られる統一投稿規定（Uniform Requirements for Manuscripts：URM）を定めている．この中の「倫理的考慮」についての項目に，「著者と貢献者」「編集者」「査読」「利益相反」「プライバシーと守秘」「被験者と実験動物の保護」についての要件が定められ，著者だけではなく出版者に求められる事柄も明記して，論文発表に関するバイアスを最小化しようと努めている．さらに査読システムを改革する動きもあり，BMJグループのような先進的な出版社では，査読者を匿名化するという一般的方法を採らず，査読者も投稿者も完全オープンな状況で査読を行うというシステムに移行している．また，BMJグループの一部の雑誌では，査読のプロセス（著者と査読者のやりとりの一部始終）がインターネット上ですべて一般公開される．これにより，査読が公正に行われたかどうか，論文出版後に確認することが可能になっている．

このように，論文発表という研究の最終段階に倫理的要件を課すること（発表倫理）が，研究実施の公正性を保証する有力な手段となるのではないかと期待される[27]．ただ現時点では，研究が登録されていても必ず発表されるという保証はなく，また，ICMJEのURMを採択している雑誌は著名誌を除けばまだ少ないのが実情である．

以上のように，研究倫理の3原則は，倫理的な手段にほぼ対応している．第1原則はインフォームド・コンセントの取得により，第2原則は倫理審査委員会承認の取得により，第3原則は発表倫理の要件を満たすことにより，遵守が促されるものと考えられる．

6.3　ダブル・スタンダードの解消を

もう一つの問題は，治験とそれ以外の臨床試験（一般臨床試験）を別扱いにするという日本独特の問題である．

米国の国家研究法の成立については先に述べたが，それに続いて欧州でも臨床研究（特に臨床試験）の法規制が進んだ．早期から臨床研究の包括的な法規制に乗り出した国はフランスであった[28]．1988年以前のフランスでは，「治療目的でない人体実験を行ってはならない」とする医師の職業倫理規定と新薬臨床試験の現実に大きな矛盾があり，臨床試験を行う医師は「いつ訴えられるかわからない」不安定な状況下に常に置かれていた．このため医学界・製薬業界からも，被験者保護のための（ひいては研究者の保護のための）規制法が求められていた．折しも人体実験スキャンダルが起こって社会的関心が高まったこともあり，1988

年12月，いわゆる「被験者保護法」が成立した．その特徴として，①適用対象がきわめて包括的なこと，②倫理審査を公的な第三者機関が行うこと，③被験者にとって直接的利益がある研究とない研究を差別化していること，④試験実施の条件，弱者保護，補償責任などをすべて法律として明文化していること，などが挙げられる．

その後，体外受精児誕生を契機に生命倫理に関する議論が起こり，1994年，「被験者保護法」を改正するとともに，新たに生命倫理に関する三法（いわゆる「人体尊重法」「移植・生殖法」「記名データ法」）が成立した．「被験者保護法」と合わせて「生命倫理四法」と呼ばれ，他に類をみない格式の高さにより諸外国の規範となっている．

2001年，欧州連合（EU）では加盟国間の医薬品臨床試験の規制調和のため「EU臨床試験指令」を公布し，各国に立法を求めた．これを受け，それまでは規制法がなかった国々でも法整備が進んでいる．たとえば，英国は1968年の薬事法以来，患者対象の臨床試験には届出・許可制度があったが，医師による自主研究は例外扱いであり，また健常人対象の試験は適用外で自主規制に委ねられてきた．しかし「EU臨床試験指令」を受け，新たな規則が2004年より施行され，倫理審査制度なども含めて臨床試験に関する包括的な法整備が進んでいる[29]．

しかるに日本では，治験は法規制されているが，一般臨床試験は依然として法の枠外にある．法的拘束力を有するのは治験のGCP省令だけであり，その他の指針には拘束力がない．研究方法に本質的な違いがないにもかかわらず，治験と一般臨床試験の扱いはまったく異なり，ダブル・スタンダード状態が続いているのである．

著者は，すべての臨床試験が法の下でGCPに準拠して行われるようになるべきだとかねてより考えてきた[30][31]．

そう考える理由にはいくつかあるが，やはり第1の理由は被験者保護である．被験者から見ると，実験に参加するという意味では，治験も一般臨床試験も何ら変わりがない．それどころか，治験よりリスクの大きい一般臨床試験も十分あり得る．GCPに準拠する治験では被験者へのリスクは最小化できるが，一般臨床試験ではその保証がない．事実，臨床試験に関わる倫理的問題の多くは，治験以外の臨床試験の中で生じている．

第2の理由は，ダブル・スタンダード状態には無駄が多いことである．治験が法規制されている背景としては，被験者保護もさることながら，研究の質を保証

しないと医薬品開発の国際競争に取り残されるという市場経済的な理由も大きい．では，治験以外の臨床試験はGCPに準拠しなくてもよいとする現状は，経済効率という点で有利なのだろうか．GCPに準拠していない臨床試験は，いくら確かな成果が得られたとしても，新しい医療技術として国から承認を受けるためのデータとしては使えない．いかに学術的に優れた研究であっても，そこで得られた知識や技術を医療現場で生かすためには，再び最初から治験としてやり直すことが求められる．これは時間的にも経済的にも大きな無駄である．一方，GCPに準拠しない臨床試験を現状のように許していると，杜撰な臨床試験が横行して誤った結果が出回ることになり，無駄どころか社会に害をもたらす．

第3に，臨床試験を適切に法規制することは，研究者の安全を守ることにもつながる．現在，診療は医師法や医療法，治験は薬事法で規定され，両方とも法的根拠を有している．ところが一般臨床試験は，これを規定した法律がないため，いわば国から公認されていない行為なのである．たとえば，今の倫理指針には補償責任などに曖昧な点が多く，研究者は常に悩まなければならない．これが法規制されれば，法的根拠のない不安定なグレイゾーンで活動している研究者の行為が公に認められ，補償制度など必要なインフラ整備も進むであろう．

臨床研究全体を法規制することに関しては，以前より賛否両論があった．一方では，単なる倫理指針では遵守しなくても制裁されないので実効性がない，したがって法規制するべきだとする主張がなされ，私案も発表されている[32]．他方，たとえガイドラインでも，遵守しないと何らかの行政上不利な取り扱い（たとえば公的研究資金が得られなくなるなど）を受けることになるため，実効性はあるという主張[33]もある．

筆者としては，GCPのような詳細な規定まで法文化する必要はないが（厳格すぎる法律は健全な研究をも妨げる可能性がある），倫理指針の根拠を与える基本法はあった方がよいと思っている．臨床研究を規制するための法律というより，健全な研究を促すために必要なことを定める法律であってほしい．具体的には，人を対象とする研究行為を法的に認め，その条件として国が認定したIRBによる倫理審査を義務づける．その基本法の下に，全行政機関共通の規則を整え，これに基づいて倫理審査を実施するのである．

研究の法規制などというと，煩瑣な手続きや他者の干渉を厭わしく思う医師・研究者の反発を招きそうだが，杜撰な研究や非倫理的な研究を淘汰し，優れた研究のみ能率よく推進するためには，誰もが認めるルールに従うことが必要である．

手続きが増えて一見遠回りに見えるが，規制に応じた研究基盤さえ整えば，結局はそちらの方が必要かつ有益な研究結果を確実に，しかも低コストで手にできる．また日本という国の信頼にもつながるということを理解するべきである．

おわりに

今日の研究倫理は戦後60年以上を費やして築かれてきたが，日本の状況はまだ未熟であり，さらなる改善と発展が望まれる．臨床研究全般を法でカバーすること，すべての臨床試験をGCPに準拠させること，倫理原則の下で指針を整理することなどが強く求められる．

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解　説

わかりやすい被験者説明文書を作成するために：オランダの取り組みの紹介

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Improving the readability of information for study subjects: The Dutch approach

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Abstract

We have translated into Japanese 1) the template of the patient information form (PIF) proposed by the Dutch Central Committee on Research involving Human Subjects (CCMO), and 2) the PIF workgroup's written advice to the CCMO. The advice has been prepared by the non-scientific members of 25 of the Dutch Medical Research Ethics Committees including one from the CCMO, which in itself is illustrative of how fundamentally different their social philosophies are from those of Japan. Also, the CCMO (a governmental body) reacts to this advice accordingly. This may be a process that cannot be mimicked by the strictly top-down Japanese society. We nevertheless hope that the current paper will lead to active discussion on the form of the PIF. Although there are differences between countries, the same principles of Good Clinical Practice are shared. We hope that readers will find valuable clues on how to improve the PIF in Japan.

Key words

PIF work group, CCMO, MREC, non-scientific member

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はじめに

今回，オランダの中央倫理委員会が作成した説明文書のテンプレート[1]と被験者説明文書作業部会が中央倫理委員会へ提出した報告書（勧告）[2]を日本語に翻訳し本誌に掲載した．国の違いはあるが，GCPという臨床試験の基本概念は同じくしており，日本における説明文書のあり方に関して参考になればと思う．

1. 被験者説明文書に関する対応

オランダでは現在，被験者説明文書（以下，説明文書）のテンプレートを中央倫理委員会が提示し，全国で活用されている．1998年に「人を対象とする医学研究に関する法律（WMO）」が制定[3]され，中央倫理委員会が発足した．中央倫理委員会の主な業務は，①特殊なタイプの研究計画書の審査，②個々の倫理委員会の認定，③認定した倫理委員会の監督，④ヒトを対象とした試験を含む全ての国内での登録された医学研究のデータ収集，⑤認定された倫理委員会による審査の質の調和と向上，などである[4]．

2004年にWMO評価部会は，書面による被験者説明には改善の余地が見受けられると判断した．WMO評価部会の判断を受けて，2005年に臨床試験倫理委員会（MREC：Medical Research Ethics Committee）委員長会議は，被験者説明文書作業部会（PIF-WG：Patient Information Form Working Group）を設立し，説明文書の読みやすさを検討した．

ここでは“説明文書を分かりやすくするには”というPIF-WGの報告書の概要と中央倫理委員会の対応を簡単に紹介する．詳しくは別掲載の日本語訳を参照していただきたい[1, 2]．

2. 現状の検討

PIF-WGは，説明文書作成補助資料と説明文書の評価の現状について検討した．その結果，下記の結論を得た．

1. 説明文書作成補助資料
   - 説明文書作成補助資料はあるが，そのほとんどが責任医師向けの資料である
   - 補助資料の質には（施設間で）ひらきが見られる
   - 責任医師が補助資料を有効活用していない（知らない，魅力を感じない）
   - 審査委員会が審査において補助資料を参考にしない
2. 説明文書の評価
   1）説明文書の目的
   - 説明文書の目的が不明瞭（免責か説明か）
   - 審査委員会には力がない．改善の余地があることも認識していない（特に国際共同臨床試験，新薬の臨床試験）．

   2）審査の対象となる事項
   - 審査委員会間で業務範囲（の認識）が異なる（改訂指示においても，審査においても）
   - 審査委員会の業務範囲（の認識）が不明瞭であるため，多施設共同試験では複数の説明文書が作成される
   - 「どうせ改訂指示が出るのだから」という認識が責任医師にある
   - 審査委員会内で，誰が説明文書の読みやすさを評価するのかが不明瞭である

   3）審査の基準
   - 審査委員会には説明文書の審査規準がない
   - 多施設共同試験の場合，審査委員会が設置されている以外の施設の委員会は，必ずしもプロトコルを審査する審査委員会の意見に従うわけではない
   - 責任医師は，審査委員会の審査が手当たり次第であると感じてしまう

3. 問題提起と対策案

PIF-WGは，調査・検討に基づき，説明文書の質に影響しうる，5つの問題点を提起した．

1. 説明文書の目的（説明すること）が不明瞭
2. 読みやすい文書の書き方についての知識の不足
3. 審査プロセス及び責任が明確化されていない上，施設間で異なる
4. 説明文書の明瞭な審査規準の欠如
5. （質の高い）作成補助が不足している

上記の問題点を改善するために，PIF-WGは下記の対策案を提言した．

1. 説明文書の目的は何か
   1) 説明文書の目的は，被験者への情報提供である．
   2) 説明文書の目的は，責任医師の司法上の免責ではなく，被験者が臨床試験に参加するか否かを慎重に決断できるために十分な情報を提供することである．
2. 読みやすい文書とは何か
   1) 標準的な説明文書は，レベル3（日本の中卒レベルに相当）で書かれていなければいけない．
   2) 12歳未満の未成年及び知的障害者（レベル1/2，まれに3）においては，これに加え適切な補足的説明が必要である．
3. 全国で統一された審査プロセス
   下記の事項を熟慮しつつ，全国で一つの，説明文書の審査に関する規定を設ける：
   1) 説明文書の作成は責任医師の責務である
   2) 説明文書の審査はMRECの責務である
   3) 各MRECにおいて，委員の一人が説明文書の読みやすさを監視する
   4) 改訂後も説明文書が指定の条件を満たしていない場合は，プロトコルは不承認となる
4. 全国で統一された説明文書の審査基準
   1) 説明文書の長さ：最長A4三枚（1,500単語，同意書，補償に関する事項，まれな副作用，臨床試験パンフレット，フローチャートを含まない）
   2) 語彙レベル：EUレベル3（日本の中卒レベルに相当）
   3) 構成：階層構成
   4) 口調：従来どおり
   5) 内容：従来どおり
5. 公式な作成補助資料の開発
   質の向上に関して，PIF-WGは下記の4つの補助資料を提案した．
   1) 説明文書の記載事項の一覧
   2) 書き方のすすめ
   3) 説明文書テンプレート
   4) 用語集

4. 中央倫理委員会の対応

中央倫理委員会はMREC委員長会議のPIF-WGの勧告を受けて，説明文書のテンプレートを作成した．説明文書の本体は最長でA4三枚（1,500単語）であること．単語数には同意文書と臨床試験パンフレット，添付する保険（補償）に関する事項，稀な副作用，フローチャート及び施設固有の情報（多施設共同試験の場合）などは含まないことが示された．

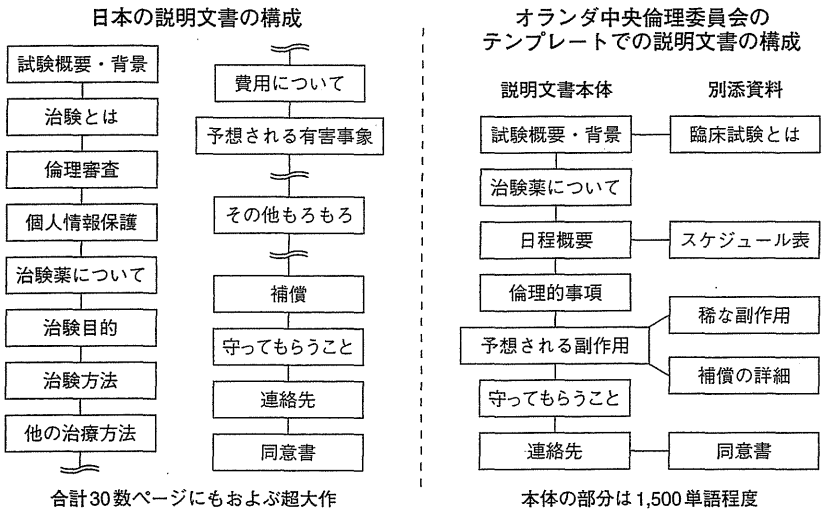
中央倫理委員会による説明文書テンプレートの日本語訳を参照されたい[1]．

今までの説明文書と新しいテンプレートを図解するとFig. 1（筆者作成）のようになる．

オランダはEU臨床試験指令に従っており，説明文書に含まれる項目はICH-GCPに記載されている項目を当然のことではあるがカバーしている．

20～30ページに及ぶ臨床試験の説明文書を理解することは，医学知識の乏しい一般のヒトにはかなり困難が伴う．説明文書は，被験者自らが臨床試験参加について判断するために必要な情報を与えることが目的であるから，読みやすいと同時

Fig. 1 Structure of typical Japanese PIF vs. Dutch CCMO template



に理解しやすい形態を考えるべきであろう.

5. 日本での対応

説明文書に関しては, 2009年12月に開催された第30回日本臨床薬理学会のワークショップ「治験／臨床研究の説明文書を作成するためのスキルアップ」で取り上げられている[5]. また, 2010年2月に松山で開かれた国際共同治験推進会議in Matsuyamaのワークショップにおいても説明文書の内容に関するディベートがあった. 説明文書の案を作成する製薬企業の担当者からは「後で問題となるのを防ぐため, できる限りの情報を載せたい」との意見があった. 訴訟大国のアメリカを考えれば無理ないことと思われるが, 医療機関側が主張する「分かりやすくすること」と会社側の「いわゆる免責」を両立させる方法を検討する時期ではないかと考える.

ICH-GCPがハーモナイズされ, 1997年にGCPを日本に定着させるために「新GCP普及定着総合研究班（主任研究者：中野重行)」が組織されたが, その中の作業班の1つにインフォームドコンセント検討作業班（班長：秋山秀樹）があった. 作業班の最終報告書には説明文書本体に加え補充説明資料の考え方が記載されている[6]. そこでの形式は基本的にはオランダの形式と類似しているが, 日本に定着普及しなかった理由を今後のためにも再検証すべきであろうと思われる.

おわりに

オランダのPIF-WGの報告書と説明文書のテンプレートを日本語に翻訳して感じたことは, 読む側に理解しやすい説明文書を作成することだけでなく, それを審査する側の適格性も併せて考慮していることである. また, 報告書の作成は24の倫理審査委員会の非専門委員が行っており, 医療機関所属者が活動している日本とは社会理念に根本的な相違が感じられる. さらに, 勧告を受けて政府機関である中央倫理委員会が対応している.

上意下達の日本文化では真似のできないプロセスと思われるが, それでも説明文書のあり方に関して積極的な論議が起こることを期待している.

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Invest New Drugs
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PHASE II STUDIES

Phase I/II study of sunitinib malate in Japanese patients with gastrointestinal stromal tumor after failure of prior treatment with imatinib mesylate

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Summary *Purpose:* To establish a recommended sunitinib dosing schedule in Japanese patients with imatinib-resistant/intolerant gastrointestinal stromal tumor (GIST) and to evaluate the efficacy, safety/tolerability, pharmacokinetics, and pharmacodynamics of sunitinib using this schedule. *Patients and methods:* In the phase I part of this open-label phase I/II trial, Japanese GIST patients received 25, 50, or 75 mg/day of sunitinib on Schedule 4/2 (4 weeks on treatment; 2 weeks off treatment) following imatinib failure. In phase II, patients received the recommended (maximum tolerated) dose on this schedule; the primary endpoint was clinical benefit rate (CBR; percent objective responses or stable disease [SD] ≥22 weeks). Additional efficacy, safety, pharmacokinetic, and biomarker analyses were performed. *Results:* In phase I (12 patients), the recommended dose was determined to be 50 mg/day. Sunitinib pharmacokinetics were similar to those observed in studies with Western patients. In the phase II part (36 patients), the CBR was 39% (95% CI: 23–57%; 11% partial responses, 28% SD ≥22 weeks). The most common treatment-related non-hematologic adverse events (AEs) were hand–foot syndrome (86%) and fatigue (67%). A trend towards a correlation between decreases from baseline in plasma soluble KIT levels and improved CB was found. *Conclusions:* The pharmacokinetics observed and clinical outcomes achieved in Japanese GIST patients on sunitinib (50 mg/day, Schedule 4/2) after imatinib failure appeared similar to those of Western patients in previous sunitinib trials. Although some serious AEs were observed, AEs were generally manageable using dose interruption/modification and/or standard medical treatments.

Keywords Sunitinib · GIST · Japanese patients · Pharmacokinetics · Biomarkers

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Introduction

Gastrointestinal stromal tumor (GIST) is a soft-tissue sarcoma that most commonly arises in the stomach or small intestine, and less frequently in the large bowel or other gastrointestinal sites [1,2]. Greater than 80% of GISTs are associated with activating mutations of KIT (stem-cell-factor receptor, CD117) [3,4], and another 5–7% express activating mutations of platelet-derived growth factor receptor alpha (PDGFR-α) [4,5].

Imatinib mesylate—a small-molecule tyrosine kinase inhibitor with selectivity for KIT and PDGFRs—is the current mainstay of treatment for metastatic or unresectable GIST. However, approximately 11–14% of GISTs are initially resistant to imatinib [6,7] and another 40–50% acquire resistance within 18–24 months of initial therapy [7,8].

Sunitinib malate (SUTENT®) is an oral multitargeted tyrosine kinase inhibitor with activity against KIT and PDGFRs, as well as vascular endothelial growth factor receptors (VEGFRs), glial cell line-derived neurotrophic factor receptor (REarranged during Transfection; RET), colony-stimulating factor 1 receptor (CSF-1R), and FMS-like tyrosine kinase-3 receptor (FLT3) (Pfizer Inc., data on file) [9–13]. Sunitinib received multinational approval for the treatment of GIST after failure of imatinib due to resistance or intolerance, based largely on the interim results of an international, randomized, double-blind, placebo-controlled phase III trial [14].

The clinical safety and efficacy of both imatinib and sunitinib in GIST have primarily been established in Western patients residing in the USA or Europe and have not been thoroughly studied in Asian patients. Fifty-six centers in 11 countries participated in the phase III trial of sunitinib in GIST, but only 15 of the 312 patients were of Asian descent (10 and 5 in the sunitinib and placebo groups, respectively). An open-label, phase I/II trial was therefore undertaken to establish a recommended dosing schedule for sunitinib in Japanese GIST patients after imatinib failure and to better evaluate the efficacy and safety of sunitinib in this patient population. In addition, the pharmacokinetic profiles of sunitinib and its active metabolite were assessed, and an initial evaluation of potential biomarkers of sunitinib activity in this patient population was performed.

Patients and methods

Patients

Japanese patients, 20–75 years of age, were required to have histologically proven metastatic or unresectable malignant GIST and confirmed failure of prior imatinib therapy, as demonstrated by disease progression (based on Response Evaluation Criteria in Solid Tumors [RECIST] [15]) or discontinuation of imatinib due to toxicity. Additional eligibility criteria included an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and adequate cardiac, hepatic, renal, coagulation, and hematologic function. Key exclusion criteria included lack of recovery from the acute toxic effects of previous anticancer therapy or imatinib treatment, discontinuation of imatinib therapy within 2 weeks or of any other approved or investigational drug for GIST within 4 weeks prior to starting sunitinib treatment, clinically significant cardiovascular events or disease in the previous 12 months, diabetes mellitus with clinical evidence of peripheral vascular disease or diabetic ulcers, or a diagnosis of any second malignancy within the previous 5 years. All patients provided written informed consent to participate in the study.

Study design

This was an open-label, single-arm, non-randomized, multicenter, dose-escalation, phase I/II trial performed in accordance with the International Conference on Harmonization Good Clinical Practice guidelines. In the phase I part of the study, patients received one 6-week treatment cycle of sunitinib (4 consecutive weeks on treatment, followed by 2 weeks off treatment; Schedule 4/2). Successive cohorts of three to six patients received doses of 25, 50, or 75 mg administered orally once daily in the morning. Patients were enrolled in the subsequent cohort if less than one-third of patients in the initial or preceding cohort had experienced a dose-limiting toxicity (DLT). A DLT was defined as a grade 4 hematologic toxicity of ≥7 days' duration or complicated by fever ≥38°C; a grade 3/4 hematologic toxicity complicated by infection, hemorrhage, or requiring blood product support, including a hematopoietic growth factor; a grade 3/4 non-hematologic event (except for asymptomatic increases in serum amylase or lipase, or nausea/vomiting or diarrhea manageable with antiemetic and antidiarrheal drugs); or evidence of left ventricular dysfunction, defined as development of congestive heart failure or decline in left ventricular ejection fraction (LVEF) by an absolute value of ≥20% from baseline and to less than the lower limit of normal (LLN). Patients experiencing a DLT during the phase I part of the study were withdrawn from sunitinib treatment but could resume dosing if the toxicity resolved and there was evidence of clinical benefit. A primary objective of the phase I part of the study was to determine a recommended dose for the phase II part by identifying the maximally tolerated dose (MTD) of sunitinib, defined as the highest dose below the dose at which the proportion of patients experiencing DLTs was ≥33.3%.

Patients continuing in the phase II part of the study from the phase I part switched to/continued on the recommended dose (50 mg/day) on Schedule 4/2 after it was determined. Newly enrolled patients in the phase II part received the recommended dose on Schedule 4/2. Any drug-related grade 3/4 adverse events developing during the phase II part were managed using standard medical treatments and/or by discontinuing drug temporarily until the event resolved sufficiently, followed by dose reduction by 12.5–25 mg for grade 3/4 non-hematologic events or grade 4 hematologic events. Criteria for permanent drug withdrawal were a need to reduce the sunitinib dose to <25 mg/day, evidence of RECIST-defined disease progression, or evidence of left ventricular dysfunction (as previously defined).

Study endpoints and assessments

The primary endpoints of the phase I part were measures of safety and pharmacokinetic parameters of sunitinib and its principal active metabolite, SU12662. Adverse events were assessed by type, grade, and relationship to study drug, with grading determined using National Cancer Institute Common Toxicity Criteria version 2.0 [16]. Serious adverse events were defined as any untoward medical occurrences that resulted in death, were life-threatening, required or prolonged hospitalization, or resulted in persistent or significant disability/incapacity or a congenital anomaly/birth defect. Safety assessments included vital signs, ECOG performance status, 12-lead electrocardiogram, echocardiogram or multiple-gated acquisition scan, and laboratory analysis of blood and urine. Pharmacokinetic parameters were determined using blood samples collected pre-dose on days 1, 2, 7, 14, 21, 28, and end of treatment (or withdrawal), and post-dose at 1, 2, 4, 6, 8, and 10 h on days 1 and 28 as well as at 24 and 48 h on day 28. Plasma concentrations of sunitinib, SU12662, and total drug (sunitinib + SU12662) were determined using a liquid chromatography/mass spectrometry method with a lower limit of detection of 0.1 ng/ml [17].

The primary endpoint of the phase II part was the clinical benefit rate, defined as the percentage of patients with RECIST-defined objective response (confirmed complete response [CR] or partial response [PR]) or stable disease (SD) ≥22 weeks. Best overall response was evaluated by the investigators and an independent extramural review committee, with the evaluations of the latter group used for the primary efficacy analysis. Secondary efficacy endpoints included objective response rate, disease control rate (proportion of patients with confirmed CR or PR, or SD ≥10 weeks), time to tumor progression (TTP), and progression-free survival (PFS). As in the phase I part, measures of safety were also recorded. In the phase II part, blood samples for pharmacokinetic analysis were collected pre-dose on days 1, 14, and 28 of cycles 1–4 (or cycles 2–4 for patients entering phase II following completion of phase I).

Plasma concentrations of soluble KIT (sKIT), soluble VEGFR-2 (sVEGFR-2), and VEGF were determined using blood samples collected pre-dose on days 1, 14, and 28 of phase I and cycles 1–4 of phase II (cycles 2–4 for patients completing phase I) and evaluated as potential biomarkers for sunitinib activity using quantitative performance-validated enzyme-linked immunosorbent assay kits (R&D Systems, Minneapolis, MN) run under Good Laboratory Practice conditions as described [18].

Statistical methods

Statistical analyses were performed on three patient populations: DLT-analysis, intention-to-treat (ITT), and per-protocol. The DLT-analysis population, used in phase I of the study, consisted of patients who experienced DLTs or who received ≥85% of the planned total dose. The ITT population, defined as all patients who received at least one dose of study drug, was used as the primary analysis set for efficacy, safety, pharmacokinetic, and biomarker analyses. The per-protocol population consisted of the ITT population after exclusion of patients because of serious deviation from inclusion/exclusion criteria, administration of prohibited concomitant medications, administration of study drug on <75% of the planned dosing days before confirming clinical benefit (CR, PR, or SD≥22 weeks) or cycle 4, or no evaluation of objective tumor response after sunitinib dosing. The per-protocol population was used as a secondary set for analysis of the primary endpoint.

Time-to-event data were assessed using Kaplan–Meier methods. TTP was defined as the period between the day of initial study treatment and the day of initial confirmation of progressive disease (PD). Data from patients who were not confirmed to have PD either during the study or before the initiation of another antitumor therapy were censored at the final confirmation of absence of PD during the study. PFS was defined as the period between the day of initial study treatment and the day of initial confirmation of PD or of death due to any cause. Data from patients who were not confirmed to have PD or to have died during the study or before the initiation of another antitumor therapy were censored at the final confirmation of absence of PD during the study. Descriptive statistics were used to evaluate pharmacokinetic parameters and potential soluble biomarkers. Relationships between changes in plasma levels of biomarkers and the antitumor effects of sunitinib were evaluated using the Wilcoxon rank-sum test.

Results

Phase I results

Patient disposition and identification of recommended dose A total of 12 patients were enrolled in the phase I part of the study: three in the 25-mg cohort, six in the 50-mg cohort, and three in the 75-mg cohort. None of the initial three patients in the 25-mg cohort or the subsequent six patients in the 50-mg cohort experienced any DLTs in the first cycle of sunitinib treatment. However, two of the three patients in the 75-mg cohort experienced DLTs leading to termination of treatment after 12 and 15 days at that dose, and the third patient's treatment was subsequently terminated on day 7 as per recommendation of the Independent Safety Data Monitoring Committee. One of the patients' DLTs included grade 3 fatigue, anorexia, hypophosphatemia, and skin reaction, while the other patient's DLTs were grade 3 decreased platelet count (complicated by a need for blood product support) and grade 3 increased aspartate transaminase (AST). Therefore, 50 mg/day was identified as the MTD and as the recommended dose for use on Schedule 4/2 in the phase II part of the trial. All three patients who received 75 mg/day of sunitinib during the phase I part resumed dosing during cycle 2 of the phase II part at the recommended dose of 50 mg/day (the two patients who had experienced DLTs resumed after 18 and 28 days, respectively). There were no other dosing interruptions or any dose reductions due to toxicity during the phase I part of the trial, although initiation of cycle 2 was delayed by 14 days in one patient on 50 mg/day due to adverse events.

Pharmacokinetics Plasma concentration–time profiles and pharmacokinetic parameters for sunitinib, SU12662, and total drug are presented in Fig. 1 and Table 1, respectively. Exposure (maximum concentration [C_{max}] and area under the concentration–time curve from 0 to 24 h [AUC_{0-24}]) to sunitinib, SU12662, and total drug increased approximately linearly with dose on day 1 (25, 50, and 75 mg) and day 28 (25 and 50 mg). By day 28, AUCs for sunitinib, SU12662, and total drug were approximately 4, 11, and 5 times as high as those on day 1, respectively. Sunitinib was absorbed slowly after administration, with a median time to C_{max} of 6–10 h. Trough plasma concentrations of sunitinib and SU12662 appeared to reach steady state by 7–14 and 14–21 days after administration, respectively (data not shown). Trough concentrations of sunitinib and SU12662 at steady state (on day 28) closely correlated with the corresponding AUC_{0-24} and C_{max} values (r^2=0.80~0.90). The oral clearance (CL/F) of sunitinib did not show dose-dependency (data not shown).

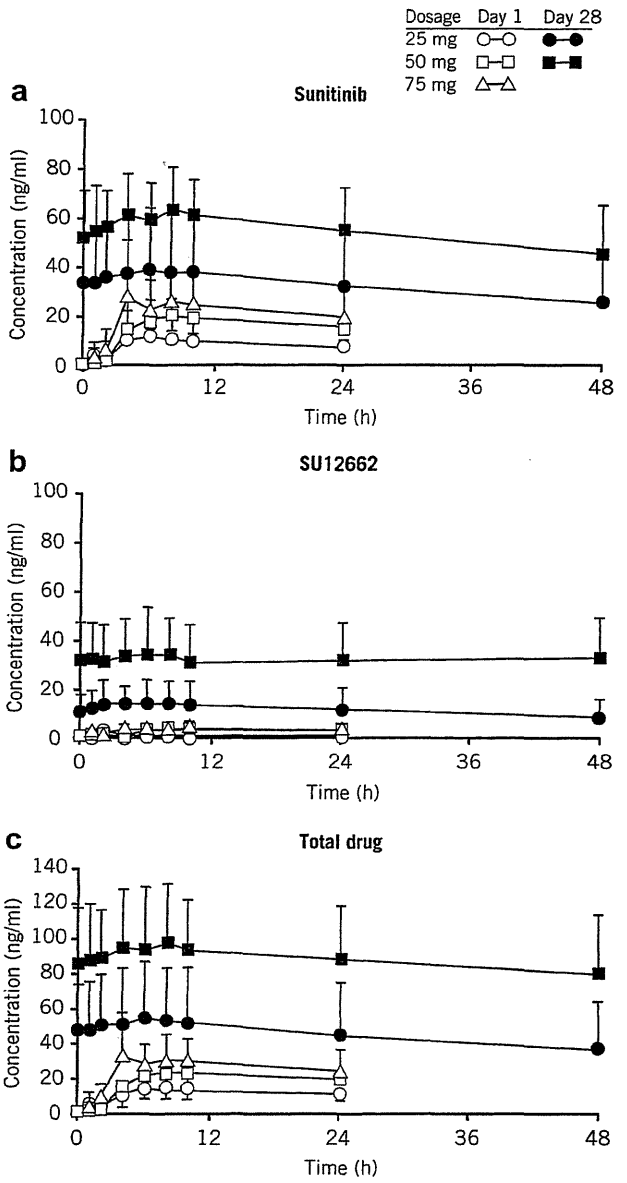

Fig. 1 Mean plasma concentration–time profiles of **a** sunitinib, **b** its active metabolite SU12662, and **c** total drug (sunitinib plus SU12662) by treatment cohort on days 1 and 28 in the phase I part of the study

Phase II results

Patient baseline characteristics, disposition, and study drug exposure Thirty-six patients were enrolled in the phase II part of the study and received sunitinib 50 mg/day on Schedule 4/2, three of whom initially received sunitinib 25 mg/day and three of whom initially received sunitinib 75 mg/day during the phase I part of the study. The ITT population comprised all 36 patients, while the per-protocol

Table 1 Pharmacokinetic parameters (mean ± standard deviation) of sunitinib, SU12662, and total drug by treatment cohort in the phase I part of the study

Parameter		Sunitinib			SU12662			Total drug		
		25 mg (n=3)	50 mg (n=6)	75 mg (n=3)	25 mg (n=3)	50 mg (n=6)	75 mg (n=3)	25 mg (n=3)	50 mg (n=6)	75 mg (n=3)
Day 1	C_{max}	12.1	22.8	32.3	2.0	4.1	4.8	14.1	26.7	37.0
	(ng/ml)	±4.9	±6.4	±20.8	±1.3	±0.9	±2.5	±6.1	±7.4	±22.1
	AUC_{0-24}	199	374	508	30.9	70.0	91.1	230	444	599
	(ng·h/ml)	±89.4	±68.9	±259	±20.6	±14.4	±45.3	±108	±82.8	±287
	T_{max}[b] (h)	6 (4–8)	7 (6–24)	8 (4–10)	6 (4–8)	9 (6–24)	10 (4–10)	6 (4–8)	7 (6–24)	8 (4–10)
Day 28[a]	C_{max}	39.5	69.3	–	15.2	38.8	–	54.0	105	–
	(ng/ml)	±25.0	±18.9		±10.2	±15.9		±32.2	±35.1	
	AUC_{0-24}	858	1,406	–	324	772	–	1,183	2,178	–
	(ng·h/ml)	±600	±364		±223	±358		±734	±702	
	T_{max}[b] (h)	10 (6–10)	6 (1–24)	–	4 (2–8)	3 (0–48)	–	6 (4–8)	6 (0–24)	–

AUC area under the concentration–time curve, C_{max} maximum concentration, T_{max} time to C_{max}

[a] Day 28 data were not collected for the 75-mg cohort due to early termination of this cohort following occurrence of dose-limiting toxicities

[b] Median (range)

population consisted of 30 patients. Six patients, comprising all of the patients in the 75-mg/day cohort and three in the 50-mg/day cohort, were excluded from the per-protocol population due to insufficient dosing.

Baseline patient characteristics, patient disposition, and exposure to study drug over both phases of the study are summarized in Table 2. Tumor progression was the primary reason for termination of imatinib therapy in 92% of patients, with the other 8% having discontinued due to imatinib intolerance. At the time of data cutoff, patients had received a median of four cycles of sunitinib (range: 2–12) at a median dose of 50 mg/day and dose intensity of 89%. Sixteen patients (44%) had dose reductions, 15 (42%) due to adverse events. Twenty-two patients (61%) discontinued sunitinib treatment, two (6%) due to adverse events and 20 (56%) due to PD. Adverse events causing discontinuation of sunitinib treatment were grade 2 decreased LVEF (one patient) and grade 4 decreased neutrophil count (one patient) that persisted despite dose reduction to 25 mg.

Efficacy The clinical benefit rate (percent objective responses or SD ≥22 weeks) based on extramural assessment of the ITT population (the primary endpoint) was 39% (95% CI: 23–57) and 40% (95% CI: 23–59) in the 50-mg cohort (Table 3). Analysis of the per-protocol population yielded similar results (data not shown). Based on extramural assessment, four patients (all in the 50-mg cohort) exhibited a RECIST-defined objective response (all PRs), yielding an objective response rate of 11% in the ITT population and 13% in the 50-mg cohort. The disease control rate (percent objective responses or SD ≥10 weeks) was 61% and 57% in the ITT population and 50-mg cohort, respectively. The median TTP was 28.3 weeks (95% CI: 22.0–39.3) in the ITT population and 27.9 weeks (95% CI: 22.0–39.3) in the 50-mg cohort; TTP and PFS were equivalent (data not shown).

Safety/tolerability All 36 patients in the ITT population experienced at least one adverse event that was considered to be treatment-related. Most adverse events were mild to moderate in intensity: 84% of all treatment-related adverse events were grade 1/2. Toxicities experienced in the study were generally manageable and reversible through careful dosing interruption, dose modification, and/or standard medical treatment. Among treatment-related non-hematologic adverse events, the most common events of any grade reported were hand–foot syndrome (86%); fatigue (67%); and diarrhea, anorexia, and skin discoloration (64%; Table 4), and the most common grade 3 events reported were hand–foot syndrome (31%) and hypertension (25%). No grade 4 events were reported among the non-hematologic adverse events listed in Table 4, and among all treatment-related non-hematologic events, only one grade 4 event (nephrotic syndrome) was reported. This event resolved after a dosing interruption of 52 days and dose reduction from 37.5 mg to 25 mg.

Hematologic and non-hematologic laboratory abnormalities are also presented in Table 4. Two incidents of grade 4 hematologic laboratory abnormalities were reported: one reduced hemoglobin concentration and one reduced neutrophil count; the former resolved after a dosing interruption of 14 days and dose reduction to 37.5 mg; the latter resulted in discontinuation, as mentioned above. The most

Table 2 Summary of patient demographics, imatinib treatment history, disposition, and study drug exposure across the phase I and II parts of the study through data cutoff

Characteristic	Treatment cohort			
	25 mg (n=3)	50 mg (n=30)	75 mg (n=3)	Total (N=36)
Median age (range), years	36 (33–54)	56 (41–74)	66 (50–68)	56 (33–74)
Sex, n (%)				
Male	2	19 (63)	3	24 (67)
Female	1	11 (37)	0	12 (33)
Median weight (range), kg	56 (48–64)	51 (40–79)	56 (51–58)	52 (40–79)
ECOG PS, n (%)				
0	3	18 (60)	2	23 (64)
1	0	12 (40)	1	13 (36)
Tumor immunohistochemistry, n (%)				
KIT-positive	3	29 (97)	3	35 (97)
CD34-positive	2	16 (53)	2	20 (56)
Imatinib treatment history				
Median duration of treatment (range), months	31 (19–32)	26 (2–46)	32 (22–38)	26 (2–46)
Primary reason for termination, n (%)				
Tumor progression	3	27 (90)	3	33 (92)
Intolerance	0	3 (10)	0	3 (8)
Most common metastatic sites, n				
Liver	3	22	3	28
Peritoneum	3	16	3	22
Lung	1	1	1	3
Ascites	2	1	0	3
Sunitinib treatment				
Median number of cycles completed (range)	10 (3–12)	4 (2–10)	5 (3–5)	4 (2–12)
Median daily dose (range), mg	25 (25–31)	50 (33–50)	52 (43–59)	50 (25–59)
Median dosing days/cycle (range)	28 (27–28)	26 (20–28)	20 (14–22)	26 (14–28)
Median dose intensity (range), %	100 (95–124)	89 (47–100)	44 (39–49)	89 (39–124)
Discontinuations, n (%)	1	18 (60)	3	22 (61)
Due to an adverse event	0	2 (7)	0	2 (6)
Due to PD	1	16 (53)	3	20 (56)
Dose reductions, n (%)	0	13 (43)	3	16 (44)
Due to an adverse event	0	13 (43)	2	15 (42)

ECOG PS Eastern Cooperative Oncology Group performance status, *PD* progressive disease

common non-hematologic laboratory abnormalities were increased AST levels (72%) and decreased albumin levels (61%). The most common grade 3/4 non-hematologic laboratory abnormalities were increased lipase (19%), increased uric acid (19%), and increased AST (11%). None of the cases of increased lipase were associated with additional signs or symptoms of pancreatitis.

In addition to hypertension, cardiovascular adverse events included a prolongation of the QTc interval to 450–<480 ms in two patients and a maximum change of 30–<60 ms from baseline QTc interval in two patients. These were not clinically significant and resolved without treatment changes. LVEF was below the LLN in three patients, two of whom experienced an absolute ≥20% decrease from baseline, which resulted in discontinuation in one patient, as mentioned above. The LVEF decrease in this latter patient ultimately abated after discontinuation. This patient also experienced cardiomyopathy, which was diagnosed by echocardiogram and magnetic resonance imaging after discontinuation and resolved after completion of the study. Two patients in the study experienced hypothyroidism (grade 1).

Nine patients (25%) experienced one or more serious treatment-related adverse events (which were abdominal pain, cardiomyopathy, gastric ulcer, hand–foot syndrome, hemorrhage, hypoglycemia, hypoproteinemia, myalgia, nephrotic syndrome, perianal abscess, reduced platelet

Table 3 Clinical response to sunitinib treatment across the phase I and II parts of the study through data cutoff

Response parameter	Treatment cohort			
	25 mg (n=3)	50 mg (n=30)	75 mg (n=3)	Total (N=36)
Tumor response, n (%)				
PR	0	4 (13)	0	4 (11)
SD	3 (100)	15 (50)	3 (100)	21 (58)
≥10 weeks	3 (100)	13 (43)	2 (67)	18 (50)
≥22 weeks	1 (33)	8 (27)	1 (33)	10 (28)
Objective response rate	0	13	0	11
95% CI		4–31		3–26
Disease control rate[a]	100	57	67	61
95% CI	–	37–75	–	44–77
Clinical benefit rate[b]	33	40	33	39
95% CI	–	23–59	–	23–57

PR partial response, *SD* stable disease

[a] Disease control rate, percent PRs + SD ≥10 weeks

[b] Clinical benefit rate, percent PRs + SD ≥22 weeks

count, and reflux esophagitis). All were reported in one patient each, except reduced platelet count, which was experienced by two patients. None of these events led to discontinuation, although the patient who experienced cardiomyopathy had already discontinued treatment due to LVEF decrease as described above. No treatment-related grade 5 events were reported in the study.

Pharmacokinetics Among patients receiving sunitinib 50 mg/day, median trough concentrations of sunitinib, SU12662, and total drug ranged from 42.3 to 59.5 ng/ml, 18.7 to 29.7 ng/ml, and 62.4 to 84.9 ng/ml, respectively, while on treatment (days 14 and 28) in cycles 1–4. Following 2 weeks off treatment, pre-dose total drug concentrations in cycles 2–4 were low, but measurable in many patients (medians: 3.0–4.0 ng/ml). Trough concentrations of sunitinib and SU12662 varied over time in a manner similar to those of total drug, corresponding to periods on and off treatment, and repeated dosing was not found to result in accumulation of plasma drug levels across four treatment cycles (data not shown).

Biomarkers Plasma levels of sKIT, sVEGFR-2, and VEGF changed in response to treatment, but only sKIT appeared to show sustained changes (data not shown). During sunitinib dosing, plasma concentrations of VEGF increased while concentrations of sVEGFR-2 decreased, but plasma concentrations of both of these biomarkers tended to return to near-baseline levels after the 2-week off-treatment period. Conversely, plasma concentrations of sKIT showed a trend for sustained decrease across both on-treatment and off-treatment periods.

Percent changes in VEGF, sVEGFR-2, and sKIT levels from baseline were compared among patient groups categorized by best overall response. There was no apparent difference in percent change of VEGF and sVEGFR-2 among the patient groups at any time point. Results for cycle 4, day 28 are shown in Table 5. Patients with an objective response and those achieving clinical benefit (objective responses or SD ≥22 weeks) showed a trend of decline in sKIT levels across cycles 1–4, while patients without objective responses exhibited only modest decreases or increases in sKIT levels (p values for clinical benefit versus no clinical benefit for cycle 4, day 28: sKIT, 0.238; VEGF, 0.459; sVEGFR-2, 0.484).

Discussion

The results of this trial of sunitinib in Japanese GIST patients following imatinib failure were highly consistent with those obtained in a number of previous sunitinib trials. The phase I part of the study yielded the same recommended dosing schedule (50 mg/day on Schedule 4/2) as that identified in prior studies of sunitinib in largely Western patients with a variety of tumor types [19–21]. In the phase II part of the study, sunitinib demonstrated similar efficacy to that previously reported in a double-blind, placebo-controlled, phase III trial also involving predominantly Western patients with imatinib-resistant/-intolerant GIST [14]. In the 50-mg cohort in the current study, 13% and 40% of patients experienced objective responses (PRs) or clinical benefit from sunitinib, respectively. By way of

Table 4 Toxicities occurring across the phase I and II parts of the study through data cutoff

Adverse event/laboratory abnormality	Treatment cohort					
	25 mg (n=3)	50 mg (n=30)			75 mg (n=3)	Total (N=36)
	Any grade[a] n	Grade 1/2 n (%)	Grade 3 n (%)	Any grade[a] n (%)	Any grade[a] n	Any grade[a] n (%)
Treatment-related non-hematologic adverse events ≥25%[b]						
Hand–foot syndrome	2	17 (57)	9 (30)	26 (87)	3	31 (86)
Fatigue	2	19 (63)	1 (3)	20 (67)	2	24 (67)
Diarrhea	2	19 (63)	0 (0)	19 (63)	2	23 (64)
Anorexia	1	19 (63)	1 (3)	20 (67)	2	23 (64)
Skin discoloration	0	21 (70)	0 (0)	21 (70)	2	23 (64)
Stomatitis	2	17 (57)	1 (3)	18 (60)	2	22 (61)
Nausea	1	13 (43)	0 (0)	13 (43)	2	16 (44)
Hypertension	0	7 (23)	7 (23)	14 (47)	2	16 (44)
Dysgeusia	1	11 (37)	0 (0)	11 (37)	2	14 (39)
Rash	1	12 (40)	0 (0)	12 (40)	1	14 (39)
Gingivitis	0	12 (40)	0 (0)	12 (40)	0	12 (33)
Abdominal pain	2	9 (30)	0 (0)	9 (30)	0	11 (31)
Cheilitis	1	9 (30)	0 (0)	9 (30)	1	11 (31)
Edema	0	9 (30)	0 (0)	9 (30)	1	10 (28)
Pigmentation disorder	0	7 (23)	0 (0)	7 (23)	2	9 (25)
Hematologic laboratory abnormalities						
Neutrophils	3	15 (50)	11 (37)	27 (90)[c]	3	33 (92)[c]
Leukocytes	3	21 (70)	5 (17)	26 (87)	3	32 (89)
Platelets	2	21 (70)	6 (20)	27 (90)	3	32 (89)
Hemoglobin	2	9 (30)	10 (33)	20 (67)[c]	3	25 (69)[c]
Lymphocytes	1	11 (37)	9 (30)	20 (67)	2	23 (64)
Non-hematologic laboratory abnormalities ≥40%[b]						
AST	2	19 (63)	3 (10)	22 (73)	2	26 (72)
Albumin	1	19 (63)	0 (0)	19 (63)	2	22 (61)
Total bilirubin	1	13 (43)	0 (0)	13 (43)	3[c]	17 (47)[c]
Alkaline phosphatase	1	9 (30)	3 (10)	12 (40)	3	16 (44)
ALT	0	12 (40)	2 (7)	14 (47)	1	15 (42)
Hyperglycemia	1	10 (33)	1 (3)	11 (37)	3	15 (42)
Phosphate	2	10 (33)	0 (0)	10 (33)	3	15 (42)

ALT alanine aminotransferase, *AST* aspartate aminotransferase

[a] No grade 4 events were reported among the treatment-related non-hematologic adverse events listed; the only grade 4 events reported among those listed were one reduced hemoglobin concentration and one reduced neutrophil count in the 50-mg cohort and one increased total bilirubin in the 75-mg cohort, as noted

[b] Based on the total population

[c] Includes one grade 4 event

comparison, the objective response and clinical benefit rates were 7% and 24%, respectively, in the phase III trial [14]. Likewise, the median TTP for the 50-mg cohort in the current study was 27.9 weeks, compared with 27.3 weeks in the phase III trial [14]. Except for ethnicity and the smaller sample size in the current study, patients in the two studies were generally comparable in terms of demographic characteristics, GIST histology, and duration of prior imatinib treatment and primary cause for discontinuation. The benefit derived from sunitinib by Japanese patients after imatinib failure is important because there are no other approved and effective second-line treatments for GIST: sunitinib remains the only approved treatment multinationally for patients with GIST after imatinib failure.

Sunitinib-related adverse events experienced by patients across both phases of the current study were predominantly

Table 5 Change from baseline of soluble protein concentrations (cycle 4, day 28) versus tumor response[a]

Soluble protein	Percent change from baseline, median (minimum, maximum)				
	PR (n=4)	SD ≥22 weeks (n=9)	Clinical benefit[b] (n=13)	SD <22 weeks + PD (n=18)	p value[c]
VEGF	365 (142, 473)	449 (49, 889)	385 (49, 889)	351 (52, 814)	0.459
sVEGFR-2	−51 (−65, −32)	−53 (−66, −20)	−53 (−66, −20)	−42 (−69, −4)	0.484
sKIT	−52 (−76, −46)	−12 (−46, 59)	−24 (−76, 59)	2 (−66, 386)	0.238

PR partial response, *PD* progressive disease, *SD* stable disease, *sKIT* soluble KIT, *sVEGFR-2* soluble VEGF receptor-2, *VEGF* vascular endothelial growth factor

[a] Last observation carried forward

[b] Clinical benefit, PR + SD ≥22 weeks

[c] Clinical benefit versus SD <22 weeks + PD, Wilcoxon rank-sum test

mild to moderate in severity; were manageable and reversible through dosing interruption, dose modification, and/or standard medical treatments; and seldom led to treatment withdrawal. Only two patients (6%) discontinued treatment due to an adverse event, consistent with previous reports of low treatment discontinuation rates due to adverse events with sunitinib therapy [14]. On the other hand, serious adverse events were reported in 25% of patients. Although these events did not result in discontinuations, this result suggests that patients should be monitored carefully. Overall, however, the safety profile observed in this study was similar to that reported in the phase III study, with fatigue and skin and gastrointestinal disorders representing the most frequent adverse events [14]. Moreover, no new adverse events were reported in this study compared with previous studies.

The pharmacokinetic results obtained in the present study were also consistent with those obtained in previous studies. In the phase I part of the study, exposure to sunitinib 50 mg on Schedule 4/2 was similar to that reported in a study of sunitinib in Western patients with various types of solid tumors [19] on day 1 (C_{max}: 22.8 versus 27.7 ng/ml; AUC_{0-24}: 374 versus 420 ng·h/ml), and day 28 (C_{max}: 69.3 versus 72.2 ng/ml; AUC_{0-24}: 1,406 versus 1,296 ng·h/ml). On the other hand, SU12662 exposure was somewhat higher in the current study than in the earlier one on day 1 (C_{max}: 4.1 versus 4.1 ng/ml; AUC_{0-24}: 70 versus 64 ng·h/ml) and day 28 (C_{max}: 38.8 versus 33.7 ng/ml; AUC_{0-24}: 772 versus 592 ng·h/ml). However, SU12662 comprised only 23–37% of total drug on day 28, resulting in total-drug exposures calculated to be approximately 15% higher in the current study, which is well within the range of exposures seen in Western patients. Median trough plasma drug concentrations obtained in the 50-mg cohort in the phase II part of the current study were above the preclinically determined effective plasma concentration of 50 ng/ml [10] throughout dosing and similar to those obtained in the phase III GIST study [14] (total drug: 62.4–84.9 versus 64.8–86.3 ng/ml, respectively). As in the phase III study, repeated dosing did not result in accumulation of sunitinib across several cycles of treatment. Taken together, these results suggest that sunitinib pharmacokinetics are comparable in Asian and Western GIST patients, consistent with the results of other analyses [22,23], and that sunitinib may be dosed similarly in both populations. Additionally, as shown in the phase I part of the study, there was a close correlation (r^2=0.80~0.90) between trough concentrations of sunitinib and SU12662 and AUC_{0-24} and C_{max} values at steady state, suggesting that trough concentration may be a useful marker of exposure.

Greater antiangiogenic effects as well as continued sensitivity of some imatinib-resistant KIT mutants have been postulated as possible explanations for sunitinib activity in GISTs resistant to imatinib. In-vitro studies using KIT constructs have demonstrated that sunitinib is capable of inhibiting the kinase activity of KIT mutants resistant to imatinib, including those commonly associated with secondary resistance [24–26]. Although patient numbers were small, a trend towards sustained decreases in plasma sKIT with sunitinib treatment was found in the current study, which correlated with improved outcomes (particularly objective responses). However, how these changes relate to antiangiogenic effects versus direct actions on mutant KIT receptors is not known. That the largest decreases were observed in patients with objective responses suggests that tumor cell loss may contribute to the decreases, although this could result from either antiangiogenic or direct antitumor effects. A correlation between decreased plasma levels of sKIT and sunitinib activity has also been reported among GIST patients who participated in the phase III trial [27], as well as in patients with metastatic breast cancer [28]. Likewise, a correlation between plasma sKIT decreases and response to imatinib in GIST has also been reported [29]. However, more work needs to be done to validate biomarkers that may be used to predict GIST response to sunitinib or other tyrosine kinase inhibitors.

In summary, the results from the present study suggest that Japanese GIST patients obtain comparable benefit from

sunitinib after failure of imatinib as did patients in the international phase III study. In addition, the results indicate that sunitinib may be dosed similarly in Asian and Western patients, and that adverse events can generally be managed by dosing interruptions, dose modifications, and/or the use of standard medical treatments. Although the present study was small and requires verification in larger controlled trials, these results provide guidance to clinicians treating Asian GIST patients after imatinib failure due to disease progression or intolerance.

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