neck cancer and 1 patient each with carcinoid tumor, thyroid cancer, and central nervous system neoplasm in part B. The response of thyroid cancer in part B is consistent with the results of a previous phase 2 study in which pazopanib monotherapy was effective against advanced differentiated thyroid cancer [19]. On the other hand, although 1 patient with GIST achieved long-term SD in part A, suggesting the potential activity of pazopanib against this disease, the efficacy of pazopanib against GIST remains uncertain because a pivotal study of pazopanib in advanced soft tissue sarcoma (PALETTE study) excluded patients with GIST [4]. Furthermore, long-term SD was obtained in 3 of 6 patients with head and neck cancer (1 of 2 patients in part A; 2 of 4 patients in part B), and 2 of 2 patients with carcinoid tumor (both in part B) had PR and long-term SD, respectively.

However, the effectiveness of pazopanib alone and in combination with lapatinib against these diseases remains unconfirmed because the evaluation of efficacy for specific types of cancer was beyond the scope of the present study.

Our findings confirmed that pazopanib monotherapy at a dose of 800 or 1,000 mg once daily and pazopanib plus lapatinib at any of the doses investigated in this study are well tolerated in Japanese patients with solid tumors. No patient had DLT, and the MTD for monotherapy and combination therapy was not determined. The PK profiles of pazopanib and lapatinib in Japanese patients were similar to those reported in non-Japanese patients. There were no consistent trends in pharmacokinetic drug interactions between pazopanib and lapatinib.

We concluded that pazopanib monotherapy at a dose of 800 mg once daily (the recommended dose for non-Japanese patients) and pazopanib plus lapatinib at any of the doses investigated in this study were appropriate for Japanese patients.

Acknowledgments Appreciation is expressed to the patients and their families, as well as the many investigators who participated in the study.

Ethical standards This study was approved by the appropriate ethics committee(s), was performed in accordance with the Declaration of Helsinki, and complied with the current laws of the country (Japan) in which it was conducted. All patients provided informed consent before inclusion in the study.

Conflict of interest This study (VEG109693; NCT00516672) was supported by research funding from GlaxoSmithKline Pharmaceuticals. Editorial assistance was provided by ProEd Communications, Inc., Beachwood, Ohio, USA, and was supported by GlaxoSmithKline. Akiko Takekura is employee but not stockholder of GSK. Kazuo is employee and stockholder of GSK. Yasutsuna Sasaki served as a consultant/advisor for Takeda-Bio, Kowa, and GlaxoSmithKline. Yuichi Ando served as a consultant/advisor for GlaxoSmithKline. The other authors have no conflicts of interest to disclose concerning this study.

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Cancer Chemother Pharmacol (2015) 75:457–464
DOI 10.1007/s00280-014-2665-8

ORIGINAL ARTICLE

Retrospective analysis of fixed dose rate infusion of gemcitabine and S-1 combination therapy (FGS) as salvage chemotherapy in patients with gemcitabine-refractory advanced pancreatic cancer: inflammation-based prognostic score predicts survival

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Received: 13 August 2014 / Accepted: 22 December 2014 / Published online: 30 December 2014

Abstract
Purpose The purpose of this study was to assess the efficacy and safety of fixed dose rate infusion of gemcitabine and S-1 combination therapy (FGS) in patients with gemcitabine (GEM)-refractory pancreatic cancer (PC) and to explore independent variables associated with survival.
Methods We retrospectively reviewed consecutive patients with GEM-refractory PC who received FGS at our institution from March 2009 to December 2013. GEM was administered by fixed dose rate intravenous infusion of 1,200 mg/m^2 as a 120-min infusion on day 1, and S-1 was administered orally twice a day at a dose of 40 mg/m^2 on days 1–7. Cycles were repeated every 14 days.
Results Sixty-one patients with GEM-refractory PC received FGS. Sixteen patients received FGS as third-line treatment. Twenty-nine patients (48 %) had a history of S-1 administration. The objective response rate was 13 %, and the disease control rate was 49 %. The median progression-free survival time was 2.7 months, and the median overall survival time was 6.0 months. Major Grade 3 or 4 adverse events included neutropenia (15 %), diarrhea (3 %), anorexia (2 %), and fatigue (2 %). A high inflammation-based prognostic score (modified Glasgow prognostic score (mGPS), which incorporates C-reactive protein and albumin), a performance status >0, and serum carbohydrate antigen 19–9 level >2,000 IU/ml were independently associated with a poor outcome.
Conclusions FGS might be effective and well tolerated as salvage chemotherapy in a practical setting. The inflammation-based prognostic score is a simple and reliable indicator of survival in the setting of salvage chemotherapy.

Keywords Pancreatic cancer · Chemotherapy · Gemcitabine refractory · Fixed dose rate infusion · S-1 · Inflammation-based prognostic score · Glasgow prognostic score

Introduction

Gemcitabine (GEM) monotherapy has been applied for advanced pancreatic cancer (PC) as a standard treatment since a randomized controlled trial demonstrated improved overall survival (OS) compared with that with fluorouracil [1]. Although various GEM-based combination regimens have been evaluated, only nab-paclitaxel or erlotinib added to GEM showed a survival benefit over GEM alone in a phase III study [2–4]. Fluorouracil/leucovorin plus irinotecan plus oxaliplatin (FOLFIRINOX), a GEM-free combination regimen, demonstrated a clear survival benefit compared with GEM for patients with metastatic PC [5]. Therefore, these combination therapies have been considered to be standard first-line therapies.

However, after disease progression during first-line chemotherapy, the options for further anticancer treatment are limited. In Japan, clinical trials of S-1 (TS-1; Taiho Pharmaceutical, Tokyo, Japan) have been conducted since the early 2000s for patients with PC. A phase II study of S-1 first-line monotherapy led to a median progression-free survival (PFS) time of 2.0 months and a median OS time of 4.5 months in GEM-refractory metastatic PC [6]. In GEM-refractory metastatic PC, a recent phase I/II study

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of fixed dose infusion (FDR) GEM and S-1 combination therapy (FGS) yielded results that demonstrated activity including a response rate of 18 %, a median PFS time of 2.8 months, and a median OS time of 7.0 months, with a favorable toxicity profile [7]. A randomized phase II study comparing GEM administration via 30-min infusion and FDR infusion showed that FDR-GEM was associated with higher intracellular drug concentrations and efficacy [8]. A phase III study E6201 designed to test two promising approaches, FDR-GEM and GEM and oxaliplatin combination therapy (GEMOX), against standard GEM showed that OS time for FDR-GEM was longer than that for standard GEM ($p = 0.04$), but the difference was not statistically significant with respect to the parameters of the study ($p < 0.025$) [9]. The results of a phase I/II study of FGS for GEM-refractory PC suggested that even after the failure of standard GEM, the increased intracellular concentration of GEM as a result of FDR infusion and/or the synergistic effect of GEM and S-1 might play an important role in the antitumor effect of FGS for advanced GEM-refractory PC.

No standard salvage chemotherapy has been established for patients with advanced PC after the failure of GEM-based treatment. It is important to clarify the prognostic factors for patients with GEM-refractory advanced PC as well as to evaluate the efficacy and safety of salvage chemotherapy. With respect to measurement of the systemic inflammatory response, the combination of C-reactive protein and albumin (the original Glasgow prognostic score and the modified Glasgow prognostic score (mGPS)) has been shown to have prognostic value in a variety of common solid tumors [10, 11]. To our knowledge, there has been no report on the relationship between the modified Glasgow prognostic score and outcome in salvage chemotherapy for advanced PC.

As noted above, FGS was reported to provide promising antitumor activity and tolerable toxicity in patients with GEM-refractory PC. However, the previous study of FGS was limited in patient number, and the efficacy and safety of FGS for patients with GEM-refractory advanced PC are not well known. The aim of the present study was to retrospectively evaluate the efficacy and safety of FGS as salvage chemotherapy for advanced GEM-refractory PC in a clinical setting and to establish a method of selecting patients who will benefit from salvage chemotherapy.

Materials and methods

The subjects were consecutive patients with advanced GEM-refractory PC who received FGS between March 2009 and December 2013 as second-line or third-line treatment at Kyorin University Hospital. We retrospectively reviewed their medical records. All patients had a pathological and clinical diagnosis of PC. Informed consent was obtained from each patient, and this retrospective study was approved by the independent ethics committee of Kyorin University School of Medicine.

Eligibility

The patient selection criteria for this study were as follows: both a pathological and clinical diagnosis of PC; disease progression under GEM-based chemotherapy; an Eastern Cooperative Oncology Group performance status (PS) of 0–2; good bone marrow function (white blood cell count $\geq$3,000/mm^3, platelet count $\geq$75,000/mm^3, and hemoglobin $\geq$8.0 g/dl); renal function (serum creatinine $\leq$1.5 mg/dl); and liver function (total bilirubin $\leq$2.0 mg/dl and transaminase levels $\leq$5 times the upper limit of the respective normal ranges). Patients who had obstructive jaundice were eligible, but only after their serum transaminase levels had decreased to within five times the upper normal limit after biliary drainage. Exclusion criteria were as follows: severe complications, such as active infection, uncontrolled diabetes, massive pleural effusion or ascites, active concomitant malignancy, or severe drug hypersensitivity.

Treatment

GEM was administered every 2 weeks by FDR intravenous infusion of 1,200 mg/m^2/120 min on day 1. S-1 was administered orally twice daily on day 1 to day 7, followed by a 1-week rest. The initial dose was determined according to the body surface area (BSA) as follows: BSA < 1.25 m^2, 80 mg/day; 1.25 m^2 $\leq$ BSA < 1.50 m^2, 100 mg/day; and BSA $\geq$ 1.50 m^2, 120 mg/day. Treatment cycles were repeated every 2 weeks until disease progression or unacceptable toxicity occurred.

Evaluation

Tumor response was assessed approximately every 2 months by contrast-enhanced computed tomography according to the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1). Toxicity was evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Laboratory variables were initially recorded as continuous variables, and later dichotomized according to the median and reference value of each variable. mGPS was constructed, using C-reactive protein and albumin, as follows: Patients with both elevated C-reactive protein ($\geq$1.0 mg/dl) and low albumin (<3.5 g/dl) were allocated a score of 2; patients in whom only C-reactive protein was elevated ($\geq$1.0 mg/dl) were allocated a score of 1, and those with normal C-reactive protein were allocated a score of 0 [11].

Table 1 Patient characteristics

	Patients ($n = 61$)	Percent (%)
Age (years)		
Median	63	
Range	37–83	
Gender		
Male	40	(66)
Female	21	(34)
ECOG performance status		
0	22	(36)
1	36	(59)
2	3	(5)
Primary tumor		
Head	29	(48)
Body/tail	32	(52)
Extent of disease		
Locally advanced	1	(2)
Metastatic	48	(79)
Recurrence after surgery	12	(20)
Metastatic site		
Liver	38	(62)
Lung	17	(28)
Peritoneum	36	(59)
Lymph node	45	(74)
Ascites	22	(36)
Prior treatment		
First Line		
GEM	37	(61)
GEM+S-1	19	(31)
GEM+erlotinib	1	(2)
GEM+ganitumab	2	(3)
GEM+nab-paclitaxel	1	(2)
S1	1	(2)
Second Line		
Yes	17	(28)
S-1	9	(15)
GEM+S-1	2	(3)
GEM	1	(2)
Clinical trial drug	3	(5)
Others	2	(3)
No	44	(72)
History of S-1 administration		
Yes	29	(48)
No	32	(52)
TTF of prior treatment (months)		
Median	6.3	
Range	0.47–32.43	
CEA (ng/ml)		
Median	8.6	
Range	0.9–1,412	
CA19-9 (IU/ml)		
Median	1,805	
Range	0.1–120,000	
ALP (IU/l)		
Median	301	
Range	147–1,429	
Alb (g/dl)		
Median	3.7	
Range	2.3–4.6	
CRP (mg/dl)		
Median	0.3	
Range	0.0–7.1	

ECOG, Eastern Cooperative Oncology Group; GEM, gemcitabine; TTF, time to treatment failure; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; ALP, alkaline phosphatase; Alb, albumin; CRP, C-reactive protein

Statistical analysis

PFS was counted from the date of treatment initiation to the date of documentation of disease progression or death, and OS was counted from the date of treatment initiation to the date of death or the last follow-up. OS and PFS were calculated using the Kaplan–Meier method. Subgroup analyses were evaluated with the log-rank test, and prognostic factors were identified by univariate analysis. Multivariate analysis was carried out using stepwise Cox proportional hazards regression modeling to identify independent prognostic factors. For the analysis of factors predictive for response to FGS, the univariate relationship between each clinical variable and the achievement of partial response was evaluated using Pearson's Chi-square test or Fisher's exact probability test. These variables were also evaluated by a multivariate logistic regression model using backward stepwise selection. The variables with p values <0.1 were selected for multivariate analysis. P values <0.05 were considered statistically significant. The SPSS statistical software program (version 20.0; SPSS, Chicago, IL, USA) was used for all statistical analyses.

Results

Between March 2009 and December 2013, 61 patients with GEM-refractory PC received FGS. The patient characteristics of the subjects are shown in Table 1. Of the 61 patients, the median age was 63 years, 40 (66 %) were male, 58 (95 %) had an ECOG PS of 0–1, and 60 (98 %) had metastatic disease. Disease progression had been confirmed before FGS in all patients. All patients had received prior GEM-based

therapy. Before FGS, 44 (72 %) received one regimen, and 17 (28 %) received two regimens. As for prior treatment regimens, 29 (48 %) had received S-1 as monotherapy or GEM plus S-1 combination therapy. Median time to treatment failure of prior treatment was 6.3 months (range 0.5–32.4).

A total of 542 courses were administered, with a median of five courses (range 1–62). Dose reduction in GEM and S-1 because of adverse events was conducted in 11 (18.0 %) and 12 (19.7 %) patients, respectively. A rest period of more than 14 days during treatment was required in 22 (36.1 %) patients. The relative dose intensity for GEM and S-1 was 92.6 and 92.3 %, respectively. FGS was discontinued in 56 (91.8 %) patients because of disease progression and in five (8.2 %) patients because of adverse events (Grade 3 cholangitis in two patients, grade 3 interstitial lung disease in one patient, grade 3 stroke in one patient, and grade 3 sick sinus syndrome in one patient). All the patients had died at the time of analysis.

After FGS treatment failure, 17 patients (27.9 %) received chemotherapy: paclitaxel in five patients, clinical trial drugs in four patients, GEM monotherapy in four patients, and others in four patients.

Toxicity

The toxic effects are summarized in Table 2. Hematologic and non-hematologic toxicity were generally mild, with grade 3 neutropenia observed in nine patients (14.8 %), grade 3 diarrhea in two patients (3.3 %), grade 3 anorexia in only one patient (1.6 %), and grade 3 fatigue in only one patient (1.6 %). Grade 3 stroke, which was irreversible, occurred in one patient (1.6 %). Other than this case, all of the adverse events were reversible. There were no treatment-related deaths.

Efficacy

Eight (13.1 %) patients showed a partial response and 22 (36.1 %) showed stable disease, resulting in an overall objective response rate of 13.1 % and a disease control rate of 49.2 %. The median OS time was 6.0 months (95 % CI 3.6–8.4), and the median PFS time was 2.7 months (95 % CI 1.9–3.5) (Fig. 1). The median OS time after the start of first-line therapy was 15.4 months.

Prognostic factors

The median survival time and p values for univariate analysis are shown in Table 3. Among these variables, ECOG performance status (PS) >0, the presence of ascites, serum carcinoembryonic antigen (CEA) level >10 ng/ml, serum carbohydrate antigen 19-9(CA19-9) level >2,000 IU/ml, serum alkaline phosphatase level (ALP) >500 IU/ml, serum albumin level (ALB) <3.5 g/dl, serum C-reactive protein (CRP) level $\geq$1.0 g/dl, and a high mGPS were significantly associated with poor survival. A previous history of S-1 administration was not a prognostic factor. The results of the Cox proportional hazards model are shown in Table 4. High mGPS, ECOG PS >0, and CA19-9 level >2,000 IU/ml were independently associated with a poor outcome.

Table 2 Toxicity according to CTCAE v 4.0

	Grade							
	1		2		3		4	
	n		*n*		*n*		*n*	
Hematologic								
Anemia	41	(67 %)	20	(33 %)	0	(0 %)	0	(0 %)
Leukopenia	12	(20 %)	11	(18 %)	7	(11 %)	0	(0 %)
Neutropenia	10	(16 %)	9	(15 %)	9	(15 %)	1	(2 %)
Thrombocytopenia	23	(38 %)	0	(0 %)	0	(0 %)	0	(0 %)
Non-hematologic						(0 %)		(0 %)
Anorexia	32	(52 %)	14	(23 %)	1	(2 %)	0	(0 %)
Nausea	21	(34 %)	11	(18 %)	0	(0 %)	0	(0 %)
Diarrhea	19	(31 %)	5	(8 %)	2	(3 %)	0	(0 %)
Oral mucositis	12	(20 %)	5	(8 %)	0	(0 %)	0	(0 %)
Fatigue	38	(62 %)	14	(23 %)	1	(2 %)	0	(0 %)
Dysgeusia	22	(36 %)	4	(7 %)	0	(0 %)	0	(0 %)
Skin hyperpigmentation	24	(39 %)	0	(0 %)	0	(0 %)	0	(0 %)
Vomiting	7	(11 %)	1	(2 %)	0	(0 %)	0	(0 %)
Constipation	11	(18 %)	9	(15 %)	0	(0 %)	0	(0 %)
Rash	3	(5 %)	1	(2 %)	0	(0 %)	0	(0 %)