厚生労働科学研究費補助金（がん臨床研究事業）
分担研究報告書
切除不能進行・再発胃がんに対する個別化治療に関する研究

研究分担者　陳　勁松　　がん研有明病院　消化器センター

研究要旨

胃癌HER2発現を免疫組織化学染色でみた場合の生検と手術標本での結果の一致性を調べ生検をいくつ行うのが適切なのかを検討した。その結果生検３個生検をすればそれ以上行った場合とで差がないことが示された。

A．研究目的
胃癌HER2発現結果は生検標本と手術標本で差があること示されている。生検数が多ければその差が少なくなるかも明らかになっていない。適切な生検個数を明らかにするため今回の検討を行った。

B．研究方法
HER2発現は免疫組織化学染色(HercepTest (DAKO))で行い後ろ向きにGastric Cancer Scoring Systemに則り HER2 score 3+30例と44例の2+, 1+, 0を検討した。同じ症例での生検標本との相同性を検討した。
（倫理面への配慮）
患者様から生検または手術前に病理サンプルを研究目的に使用することに関する同意書を文書にて得られた症例を対象にした

C．研究結果
Results:生検個数は平均3.13(1-6)/case。生検と手術標本でのHER2結果の一致率としてはHER2 3+, 2+ and 1+ or 0groupで各々 80.0%、 47.8% and 47.6%であった。生検標本毎の一致率は各々73.5%, 34.7% and 69.1%であった。HER2陽性群では陰性群にくらべ一致率は有意に高かった。生検を３個行った場合と４個以上では一致率に差は観られなかった。

D．考察
今回の研究は後ろ向きの少数例での検討であり確定的なことを言うことはできない。HER2免疫染色の条件の差も影響があると思われる。また、今回はFISH検査を加えたの検討は行っていない。
HER2 3+ surgical(-) biopsy(+) 症例でのtrastuzumabの効果は不明である。

E．結論
今回の検討の結果、胃癌HER2発現を免疫組織化学検査で検討する場合生検を３個行うとそれ以上行った場合とで手術標本での結果の一致性に差がないことが示された。

F．研究発表
1．論文発表
作成中

2．学会発表
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E. Shinozaki, N. Yamamoto, K. Chin, M. Ogura, K. Takagi, M. Ozaka, S. Matsusaka, M. Suenaga, N. Mizunuma, K. Hatake, T. Yamaguchi
Cancer Institute Hospital, GI cancer center, Department of Pathology, Medical Oncology Tokyo, Japan

G．知的財産等の出願・登録状況（予定を含む。）
1.特許取得
未

2.実用新案登録
未

厚生労働科学研究費補助金（がん臨床研究事業）
分担研究報告書
切除不能進行・再発胃がんに対する個別化治療に関する研究

研究分担者　　神奈川県立がんセンター　消化器内科　医長　中山昇典

研究要旨
Her2 陰性の切除不能進行再発胃癌患者を対象に、ドセタキセル＋シスプラチン＋S-1 併用療法（DCS 療法）を試験治療とし、Her2 陰性例での標準治療である S-1＋シスプラチン(CS)療法に対する優越性をランダム化比較第三相試験にて検証するとともに、組織型における治療効果の違いについても探索的な検討を行う。

A．研究目的

現在のHer2陰性の切除不能進行胃癌に対する標準化学療法はS-1+シスプラチン(CS)療法である。我々は北里大学との共同研究で、このCS療法の効果をさらに向上することを目的に、ドセタキセルを上乗せしたDCS療法の有用性を報告してきた。本研究の主目的は、現在の標準治療であるCS療法に対するDCS試験療法の優越性を検証する第III相比較試験である。また、今回は個別化治療として組織型に着目し、予め組織型を相別化因子に加えて、未分化型腺癌と分化型腺癌で治療効果に違いが出るのかを探索的に検証することも目的とした試験である。我々も本試験に参加している。

B．研究方法

JCOG胃がんグループによる多施設共同の第III相比較試験(JCOG1013)を行う。

（倫理面への配慮）

本試験に関するすべての研究者はヘルシンキ宣言および「臨床研究に関する倫理指針（平成20年厚生労働省告示415号）」に従って本試験を実施する。

本試験における「医療機関」は上記指針における「臨床研究機関」に対応している。

C．研究結果

本試験のプロトコール作成が終了し、JCOG運営委員会の二次審査を通過した。このため、当院でのＩＲＢに提出し、承認後登録開始の予定である。

D．考察

E．結論

現在は、胃癌治療においてHer2の切除不能進行胃癌という存在が明らかに成り、それによって治療方法を変えることの必要性も証明されている。しかし、Her2陽性の切除不能進行胃癌は10%であるため、90%の Her2陰性の切除不能進行胃癌の更なる治療開発は重要である。現在S-1+Cisplatinが標準治療であるが、我々はDocetaxelを加えたDCS療法について第Ⅰ/Ⅱ相試験を行い有用性について報告してきた。また第Ⅱ相試験の少人数であるが、未分化型腺癌と分化型腺癌で治療効果に違いについても報告してきた。このため現在の標準治療に対するDCS療法について第Ⅲ相試験で検討することは重要である。

F．研究発表

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本研究に間接的に関連するものについては別紙参照

2．学会発表

1．第 83 回日本胃癌学会　パネルディスカッション
中山 昇典、小泉　和三郎、西村 賢、樋口 勝彦、佐々木 徹、田辺 聡、高木 精一、東　瑞智、堅田 親利、中谷　研斗、石戸　謙次、柳田　直毅、本橋 修：「進行・再発胃癌に対する docetaxel/cisplatin/S-1(DCS)療法(KDOG0601 P2)：長期解析結果」
本研究に間接的に関連するものについては別紙参照。

G．知的財産等の出願・登録状況（予定を含む。）

1. 特許取得
特記すべきことなし
2. 実用新案登録
特記すべきことなし
3. その他
特記すべきことなし

厚生労働科学研究費補助金（がん臨床研究事業）
分担研究報告書
切除不能進行・再発胃がんに対する個別化治療に関する研究

研究分担者　　堀田　洋介　　富山県立中央病院　外来化学療法科医長

研究要旨
ドセタキセル+シスプラチン+S1併用療法（DCS療法）を試験治療とし、標準治療であるS1/シスプラチン療法に対する優越性をランダム化比較第Ⅲ相試験の開始を準備中

A．研究目的

切除不能・再発進行胃がんに対する新たな標準治療を確立するために、ドセタキセル+シスプラチン+S-1併用療法（DCS療法）を試験治療とし、標準治療であるS-1/シスプラチン療法に対する優越性をランダム化比較第Ⅲ相試験で検証する。また、個別化医療を目指して組織型別による効果の差も検討する。

B．研究方法

多施設共同ランダム化比較第Ⅲ相試験

（倫理面への配慮）

当施設の倫理審査委員会での承認を取得、対象患者には書面で同意を得て登録する予定である。

C．研究結果

班会議などを通じてプロトコール作成に関与、プロトコール完成後は施設での承認を得次第、試験を開始する予定。

D．考察

本邦ではS-1+シスプラチンが標準治療と認識されているが、ドセタキセルを加えたDCS療法は、良好な第Ⅱ相試験の結果が報告されており、期待される治療法である。本邦で行われてきたS-1を含む胃癌に対する第Ⅲ相試験を統合してみると組織型による治療選択の可能性が考えられる事から、本試験においては治療効果を組織型によるサブグループで解析する予定であり、胃癌における個別化治療の重要な先駆けとなる試験と考える。

E．結論

切除不能・再発胃癌に対するDCS療法は、現時点で本邦で最も有望な治療法の一つであり、個別化治療の選択肢としても期待できる。プロトコールを確定後、症例登録を開始する予定である。

F．研究発表

1．論文発表

本研究に直接関連するものなし。

本研究に間接的ではあるが関連するものについては別紙参照

2．学会発表

本研究に直接関連するものなし。

本研究に間接的ではあるが関連するものについては下記参照

1．織田典明、堀田洋介、木田明彦、藤原　秀、平井　聡、島谷明義、松田耕一郎、平松活志、松田　充、荻野英朗、野田八嗣
「術後14年目に大腸転移を来たした胃癌の一例」
第97回日本消化器病学会総会（2011.5）

2．堀田洋介、木田明彦、藤原　秀、平井　聡、島谷明義、松田耕一郎、平松活志、松田　充、荻野英朗、野田八嗣
「Antiemetic effect of including aprepitant in the chemotherapeutic regimen for advanced gastrointestinal cancer patients.」
第9回日本臨床腫瘍学会学術集会(2011.7)

G．知的財産等の出願・登録状況（予定を含む。）

1．特許取得

なし

2．実用新案登録

なし

3．その他

特記すべき事なし

厚生労働科学研究費補助金（がん臨床研究事業）
分担研究報告書
切除不能進行・再発胃がんに対する個別化治療に関する研究

研究分担者　　静岡県立総合病院　腫瘍内科　医長　多久佳成

研究要旨
切除不能進行再発胃癌患者を対象に、ドセタキセル＋シスプラチン＋S-1 併用療法（DCS 療法）を試験治療とし、標準治療である S-1＋シスプラチン(CS)療法に対する優越性をランダム化比較にて検証するとともに、組織型における治療効果の違いについても探索的な検討を行う。

A．研究目的

現在の切除不能進行胃癌に対する標準化学療法はS-1+シスプラチン(CS)療法である。近年では、このCS療法の効果をさらに向上することを目的に、ドセタキセルを上乗せしたDCS療法の有用性が示唆されている。本研究の主目的は、現在の標準治療であるCS療法に対するDCS試験療法の優越性を検証する第III相比較試験である。また、今回は個別化治療として組織型に着目し、予め組織型を相別化因子に加えて、未分化型腺癌と分化型腺癌で治療効果に違いが出るのかを探索的に検証することも目的とした試験である。

B．研究方法

JCOG胃がんグループによる多施設共同の第III相比較試験(JCOG1013)を行う。

（目的）

Primary endpoint:全生存期間、
key secondary endpoint:分化型腺癌/未分化型腺癌のサブグループ毎の全生存期間

（倫理面への配慮）

本試験に関するすべての研究者はヘルシンキ宣言および「臨床研究に関する倫理指針（平成20年厚生労働省告示415号）」に従って本試験を実施する。

C．研究結果

本試験のプロトコールの倫理審査委員会承認をまち、試験開始予定である。

D．考察

現時点での同試験開始に特に問題はないと判断している。

E．結論

胃癌治療においてHer2陽性例に対しTrastuzumabの有効性が示され、患者への個別化医療に期待が寄せられている。本試験の様に、胃癌の組織型により治療効果が変わる可能性を検討することは、今後の治療開発においても大変有意義なものであると考える。

F．研究発表

1．論文発表

関連した発表を行っておりません。

2．学会発表

関連した発表を行っておりません。

G．知的財産等の出願・登録状況（予定を含む。）

1.特許取得
特記すべきことなし
2.実用新案登録
特記すべきことなし
3.その他
特記すべきことなし

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分担研究報告書
切除不能進行・再発胃がんに対する個別化治療に関する研究

研究分担者　静岡県立静岡がんセンター　消化器内科　科部長　安井博史

研究要旨
切除不能進行再発胃癌患者を対象に、ドセタキセル＋シスプラチン＋S-1 併用療法（DCS 療法）を試験治療とし、標準治療である S-1＋シスプラチン(CS)療法に対する優越性をランダム化比較にて検証するとともに、組織型における治療効果の違いについても探索的な検討を行う。

A．研究目的

現在の切除不能進行胃癌に対する標準化学療法はS-1+シスプラチン(CS)療法である。近年では、このCS療法の効果をさらに向上することを目的に、ドセタキセルを上乗せしたDCS療法の有用性が示唆されている。本研究の主目的は、現在の標準治療であるCS療法に対するDCS試験療法の優越性を検証する第III相比較試験である。また、今回は個別化治療として組織型に着目し、予め組織型を相別化因子に加えて、未分化型腺癌と分化型腺癌で治療効果に違いが出るのかを探索的に検証することも目的とした試験である。我々も本試験に参加している。

B．研究方法

JCOG胃がんグループによる多施設共同の第III相比較試験(JCOG1013)を行う。

（目的）

Primary endpoint:全生存期間、
key secondary endpoint:分化型腺癌/未分化型腺癌のサブグループ毎の全生存期間

（倫理面への配慮）

本試験に関するすべての研究者はヘルシンキ宣言および「臨床研究に関する倫理指針（平成20年厚生労働省告示415号）」に従って本試験を実施する。
本試験における「医療機関」は上記指針における「臨床研究機関」に対応している。

C．研究結果

本試験のプロトコール作成が終了し、まもなく試験開始となる予定である。

D．考察

E．結論

現在は、胃癌治療においてHer2陽性胃癌という存在が明らかに成り、それによって治療方法を変えることの必要性も証明されている。このように、癌の性状、組織型により治療効果が変わる可能性を検討することは、大変有意義であると考える。

F．研究発表

1．論文発表

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2．学会発表

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2．日本癌治療学会総会、ワークショップ、「切除不能・再発胃癌に対する 2 次治療としての ABI-007（3 週毎投与法）第 II 相試験」
3．第35回日本眼科手術学会総会　シンポジウム（増えています。抗がん剤による眼表面と涙道障害）、「本邦の消化器がん化学療法におけるS-1の位置づけ」

G．知的財産等の出願・登録状況（予定を含む。）

1. 特許取得
特記すべきことなし
2. 実用新案登録
特記すべきことなし
3. その他
特記すべきことなし

厚生労働科学研究費補助金（がん臨床研究事業）
分担研究報告書
切除不能進行・再発胃がんに対する個別化治療に関する研究

研究分担者　安井久晃　　京都医療センター　腫瘍内科診療科長

研究要旨
　ドセタキセル+シスプラチン+Ｓ-1併用療法（DCS療法）を試験治療とし、標準治療であるS-1/シスプラチン療法に対する優越性を検証するランダム化比較第III相試験がまもなく登録開始予定である。

Ａ．研究目的
　切除不能・再発進行胃がんに対する新たな標準治療を確立するために、Docetaxel+Cisplatin+Ｓ-1併用療法（DCS療法）を試験治療とし、標準治療であるS-1+Cisplatin療法に対する優越性を第III相試験で検証する。Key Secondary Endpointとして個別化医療を目指して組織型別による効果の差も検討する。さらには、治療前のホルマリン固定組織を用いて抗がん剤感受性因子の遺伝子発現を検索し、治療選択因子を探索的に検索する。

Ｂ．研究方法
　前向きの多施設共同ランダム化比較第III相試験。
（倫理面への配慮）
　本臨床試験は参加施設の倫理審査委員会の承認を必須とし、対象患者には同意を得る予定である。遺伝子検索についても別個に同意を取得する。

Ｃ．研究結果
　日本臨床腫瘍研究グループ(JCOG)の胃がんグループにてプロトコールが検討された。プロトコールコンセプトはH22年12月18日のJCOG運営委員会にて承認された。その後、班会議などで参加施設の意見を集約しながらH24年2月に完成した。間もなく試験が開始される予定である。

Ｄ．考察
　現在、世界的に切除不能・再発胃癌に対する標準的化学療法はﾌｯｶﾋﾟﾘﾐｼﾞﾝ+ﾌﾟﾗﾁﾅ製剤の併用(CF)療法である。この2剤併用療法にDocetaxelを加えたDCF療法のみがCF療法に対して全生存期間において優越性を示したが、高い毒性のため一般的には受け入れられていない。本邦ではS-1+Cisplatinが標準治療であるが、Docetaxelを加えたDCS療法の良好な第II相試験の結果が報告されている。胃癌に対する分子標的薬としてHerceptinの有効性が報告されたが、Her-2陽性胃癌は10%程度であり、胃癌全体の成績向上にはつながらない。さらには、BevacizumabやPanitumumabを用いた一次治療での上乗せ効果は示されなかった。これらの状況を考えると現時点ではDCS療法が最も期待の持てる治療法である。しかし、DCS療法が毒性を伴うことは明らかであり、3剤併用療法により大きな効果が得られる症例を選択することは重要な課題である。本邦で行われたS-1を含む第III相試験を統合すると、組織型による治療選択の可能性が考えられるため、本試験においても検討する。

Ｅ．結論
　切除不能・再発胃癌に対する化学療法の進歩を考えると、個別化を含むDCS療法は、現時点で本邦にて実行可能な最も有望な治療法であると思われる。来年度早期から症例登録を開始する予定である。

Ｆ．研究発表
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2．学会発表
本研究に直接関連するものなし。

Ｇ．知的財産等の出願・登録状況（予定を含む。）
1. 特許取得
　なし
2. 実用新案登録
　なし
3. その他
　特記すべきことなし

厚生労働科学研究費補助金（がん臨床研究事業）
分担研究報告書
切除不能進行・再発胃がんに対する個別化治療に関する研究

研究分担者　　佐藤　太郎

研究要旨

分担研究として、胃癌個別化治療のプロトコールの検討、国際共同治験における日本人のデータ解析などを行う

A．研究目的

胃癌の個別化治療に関する研究として、バイオマーカーの探索、臨床薬理学的研究を行う

B．研究方法
日本人の国際共同試験に登録された胃癌患者のデータを解析し、有効性安全性の研究、二次治療でイリノテカンの投与を行う患者のPKデータを解析する
（倫理面への配慮）ヘルシンキ宣言にのっとり、IRBの承認を得、臨床試験に文書での同意をえた患者のデータの解析をおこなっている

C．研究結果
胃癌治療における、カペシタビン、シスプラチン併用療法の安全性の確認が行われ、イリノテカンの投与時のUGT1A1の意義をが確認された

D．考察
世界標準治療である、カペシタビンとシスプラチンが日本人患者にも有効に投与できることから、国際共同治験、新薬開発の基盤となるデータの確立ができたと考える

E．結論

F．研究発表
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G．知的財産等の出願・登録状況（予定を含む。）
1．特許取得

2．実用新案登録

3．その他

厚生労働科学研究費補助金（がん臨床研究事業）
分担研究報告書
切除不能進行・再発胃がんに対する個別化治療に関する研究

研究分担者　　大阪府立成人病センター　臨床腫瘍科　副部長　杉本直俊

研究要旨
切除不能進行再発胃癌患者を対象に、ドセタキセル＋シスプラチン＋S-1 併用療法（DCS 療法）を試験治療とし、標準治療である S-1＋シスプラチン(CS)療法に対する優越性をランダム化比較にて検証するとともに、組織型における治療効果の違いについても探索的な検討を行う。

A．研究目的

現在の切除不能進行胃癌に対する標準化学療法はS-1+シスプラチン(CS)療法である。近年では、このCS療法の効果をさらに向上することを目的に、ドセタキセルを併用したDCS療法の有用性が示唆されている。本研究は、現在の標準治療であるCS療法に対して試験治療であるDCS療法の優越性を検証する第III相比較試験である。さらに、今回は個別化治療として組織型に着目し、予め組織型を相別化因子に加えて、未分化型腺癌と分化型腺癌で治療効果に違いが出るのかを探索的に検証することも目的としている。

B．研究方法

JCOG胃がんグループによる多施設共同の第III相比較試験(JCOG1013)を行う。

（目的）

Primary endpoint:全生存期間、

key secondary endpoint:分化型腺癌/未分化型腺癌のサブグループ毎の全生存期間

（倫理面への配慮）

本試験に関するすべての研究者はヘルシンキ宣言および「臨床研究に関する倫理指針（平成20年厚生労働省告示415号）」に従って本試験を実施する。

本試験における「医療機関」は上記指針における「臨床研究機関」に対応している。

C．研究結果

本試験のプロトコール作成が終了し、まもなく試験開始となる予定である。

D．考察

E．結論

現在は、胃癌治療においてHer2陽性胃癌という存在が明らかに成り、それによって治療方法を変えることの必要性も証明されている。このように、癌の性状、組織型により治療効果が変わる可能性を検討することは、大変有意義であると考える。

F．研究発表

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G．知的財産等の出願・登録状況（予定を含む。）

1.特許取得

特記すべきことなし

2.実用新案登録

特記すべきことなし

3.その他

特記すべきことなし

研究成果の刊行に関する一覧表

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雑誌

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DOI 10.1007/s10147-010-0135-9

ORIGINAL ARTICLE

Systemic chemotherapy for peritoneal disseminated gastric cancer with inadequate oral intake: a retrospective study

Satoru Iwasa · Takako Eguchi Nakajima · Kenichi Nakamura · Atsuo Takashima · Ken Kato · Tetsuya Hamaguchi · Yasuhide Yamada · Yasuhiro Shimada

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Abstract
Background Oral fluoropyrimidines are widely used as standard treatment for gastric cancer, but peritoneal disseminated gastric cancer patients are often ineligible for chemotherapy using oral anticancer agents because of inadequate oral intake. The purpose of this study was to evaluate the treatment outcome and identify the prognostic factors in gastric cancer patients with inadequate oral intake resulting from peritoneal dissemination.
Methods Seventy-nine patients with peritoneal disseminated gastric cancer receiving systemic chemotherapy as the first-line treatment option at our hospital between April 1999 and December 2006, and who were administered intravenous drip infusion because of inadequate oral intake, were retrospectively analyzed.
Results All patients received 5-fluorouracil (5-FU)-based chemotherapy. Of the 79 treated patients, 71 had ascites as peritoneal dissemination and the remaining 8 had only gastrointestinal stenosis without ascites. Eleven (15%) patients showed an improvement in ascites. Proportion of oral intake improvement was 33%. Median time to progression and overall survival time was 1.7 months [95% confidence interval (CI), 0.9–2.4 months] and 3.3 months (95% CI, 2.1–4.5 months), respectively. Four independent poor prognostic factors were identified in multivariate analysis: serum albumin < 3.0 g/dl [hazard ratio (HR) 1.69, $P = 0.03$], performance status ≥ 3 (HR 1.78, $P = 0.05$), massive ascites (HR 1.79, $P = 0.04$), and serum C-reactive protein ≥ 2.0 mg/dl (HR 2.03, $P < 0.01$).
Conclusion The efficacy of 5-FU-based chemotherapy for peritoneal disseminated gastric cancer patients with inadequate oral intake was unsatisfactory.

Keywords Gastric cancer · Peritoneal metastasis · Inadequate oral intake · Chemotherapy

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Introduction

Although the incidence and mortality rate of gastric cancer has decreased dramatically over the past several decades, gastric cancer remains one of the most common malignancies in the world, especially in Asia [1]. Gastric cancer can spread through various routes such as by local extension of direct serosal invasion, involvement of lymphatics, and distant metastasis through vascular diffusion. Peritoneal dissemination occurs mainly as a result of direct serosal invasion, omentum and peritoneal seeding, and/or lymphatic spread. Peritoneal dissemination is a common reason why gastric cancer cannot be resected [2]. Moreover, peritoneal recurrence after curative resection is identified as a major type (29–44%) of recurrence [3, 4]. Peritoneal dissemination may cause serious clinical complications, such as intestinal obstruction, massive ascites, obstructive jaundice, and hydronephrosis. These complications are associated with abdominal pain, abdominal fullness, vomiting, and malnutrition, leading to an extremely poor quality of life for the patient.

Recently, several phase III trials demonstrated that orally administered fluoropyrimidines, S-1 (containing

tegafur, 5-chloro-2,4-dihydroxypyridine, and potassium oxonate) or capecitabine, were not inferior to infusional 5-fluorouracil (5-FU) in advanced gastric cancer, so further clinical trials will demand greater feasibility of oral intake [5–7]. However, patients with severe peritoneal dissemination are excluded from drug development in accordance with inadequate oral intake. It is necessary to establish a treatment strategy for peritoneal disseminated gastric cancer patients with inadequate oral intake.

We retrospectively investigated the treatment outcome and prognostic factors in peritoneal disseminated gastric cancer patients with inadequate oral intake to determine the appropriate treatment strategy.

Patients and methods

Patients

Patients who received first-line chemotherapy treatment for gastric cancer at the National Cancer Center Hospital in Tokyo between April 1999 and December 2006 were retrospectively selected for this study according to the following criteria: (1) histological confirmation of adenocarcinoma as gastric primary lesion; (2) Stage IV disease or postoperative recurrence; (3) histological and/or radiologic confirmation of peritoneal dissemination; (4) no prior chemotherapy or radiotherapy; and (5) inadequate oral intake. We defined inadequate oral intake as requiring an intravenous drip infusion that had indeed been done. Patients who were administered an intravenous drip infusion for the purpose of renal protection or as a drug administration route such as for morphine were excluded.

Pretreatment clinical variables were evaluated: age (younger than 65 years of age or 65 years and older), gender (male or female), Eastern Cooperative Oncology Group (ECOG) performance status (PS) (0–2 or $\geq$3), serum albumin ($<$3.0 or $\geq$3.0 g/dl), serum C-reactive protein (CRP, $<$2.0 or $\geq$2.0 mg/dl), tumor histological type (diffuse or others), primary lesion status (present or absent), disease status (Stage IV or recurrence), ascites (massive or non-massive), number of metastatic sites (1 or $\geq$2), and the 5-FU administration method (bolus or continuous). Ascites was defined as four levels: none, mild, moderate, or massive. None was defined as undetected by computed tomography (CT) scan; mild ascites was localized in only one area such as the pelvic cavity or surface of the liver; moderate ascites did not correspond to either mild or massive ascites; and massive ascites extended continuously from the pelvic cavity to the upper abdominal cavity.

This retrospective study was approved by the National Cancer Center Institutional Review Board and conducted in accordance with ethical principles stated in Japanese ethics guidelines for epidemiological studies.

Assessment of response

Responses were evaluated using the Response Evaluation Criteria in Solid Tumors. Ascites response was evaluated as follows: disappearance was defined as ascites unidentifiable by CT scan, decrease was defined as ascites decrease of more than one level, no change was defined as ascites remaining at the pretreatment level, and increase was defined as ascites increase of more than one level or ascites becoming clinically apparent. Oral intake improvement was defined as sufficient ingestion for 7 days or more without an intravenous drip infusion.

Statistical methods

In univariate analysis, cumulative survival proportions were calculated using the Kaplan–Meier method, and any differences were evaluated using the log-rank test. Only those variables that achieved statistical significance in univariate analysis were subsequently evaluated in multivariate analysis using Cox's proportional hazard model. Progression-free survival (PFS) and overall survival (OS) were calculated using the Kaplan–Meier method. PFS was calculated from the date of the first treatment to the date of disease progression, death, or final follow-up. OS was calculated from the date of the first treatment to the date of death or final follow-up. All statistical analyses were performed using Dr. SPSS II software (SPSS Japan, Tokyo, Japan). All P values presented in this report are of the two-tailed type. Differences with a P value $\leq$0.05 were considered significant.

Results

Patients and characteristics

From April 1999 to December 2006, a total of 1,747 consecutive patients with gastric cancer underwent systemic chemotherapy at the National Cancer Center Hospital in Tokyo. Of these, 340 patients with peritoneal metastasis underwent systemic chemotherapy as first-line treatment. Of these 340 patients, 82 patients had received an intravenous drip infusion before chemotherapy. However, 3 patients were excluded because of the usage of infusion as an opioid administration route. The remaining 79 patients were thus identified as participants in this study. The patient characteristics are summarized in Table 1. All patients had baseline Eastern Cooperative Oncology Group (ECOG) performance status (PS) greater than 1.

Table 1 Patient characteristics

Characteristics	*N*	%
Gender		
Male	43	54
Female	36	46
Age (years)		
Median	58	
Range	20–77	
ECOG performance status		
0	0	0
1	27	34
2	33	42
3	19	24
Disease status		
Unresectable	59	75
Recurrent	20	25
Primary tumor		
Present	46	58
Absent	33	42
Histological type		
Diffuse type	71	90
Intestinal type	4	5
Other not specified	4	5
Number of metastatic sites		
1	49	62
≥2	30	38
Ascites		
None	8	10
Mild	34	43
Moderate	16	20
Massive	21	27
Treatment regimen		
Standard 5-FU ci	10	13
Low-dose 5-FU ci	12	15
MTX/5-FU	56	71
5-FU/L-LV	1	1

Chemotherapy

First-line chemotherapy was based on 5-FU in all patients. 5-FU-based regimens of bolus administration were methotrexate (MTX)/5-FU and 5-FU/L-leucovorin (L-LV; or *l*-LV) therapy. The MTX/5-FU therapy consisted of weekly MTX [100 mg/m^2 administered intravenously (i.v.) as bolus] followed by 5-FU (600 mg/m^2 i.v. bolus) at 3-h intervals (Fig. 1a, b). The 5-FU/L-LV therapy consisted of weekly L-LV (200 mg/m^2 2-h i.v. infusion) plus 5-FU (500 mg/m^2 i.v. bolus). The continuous 5-FU regimen included two different schedules: low-dose continuous infusion (ci) of a daily i.v. infusion of 5-FU (300 mg/m^2 24-h ci) and standard 5-FU ci (800 mg/m^2 24-h ci on days 1–5, q4w) (Fig. 1c, d). Median number (range) of each chemotherapy was 4 times (1–41 times) in MTX/5-FU, 6 times in 5-FU/L-LV, and 2 times (1–4 times) in standard 5-FU ci; median administration of low-dose 5-FU ci was 24 days (4–299 days).

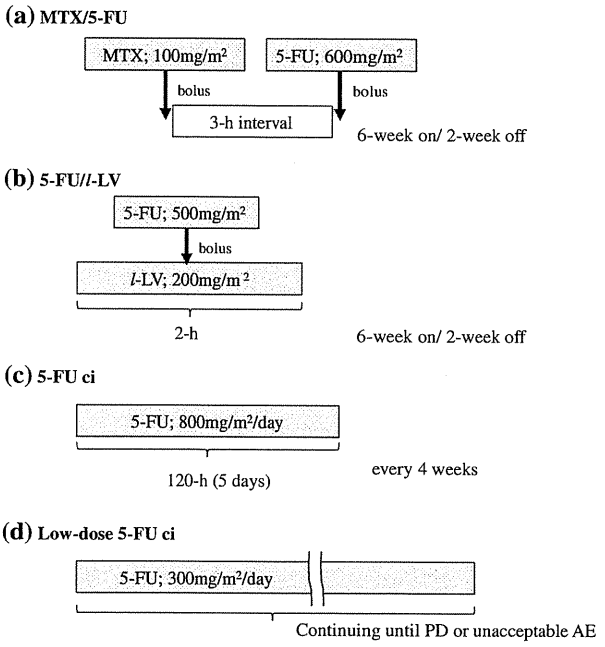

Fig. 1 5-Fluorouracil (*5-FU*)-based regimens used in the current study. *MTX*, methotrexate; *L-LV* (*l-LV*), L-leucovorin; *PD*, progressive disease; *AE*, adverse event; *ci*, continuous infusion

Efficacy

Seventy-one (90%) of the 79 patients had evaluable ascites at initial diagnosis. The remaining 8 (10%) patients had gastrointestinal stenosis without ascites. Objective improvement in ascites was observed in 11 patients [15%, 95% confidence interval (CI) 8–26%]: 2 (3%) patients achieved disappearance of ascites and 9 (13%) patients had a decrease of ascites. Twenty-eight patients showed no change of ascites and 14 patients had an increase of ascites. The remaining 26 patients were not assessable because of the unavailability of posttreatment radiologic images, except for evident clinical disease progression that is unnecessary for radiologic evaluation (11 patients), transfer to other hospitals (7 patients), refusal (7 patients), and early death (1 patient). Oral intake improvement was observed in 26 patients (33%, 95% CI 23–44%). Two patients were excluded from analysis because they underwent endoscopic stent placement or ileostomy during chemotherapy. The most frequent reason for treatment discontinuation was disease progression (77%), followed by hospital transfer

Table 2 Treatment discontinuation

Category	*N*	%
Progressive disease (PD)	61	77
Ascites	20	
Gastrointestinal stenosis	17	
Obstructive jaundice	4	
Hydronephrosis	4	
Pleural effusion	3	
Lymphangitis	1	
Bone metastasis	1	
Target lesions	5	
Clinical PD	6	
Unacceptable toxicity	5	6
Treatment-related death	2	3
Others[a]	11	14

[a] Ten patients transferred to other hospitals and 1 provided no follow-up

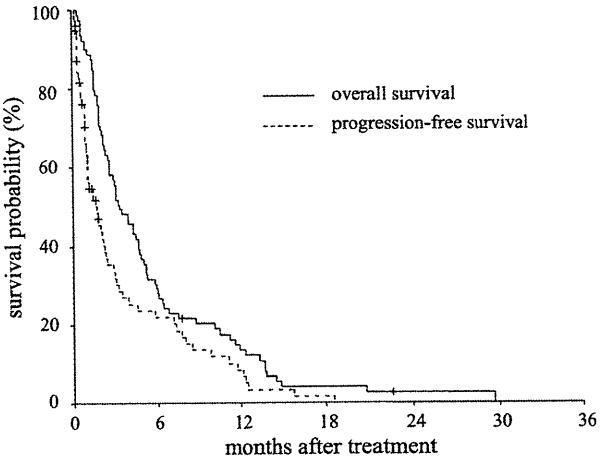

Fig. 2 Overall survival (*continuous line*) and progression-free survival (*dotted line*) in the 79 patients. The *marks on the curves* indicate censored cases

with stable disease (13%), unacceptable toxicity (6%), treatment-related death (3%), and loss of follow-up (1%) (Table 2). Among the 61 patients with disease progression, only 17 patients received second-line chemotherapy treatment, which consisted of a regimen of taxanes for 12 patients, MTX/5-FU for 2 patients, 5-FU ci for 2 patients, and mitomycin for 1 patient.

Seventy-seven patients had died at a median follow-up time of 3.3 months (range, 0.4–29.7 months). Twenty (25%) patients died within 30 days after the last administration of first-line chemotherapy. Of these 20 patients, 17 patients died of disease progression, 2 patients died of treatment-related causes, and 1 patient died of aspiration pneumonia. As to treatment-related death, both patients developed septic shock with febrile neutropenia. Median PFS and median OS for all patients were 1.7 months (95% CI, 0.9–2.4 months) and 3.3 months (95% CI, 2.1–4.5 months), respectively (Fig. 2).

Prognostic factors

In univariate analysis, five variables were identified as significantly associated with shorter survival time (Table 3A): serum CRP level of $\geq$2.0 mg/dl ($P < 0.001$), performance status of $\geq$3 ($P < 0.001$), serum albumin level of <3.0 g/dl ($P = 0.004$), massive ascites ($P = 0.004$), and number of metastatic sites of $\geq$2 ($P = 0.049$). The results of multivariate analysis are given in Table 3B. Elevated serum CRP level, low serum albumin level, poor performance status, and massive ascites were found to be significantly poor prognostic factors in multivariate analysis. The results of forward and backward stepwise regression procedures remained the same. The patients were then classified into three groups according to the prognostic index, as follows: good prognosis with none of the four prognostic factors (group 1, $n = 26$); intermediate prognosis with one or two of the poor prognostic factors (group 2, $n = 39$); or poor prognosis with three or four prognostic factors (group 3, $n = 14$). The survival curves for the three groups are shown in Fig. 3. The median survival time in the good, intermediate, and poor prognosis groups was 6.0, 3.1, and 1.4 months, respectively. There were significant differences in survival time among the three groups ($P < 0.015$).

Discussion

This study demonstrated that median OS of peritoneal disseminated gastric cancer patients with inadequate oral intake receiving first-line systemic chemotherapy was 3.3 months. Serum CRP level $\geq$2.0 mg/dl, serum albumin level <3.0 g/dl, massive ascites, and poor performance status (PS $\geq$ 3) were independent prognostic factors. To the best of our knowledge, this is the first study identifying the treatment outcome and prognostic factors in gastric cancer patients with inadequate oral intake resulting from peritoneal dissemination, treated by systemic chemotherapy.

Gastric cancer patients with peritoneal dissemination have been excluded from the eligibility criteria in most clinical trials because of the absence of measurable lesions and potential severe complications such as massive ascites, hydronephrosis, obstructive jaundice, and intestinal obstruction. Moreover, because peritoneal dissemination causes inadequate oral intake, it is difficult to continue chemotherapy using oral anticancer agents. Recent phase III trials demonstrated that chemotherapy using oral

Table 3 Pretreatment factors associated with the outcome

Variable	N	P value
(A) Univariate analysis		
Gender		
Male	43	0.06
Female	36	
Age		
≥65	18	0.08
<65	61	
ECOG PS		
0–2	60	<0.001
3	19	
Disease status		
Unresectable	20	0.52
Recurrent	59	
Histology		
Diffuse type	71	0.07
Non-diffuse type	8	
Primary tumor		
Present	46	0.81
Absent	33	
Number of metastatic sites		
1	49	0.049
≥2	30	
Ascites		
Non-massive	58	0.004
Massive	21	
Treatment regimen		
5-FU bolus	57	0.38
5-FU ci	22	
Albumin (g/dl)		
<3.0	31	0.004
≥3.0	48	
C-reactive protein (mg/dl)		
≥2.0	33	<0.001
<2.0	46	

Variable	N	Hazard ratio (95% CI)	P value
(B) Multivariate analysis			
ECOG PS			
0–2	60	1	0.05
3	19	1.78 (1.001–3.17)	
Number of metastatic sites			
1	49	1	0.14
≥2	30	1.32 (0.91–1.91)	
Ascites			
Non-massive	58	1	0.04
Massive	21	1.79 (1.04–3.08)	
Albumin (g/dl)			
≥3.0	48	1	0.03
<3.0	31	1.69 (1.05–2.73)	
C-reactive protein (mg/dl)			
<2.0	46	1	<0.01
≥2.0	33	2.03 (1.25–3.31)	

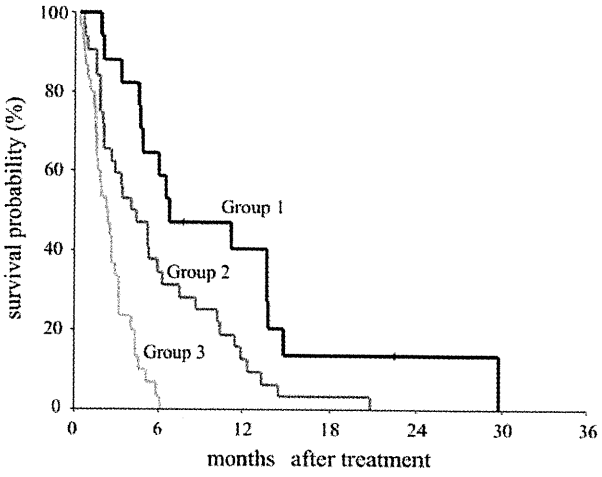

Fig. 3 Survival curves for the three groups determined by prognostic index: group 1, good prognosis (26 patients); group 2, intermediate prognosis (39 patients); group 3, poor prognosis (14 patients). The *marks on the curves* indicate censored cases

fluoropyrimidines, such as capecitabine or S-1, has efficacy results comparable to 5-fluorouracil-based chemotherapy [5, 7]. Patients with inadequate oral intake are subject to the exclusion criteria in the treatment protocol, and most of them must receive 5-FU-based chemotherapy as an intravenous administration. Although 5-FU is one of the most commonly used drugs in patients with gastrointestinal malignancies, systemic chemotherapy of 5-FU has a limited response rate. Therefore, we need to develop novel chemotherapeutic regimens to provide significant benefits at the initial stage of therapy to control the symptoms and improve the quality of life in gastric cancer patients who have severe peritoneal dissemination.

Regarding the host-related factors, good performance status, absence of ascites, serum CRP level <2.0 mg/dl, and serum albumin level ≥3.0 g/dl were found to be favorable prognostic factors by multivariate analysis. Presence of ascites and high serum CRP level were identified as being significantly associated with shorter survival times in the multivariate analysis, and these findings are compatible with previous reports [8, 9]. Moreover, performance status is one of the best known prognostic factors in most cancers beyond gastric cancer. For clinical application of these findings, we can directly predict the survival curve of each patient. These survival curves can be easily calculated because they are based on variables obtained during routine clinical examinations. These findings, therefore, can be used to stratify peritoneal disseminated gastric cancer patients with inadequate oral intake before systemic chemotherapy according to predicted survival. Accordingly, patients with a good prognosis may obtain sufficient treatment efficacy and survival with 5-FU-based chemotherapy as the first-line treatment. In contrast,

patients with a poor prognosis may be treated with palliative care only because of the extremely short median survival (1.4 months) expected, or may be treated with other, more intensive chemotherapy. Systemic chemotherapy for gastric cancer has recently become an important focus, because new anticancer agents, such as oxaliplatin and taxanes, have been proven to confer a survival benefit and to show promise as standard anticancer agents for patients with gastric cancer [6, 10, 11]. Especially in gastric cancer with peritoneal dissemination, paclitaxel is recognized as an effective agent because of its high molecular weight and bulky molecular structure, delaying its clearance from the peritoneal cavity [12–14]. A randomized phase II trial (JCOG 0407) comparing best available 5-FU versus weekly paclitaxel is now ongoing for fluoropyrimidine-resistant gastric cancer with peritoneal dissemination. Oxaliplatin tends to be selected as a substitute for cisplatin in cases of peritoneal dissemination with a certain amount of ascites because oxaliplatin does not require extensive hydration [15]. To improve treatment efficacy, further chemotherapy regimens, such as combination therapy comprising 5-FU and taxane or oxaliplatin, remain as challenges to be met by further detailed investigations for peritoneal disseminated gastric cancer patients with inadequate oral intake. These findings may be helpful in predicting the life expectancy in peritoneal disseminated gastric cancer patients with inadequate oral intake who are treated with 5-FU-based chemotherapy.

In conclusion, this study demonstrated that the efficacy of 5-FU-based chemotherapy as the first-line treatment against peritoneal disseminated gastric cancer with inadequate oral intake was unsatisfactory. Patients receiving chemotherapy safely could be selected depending on some prognostic markers: PS, amount of ascites, serum CRP, and serum albumin. Systemic chemotherapy should be recommended with caution to patients with poor prognostic factors considering the risk–benefit balance. Further development of new regimens without oral anticancer agents is necessary to improve the quality of life and prognosis in this patient population.

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Conflict of interest We have no conflicts of interest to declare.

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ORIGINAL ARTICLE

Management of adjuvant S-1 therapy after curative resection of gastric cancer: dose reduction and treatment schedule modification

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Abstract
Background The aim of this study was to determine the optimal management of adjuvant S-1 therapy for stage II or III gastric cancer, encompassing the details of dose reduction and treatment schedule modification.
Methods We retrospectively examined 97 patients with stage II or III gastric cancer who received S-1 chemotherapy following gastrectomy between January 2003 and December 2007. S-1 (80 mg/m^2 per day) was orally administered twice daily for 4 weeks, followed by a 2-week rest. As a rule, treatment was continued for 1 year after gastrectomy. Dose reduction or treatment schedule modification was performed according to toxicity profiles.
Results Among the 97 patients, 57 (59%) underwent dose reduction at least once and 39 (40%) received treatment schedule modification. Of the 57 patients who required dose reduction, 45 (79%) underwent reduction within 3 months of the beginning of treatment. The most common reasons for dose reduction were anorexia (47%), followed by diarrhea (32%), leukopenia (24%), and rash (16%), with the reasons overlapping. Although the difference in the requirement for dose reduction was not significant, patients with a low creatinine clearance level or those who underwent total gastrectomy had a greater tendency to require dose reduction. The duration of the S-1 treatment period was at least 3 months in 88% of the patients, at least 6 months in 82%, and the planned 1-year period in 73% of the patients.
Conclusions In most patients, the planned 1-year adjuvant S-1 therapy for stage II or III gastric cancer could be completed by modifying the dose reduction and treatment schedule.

Keywords S-1 · Adjuvant chemotherapy · Gastric cancer

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Introduction

Gastric cancer remains one of the leading causes of cancer-related deaths, the mortality rate of which ranks second worldwide [1]. Although surgery remains the sole mainstay of any curative treatment, the relapse rate is high and survival remains low even after surgical resection with curative intent. To prevent relapse and increase the survival rate, several types of adjuvant treatments have been administered. The rationale for using adjuvant treatment after curative resection remains controversial worldwide. In the United States, adjuvant chemoradiotherapy has become a standard treatment [2], and in Europe, perioperative chemotherapy has been established as a standard treatment [3]. On the other hand, in Japan, oral anticancer agents have been investigated for decades as postoperative adjuvant chemotherapy without sufficiently robust evidence for their efficacy. The different approaches in Europe, the United States, and Japan regarding adjuvant chemotherapy for gastric cancer may be attributable to differences in surgical approaches. In Europe and the United States, the standard surgical treatment is gastrectomy plus D0 or D1 lymphadenectomy, and chemoradiotherapy appears to be effective for local control after curative resection. In Japan, however, the established standard surgical treatment for gastric cancer is gastrectomy plus D2

lymphadenectomy [4]. The role of adjuvant chemotherapy is to control distant or peritoneal recurrences. Against this background, adjuvant chemotherapy using oral fluorinated pyrimidines has been most widely used in both clinical practice and clinical trials [5, 6], although it remains unclear which specific treatment is effective.

S-1 is an effective derivative of 5-fluorouracil (5-FU) that combines tegafur with two modulators of 5-FU metabolism; namely, 5-chloro-2,4-dihydroxypyridine (CDHP), a reversible inhibitor of dihydropyrimidine dehydrogenase (DPD), and potassium oxonate, in a molar ratio of 1:0.4:1 [7]. Tegafur, an oral prodrug of 5-FU, is gradually converted to 5-FU and rapidly metabolized by DPD in the liver. The maximum concentration (Cmax) and area under the concentration time curve (AUC) of 5-FU in plasma during S-1 treatment have been found to be higher than the steady-state concentration and AUC of 5-FU in plasma during protracted intravenous infusion of 5-FU at 250 mg/m^2 per day [8]. Recently, the Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer (ACTS-GC) was performed [9]. This was a large randomized controlled trial comparing surgery alone versus surgery plus adjuvant chemotherapy. Following the ACTS-GC trial, S-1 administration for 1 year after curative surgery increased both overall and relapse-free survival compared with surgery alone. Thus, S-1 has become widely used in Japan not only for unresectable recurrent or metastatic tumors but also for disease-free patients after curative surgery for gastric cancer.

In the ACTS-GC trial, even though the major grade 3/4 toxicities included only anorexia (6.0%), nausea (3.7%), and diarrhea (3.1%), the percentage of patients who completed the planned 1-year S-1 treatment was only 65.8%. In addition, dose modification was performed in 42.4% of the patients, although details of the reasons for such modification were not provided. We therefore retrospectively investigated the details of dose reduction and schedule modification in patients with adjuvant S-1 therapy after curative resection of gastric cancer.

Patients and methods

Between January 2003 and December 2007, we retrospectively analyzed a total of 97 patients with stage II or III gastric cancer who received S-1 therapy after gastrectomy at the National Cancer Center Hospital, Tokyo. The clinicopathologic findings were determined in accordance with the *Japanese classification of gastric carcinoma* [10]. We regarded S-1 administration that started within 90 days after surgery as an acceptable period because this was a retrospective study, and because oncologists should consider starting adjuvant chemotherapy as soon as possible after gastrectomy (within 6 weeks) in order to eliminate micrometastases. There is no clear evidence for this 90-day period, but it is approximately twice the starting limit of the ACTS-GC study. Moreover, because the period of adjuvant S-1 therapy was 1 year, this study was intended for patients who had started adjuvant S-1 therapy 1 year or more before the time of analysis. In principle, S-1 was administered orally at 40 mg (body surface area [BSA] < 1.25 m^2), 50 mg (BSA 1.25–1.50 m^2), and 60 mg (BSA > 1.50 m^2) twice daily for 4 weeks, followed by a 2-week rest. However, a reduction of the starting dose was allowed at the physician's discretion; for example, when patients had postoperative gastrointestinal symptoms, poor general condition, or myelosuppression. S-1 administration was continued until 1 year after gastrectomy if there was no evidence of tumor recurrence or unacceptable toxicity. The dose or treatment schedule was modified at the physician's discretion according to toxicity profiles. In principle, we recommended that the schedule be changed from a 4-week administration followed by a 2-week rest to a 2-week administration followed by a 1-week rest if patients could take S-1 twice per day completely without S-1 skip but had severe gastrointestinal symptoms or myelosuppression during the first 2 weeks, and the dose was reduced (1 level down) if sufficient S-1 could not be administered to the patients due to adverse events during first 2 weeks. Nevertheless, we recommended a further dose reduction of S-1 (2 levels down) or 2-week administration followed by a 1-week rest when patients could not continue S-1 by adjusting first step dose or schedule modification. Furthermore, we attempted a 2-week administration followed by a 2-week rest or a 3-week administration followed by a 2-week rest if the treatment was not successful. We also allowed low doses such as 60 mg/day when we could not manage adverse events with a reduction to 80 mg/day.

The cumulative incidence of dose reduction was calculated by the Kaplan–Meier method, censoring at the date of treatment discontinuation caused by postoperative recurrence or adverse events. Statistical analysis was performed using Dr SPSS II (SPSS Japan, Tokyo, Japan). All statistical comparisons were two-sided and $P \leq 0.05$ was considered significant. Treatment-related toxicities were assessed using the Common Terminology Criteria for Adverse Events version 3.0.

This study was approved by the institutional review board of the National Cancer Center and was conducted in accordance with the ethical principles stated in Japanese ethics guidelines for epidemiological studies.

Results

Patient characteristics

The characteristics of the patients are shown in Table 1. Forty patients underwent total gastrectomy, 54 had distal

Table 1 Patient characteristics ($n = 97$)

	n (%)
Age (years)	
Median	59
Range	35–80
Sex	
Male	63 (65)
Female	34 (35)
ECOG performance status	
0	60 (62)
1	37 (38)
Stage, Japanese classification	
II	50 (52)
IIIA	29 (30)
IIIB	18 (19)
Surgical procedure	
Total gastrectomy	40 (41)
Subtotal gastrectomy	57 (59)
Creatinine clearance (ml/min)	
<60	10 (10)
6–80	29 (30)
>80	58 (60)
Initial dose of S-1 (mg/body)	
80	11 (11)
100	35 (36)
120	51 (53)

Creatinine clearance was calculated using the Cockroft–Gault formula. Percentages might not add up to 100% due to rounding

ECOG Eastern Cooperative Oncology Group

gastrectomy, and the remaining 3 underwent pylorus-preserving gastrectomy. Of 19 patients receiving dose reduction at the initial administration, 6 showed inadequate food intake after gastrectomy, 5 had leucopenia and were judged unfit to start at the standard dose, 1 developed pancreatic fistula as a postsurgical complication, and 1 had borderline BSA (This patient had BSA of 1.51, so physician selected S-1 100 mg/day in consideration of postsurgical condition); the reasons for the dose reduction in the remaining 6 patients were unknown. Of the 97 patients enrolled, 62 patients exceeded the 6-week starting time limit of the ACTS-GC study. The reasons were pancreatic fistula in 6 patients, gastrointestinal symptoms in 5 patients, poor oral intake in 3 patients, poor general condition in 3 patients, another treatment in 2 patients (dental therapy in 1 and treatment for early bladder cancer in the other), anastomotic stenosis in 1 patient, ileus in 1 patient, colitis in 1 patient, delay of pathological confirmation in 1 patient, and by patient request for 1 patient; and the remaining 38 patients delayed seeking an examination at the outpatient clinic by about 1 or 2 weeks.

Table 2 Adverse events ($n = 97$)

	No. of patients				%	%
	G1	G2	G3	G4	All G	G3/4
Hematological toxicity						
Leukopenia	35	35	1	0	73	1
Neutropenia	18	36	22	1	79	24
Anemia	66	20	1	0	90	1
Thrombocytopenia	18	2	0	0	21	0
Nonhematological toxicity						
Anorexia	67	11	3	0	84	3
Nausea	43	5	0	0	49	0
Vomiting	14	2	0	0	17	0
Mucositis	35	4	0	0	40	0
Diarrhea	53	10	2	0	67	2
Fatigue	65	4	1	0	72	1
Rash	27	3	1	0	32	1
Pigmentation	40	4	–	–	45	–
Hand-foot syndrome	11	2	1	–	14	1
Watery eyes	6	5	1	–	12	1
Taste alteration	13	5	–	–	19	–
Hypoalbuminemia	23	2	1	0	27	1
Hyperbilirubinemia	33	10	1	0	45	1
AST	27	3	2	0	33	2
ALT	22	2	2	0	27	2
ALP	16	0	0	0	17	0
Creatinine	6	1	0	0	7	0

G grade, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *ALP* alkaline phosphatase

Safety

S-1 chemotherapy adverse events, which involved grade 1/2 intensity in the majority of cases, are summarized in Table 2. The most common hematological adverse event was neutropenia, occurring at grade 3/4 intensity in 23 patients (24%). Only 1 patient developed grade 3 febrile neutropenia. Nonhematological toxicity was frequent but rarely severe. Taste alteration and watery eyes, which occurred consistently with repeated courses of therapy, were experienced by 18 (19%) and 12 (12%) patients, respectively, and occasionally a few patients needed dose reduction or treatment discontinuation. There were no treatment-related deaths.

Treatment administration

The median follow-up period after gastrectomy was 43.0 months (range 5.3–73.4 months). Among the 97 patients analyzed, 57 (59%) received dose reduction at least once and 39 (40%) underwent schedule modification during the planned 1-year treatment. Of the 57 patients

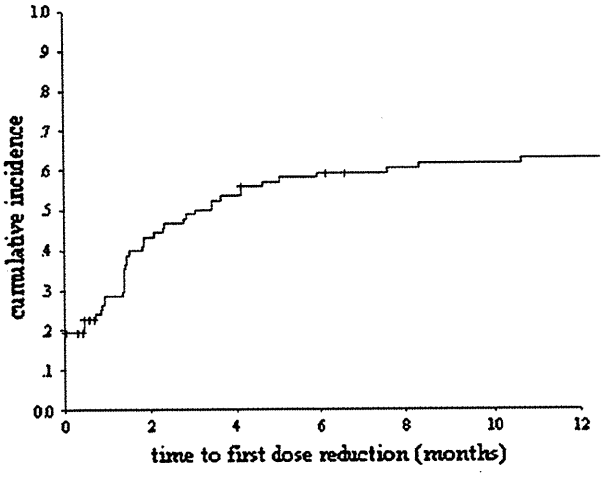

Fig. 1 Cumulative incidence of the time to first dose reduction

Table 3 Reasons for dose reduction ($n = 57$)

Pretreatment dose reduction	19 (33%)
Inadequate food intake	6
Leukopenia	5
Pancreatic fistula	1
Borderline BSA*	1
Unknown	6
Dose reduction during the treatment	38 (67%)
Gastrointestinal toxicities	
Anorexia	18
Diarrhea	12
Nausea/vomiting	5
Mucositis	2
Abdominal pain	1
Others	
Leukopenia/neutropenia	9
Rash	6
Fatigue	3
Taste alteration	3
Liver dysfunction	2
Watery eyes	1

The percentages and numbers do not balance because of overlapping reasons for dose reduction during the treatment

BSA body surface area

* 1 patient with borderline BSA had BSA of 1.51, so physician selected S-1 100 mg/day in consideration of postsurgical condition

who required dose reduction, 45 (79%) underwent the reduction within 3 months of starting the treatment. The median time to the first dose reduction was 1.4 months (range 0–10.6 months). The time to dose reduction is shown graphically in Fig. 1. The most common reasons for dose reduction during the treatment period were anorexia

Table 4 Reasons for treatment discontinuation ($n = 26$)

Adverse events	20 (77%)
Gastrointestinal toxicities	14
Anorexia	6
Diarrhea	3
Nausea/vomiting	3
Abdominal pain	1
Mucositis	1
Others	
Fatigue	3
Leukopenia/neutropenia	2
Watery eyes	2
Taste alteration	2
Rash	1
Hand–foot syndrome	1
Pigmentation	1
Liver function	1
Dyspnea	1
Recurrence	2 (8%)
Others	4 (15%)

The numbers do not balance because of overlapping reasons for treatment discontinuation

(47%), followed by diarrhea (32%), leukopenia (24%), and rash (16%) with reasons overlapping (Table 3). Of the 39 patients who required schedule modification, 22 patients underwent a 2-week administration followed by a 1-week rest, 19 patients had a 2-week administration followed by a 2-week rest, and 2 patients had a 3-week administration followed by a 2-week rest (including the 4 patients who underwent two modifications, i.e., a 2-week administration followed by a 1-week rest, and a 2-week administration followed by a 2-week rest in 3 patients, and a 3-week administration followed by a 2-week rest and a 2-week administration followed by a 2-week rest in 1 patient).

A total of 60 patients required dose reduction and/or schedule modification, and 32 patients underwent remodification after their initial modification (the number of modifications was 1 in 28 patients, 2 in 22 patients, 3 in 9 patients, and 4 in 1 patient). No patients were rechallenged with the initial dose after undergoing dose reduction due to adverse events during the adjuvant chemotherapy. The relative administration day, defined as the ratio of actual administration days to planned administration days, was 83.8%, and we regarded relative number of administration days assuming that was reckoned from the start date of actual S-1 administration, not within 6 weeks after surgery specified in ACTS-GC. The relative dose intensity, defined as the ratio of the actual cumulative dose to the planned cumulative dose, was 69.1%. The percentage of patients who continued treatment for at least 3 months was 88%, that of patients who continued treatment for at least 6 months was 82%, and that