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State of the art 2

世界各地で行われてきた臨床試験において，ベースとなるコントロール治療に大きな違いが存在することから，残念ながら世界の誰もが認める標準的治療法は存在しない。また保険償還システムの違いから二次治療以降の生存期間にも地域間差が認められている。今後一次治療における分子標的薬剤の開発を考えた場合，二次治療以降の地域間差は避けては通れない大きな問題となる可能性がある。

SPIRITS 試験／FLAGS 試験／TS-1 ＋シスプラチン／二次治療／保険償還

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1 標準的治療法の地域間差

1. わが国の標準的治療が世界の標準的治療となるか？ －TS-1＋シスプラチン－

近年わが国から，切除不能進行・再発胃癌に対する標準的治療を確立する上で，重要な臨床試験の報告が行われた。それら試験結果の中で，JCOG9912試験（5-FU vs. イリノテカン＋シスプラチン vs. TS-1）で，TS-1の5-FUに対する非劣性が示されたこと，およびSPIRITS試験（TS-1 vs. TS-1＋シスプラチン）で，TS-1＋シスプラチンのTS-1に対する優越性が示されたことが，重要なポイントとしてあげられる[1,2]。これら2つの試験結果から，一次治療法としてTS-1＋シスプラチンがわが国において推奨されることになった。ではTS-1＋シスプラチンは，世界的にも標準的治療として受け入れられているのであろうか？その答えは残念ながらNOである（表1）。グローバルトライアルとして行われたFLAGS試験（5-FU＋シスプラチン vs. TS-1＋シスプラチン）の結果，TS-1＋シスプラチンは，5-FU＋シスプラチンに対して優越性を示すことができず，世界標準にはなれなかった[3]。もともとTS-1は，5-FU系の経口抗癌剤であり，利便性で優れていることから，製薬会社サイドは当初，FDAに対して非劣性デザインで申請試験を行いたい旨の申し入れを行った。しかしTS-1は，3つの薬品（テガフール，ギメラシル，オテラシルカリウム）からなる合剤であり，TS-1自体がすでに多剤併用と見なされ，最終的に優越性試験での実施しか選択の余地はなかったのである。

FLAGS試験は，アジアを除く世界の国々が参加して行われた，まさにグローバルトライアルである。このトライアルにおけるサブセット解析には，注目すべき点がいくつか存在する。なかでも極めて興味深い点は，治療成績の地域間差である。特に米国におけるTS-1＋シスプラチンの治療成績は，極めて良好であった。その一方で，南米の治療成績は極めて悪く，米国とは正反対の結果であった。その要因の1つとして考えられるのが，TS-1に対する慣れ，つまり副作用コントロールに違いがなかったかということである。注射剤と違い，経口剤は自宅での治療期間がメインであり，副作用をうまくコントロールすることが治療を継続する上で重要である。そのためには行き届いた患者教育および管理が必要である。欧米におけるTS-1＋シスプラチンの第Ⅰ/Ⅱ相試験は，米国のM. D. Anderson Cancer CenterのAjaniらが中心となって行い，その成績は極めて良好であった。この試験に参加した施設は，米国でも臨床試験に慣れた質の高い施設ばかりで，FLAGS試験を開始する前に，TS-1＋シスプラチンを十分手の内に入れていたと考えられる。一方，南米の施設は，TS-1＋シスプラチンの臨床経験もなく，また米国の施設ほど臨床試験のサポート体制が整備されているとは言い難い。その違いがFLAGS試験の地域間差に影響を及ぼした可能性は否定できない。この事実はまさしく胃癌化学療法に地域間差が存在することを示した好例といえるだろう。

2. 欧米の標準的治療がわが国の標準的治療になりえるか？ －ECFおよびDCF－

NCCNガイドラインを紐解いてみると，ECF（エピルビシン＋シスプラチン＋5-FU）とDCF（ドセタキセ

表1 SPIRITS試験とFLAGS試験におけるTS-1＋シスプラチン療法の治療成績

	奏効率（%）	無増悪生存期間（カ月）	生存期間中央値（カ月）	二次治療への移行率（%）
SPIRITS試験[2]	54	6.0	13.0	75
FLAGS試験[3]	29.1	4.8	8.6	31

ル＋シスプラチン＋5-FU）が，一次治療として推奨されており，欧米における標準的治療として位置付けられている。しかしECFやDCFが，標準的治療として位置付けられるまでの過程がわが国と異なっていることに注目したい。これまで欧米では，わが国のように単剤（5-FUもしくはTS-1）をコントロールにおいた比較試験ではなく，多剤併用療法同士の比較試験が，数多く行われてきた（表2）。欧州を代表する臨床試験グループであるEuropean Organization for Research and Treatment of Cancer（EORTC）は，FAM（5-FU＋adriamicin＋マイトマイシンC）をreference armにしたFAM vs. FAMTX（5-FU＋adriamicin＋メトトレキサート）の無作為化比較試験を最初に行った。この試験においてFAMTXが，奏効率および生存期間で優れていたため，一時期，欧米の標準的治療と目された[4]。しかしその後EORTCが行ったFAMTX vs. ELF（エトポシド＋5-FU＋LV）vs. FP（5-FU＋シスプラチン）の3群比較で，奏効率および全生存期間において3群間に有意な差を認めなかったため，推奨できる標準的治療がないと結論付けている[5]。この試験で検証されたFP療法は，同時期にわが国で行われたJCOG9205試験において，5-FU単独を生存において上回ることができなかった[6]。しかも5-FU単独の毒性が軽微であったことから，わが国では単剤をコントロールにおいた試験にこだわり，前述した2つの試験結果によって標準的治療としてのTS-1＋シスプラチンに至ったのである。

一方欧米では，イギリスを中心に行われたMRC試験において，ECF（エピルビシン＋シスプラチン＋5-FU）が前述したFAMTXに比べて，有意に全生存期間を改善したことにより，イギリスの文化圏ではECFが標準的治療となった[7]。しかし米国ならびに一部の欧州の国々では，FPに対するエピルビシンの上乗せが検証されていないことから，日常診療には積極的にECFを取り入れていない。

FPにドセタキセルの上乗せを検証したV325試験（DCF vs. FP）において，FPに対するDCFの優越性が示された[8]。この結果，DCFは欧米で推奨できる一次治療のひとつとなっている。しかしながらDCFは，毒性に問題があることが指摘されており，欧米における実臨床では，オリジナルのDCFではなくmodified DCFが幅広く行われている。このDCFも世界的にみれば必ずしも，世界共通の標準的治療法として認められていないのが現状である。ましてわが国においては，TS-1＋シスプラチンの2剤併用が標準的治療として確立されたばかりである。現在，TS-1＋シスプラチンに

表2　欧米における重要な無作為化比較試験（併用療法 vs. 併用療法）

臨床試験	治療法	症例数	奏効率（%）	p値	生存期間中央値（カ月）	p値
EORTC試験（1991年）	FAM	103	9	p＝＜0.0001	7.2	p＝0.004
	FAMTX	105	41		10.5	
Webbらによる試験（1997年）	FAMTX	130	21	p＝0.0002	5.7	p＝0.0009
	ECF	126	45		8.9	
EORTC試験（2000年）	FAMTX	133	12	NS	6.7	NS
	ELF	132	9		7.2	
	FP	134	20		7.2	
V325試験（2006年）	DCF	221	38.7	p＝0.012	9.2	p＝0.02
	FP	224	23.2		8.6	

ドセタキセルを併用したDCSに関する第Ⅱ相試験の良好な治療成績がいくつか報告されているが，今後，2剤vs. 3剤の比較試験（例えばTS-1＋シスプラチンvs. DCS）を行うか否かは，分子標的薬剤の開発も絡んで不透明な状況である。

2 二次治療における地域間差 ―保険償還システムの違い―

わが国で行われたSPIRITS試験と，グローバル試験として行われたFLAGS試験を比較すると，二次治療の地域間差について興味深い点が浮かび上がってきた。それは，両者の二次治療への移行率の差が顕著なことである。わが国のSPIRITS試験の二次治療への移行率は75％と高率なのに対し，グローバルトライアルであるFLAGS試験では，わずか31％の移行率にしかすぎなかった。この移行率の低さは，近年報告された他の試験においても共通して認められている。前述したわが国で行われたJCOG9912試験の二次治療への移行率は，全体で80％弱と極めて高いのに対し，イギリスを中心に行われたREAL-2試験では，わずか15％の移行率にすぎなかった。この背景には，わが国とその他の国々では保険償還システムに大きな違いがあることに注意を払う必要がある。特にイギリスでは，二次治療が保険で認められていないため，一次治療が極めて重要である。近年わが国から報告された第Ⅲ相試験の生存期間中央値は，欧米から報告されたそれと比べて2～3ヵ月長い傾向がある。それには保険償還システムの違いが，大きく関与していると考えられる。

3 地域間差がもたらす新たな問題 ―日韓が参加するグローバルトライアルにおける問題―

ASCO2009で，ToGA試験の結果が報告された[9]。ToGA試験は，HER2陽性の進行胃癌患者の一次治療にトラスツズマブを追加することのベネフィットを検証した試験である。適格基準を満たした584例を5-FUまたはカペシタビン＋シスプラチン（FC群：290例），5-FUまたはカペシタビン＋シスプラチン＋トラスツズマブ（FC＋T群：294例）に無作為割り付けした。生存期間中央値は，FC群（11.1ヵ月）に比べ，FC＋T群（13.8ヵ月）で有意に長く（p＝0.0046），HER2陽性・進行胃癌に対するトラスツズマブの有用性が示されている。この試験において興味深い点は，サブセット解析における生存期間の地域間差であろう。ToGA試験では，アジアにおけるトラスツズマブの生存期間に対するインパクトは小さく，南米における生存期間に対するインパクトは極めて大きかった。この理由を考えてみると，前述した二次治療の地域間差が第一に考えられる。この試験の登録の半分近くは，韓国ならびにわが国から行われていた。日韓両国は，実臨床において二次治療を積極的に行っている地域である。一方で南米では二次治療が行われることは少ない。よって南米では，一次治療のインパクト，すなわちトラスツズマブのインパクトが大きくなったと考えられる。現在，胃癌における分子標的治療薬の開発は，日韓がメインとなって行われている。その日韓が多くの患者を登録した場合，二次治療以降の生存が長いことから，主要評価項目が全生存期間だと有意な差がつき難いという新たな問題に直面しつつある。

今後，一次治療における分子標的薬剤の開発を考えた場合，二次治療以降の地域間差は避けては通れない大きな問題となる可能性がある。

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Q11 胃がん―切除不能進行・再発胃がん―

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point

- 切除不能進行・再発胃がんに対する分子標的治療薬の開発がグローバルトライアルとして行われている.
- 我が国と欧米の標準的治療に対する考え方に違いがある.
- グローバルトライアルを行った結果,『地域間差』があることが明らかとなった.
- 我が国と違い,欧米では二次治療への移行率が低い.

Q 切除不能進行・再発胃がんでは,どういった点が今いちばん話題になっているでしょうか？

A 近年,我が国から切除不能進行・再発胃がんに対する標準的治療を確立するうえで重要な臨床試験の結果が報告されました.なかでもJCOG9912試験(5-FU vs CPT-11＋CDDP vs S-1)でS-1の5-FUに対する非劣性が示されたこと[1],SPIRITS試験(S-1 vs S-1＋CDDP)でS-1＋CDDPのS-1単独に対する優越性が示されたことにより[2],我が国における一次治療法としてS-1＋CDDPが推奨されることになりました.現在さらなる治療効果の向上を目指して,他臓器がんと同じく胃がんの領域においても,分子標的治療薬の開発が積極的に行われています.

Q 切除不能進行・再発胃がんでは,我が国の標準的治療と欧米の標準的治療には違いがあるのですか？

A 我が国の標準的治療となったS-1＋CDDPは,世界的にも標準的治療として受け入れられているのでしょうか？答えは残念ながらNoです.グローバルトライアルとして行われたFLAGS Trial(5-FU＋CDDP vs S-1＋CDDP)の結果,S-1＋CDDPが5-FU＋CDDPに対して優越性を示すことができませんでした[3].もともとS-1は5-FU系の経口抗がん剤であり,利便性で優れていることから,当初製薬会社やPMDA(医薬品医療機器総合機構)に対して非劣性デザインで承認試験を行った旨の申し入れを行いました.しかし,S-1はすでに多くの薬品(オキサリプラチン,シスプラチン,カルボプラチン,イリノテカン,ドセタキセル,パクリタキセル)と

剤であり，S-1 自体がすでに多剤併用と見なされ，最終的に優越性試験での実施に至る経緯はなかったようです．その結果，S-1＋CDDP は世界共通の標準的治療にはなりえなかったのです．

Q 欧米での標準的治療法を教えてください

A 有名な MOOT ガイドラインを紐解くと，ECF（エピルビシン＋CDDP＋5-FU）と DCF（ドセタキセル＋CDDP＋5-FU）が一次治療として推奨されており，欧米における標準的治療として位置付けられています．しかし ECF や DCF が標準的治療として位置付けられるまでの過程が，我が国とは異なっていることに注意してください．欧米では，我が国のように単剤（5-FU or S-1）をコントロールにおいた比較試験ではなく，多剤併用療法同士の比較試験によってエビデンスがつくられてきました．

UK を中心に行われた試験において，ECF が，FAMTX（5-FU＋アドリアマイシン＋MTX）に比べて優越性を示したことにより，UK 圏の文化圏では ECF が標準的治療となっています[4]．しかし米国などの一部の欧州の国々では，FP（5-FU＋CDDP）に対するエピルビシンの上乗せが検証されていないことから，積極的に ECF を日常診療には取り入れてはいません．米国ではドセタキセルの上乗せを検証した V325 試験（DCF vs FP）において，FP に対する DCF の優越性が示されたことにより，欧米で推奨できる一次治療の一つとなりました[5]．しかし DCF は，毒性に問題があることが指摘されており，実際欧米における実臨床では，オリジナルの DCF ではなく，modified DCF が幅広く行われています．

Q 切除不能進行・再発胃がんにおける分子標的治療薬の現状について教えてください

A ASCO2009 で ToGA 試験の結果が報告されました．この試験は，HER2 陽性の進行胃がん患者の一次治療にトラスツズマブを追加することのベネフィットを検証した試験です．適格基準を満たした 584 例を 5-FU またはカペシタビン＋CDDP（FC 群：290 例），5-FU またはカペシタビン＋CDDP＋トラスツズマブ（FC＋T 群：294 例）に無作為割付けしました．全生存期間中央値は，FC 群（11.1 ヵ月）に比べ，FC＋T 群（13.8 ヵ月）で有意に長く（$p=0.0046$），HER2 陽性胃がんに対するトラスツズマブの有用性が示されました[6]．胃がんに対するトラスツズマブの使用が認められれば，今後一次治療を行う前に必ず HER2 陽性胃がんか否かをチェックする必要がありますね．

また ASCO2010 において JAVELIN 試験の結果が報告され，注目を集めました．この試験は，カペシタビン/5-FU＋CDDP 療法に抗 VEGF 抗体薬であるベバシズマブの上乗せ効果を検証する目的で実施されました．全体で 774 例もの患者さんが参加され，そのうち 49%がアジアから，29%が欧州から，19%が北米から登録しました．その結

果は，主要評価項目である全生存において［ ］で差が認められなかったという残念な結果となりました．また，その治療成績に「地域間差」があることが浮き彫りとなりました．

Q グローバルトライアルにおける「地域間差」とはなんですか？

A 我が国で行われたSPIRITS試験とグローバル試験として行われたFLAGS trialを比較してみましょう．すると，二次治療の地域間差について興味深い点が浮かび上がってきます．それは両者の二次治療への移行率の差が顕著なことです．SPIRITS試験の二次治療への移行率は75%と高率なのに対し，グローバルトライアルであるFLAGS trialでは，わずか31%の移行率にしかすぎません．この移行率の低さは，近年報告された他の試験においても共通して認められています．

ToGA試験においても，アジアにおけるトラスツズマブの生存に対するインパクトは小さく，南米における生存に対するインパクトは極めて大きなものがありました．この理由を考えてみると，前述した二次治療の地域間差が第一に考えられます．この試験の登録の半分近くは，韓国ならびに我が国から行われています．日韓は，実臨床において二次治療を積極的に行っている地域ですが，南米では二次治療が行われることは少ない地域です．よって南米では，一次治療のインパクト，すなわちトラスツズマブのインパクトが大きくなったと考えられます．現在胃がんにおける分子標的治療薬の開発は，日韓がメインとなっていますが，多くの患者が日韓から登録された場合，二次治療以降の生存が長いことから，主要評価項目が全生存期間だと有意な差がつきにくいという新たな問題が生まれています．これからは，従来どおりのグローバルトライアルを積極的に展開すべきなのか，practice cultureが同じ地域でのトライアルを計画すべきなのか慎重に考えないといけないと思われます．

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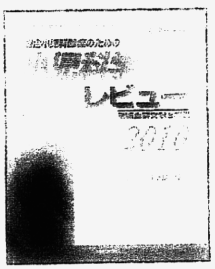

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Ⅳ．進行・再発大腸癌に対する標準的化学療法

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〔*Jpn J Cancer Chemother* **37**(11): 2085-2086, *November*, 2010〕

大腸癌領域に分子標的治療薬が導入されてある程度の時間が経過し，各薬剤の特性が明らかとなってきた。今後しばらくは新薬の導入予定がなく，現在使用可能な薬剤を患者の病態に応じていかに提供するのがベストかを問う時代になってきたと思われる。わが国の大腸癌治療ガイドラインも2010年7月に改訂され，first-lineの選択肢はNCCNのpractice guidelineとほぼ同様となった。これら多くの治療選択肢は実臨床における標準的治療として位置付けられるものであり，正に患者個々の病態に応じた選択が可能であることを意味している。

1．First-line治療をどのように選択するのか

患者の治療目標は，患者個々によって違いがあって当然である。その治療目標によってaggressive approachが必要か，あるいはnon-aggressive approachが必要かを見極める必要がある。図1に最近欧米で考えられているfirst-lineの治療戦略を示す。first-line治療においてaggressive approachが必要か否かを見極める上で，第一に治癒切除の可能性がないかどうかを検討することが重要である。治癒切除が可能な症例では，当然腫瘍縮小効果の高いaggressive approachを選択すべきである。次に，治癒切除が不可能と考えられる症例においてもaggressive approachが必要なケースがある。それは腫瘍随伴症状のある症例である。さらに腫瘍随伴症状がない症例においても，腫瘍量の多い症例や急激な臨床経過をたどることが予想される症例ではaggressive approachが必要となろう。それ以外の症例はnon-aggressive approachで十分対応可能である。

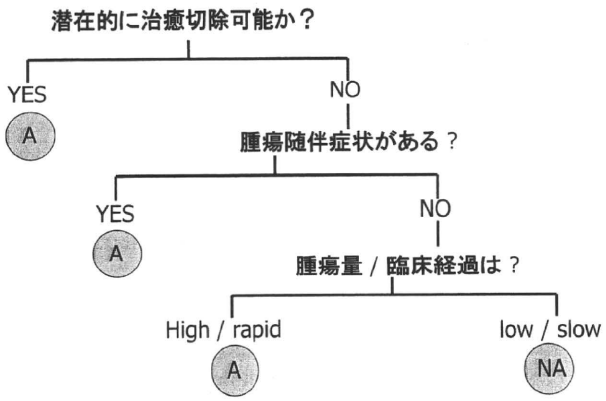

図1　First-line治療の選択
A: aggressive approach，NA: non-aggressive approach

2．Aggressive approachの選択

前述したようにaggressive approachが必要な症例は，いい換えれば急速な腫瘍縮小が不可欠の症例である。その場合のbaseline regimenとなるのはFOLFOXあるいはFOLFIRIである。それらbaseline regimenにどの分子標的治療薬を併用すべきか議論のあるところである。抗EGFR抗体薬のcetuximabやpanitumumabは，*K-RAS* wild typeの場合に限りその効果が期待できる。これまでに行われたfirst-lineの検証試験の結果から，*K-RAS* wild typeの症例においては，抗EGFR抗体薬の方がbaseline regimenに対する奏効率の上乗せが期待できる（表1）。よって*K-RAS* wild typeの症例でaggressive approachが必要な症例は，抗EGFR抗体薬の選択がreasonableな選択だと思われる[1-3]。

その一方で，抗VEGF抗体薬のbevacizumabは，*K-RAS* statusに関係なく効果が期待できる。*K-RAS* mutantでaggressive approachが必要な症例は，治癒切除を目標にする症例か否かでその選択が違ってくるかもしれない。つまり最終的に治癒切除を目標とした症例においては，bevacizumabをbaseline regimenと併用するか否かで現状意見が分かれているからである。その根拠として，bevacizumabの検証試験であるNO16966試験の奏効率において，bevacizumabの上乗せがまったく認められなかった点があげられる[1]。この試験結果と手術時期を遅らせる必要性から，たとえ*K-RAS* mutantの症例であったとしてもconversion therapyにおいてbeva-

表1　一次療法における各抗体薬併用による奏効率の上乗せ

	baseline regimen	control群	抗体薬併用群
NO16966試験（bevacizumab）	FOLFOX	36%	38%
	XELOX	39%	37%
CRYSTAL試験（cetuximab）	FOLFIRI	40%	57%
PRIME試験（panitumumab）	FOLFOX	48%	55%

cizumabは必要ないと考える欧米の研究者も多い。逆に*K-RAS* mutantにおいて，治癒切除を目標としないaggressive approachが必要な症例の場合は，bevacizumab併用を否定する理由は見当たらず，baseline regimenへのbevacizumabの併用がベターな選択と考えられる。

3．Non-aggressive approachの選択

non-aggressive approachで対応可能な症例としては，治癒切除が望めず腫瘍量のそれほど多くない，腫瘍増殖スピードのslowな症例があげられる。そういった症例の治療目標は，QOLを維持した状態での生存期間の延長であり，できる限り低い毒性での延命が求められる。実際に有効性を落とさずに毒性を抑える試みとしてOPTIMOX試験がある[4,5]。日常臨床で使用される頻度の多いFOLFOXの最大の問題点である神経毒性を軽減するためにOxaliplatinを6コース限定で使用し，そのあと5-FU/LVによる維持療法を行い，可能であればFOLFOXを再導入するといった戦略である。このOPTIMOXコンセプトによって腫瘍をコントロールする期間を減弱することなく，Oxaliplatinによるgrade 3以上の神経毒性が軽減され，患者のQOL向上につながった。

同じくQOL維持における分子標的治療薬の役割を考える上で重要な発表が2010年ASCOで報告されている。これはスペインのTTDグループが報告したMACRO試験で，XELOX＋bevacizumabをPDまで続ける群をコントロールにして，XELOX＋bevacizumabを6コース行い，その後に維持療法としてbevacizumab単独を投与する群の非劣性を検討した試験である[6]。残念ながら統計学的には，bevacizumab単独群の非劣性は証明されなかったが，QOLを強く意識した極めてチャレンジングな興味深い試験であった。今後わが国においても，患者のQOL向上をめざした臨床試験を考えていく必要があると思われる。

いくつかの臨床試験の結果から，bevacizumabの上乗せ効果を無増悪生存期間におけるハザード比でみた場合，5-FU/LV（RPMI）＞IFL＞capecitabine＞XELOX＞FOLFOXの順となる。単純に考えると，5-FU/LVとの併用で最大の効果が得られ（ハザード比0.49），逆に実臨床で頻用されることの多いFOLFOXにおいて上乗せ効果が最も弱い（ハザード比0.89）。もちろん毒性の点からいえば5-FU/LV＋bevacizumabはless toxic regimenであり，sequential approachで残りのkey drugsを使い切ることが可能であれば，baseline regimenを必ずしもcombination regimenにする必要はないと思われる。以前，細胞毒性を有する抗癌剤の使用に際し，毒性軽減を考えてsequenceとcombinationの比較が検討され，両者には大差がないことが報告されている[7,8]。そこにさらに分子標的治療薬が加わった今，毒性軽減を目指したsequential approachが同様に成り立つのか興味深いところである。極論すれば，腫瘍量の少ない無症状の患者においては，そういったsequenceの戦略が一番フィットするのではないかと考える。

おわりに

分子標的治療薬の登場によって飛躍的に治療選択肢が増え，種々のガイドラインに記載されているように，様々な治療のオプション選択が可能となった。実際の臨床においては，決して画一的な治療選択をすべきではなく，病態に応じた治療選択が重要な時代になりつつある。それを実践していくには，まず一次治療開始前にaggressive approachが必要な症例かどうかを見極めることが重要である。

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Review Article: Molecular Target Treatment

Current Status and Problems in Development of Molecular Target Agents for Gastrointestinal Malignancy in Japan

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Since late 1990s, many molecular target agents have been introduced to clinical trials for various kinds of tumors, and some of them showing significant benefits have been approved. However, these global trials were mainly conducted outside Japan, and the 'drag lag' has been a serious problem in Japan recently. Nowadays, Japanese institutions have been participating in some global trials, and the drug lags are getting shorter. For colorectal cancer, molecular target agents such as bevacizumab and cetuximab have been approved in Japan, resulting in improved clinical outcomes. For gastric cancer, Japanese institutions not only contribute to the global Phase III trials of trastuzumab and bevacizumab but also show leadership in the early development of other new agents. For pancreatic cancer, only erlotinib has shown a survival benefit in these 10 years. Worldwide approach including Japan is warranted to achieve better clinical outcomes. For liver cancer, although Japanese institutions did not participate even in the Asian trial of sorafenib, it has been approved in Japan. For esophageal cancer, because there has been no new molecular target agents developed by pharmaceutical companies, investigator-initiated registration trial will play an important role. For all gastrointestinal malignancies, molecular target agents have made a progress in their treatments. In the near future, Japanese institutions will participate in more and more global trials and should play a specific role in worldwide drug development. Furthermore, the optimal use of these new drugs, molecular target agents, based on the daily practice should also be explored in Japan.

Key words: development – molecular target agent – gastrointestinal malignancy

INTRODUCTION

Since late 1990s, many molecular target agents have been introduced to clinical trials for various kinds of tumors, and some of them showing significant benefits have been approved. Actually, molecular target agents have made a remarkable progress in treatment of gastrointestinal malignancies and been widely used in clinical practice worldwide. In the past, the global trials were conducted mainly outside Japan, and thereafter independent studies, mainly Phase II, were added for registration in Japan after approval in Western countries. These independent registration trials caused the 'drag lag', and it has been a serious problem in Japan recently. After the guideline regarding to clinical evaluation of drugs for malignant disease was revised, Phase III trials are mandatory for common malignancies such as lung, gastric, colorectal, liver and breast cancers, whereas data of clinical trials conducted overseas are acceptable in Japan. Nowadays, many pharmaceutical companies have been including Japanese institutions in global clinical trials. However, there are merits and problems in these development and approval methods, depending on cancer types and developing stages. Furthermore, there should be roles for Japanese institutions to play from the global point of view as a part of ICH (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use).

COLORECTAL CANCER

Until recent days, chemotherapy for metastatic colorectal cancer in Japan was far behind from Western countries, not

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only with molecular target agents but also with cytotoxic agents. Until 2004, in Japan, the most active regimen had been IFL (1) which comprised bolus 5-fluorouracil (5-FU)/leucovorin and drip infusion of irinotecan (CPT-11) even after N9741 trial showed that FOLFOX, which is based on infusional 5-FU and combination with oxaliplatin, regimen showed a survival benefit over IFL (2). Although CPT-11 was approved for colorectal cancer in 1994, 2 years earlier than the USA, delay in approval of leucovorin (1999), oxaliplatin (2005) and infusional 5-FU with leucovorin (2004) had been limiting clinical practice for metastatic colorectal cancer in Japan (Table 1). It seemed to be unusual that oxaliplatin in combination with infusional 5-FU was approved without any data of FOLFOX regimens in Japanese population.

Recently, molecular target agents such as bevacizumab (3–5) and cetuximab (6–8) have been playing an important role for managing patients with metastatic colorectal cancer. Bevacizumab added to IFL regimen showed a remarkable survival benefit over IFL alone (3), in the first-line chemotherapy and so did it in the second-line chemotherapy combined with FOLFOX regimen (5). In Japan, only one study investigating its feasibility in combination with XELOX regimen was conducted for registration. As a result, the approval of bevacizumab was delayed by 3 years compared with the USA. Cetuximab showed a survival benefit in the third line compared with best supportive care (6), and longer progression survival time in combination with FOLFIRI and CPT-11 in the first (7) and second lines (8), respectively. In Japan, after its Phase I studies of monotherapy (9) and combination therapy with CPT-11 (10) had been conducted, it was approved in 2008, 4 years later than the USA. Although it has been widely accepted that cetuximab shows no activity to the patients whose tumors has K-ras mutation (11), the K-ras mutation test has not been approved in Japan.

Until early 2000, the drug lag between Japan and Western countries had been awfully large, and recently, it has been getting shorter. Now, some Japanese patients are enrolled to the global Phase III studies investigating new drugs to get approval worldwide. However, Phase I studies are still delayed from global ones, and it seems obligate to reach the same target dose in Japanese Phase I studies, although there might be ethnic differences in feasibility. In the near future, Phase I studies of new drugs should be started simultaneously also in Japan.

In conclusion, chemotherapy for colorectal cancer in clinical practice in Japan has caught up with Western countries while there has been no recent progress globally (12). Japanese institutions should participate in the development of new drugs from the early stages.

Table 1. Drug approval for colorectal cancer in Japan and in the USA

Agents	Approval	
	Japan	USA
5-FU/leucovorin	1999	1980s
Irinotecan	1994	1996
Capecitabine	2007	2001
Oxaliplatin	2005	2002
Cetuximab	2008	2004
Bevacizumab	2007	2004

5-FU, 5-fluorouracil.

GASTRIC CANCER

In spite of the several reports of Japanese large Phase III trials (13–15) for advanced gastric cancer which has established a standard chemotherapy in Japan, they have only a little impact worldwide because they contained S-1 which did not show a survival benefit over 5-FU combined with cisplatin (CDDP) in FLAGS trial (16). Therefore, the standard practice for advanced gastric cancer in Japan is a little bit different from that in Western countries, where capecitabine and/or oxaliplatin has been used widely. Although neither of these new drugs is approved in Japan, we should accept the control arm based on capecitabine in the global Phase III trials.

Although clinical trials for gastric cancer were conducted separately between Asian and Western countries in 1990s, the number of global studies focusing on gastric cancer which include both Asian and Western countries has been remarkably increasing. ToGA trial (17), which showed a survival benefit of trastuzumab added to combination chemotherapy with 5-FU (capecitabine or continuous infusion of 5-FU) and CDDP for the patients with Her-2-positive gastric cancer, is the first global study to which many Japanese patients with gastric cancer were enrolled. Because the frequency of Her-2-positive gastric cancer is reported to be around 20% among all gastric cancers (18), it was necessary to screen very large number of patients ($n = 3807$) for enrollment. Asian countries where the incidences of gastric cancer are high play an important role for this study, and actually, Korea and Japan were the first and the second contributors. As for bevacizumab, the enrollment to the Phase III study, comparing between combination chemotherapies with and without bevacizumab based on the 5-FU (capecitabine or continuous infusion of 5-FU) plus CDDP, has been completed, and the final results are planned to be published in 2010. Japanese institutions enrolled the most patients to this study all over the world. Now, there are three global Phase III trials on-going, in which cetuximab (19) for the first line, lapatinib (20) for the second line and everolimus (21) compared with best supportive care are investigated.

As for the early development of molecular target agents for gastric cancer, there are many Phase I and II trials both in monotherapy and in combination chemotherapy conducted in Japan such as nimotuzumab (22) (EGFR inhibitor), axitinib (23), cediranib (24), sunitinib (25), aflibercept (26) (angiogenesis inhibitor), heat shock protein inhibitor, c-met

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inhibitor, insulin-like growth factor inhibitor and so on (Table 2). Among them, the Phase I and II studies of everolimus were initiated in Japan, and now they have proceeded to the global Phase III trial.

In conclusion, Japan has become one of leaders contributing not only to global Phase III studies but also to the early development of molecular target agents for gastric cancer.

PANCREATIC CANCER

Since gemcitabine (GEM) showed a survival benefit over 5-FU alone (27), it has been a standard care for advanced pancreatic cancer worldwide. In Japan, GEM was approved only after a Phase I study of a very small number of patients (28). Although several Phase III trials investigating combination chemotherapies of GEM with other drugs, including molecular target agents (Table 3) such as bevacizumab (29) and cetuximab (30), were conducted, only erlotinib (tyrosine kinase inhibitor of EGFR) showed a modest survival benefit (31). It was after getting the result of this Phase III when a Phase II trial of combination chemotherapy with GEM and erlotinib was started in Japan. Furthermore, pneumonitis due to this combination chemotherapy is considered to be a big problem in Japan, although there are no differences in its incidence and severity (32).

Recently, Japan was the second contributor to enrollment of patients to the Phase III trial comparing GEM plus axitinib with GEM alone. Although axitinib could not unfortunately show a survival benefit (33), this trial was the first global Phase III trial that many Japanese patients with pancreatic cancer were enrolled. Although the potential of patient accrual from Japan was demonstrated in the axitinib study, Japanese institutions have been participating to none of the other global Phase III trials since then.

During the similar period to the global Phase III of erlotinib, a Phase II studies of S-1 (34) with and without GEM (35) showed very promising results, and a Phase III trial with two pair comparisons investigating the non-inferiority of S-1 and the superiority of S-1 plus GEM to GEM alone has been conducted in Japan. If the combination chemotherapy of S-1 plus GEM could show a survival benefit over GEM alone, S-1 plus GEM would be a new standard care for advanced pancreatic cancer at least in Japan. Then, however, because S-1 is not accepted worldwide, it is afraid that difference in the standard care might make it more difficult for Japanese institutions to participate in the future global trials based on the monotherapy with GEM.

In 2008, CONKO group reported the results of Phase III trial comparing between infusional 5-FU with and without oxaliplatin in the second-line setting after failure in GEM (36), resulting in a longer survival with oxaliplatin. And NCCN guideline adopted this therapy in the second-line setting after failure in GEM. In Japan, a Phase III study comparing S-1 plus oxaliplatin with S-1 is underway.

In conclusion, the introduction of new drugs to Japan has been delayed in spite of the fact that there has been no progress except for erlotinib. Although there is no difference in the incidence of pancreatic cancer between Japan and Western countries, worldwide collaboration is warranted for the development of new drugs for advanced pancreatic cancer.

Table 2. Clinical trials of molecular target agents for gastric cancer in Japan

Agent	Mechanism	Phase	Combination
Gefitinib	TKI of EGFR	Stop	—
Lapatinib	TKI of Her-1,2	III	Paclitaxel
Nimotuzumab	MoAb to EGFR	rII	Irinotecan
Cetuximab	MoAb to EGFR	III	Capecitabine + cisplatin
Trastuzumab	MoAb to Her-2	III	Capecitabine + cisplatin
Bevacizumab	MoAb to VEGF	III	Capecitabine + cisplatin
Aflibercept	VEGF trap	I	S-1
Sunitinib	Multiple TKI	I	S-1 + cisplatin
Cediranib	TKI of VEGFR	I	S-1/capecitabine + cisplatin
Everolimus	mTOR inhibitor	III	—
TSU-68	TKI of VEGFR	rII	S-1 + cisplatin
ARQ197	cMET inhibitor	II	—
Sorafenib	Raf inhibitor	I	S-1 + cisplatin

TKI, tyrosine kinase inhibitor; EGFR, epidermal growth factor receptor; MoAb, monoclonal antibody; VEGF, vascular endothelial growth factor; mTOR, mammalian target of rapamycin.

Table 3. Recent Phase III trials of molecular target agents for pancreatic cancer

Regimens	*n*	MST (months)	*P* value
GEM + marimastat	120	5.4	0.95
GEM	119	5.4	
GEM + tipifarnib	334	6.3	0.75
GEM	342	6.0	
GEM + erlotinib	285	6.2	0.04
GEM	284	5.9	
GEM + cetuximab	369	6.4	0.14
GEM	366	5.9	
GEM + bevacizumab	302	6.1	0.78
GEM	300	5.8	
GEM + erlotinib + bevacizumab	306	7.1	0.21
GEM + erlotinib	301	6.0	

MST, median survival time; GEM, gemcitabine.

LIVER CANCER

Treatment of liver cancer [hepatocellular carcinoma (HCC)] comprises multimodality such as resection (transplantation), ablation, trans-arterial chemo-embolization (TACE) and

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systemic chemotherapy, and treatment selection seems to be difficult and complicated according to the liver function, number, sites and size of tumors. Furthermore, it was considered that HCC is not sensitive to cytotoxic agents because of their low response rates and substantial toxicities due to liver dysfunction.

Recently, systemic chemotherapy for HCC has entered the new era, molecular target agents. In SHARP trial conducted in Western countries, sorafenib showed a survival benefit over best supportive care in the patients with HCC who were not indicated local therapies (37). It is well known that the etiology of HCC differ between Asian and Western countries. The Asian Phase III trial (38) was also conducted, showing similar results to those of SHARP trial. However, Japanese institutions did not participate in this Asian trial and conducted a clinical trial of sorafenib following TACE in Japan. Sorafenib was approved before the result of the Japanese trial was disclosed.

Nowadays, while a couple of global clinical trials investigating molecular target agents, such as sunitinib and RAD001, for HCC, Japanese institutions do not participated in them. In fact, Asian doctors outside Japan say that Japanese patients seem to be different in the etiology, hepatitis virus B and C, in anti-viral therapy and in basic liver function, it is extremely afraid that Japan might be isolated in the clinical trials for HCC.

In conclusion, the role of systemic chemotherapy with new molecular target agents is getting larger and larger for HCC. Although other Asian countries contribute to development of them, Japanese institutions should also participate in global trials for HCC.

ESOPHAGEAL CANCER

Multimodality treatment is generally performed for resectable esophageal cancer worldwide. Recent clinical trials have been focusing on treatment strategy such as comparison between neoadjuvant and adjuvant chemotherapy (39), between with and without neoadjuvant chemoradiation therapy (40), and between definitive and neoadjuvant chemoradiation therapy (41). In Japan, JCOG9907 trial (39) showed that neoadjuvant chemotherapy followed by surgery resulted in a 5-year survival rate about 60% higher than adjuvant chemotherapy, whereas definitive chemoradiation therapy whose 5-year survival rate was 37% (JCOG9906) (42). Thus, it is considered that chemoradiation therapy have some problems: (i) poor local control and (ii) late radiation toxicities. New drug development is a key to solve the problem of efficacy. However, there have been very few new drugs developed for esophageal cancer, and 5-FU and CDDP have been still key drugs for a long time.

The reluctance of pharmaceutical companies to new drug development for esophageal cancer is caused by a low incidence of the disease, complicated multimodality treatment and severe adverse events. Thus, investigator-initiated registration trial is underway, such as cetuximab in RTOG and S-1 in JCOG (Japan Clinical Oncology Group). It seems extremely hard for Japanese institutions to participate in the RTOG study because they have to satisfy both Japanese regulation (Good Clinical Practice) and RTOG requirement by themselves. Furthermore, the majority of esophageal cancers in Japan are squamous cell carcinoma histologically, whereas more than half in Western countries were adenocarcinoma. Therefore, it is afraid that the evidence established in Western countries may not be introduced to Japan directly.

In conclusion, new drugs including molecular target agents have been hardly developed worldwide as well as in Japan.

CONCLUSION

Recent development of molecular target agents has made a progress in the treatment of gastrointestinal malignancies, resulting in better clinical outcomes. Japanese institutions should participate in global trials to eliminate drug lag and has to play a specific role in worldwide drug development from the point of ICH. Furthermore, because these trials aim to the approval of new drugs based on the global standard, their optimal use based on the daily practice should also be explored in Japan.

Conflict of interest statement

None declared.

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ORIGINAL ARTICLE

Comparison of combination chemotherapy with irinotecan and cisplatin regimen administered every 2 or 4 weeks in pretreated patients with unresectable or recurrent gastric cancer: retrospective analysis

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Abstract
Background Efficacy and safety of irinotecan and cisplatin administration every 2 weeks (biweekly regimen) or 4 weeks (4-weekly regimen) in patients with pretreated unresectable or recurrent gastric cancer was retrospectively evaluated.
Methods Study patients comprised two cohorts: cohort 1, consisting of 31 patients received chemotherapy on a 4-weekly regimen; and cohort 2, consisting of 32 patients received chemotherapy on a biweekly regimen. In cohort 1, patients received irinotecan (70 mg/m^2) on days 1 and 15 and cisplatin (80 mg/m^2) on day 1 every 4 weeks; in cohort 2, patients received irinotecan (60 mg/m^2) on day 1 and cisplatin (30 mg/m^2) on day 1 every 2 weeks.
Results Response rates were for cohorts 1 and 2 were 26% (7/27) and 28% (7/25) in patients with measurable lesions, median progression-free survivals were 3.5 and 4.3 months, and median survival times after irinotecan and cisplatin initiation were 9.5 and 10.1 months, respectively. The incidence of grades 3 and 4 hematological toxicities in cohorts 1 and 2 were 74% and 44% for leukopenia, 81% and 53% for neutropenia, and 45% and 28% for anemia, respectively. Incidences of grades 3 and 4 nonhematological toxicities were 23% and 12% for nausea, 23% and 9% for vomiting, 19% and 12% for anorexia, and 6% and 6% for febrile neutropenia, respectively.
Conclusion Irinotecan plus cisplatin chemotherapy administered on a biweekly regimen was comparable in efficacy to a 4-weekly regimen and might be more feasible than the 4-weekly regimen.

Keywords Irinotecan · Cisplatin · Pretreated · Gastric cancer

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Introduction

Gastric cancer is a major cause of death from cancer worldwide and remains the second most common cause in Japan of cancer-related death. For patients with unresectable or recurrent gastric cancer, the main therapeutic option is palliative chemotherapy. Chemotherapy treatment with 5-fluorouracil (5-FU) has been shown to have a survival benefit over best supportive care (BSC) [1–3] and is widely used. Recently, two pivotal phase III studies conducted in Japan were reported. The first, the Japan Clinical Oncology Group (JCOG) 9912 trial revealed no inferiority of S-1 alone to 5-FU alone and failed to demonstrate superiority of irinotecan (CPT-11) plus cisplatin (CDDP) to 5-FU alone in terms of overall survival (OS) [4]. The study concluded that S-1 alone could replace continuous 5-FU infusion for treating advanced gastric cancer. The second study was the Randomized phase III study of S-1 alone versus S-1 + cisplatin in the treatment for advanced gastric cancer (SPIRITS) trial, which showed superiority of S-1 plus CDDP to S-1 alone in terms of overall survival [5]. From these results, S-1 plus CDDP has been recognized in Japan as the standard first-line chemotherapy for unresectable and recurrent gastric cancer. In an adjuvant setting, the Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer (ACTS-GC) trial reported that adjuvant therapy

with S-1 showed a better survival outcome than surgery alone in patients with stage II or III gastric cancer who had undergone gastrectomy with extended (D2) lymph-node dissection [6]. Based on the results of that study, S-1 alone is recognized in Japan as the standard adjuvant chemotherapy for stage II or III gastric cancer. These studies indicate that S-1 is a key drug for the initial treatment of gastric cancer. However, although a considerable number of patients experience disease progression or recurrence during or after initial therapy, a standard chemotherapy regimen after failure in initial therapy containing S-1 has not yet been established.

CPT-11 is a semisynthetic compound derived from the plant alkaloid camptothecin, which is extracted from *Camptotheca acuminate*. This compound inhibits DNA topoisomerase I [7]. Recently, Thuss-Patience et al. [8] reported a phase III study comparing CPT-11 to BSC as a second-line therapy for advanced gastric cancer. Although the trial was closed prematurely because of poor accrual, this study suggested a survival benefit of second-line chemotherapy by CPT-11 alone [OS 123 vs. 73 days, $p = 0.023$; hazard ratio (HR) 0.48; 95% confidence interval (CI) 0.25–0.92]. Thus, CPT-11 can be considered an option for second-line therapy. In our hospital, CPT-11 is preferred in second-line settings unless the patient has a contraindication for CPT-11 therapy, such as intestinal obstruction due to peritoneal dissemination. In particular, combination chemotherapy with CPT-11 plus CDDP is frequently used after failure of S-1 monotherapy.

Combination chemotherapy with CPT-11 and CDDP administered every 4 weeks (4-weekly regimen) was reported by Boku et al. [9]. CPT-11 (70 mg/m^2) was administered on days 1 and 15 and CDDP (80 mg/m^2) on day 1 by intravenous infusion every 4 weeks. The response rate (RR) when administered as a first-line therapy for advanced gastric cancer was 59%, and the median survival time (MST) was 12.3 months. Additionally, Ueda et al. [10] reported a RR of 28%, a median time to progression of 3.5 months, and a MST of 9.4 months when administered to patients with pretreated gastric cancer. Subsequently, a regimen comprised of CPT-11 (60 mg/m^2) on day 1 and CDDP (30 mg/m^2) on day 1 every 2 weeks (biweekly regimen) was reported by Koizumi et al. [11]. The response for this regimen in second-line therapy for advanced gastric cancer was 20%, and MST was 9.1 months.

As for toxicities, the biweekly regimen seems to be less toxic than the 4-weekly regimen. After Koizumi et al.'s report, biweekly regimen was adopted at our institution in 2007 (with the approval of the clinical practice committee of Shizuoka Cancer Center) for treating patients with pretreated advanced gastric cancer. However, these two regimens, every 2 or 4 weeks, have not been compared. The objective of this retrospective study was to historically compare the efficacy and safety between CPT-11 plus CDDP administered on a biweekly and 4-weekly regimen in patients with pretreated advanced gastric cancer.

Patients and methods

Patients

Sixty-three patients with unresectable or recurrent gastric cancer were treated with CPT-11 plus CDDP administered on either a biweekly or 4-weekly regimen between September 2002 and July 2009. Thirty-one patients were treated on the 4-weekly regimen (cohort 1), which was initiated before May 2007; 32 patients were treated on the biweekly regimen (cohort 2) between February 2007 and July 2009. Selection criteria for this retrospective analysis were: (1) histological diagnosis of adenocarcinoma, (2) history of having undergone one or two prior chemotherapy regimens that did not contain either CPT-11 or CDDP, (3) age $\leq$75 years, (4) Eastern Cooperative Oncology Group Performance Status (ECOG PS) $\leq$2, (5) preserved organ functions [bone marrow: white blood cell (WBC) count $\geq$3,000/μl and platelet count $\geq$10,000/μl; hepatic function: serum bilirubin level $\leq$1.5 mg/dl, serum transaminase level $\leq$2.5$\times$ the upper limit of the normal range; renal function: serum creatinine level $\leq$1.5 mg/dl, and blood urea nitrogen level $\leq$25 mg/dl), (6) no other serious diseases, (7) no other active malignancy, and (8) provision of written informed consent for treatment.

Treatment methods

In cohort 1, CPT-11 (70 mg/m^2) was administered by intravenous infusion for 90 min on day 1 followed by a 2-h interval and then intravenous infusion of CDDP (80 mg/m^2) for 120 min. The same dose of CPT-11 was administered on day 15. This treatment was repeated every 4 weeks. In cohort 2, CPT-11 (60 mg/m^2) was administered by intravenous infusion for 90 min, followed by CDDP (30 mg/m^2) for 120 min on day 1. This treatment was repeated every 2 weeks. Treatments in both cohorts were continued until disease progression, patient's refusal, or unacceptable toxicity. Treatments were given after confirming a leukocyte count $\geq$3,000/μl, a platelet count $\geq$100,000/μl, grade 0 diarrhea, and absence of infection on day 1. In cohort 1, if the patient had a leukocyte count $<$3,000, a platelet count $<$100,000, diarrhea of grade 1 or higher, or an infection on day 15, then administration of CPT-11 on day 15 was postponed until the patient had recovered from these adverse reactions. If these adverse reactions persisted beyond day 22, then the CPT-11 dosage scheduled on day 15 was skipped. If a hematological

adverse reaction of grade 4 or a nonhematological adverse reaction of grade 3 or higher occurred, then administration of CPT-11 on day 15 was skipped, and the subsequent dose of CPT-11 was reduced to 60 mg/m^2. In cohort 2, if the patient had a leukocyte count <3,000, a platelet count <100,000, diarrhea of grade 1 or higher, or an infection on day 1, administration of CPT-11 and CDDP was postponed until the patient had recovered from these adverse reactions. If these adverse reactions continued beyond day 22 or if a hematological adverse reaction of grade 4 or a nonhematological adverse reaction of grade 3 or higher occurred, then the subsequent dose of CPT-11 was reduced to 50 mg/m^2.

Evaluation

Response was assessed using computed tomography (CT) every 1 or 2 months, and the results were evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST v.1.0) [12]. Toxicities were evaluated according to the Common Toxicity Criteria for Adverse Events version 3.0 (CTCAE 3.0). Progression-free survival (PFS) was calculated using the Kaplan–Meier method as the period from the date of treatment initiation (CPT-11 plus CDDP) until the first observation of disease progression or death from any cause. Similarly, overall survival was calculated as the period from the date of treatment initiation until the date of death or the last confirmed date of survival (censored).

Results

Patient characteristics

Thirty-one patients in cohort 1 and 32 patients in cohort 2 received CPT-11 plus CDDP administered on a 4-weekly or biweekly regimen, respectively. Patient characteristics are summarized in Table 1. Whereas most patients had a good PS, the proportion of patients with PS 2 was larger in cohort 2 than in cohort 1. All previous therapies are summarized in Table 2. The proportion of patients receiving CPT-11 plus CDDP as a third-line treatment was larger in cohort 2 than in cohort 1.

Table 1 Patient characteristics

	Four-weekly regimen cohort 1	Biweekly regimen cohort 2
No. of patients	31	32
Age		
Median (range)	58 (37–75)	66 (40–76)
Sex		
Male/female	25/6	21/11
ECOG performance status		
0/1/2	15/14/2	14/11/7
Macroscopic type		
1,2/3,4/unknown	6/18/7	8/19/5
Histological type		
Intestinal/diffuse/unknown	16/12/3	13/15/4
No. of metastatic sites		
0,1/2/≥3	15/12/4	14/12/6
Metastatic site		
Lymph node	22	17
Peritoneal dissemination	13	16
Liver	8	12
Lung	4	3
Bone	0	2

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Table 2 Previous chemotherapeutic regimen

	Four-weekly regimen cohort 1 No. of patients	Biweekly regimen cohort 2 No. of patients
No. of prior regimens		
1/2	26/5	18/14
Prior therapy		
Oral fluoropyrimidine	18	27
Paclitaxel	3	10
5-FU bolus (MTX + 5-FU)	5	5
5-FU CIV	10	2
Others	0	2

5-FU 5-fluorouracil, *MTX* methotrexate, *CIV* continuous intravenous infusion

Response and survival

Responses are summarized in Table 3. Twenty-seven patients in cohort 1 and 25 in cohort 2 had measurable lesions, respectively. Seven patients (26%) in cohort 1 and 7 (28%) in cohort 2 achieved a partial response (PR). Ten patients (37%) in cohort 1 and 9 (36%) in cohort 2 showed stable disease (SD). Thus, the RR in cohorts 1 and 2 were 26% and 28%, and disease control rates were 63% and 64%, respectively. At the time of analysis, treatment was continued in one patient in cohort 2. The median PFS for cohorts 1 and 2 were 3.5 and 4.3 months, respectively (Figs. 1, 2), and MSTs were 9.5 and 10.1 months, respectively (Figs. 3, 4).

Toxicity

Grade 3 and 4 toxicities observed in each cohort are summarized in Table 4. Incidence in cohorts 1 and 2 were