のガイドラインは欧米よりかなりintensiveであると考えられていたが，欧米も最近のメタアナリシスの結果を踏まえてintensiveなものにかわりつつある．ASCO2000年版やESMO2003年版のガイドラインでは，胸部X線検査やCT検査などの定期的な画像検査は推奨されていなかったが，ASCO2005年版やESMO2007年版では再発高リスク症例に対し，術後3年間は年1回のCT検査が推奨されるようになった．本邦の『大腸癌治療ガイドライン』においても2005年版は肺転移に関しては胸部X線検査を推奨し，疑診例には胸部CTを，あるいは肝転移に関しても腹部超音波検査を推奨し，疑診例に腹部CTまたは腹部MRIを行うと記載してあったが，2009年版以降はこれらについても胸部・腹部CTを推奨するように変化してきている．本邦と欧米のガイドラインにおけるサーベイランスの違いは，欧米では以前よりintensiveに変わったとはいえ，術後3年のみ1年に1回のCT検査と本邦では基本術後5年間半年に1回のCT検査とでは，検査方法は一緒であるが，検査間隔が大きく異なっている．また本邦のガイドラインではstageによって，あるいは結腸と直腸で分けている点が大きく異なる．

Ⅶ 本邦における標準的サーベイランス（大腸癌治療ガイドライン医師用2010年版を基に）

1 サーベイランスの対象症例

Sage 0（pM癌）は，切除断端に癌が陰性であれば，サーベイランスは不要である．ただし，切除断端の評価が困難な場合は，半年～1年後に大腸内視鏡検査を行い，局所再発の有無を調べる．

Stage Ⅰ以上では進行度と再発臓器の特徴に合わせたサーベイランスを行う．前述のごとくstage Ⅰ，Ⅱ症例は術後再発率がStage Ⅲより低いため，若干サーベイランスの頻度を少なくしている（表3，5）．

2 サーベイランスの期間

前述の「大腸癌術後のフォローアップに関する研究」の解析結果によると，術後5年以降の再発は5,230例中わずか33例（0.63%）であった．この結果から，医療経済的な面も考慮し，サーベイランス期間は術後5年でよいとされるが，肺に関しては術後5年経過後も再発をきたすおそれがあるため注意が必要である（表2，4）．

3 サーベイランスの検査法と間隔（表3，5）

1）問診・診察

問診によって血便や腸閉塞症状の出現，視触診によってリンパ節腫大や腹壁腫瘤，腹水を確認することで再発の診断に繋がる．特に直腸指診は前方切除後の吻合部再発や，ダグラス窩に存在する腹膜播種病巣の診断に有用である．『大腸癌治療ガイドライン医師用2010年版』では術後3年までは3カ月ごと，それ以降5年まで6カ月ごとの問診・診察が推奨されている．

2）腫瘍マーカー

血中癌胎児性抗原（carcinoembryonic antigen：CEA）のモニタリングが治癒切除可能な再発病変の早期発見に有用であることが示されている．CEAの定期的な測定は，すべてのガイドラインにおいて共通して推奨されているサーベイランスの検査法である．CA19-9値測定の意義は臨床試験では明らかにされていないが，本邦ではCEA値とともに推奨されているサーベイランス検査法である．術後3年までは3カ月ごと，それ以降5年まで6カ月ごとが推奨される．

3）胸部X線検査

小さな肺転移巣は胸部X線検査では検出が難しい．術後サーベイランスに胸部X線検査を行うことに関してはcontroversialである．『大腸癌治療ガイドライン2005年版』では肺再発検出検査法として胸部単純X線検査と胸部CTが併記されていたが，『大腸癌治療ガイドライン2009年版』からは胸部CT検査が推奨されている．

4）腹部超音波検査

肝臓は初発再発部位として最も頻度が高く，外科治療が有効な臓器である．ESMOガイドラインでは術後3年間を6カ月ごと，以後は1年ごと術後5年まで腹部超音波検査が推奨されている．本邦においても腹部超音波検査は肝転移のスクリーニング検査として頻用されており，『大腸癌治療ガイドライン2005年版』では肝再発のサーベイランス手段として重視

されていたが，本検査は検出感度が検者の技量によって異なり，また腸管ガスの影響を受けやすいなどの理由により，『大腸癌治療ガイドライン2009年版』以降では超音波検査よりもCT検査が推奨されている．また，腹腔内リンパ節再発や腹膜播種巣の客観的評価にもCT検査は有用と考えられる．

5）CT検査（胸部，腹部，骨盤）

前述したように，『大腸癌治療ガイドライン2009年版』以降では肺再発，肝再発，局所再発などのサーベイランス検査法としてCT検査を，基本術後5年間6カ月に1回施行することが推奨されている．ASCO，ESMO，NCCNの各ガイドラインではCT検査の適応は再発高リスク群のみを対象とし，術後3年間1年に1回行うことを推奨している．

6）大腸内視鏡検査

術後初回の内視鏡検査時期に関し，NCCNとESMOのガイドラインでは術後1年目，ASCOガイドラインでは術後3年目としている．『大腸癌治療ガイドライン医師用2010年版』で推奨されている術後初回の大腸内視鏡検査は術後1年目であるが，術前に腫瘍口側の検索が不十分であった場合は術後6カ月以内に行い，残存大腸の精査をすることを推奨している．大腸癌の術後に本検査を行う目的は結腸癌では異時性大腸腫瘍の検索であるが，直腸癌では吻合部再発の検索も重要な目的である．NCCNガイドラインでは低位前方切除後は術後5年間，6カ月ごとの直腸鏡検査を推奨している．『大腸癌治療ガイドライン医師用2010年版』で直腸癌術後には術後3年まで年に1回の検査が推奨されている．

7）MRI検査

定期的に行うサーベイランスの検査法としてMRI検査はいずれのガイドラインにおいても推奨されていないが，肝転移や骨盤内局所再発の確定診断に有用であることから，MRI検査はCT検査などで再発が疑われた症例の精査手段として位置づけられている．

8）PET/CT検査

PET/CT検査においても定期的に行うサーベイランスの検査法としては推奨されていない．しかし再発疑診断症例での診断法として使用されたり，腫瘍マーカーが高値となり，再発が疑われるが，CT検査で明らかな再発巣を指摘されない場合のスクリーニングとして行うことがある．

Ⅷ おわりに

わが国で推奨される比較的intensiveなサーベイランス方法が治療成績に寄与するのかは今後検証すべき重要な課題であり，医療経済の視点から必要最小限の検査で効率よく大腸癌術後再発を発見できることが理想である．現状では術後サーベイランスが再発早期発見，再発巣切除率向上，そして予後改善に寄与することを認識し，原発巣の部位や進行度による再発様式の特徴を考慮した定期的なサーベイランスを計画することが期待される．

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外来癌化学療法

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外来抗癌療法治療の実際

大腸癌に対するチーム医療で行う外来化学療法
―術後補助化学療法を中心に―

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はじめに

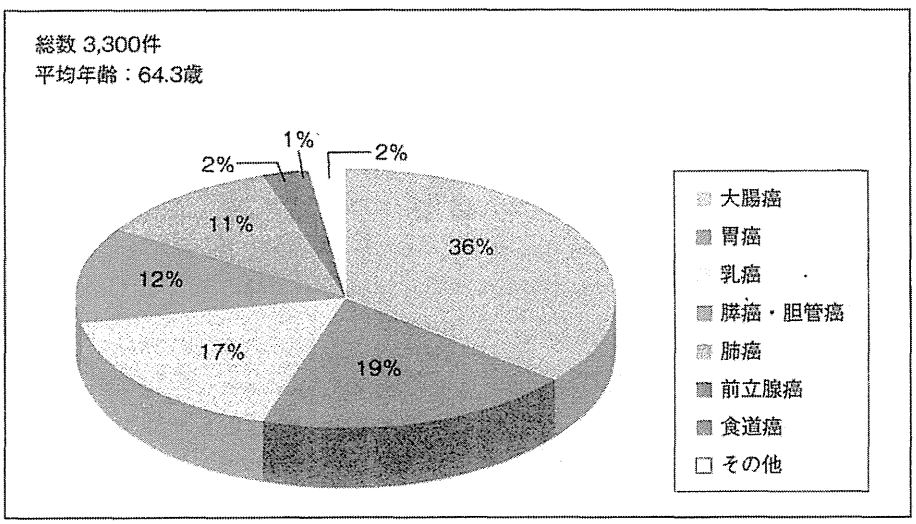
大腸癌化学療法は切除不能例に対する化学療法の発展に伴い，術後補助化学療法においても近年大きく進歩を遂げている．大腸癌の標準治療は外科的切除であるが，進行した癌に対しては，治癒(無再発)を目指して術後補助化学療法が施行される．大腸癌研究会によると結腸癌と直腸癌をあわせた大腸癌のステージ別5年生存率ではStage0：94.3%，StageⅠ：90.6%，StageⅡ：81.2%，StageⅢa：71.4%，StageⅢb：56.0%，StageⅣ：13.2%と報告され[1]，術後補助療法の適応となるStageⅢのなかでもStageⅢbは特に再発のリスクが高いと考えられる．当初切除不能例に使用されていたFOLFOX療法やXELOX療法が術後補助化学療法として使用可能となり，どのような症例に，これらの治療を行うかがトピックスである．

本稿では術後補助療法の変遷として最近のエビデンスをまとめ，近年，使用頻度が増加しているXELOX療法について症例を提示し，有害事象対策を中心としたチーム医療の実際を具体的に示す．また，当院における外来化学療法における工夫として，薬剤師による血液検査実施後から医師による診察までの間における患者面談(以下，診察前面談)を実施しており，これについても紹介する．

当院の外来化学療法室

当院は614床を有する大学附属病院で，岐阜県のがん診

図1　岐阜大学医学部附属病院外来化学療法室(2011年度)



療連携拠点病院である．外来化学療法室は2005年に開設され，13床(ベッド8台，リクライニングチェア5台)で稼働している．医師：2名(専門外来＋化学療法室担当医)，薬剤師：3名(がん専門薬剤師1名)，看護師：8名(がん化学療法認定看護師1名)で構成されている．2013年5月には外来化学療法棟が建設され31床に増床する予定である．2011年度は総数3,300件が外来化学療法室で化学療法を施行された．そのうち，大腸癌に関する化学療法は36%と最も多く，切除不能大腸癌症例のみならず，術後補助化学療法症例の化学療法室使用も増加してきている(図1)．

よって大腸癌の術後補助化学療法について述べる．

大腸癌ガイドラインに示される術後補助化学療法の標準治療とその変遷

日本の大腸癌治療ガイドライン[1]では，図2に示すように①5-フルオロウラシル(5-FU)＋ホリナート(LV)療法，②テガフール・ウラシル(UFT)＋LV療法，③カペシタビン(CAP)療法，④FOLFOX4療法またはmFOLFOX6療法が，そして最近では大腸癌治療ガイドラインweb版にて⑤XELOX療法も術後補助化学療法として推奨されている．また，④に関しては外来で化学療法を行う場合はmFOLFOX6療法が汎用されている．大腸癌の術後補助化学療法の推移を臨床試験が行われたエビデンスに基づいて示すと図3となる[2]．

大腸癌の術後補助化学療法の標準治療として，1990年代に5-FU＋LV療法が確立し，その後，欧米では，NSABP-C-06試験やX-ACT試験の結果から経口FU系抗癌薬であるUFT＋LV療法やCAP療法が静注5-FU＋LV療法と同等であることが示された．国内においても5-FU＋LV療法 vs UFT＋LV療法とのランダム化比較試験(JCOG 0205試験)が施行され，最終結果がASCO2012にて発表さ

図2 大腸癌術後補助化学療法

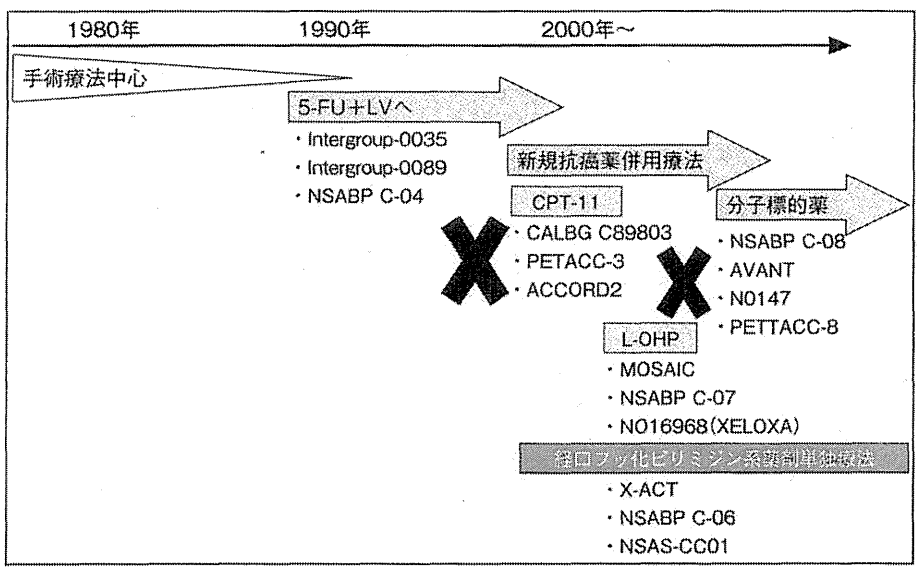
推奨される療法
- ①5-FU+LV療法
- ②UFT+LV療法
- ③CAP療法
- ④FOLFOX4またはmFOLFOX6療法
- ⑤CapeOX(XELOX)療法*

推奨される投与期間
- 6ヵ月を原則とする

＊：大腸癌治療ガイドラインWeb版(http://www.jsccr.jp/guideline/2010/index_guide.html)に記載

(文献1より引用)

図3 大腸癌に対する術後補助化学療法の変遷



(文献2より改変引用)

れており，UFT＋LV療法は5-FU＋LV療法と同等であることが報告された．

また，欧米ではMOSAIC試験やNSABPC-07試験の結果によりオキサリプラチン(L-OHP)＋5-FU＋LV併用療法の有効性が示され，StageⅢ結腸癌に対する術後補助化学療法としてFOLFOX療法が推奨されている．さらに，近年ではNO16968/XELOXA試験によりL-OHPベースレジメンであるXELOX療法が5-FU＋LV療法より優越性を示したため，CapeOX（XELOX)療法がガイドラインで推奨されるようになっている．

一方，StageⅢ大腸癌に対し術後補助療法としてLV5FU2療法とイリノテカン(CPT-11)を追加したFOLFIRI療法を比較した第Ⅲ相ランダム化比較試験：PETACC-3の結果はnegativeであり，他のCPT-11ベースレジメンの臨床試験であるCALBG C89803試験やACCORD2 試験もnegativeな結果であったため，大腸癌に対する術後補助療法としてCPT-11ベースレジメンは有用ではないとされた．

さらに，切除不能大腸癌に有効であることが示されている分子標的薬であるベバシズマブ(BV)やセツキシマブを併用した臨床試験も行われ，NSABP C-08試験，AVANT試験は術後補助療法としてL-OHPベースレジメン(FOLFOX療法/XELOX療法)に抗VEGF抗体であるBVの上乗せ効果をみた臨床試験であるが，いずれの試験もBVの上乗せ効果は認めなかった．また，抗EGFR抗体であるセツキシマブに関してはN0147試験，PETACC-8試験でFOLFOX療法に対しセツキシマブの上乗せ効果を検討したが，どちらの臨床試験もnegativeな試験であった．よって，術後補助療法としてこれらの分子標的薬の上乗せ効果は認めず，有用ではないとされている．

これらの臨床試験の結果より欧米のガイドラインが作成されており，日本のガイドラインもこれらの欧米のエビデンスにより構成されている．

このなかでキーとなる代表的な臨床試験についていくつか紹介する．

1．X-ACT試験[3]

X-ACT試験はStageⅢ結腸癌を対象としたCAP療法と5-FU＋LV療法とのランダム化第Ⅲ相比較試験として行われた．無再発生存期間，および全生存期間(overall survival：OS)で同等以上とその有効性が示された．また，その後5年生存率の結果が報告され，CAP療法で71.4％，5-FU＋LVで68.4％であった．有害事象では手足症候群(hand-foot syndrome：HFS)の発生割合がCAP療法群で多いのに対し，他のGrade3, 4の有害事象は少なかった．

2．JCOG0205試験

JCOG0205試験はStageⅢの大腸癌を対象とした5-FU＋LV療法とUFT＋LV療法とのランダム化第Ⅲ相比較試験である．その結果が，ASCO2012でUFT＋LV療法の5-FU＋LV療法に対する非劣性が証明されたと報告された．全体の3年無病生存期間(disease-free survival：DFS)は78.6％(UFT＋LV群が77.8％，5-FU＋LV群が79.3％)で，5年全生存期間は全体で87.9％（UFT＋LV群が87.5％，5-FU＋LV群が88.4％)であった．

3．MOSAIC試験[4]

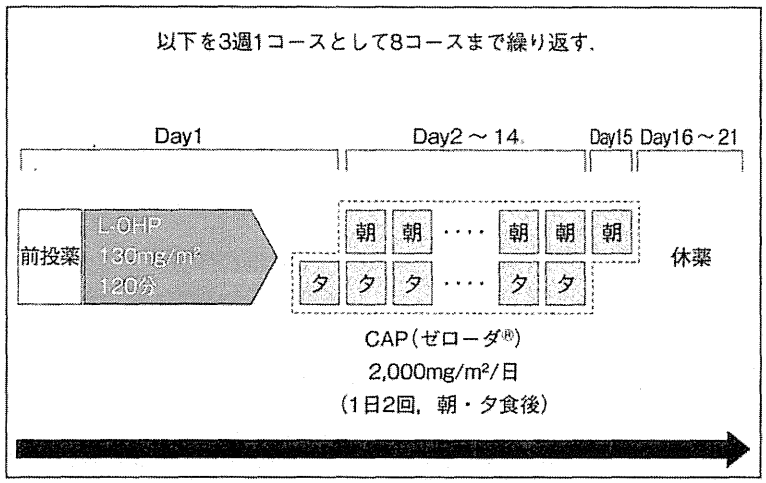
MOSAIC試験はStageⅡ/Ⅲ結腸癌に対する補助療法としてFOLFOX4療法とLV5FU2療法の第Ⅲ相ランダム化比較試験である．5年の時点でのDFS率はFOLFOX4療法：73.3％，LV5FU2療法：67.4％(p＝0.003)，また，6年OSはそれぞれ78.5％，76.0％(p＝0.046)とFOLFOX4療法はこれまでの標準治療とされたLV5FU2療法より有意に優れていた．特にStageⅢ症例の6年OSはそれぞれ72.9％，68.7％と有意な改善を認めたが，StageⅡ症例では有意でなかった．

4．NO16968/XELOXA試験[5][6]

NO16968/XELOXA試験は，StageⅢ結腸癌における術後補助化学療法としてXELOX療法と急速静注5-FU＋LV療法の第Ⅲ相比較試験である．ESMO2009でDFSに関して3年DFS率はXELOX療法と急速静注5-FU＋LV療法でそれぞれ70.9％，66.5％，5年DFS率はそれぞれ66.1％，59.8％であり，XELOX療法群で有意に改善した(p＝0.0045)と報告された．

FOLFOX療法/ XELOX療法は5-FU＋LV療法よりDFS，OSで有意に優れている．しかしながらL-OHPによる残存する末梢神経障害の報告がある．よって，日本でのエビデンス構築が必要と考えられ，日本においてJFMC41，JFMC47試験にてL-OHPベースレジメンによる

図4 CapeOX(XELOX療法)-治療スケジュール-



第Ⅲ相臨床試験が行われている. MOSAIC試験とNO16968/XELOXA試験の結果より, XELOX療法はFOLFOX療法と比べ, 下痢やHFSはやや高率であったが, 好中球減少は軽度であり, 安全性は優れていた. さらに, XELOX療法はFOLFOX療法でのCVポート留置や5-FUの2日間持続静注が不要であり, 患者の負担軽減や, 医療従事者にとっても労力の軽減が可能となる. 今後XELOX療法はStageⅢ結腸癌の術後補助療法として有用な治療法となることが期待される.

当科での現在の基本的な治療方針

図2で示すように日本の治療ガイドラインで推奨される5個のレジメンが使用可能である. まず, ①の急速静注5-FU+LV療法の治療効果は②UFT+LV療法や③CAP療法と同等で, ②③は経口薬で利便性が高いことからQOLを考慮し, 急速静注5-FU+LV療法を最近用いることはほとんどない. ④⑤のL-OHPベースのFOLFOX療法やXELOX療法を, ②③の経口薬であるUFT+LV療法やCAP療法と比較すると, 効果で優る可能性があるが, 有害事象も強いと考えている. よって再発高リスクと判断し, 全身状態(performance status：PS)がよく, 若年者の場合は当科では積極的にFOLFOX療法やXELOX療法を用い, 1人でも多くの患者が治癒できることを期待している. 日本での臨床試験であるJCOG0205の結果より, 5-FU+LV療法とUFT+LV療法の3年DFSはそれぞれ79.3%, 77.8%, 5年OSはそれぞれ88.4%, 87.5%であった. 全体の3年DFS, 5年OSはそれぞれ78.6%, 87.9%と欧米のMOSAIC試験やXELOXA試験と比較するとL-OHPを使用しなくても同等以上の成績を示しているから, StageⅢ全症例にL-OHPを使用するかどうかは疑問ではある. しかしながらTNM分類を用いると, 日本の成績でも3年DFSは5-FU+LV療法, UFT+LV療法全体でStageⅢa, StageⅢb, StageⅢcはそれぞれ91.6%, 79.7%, 62.6%であったことより, StageⅢb, StageⅢcは少なくともL-OHPを使用してもよいのではと考えている. しかし, FOLFOX療法・XELOX療法による蓄積性末梢神経毒性のデメリットや医療コストも考慮する必要がある. また, 今後実臨床ではFOLFOX療法から利便性を重視したXELOX療法が普及すると予測される. XELOX療法は図4で示すように, 経口抗癌薬をベースにするため, FOLFOX療法と比較し, 点滴時間の短縮とCVポートやインフュージョンポンプが不要となる. また, 3週が1コースとなるため外来通院回数も少ないという利点がある. これらより身体的自由度が増し, 患者の利便性は向上することから当院においても大腸癌術後補助化学療法としてXELOX療法施行例が増加している.

ここで大腸癌術後補助化学療法としてXELOX療法例を呈示する.

チーム医療としてXELOX療法の場合の医師・薬剤師・看護師の役割を具体的に示すと図5となり, 当院では多職

図5 チーム医療としての医師・薬剤師・看護師の役割

術後補助療法としてXELOX療法の場合

■外来化学療法室における医師の役割
▶治療方針の決定
▶チーム内の統率

■外来化学療法室における薬剤師による服薬指導
～指導の内容～
▶点滴・内服薬の内容・スケジュール
▶有害事象の説明と対策
・制吐対策
・L-OHPによる末梢神経障害対策
・HFS対策
・下痢・口内炎対策

■外来化学療法室における看護師による有害事象対策と精神的ケア
▶HFSの評価や保湿剤などの指導
▶コンプライアンスの確認

種が各専門領域を尊重しながらいかに患者にかかわっているか説明する.

Case study

患者：50代男性，PS0
診断・術式：S状結腸癌の診断にてS状結腸切除術＋D3リンパ節郭清施行
最終診断：S状結腸癌　SE，N2，P0，H0，M0 tub2，ly1，v3 StageⅢb

StageⅢbであったため大腸癌に対する術後化学療法を施行することとした.

化学療法の選択基準：大腸癌治療ガイドラインで推奨されているレジメンを呈示．静脈侵襲高度で漿膜浸潤を認めるStageⅢb大腸癌で再発リスクは高いと判断した．以上より，UFT＋LV療法やCAP療法の経口薬とL-OHPベースレジメンの治療説明を行った．有効性と有害事象，治療スケジュールについて医師より説明した.

PS0で，元気な若年男性であり，相談のうえ，再発リスクを心配され，L-OHPベースレジメンを選択された．次にFOLFOX療法か，XELOX療法で選択することとした．利便性を考慮し，3週間に一度で，ポンプフリーでCVポート留置が基本的に必要ないXELOX療法を選択された．ここで示した治療方針の決定は医師により行われる(図4).

XELOX療法の投与方法は，図4で示すように，術後補助療法ではL-OHPを2時間で点滴投与し，CAP(商品名：ゼローダ®)を1日2回2週間内服し1週間休薬する．これを1コースとし合計8コースを約6ヵ月間で施行することを説明する．L-OHP投与前に制吐対策として，5-HT_3受容体拮抗薬とデキサメタゾン(DEX)注射薬9.9mgを同時に投与することも医師・薬剤師から説明する．これら前投薬に関し制吐対策が不十分であるときは，アプレピタント(イメンド®)を追加したり，パロノセトロン(アロキシ®)に変更したりする．遅発性嘔気・嘔吐に対してはDEXの内服や他の制吐補助薬を使用する．点滴・内服薬の内容・スケジュールに関する服薬指導は主に薬剤師の仕事であり，詳細に患者に説明する(図4).
有害事象の説明：
①CAPによるHFSとL-OHPによる末梢神経障害，両者によって起こる消化器症状への注意が必要である.
②特にHFSは保湿剤(ヒルドイド®やウレパール®)やステロイド軟膏によるセルフケアができるかどうかが治療継続の可否に重要.
③HFSでGrade2の有害事象，つまり痛みが出現したら服薬中止.
④3週間と比較的長い通院期間となるため，HFSが悪化した場合は気軽に病院に連絡できるよう説明する.

上記の有害事象の説明と対策に関しても主に薬剤師の役割で，必要な処方薬に関しては医師と相談し，薬剤師の処方提案に基づいて医師が処方する(図4).

初回投与

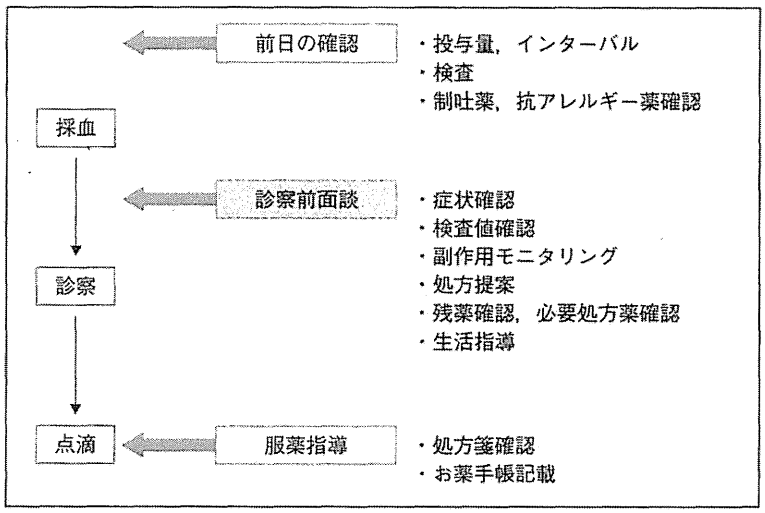
L-OHP　130mg/m^2(Day1)
CAP　2,000mg/m^2/Day×14日(Day1夕～15朝)

前投薬はグラニセトロン注射薬(カイトリル®)3mg，DEX注射薬(デカドロン®)9.9mg(Day1)点滴とし，DEX内服薬(デカドロン®)4mg分2をDay2～3に内服.

1コース目：Day8にGrade3の食欲不振・悪心，Grade2味覚異常，Grade1下痢，Grade1嘔吐を認めた．薬剤師と相談し，オランザピン5mg投与にて悪心は著明に改善．末梢神経障害Grade1冷感刺激時のみ.

2コース目：前コースにてGrade3の食欲不振・悪心を認

図6 診察前面談の流れ



めたが，薬剤師・医師および患者と相談し，制吐対策をしっかりと行うこととし，減量せず治療継続．前投薬にアプレピタント125mg内服を追加．Day2～3はDEX4mg分2，アプレピタント80mgとし，オランザピン5mgを7日間投与とした．その後，食欲不振，悪心，味覚異常の有害事象は消失．Day2～7にGrade2の下痢を認めたが，ミヤBM®3g分3で軽快．末梢神経障害Grade1．

3コース目：Grade2の好中球減少で2週間治療延期し開始．血管痛を認め，温罨法で対処．末梢神経障害Grade1，Day2～14までGrade1の下痢(4～5回/日)あり．

4コース目：血管痛で温罨法施行．Day3～14までGrade1の下痢あり．末梢神経障害Grade1．

5コース目：血管痛で温罨法施行．Day3～14までGrade1の下痢あり．末梢神経障害Grade1．

6コース目：ロペラミド2Cp分2処方とし，下痢の回数は減少．末梢神経障害Grade1．

7コース目：本コースから血管痛に対し温罨法とDEXを混注した．末梢神経障害Grade1．

8コース目：足のしびれが持続し，末梢神経障害Grade2．

この8コースを施行している間，看護師は外来化学療法室で精神的ケアを行い，CAPによるHFSの評価・対策の指導を行っている．この症例ではHFSの有害事象を認めなかったが，通常HFSの有害事象のGrading評価や保湿剤などの指導を行い，内服薬であるためコンプライアンスはよいかどうか，あるいは減量・休薬があるときはそれらの指導も行っている．この症例において血管痛対策は看護師が中心となり施行された(図4)．

現在，術後1年経過し，明らかな再発なし．末梢神経障害の残存なし．

外来化学療法室を利用する症例が増加してきている現在，外来化学療法をさらに効率よく機能させるために，当院では新たな試みとして薬剤師の診察前面談を2008年4月より始めた．上記症例も各コース有害事象のGradingはまずは薬剤師の診察前面談で行われ，医師の確認で最終Gradingが確定され，有害事象に対する処方提案もこの薬剤師の診察前面談で行われている．これについて解説する．

薬剤師の診察前面談(図6)

患者が外来化学療法を施行するにあたりまず採血を行う．検査データがそろい医師の診察が行われるまでには約1時間の待ち時間があるため，その間に薬剤師が面談を行う．面談では患者日誌や患者の訴えから情報を収集し，診察による症状の把握と有害事象の確認が行われる．対策が必要と考えられた場合には，処方の提案が行われる．その他には残薬の確認による処方薬の調節や必要薬の処方依頼などが実施される．これら医師への報告はSOAP形式で電子カルテに記入され(図7)，患者の評価は，

有害事象共通用語基準や，numerical rating scaleを用いて行われる．上記のcase studyの症例に関してもコース開始前の薬剤師による診察前面談にて有害事象のGradingの評価を行い，処方提案がされている．よって，医師は患者を診察する前に患者状態や副作用の出現状況を把握することができ，必要な処方薬，化学療法の延期・休薬・減量などの判断が容易になり，診察時間の短縮に繋がっている．また，各職種が専門性を生かし異なる視点から，患者の評価を行うため，症状のダブルチェックだけでなく，有効かつ安全で，患者のQOLに配慮した治療の提供が可能となっている．

おわりに

抗癌薬の有害事象を回避・軽減することにより，患者のQOL低下を防ぐとともに，治療完遂率を高めて治療効果の向上に貢献するとの信念に基づいて，当院外来化学療法室は各職種のコミュニケーションよく，最適の化学療法を患者に提供する努力をしている．医師以外の職種である薬剤師や看護師においても，自分達の役割を全うするモチベーションをもち，仕事をしている．外来化学療法室における化学療法が効率よく，安全に行われるにはやはりチーム医療はかかせないと考える．

今回は大腸癌補助化学療法の変遷をエビデンスに基づいて解説し，当科での治療方針について述べた．また，当院での薬剤師における診察前面談やチーム医療における医師・薬剤師・看護師の役割について最近増加しているレジメンであるXELOX療法を用いて説明した．

図7　薬剤師による診察前面談の電子カルテ記入例

#0 薬剤師 薬剤

S
3日目から気持ち悪くなって吐き気は5日間くらい続きました。
3日戻す日がありました。
口内炎はなく、便が水っぽい日はありましたが、排便回数の増加は特にありませんでした。
冷感刺激による痺れが4日目くらいまで手と喉にありました。血管の痛みも4日目までありました。
手の皮がめくれましたがすぐに治りました。

O
食欲不振 (-)
悪心 G2(遅):Day3-7
嘔吐 G1(遅):day3,4,6
味覚異常 G1
口内炎 (-)
便秘 (-)
下痢 (-)
末梢神経障害 G1:冷感刺激のみ。手、咽頭→Day1-4
HFS G1:day3-7
血管痛 G1:Day1-7
ノバミン錠 day2-8頓服使用

A
G2の悪心(R11)とG1の嘔吐が発現しております。
イメンドの追加をお願いいたします。
その他の副作用は許容内です。手の保湿、冷感刺激の回避等再度指導いたしました。

P
【希望薬】
イメンド125mgCp→急変オーダー
イメンド80mgCp 1Cp/朝食後 2日間
デカドロン錠0.5mg 8錠/朝昼食後 2日間
ヒルドイドソフト軟膏 3本
ノバミン 1錠/回 悪心(R11)時 10回分

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ORIGINAL ARTICLE

Reporting patient characteristics and stratification factors in randomized trials of systemic chemotherapy for advanced gastric cancer

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Abstract
Background There is no consensus on which patient characteristics are the most suitable to report or to be used as stratification factors in clinical trials for advanced gastric cancer (AGC), to our knowledge.
Methods We conducted a comprehensive review of published randomized trials for AGC to examine the patient characteristics that were reported.
Results Among the 67 analyzed trials, age, gender, performance status, proportion of patients with measurable disease, and previous gastrectomy were frequently reported (>69%). Histology, number of disease sites, and adjuvant treatment were reported in less than 50% of trials. Although the reporting of second-line chemotherapy has increased in recent trials, it remains at less than 50%. Notably, recent trials have tended to include patients with better performance status and less locally advanced disease, with Asian trials more frequently including patients with more diffuse histology and less locally advanced disease or liver metastasis than non-Asian trials. Stratification was conducted in approximately 60% of the trials, using quite variable stratifying factors.
Conclusion Inconsistency exists in the reporting of patient characteristics, the characteristics themselves, and the use of stratification factors in clinical trials for AGC. A consensus set of important patient characteristics and strata may be necessary to conduct and interpret quality randomized studies.

Keywords Chemotherapy · Gastric cancer · Prognostic factor · Randomized trial · Stratification

Introduction

Gastric cancer remains one of the most common malignancies and leading causes of cancer death worldwide [1]. Although the most effective treatment for localized disease is surgery, approximately half of all patients with advanced-stage disease experience recurrence following curative resection. The prognosis of patients with advanced or recurrent gastric cancer (AGC) remains poor, with commonly used combination chemotherapy regimens, consisting of a fluoropyrimidine plus a platinum agent with or without docetaxel or anthracyclines, leading to a median survival of only 1 year [2–8]. Therefore, the development of novel anticancer agents or strategies for the treatment for AGC is urgently required; however, for the evaluation of such agents and treatments, it is critical to conduct effective randomized trials.

Reflecting the relatively high incidence of gastric cancer worldwide, numerous clinical trials have been conducted in multiple countries or as part of global studies [7, 8]. These clinical trials have displayed surprising heterogeneity in overall survival (OS) even if patients with similar stages of unresectable AGC are targeted. Although several identified prognostic factors in patient characteristics and practice

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patterns, including surgery and chemotherapy, are thought to partially contribute to the observed heterogeneity [9], the exact reason for this heterogeneity is unknown.

A number of reports have evaluated prognostic factors in AGC patients who underwent chemotherapy [10–14]. For example, the recent Global Advanced/Adjuvant Stomach Tumor Research through International Collaboration (GASTRIC) project confirmed the impact of performance status (PS), disease status (metastatic vs. locally recurrence vs. locally advanced), number of metastatic organs, location of metastasis, and prior surgery on the survival of AGC based on individual patient data analysis of previous randomized studies [10]. In addition, Chau et al. [11] identified four independent prognostic factors for poor AGC survival: PS $\geq$ 2, liver metastasis, peritoneal metastasis, and increased serum alkaline phosphatase (ALP) levels, which were subsequently used to classify patients into three risk groups (Royal Marsden hospital prognostic index) that were validated in a large phase III trial [12]. The prognostic factors for AGC identified to date also serve as important stratification factors in randomized trials to exclude possible confounding variables. To our knowledge, however, there is no consensus as to the specific patient characteristics that are most suitable to report or to be used as stratification factors in clinical trials for AGC.

Here, we report the results of a comprehensive review of published randomized trials for AGC that we conducted to investigate the patient characteristics and stratification factors that have been evaluated and reported. We also examined differences in previous studies according to trial period and region.

Materials and methods

Search for studies

We conducted a literature search for randomized clinical trials of AGC through computer-based searches of the Medline database (January 1966 and December 2010) and searches of abstracts from conference proceedings of the American Society of Clinical Oncology (1995–2010), and the European Cancer Conference and European Society for Medical Oncology (1995–2010). Search key words included: "gastric cancer," "randomized", "advanced or metastatic", and "chemotherapy." The search was also guided by a thorough examination of reference lists from original and review articles.

Procedures

Two investigators (Kohei Shitara and Keitaro Matsuo) extracted data in accordance with the Quality of Reporting of Meta-analyses (QUORUM) guidelines [15]. Randomized trials of systemic chemotherapy for patients with histologically confirmed AGC (metastatic or unresectable locally advanced disease) of the stomach or gastroesophageal junction were included in the analyses. Trials that compared chemotherapy with best supportive care were also included, as were those which included patients with adenocarcinoma of the distal esophagus. Exclusion criteria included trials designed to assess combined modality treatments, including radiotherapy and surgery (neoadjuvant or adjuvant chemotherapies); and those in which patients were pretreated with systemic chemotherapy. Unpublished trials and trials published in non-English languages were also excluded from this analysis.

For each trial, the reporting of patient characteristics and stratification factors was extracted. As trial characteristics, the following information was extracted: first author's name, year of publication, trial design (randomized phase II or III, if reported), trial location, number of enrolled patients, and treatment regimens. As patient characteristics, the following information was extracted (if reported): age; gender; PS; histology (e.g., diffuse or intestinal type); disease status (e.g., advanced or recurrent disease); primary tumor location (e.g., stomach or gastroesophageal junction); extension of disease (e.g., locally advanced or metastatic); previous gastrectomy, adjuvant chemotherapy, and radiotherapy; sites of metastases (e.g., peritoneum, liver, and lymph node); number of metastatic organs; and proportion of patients with measurable disease. The proportion of patients who received second-line chemotherapy was also extracted. All data were checked for internal consistency.

Statistical methods

Differences in the reporting of patient characteristics according to trial period (before vs. after 2004) and trial region (Asian vs. non-Asian trials) were assessed by the χ^2 test or Fisher's exact test, as appropriate. Because there was no definitive cut-off time for performing trend analysis, we divided the period at 2004 as this led to the number of trials (36 vs. 31 trials) and number of patients being almost equally distributed in the two periods. Median values for patient characteristics were calculated for each trial and the combined patient population. Differences in patient characteristics according to region or trial period were evaluated using the Mann–Whitney test. Use of stratification factors according to trial period or region was evaluated with the χ^2 test or Fisher's exact test as appropriate. Statistical analyses were performed using STATA ver. 10 (StataCorp. LP; College Station, TX, USA). All tests were two-sided, and P values of less than 0.05 were considered statistically significant.

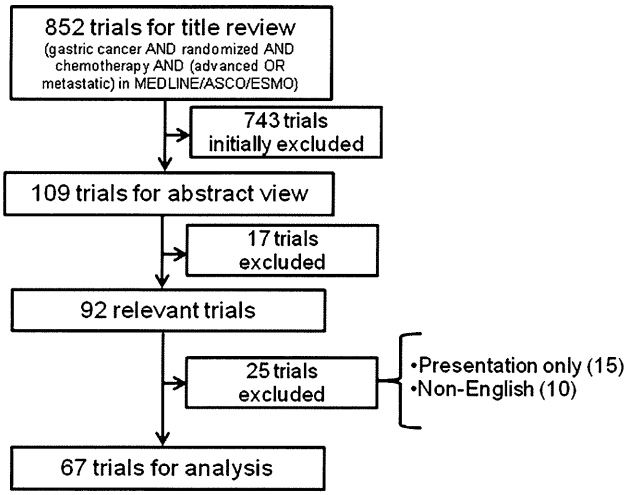

Fig. 1 Selection process for trials. An initial literature search for randomized clinical trials of advanced gastric cancer (AGC) identified a total of 852 potentially relevant reports, of which 743 were excluded on examination of titles. After review of the abstracts of the remaining studies, 67 randomized trials, with a total of 153 treatment arms and 12,656 patients were identified as eligible for analysis. *ASCO* American Society of Clinical Oncology, *ESMO* European Society for Medical Oncology

Results

Study selection

Our extensive literature search yielded a total of 852 potentially relevant reports, of which 743 were initially excluded on examination of titles (Fig. 1). After review of the abstracts of the remaining studies, 67 randomized trials, with a total of 153 treatment arms and 12,656 patients were identified as eligible for analysis (Supplement 1). Table 1 summarizes the characteristics of the 67 selected clinical trials, which consisted of 23 and 30 randomized phase II and III trials, respectively, and 14 trials that did not report the trial phase.

Patient characteristics reported in trials

Table 2 summarizes the patient characteristics reported in the 67 clinical trials included in the analysis. Two global studies that included Asian countries were excluded when comparing trials in Asia and non-Asian countries.

Age, gender, and PS

All 67 clinical trials provided information of patient age, with nearly all (94%) providing a median value, and four trials providing categorized values. One trial targeted elderly patients (>70 years). Gender information was reported by all but one trial. Sixty-four trials (96%) provided information regarding PS, with 46 reporting Eastern Cooperative Oncology Group (ECOG)/WHO PS classifications and the other 17 using the Karnofsky Performance Scale (KPS). Considerable PS variability was detected among the trial patients, as follows: PS 0–1, 4 trials; PS 0–2, 25 trials; and PS 0–3, 17 trials; and KPS 100–80, 1 trial; KPS 100–70, 5 trials; KPS 100–60, 7 trials; and KPS 100–50, 4 trials. Among the trials that used ECOG PS, 22 reported ECOG PS 0 versus 1 versus 2, whereas the other studies reported PS 0 and 1 without discrimination. No significant differences in reporting were detected in the trial period or region for PS, age, and gender.

Table 1 Characteristics of the 67 clinical trials analyzed in the present study

Characteristic	*N*	%
Reported year		
Before 2004	36	54
2004–2010	31	46
Trial setting		
Phase II	23	34
Phase III	30	45
Not indicated	14	21
Number of patients		
<100	28	42
100–300	28	42
>300	11	16
Trial area		
Asia	14	21
North America	12	18
Europe	31	46
Other	6	9
North America and Europe	2	3
Global, including Asia	2	3

Disease characteristics

The proportion of patients with measurable disease was reported in 69% of trials, with half including only patients with at least one measurable disease. Extension of disease and disease status were reported in 57 and 27% of trials, respectively. The location of metastases was reported in 64% of trials; the liver was the most commonly reported site, followed by the peritoneum. Histology and the number of metastatic organs were not reported in more than half of the trials. The Lauren classification (intestinal or diffuse type) was used in 12 trials, while classifications such as the American Joint Committee on Cancer grading system (well- or poorly differentiated adenocarcinoma, etc.) were used in 18 trials. The location of primary tumors was reported in 26 trials (39%), with 17 trials including not only gastric cancer, but also esophagogastric junction or

Table 2 Reported patient characteristics in the 67 clinical trials analyzed in the present study

Characteristic	Reported studies (%)	Reported year			Area of trial[a]		
		Before 2004 ($n = 36$)	After 2004 ($n = 31$)	P value[†]	Non-Asian ($n = 51$)	Asian ($n = 14$)	P value[†]
Age	67 (100)	36 (100)	31 (100)	ns	51 (100)	14 (100)	ns
Gender	66 (99)	35 (97)	31 (100)	ns	50 (98)	14 (100)	ns
PS	64 (96)	34 (94)	30 (97)	ns	48 (94)	14 (100)	ns
Measurable disease	46 (69)	21 (58)	25 (81)	0.05	35 (69)	9 (64)	ns
Metastatic site	43 (64)	22 (61)	21 (68)	ns	33 (65)	9 (64)	ns
Disease extension (local or metastatic)	38 (57)	19 (53)	19 (61)	ns	33 (65)	5 (36)	ns
Histology	30 (45)	12 (33)	18 (58)	0.04	20 (39)	9 (64)	ns
Location of primary tumor	26 (39)	8 (22)	18 (58)	≤0.01	24 (47)	1 (7)	≤0.01
Number of metastatic organs	25 (37)	5 (14)	20 (65)	≤0.01	18 (35)	5 (36)	ns
Disease status (advanced or recurrent)	18 (27)	5 (14)	13 (42)	ns	13 (25)	5 (36)	ns
Previous gastrectomy	46 (69)	21 (58)	25 (81)	0.05	32 (63)	12 (86)	ns
Previous adjuvant chemotherapy	16 (24)	0 (0)	16 (52)	≤0.01	6 (12)	9 (64)	≤0.01
Previous radiotherapy	11 (16)	3 (8)	8 (26)	ns	9 (17)	1 (7)	ns
Second-line chemotherapy	18 (27)	3 (8)	15 (48)	≤0.01	10 (20)	6 (43)	ns

ns not significant, *PS* performance status

[a] Excluded two global studies

[†] Statistical analyses were performed using the χ^2 test or Fisher's exact test, with the level of significance set at $P < 0.05$ (underlined)

esophageal cancer. The frequency of reporting these characteristics appeared to be increasing in more recent trials, although most examined characteristics were reported in less than 60% of the trials (Table 2). Only primary tumor location was more frequently reported in non-Asian than Asian trials, and no other significant differences in reporting of disease characteristics were observed based on trial area.

The other reported patient characteristics were as follows: weight loss ($n = 12$; 18%); any symptoms (anorexia, dysphasia, etc., $n = 7$; 10%); body surface area ($n = 3$; 4%); ethnic groups ($n = 2$; 3%); hemoglobin level ($n = 4$; 6%); serum ALP level ($n = 3$; 4%); comorbidities ($n = 3$; 4%), and Royal Marsden hospital prognostic index ($n = 1$; 1%).

Previous treatment and second-line chemotherapy

An indication of the proportion of patients with previous gastrectomy was reported in 69% of trials, with the curability of gastrectomy (curative or palliative with residual disease) specified in approximately 50% of trials. Previous adjuvant chemotherapy and radiotherapy were infrequently reported (24 and 16% of trials, respectively). Second-line chemotherapy was also reported with low frequency (27% of trials), and was typically indicated in the text, rather than being included in patient characteristic tables. The reporting of previous treatment and second-line chemotherapies was found to be increasing in recent trials, although more than half did not include information related to second-line chemotherapy. In addition, Asian trials more commonly reported the use of adjuvant chemotherapy than non-Asian trials.

Patient characteristics of the combined trial population

The characteristics of the 12,656 AGC patients were calculated based on the reported values in each of the 67 clinical trials (Table 3). Recent trials included more patients with better PS (ECOG PS 0–1; 94 vs. 64%; $P < 0.01$) and less locally advanced disease (4 vs. 27%) than older trials. Asian trials included more patients with diffuse histology than non-Asian trials (53 vs. 34%; $P < 0.01$), while patients with liver metastasis (43 vs. 31%; $P = 0.01$) or locally advanced disease (15 vs. 3%; $P = 0.04$) were more common in non-Asian trials. Second-line chemotherapy was more commonly used in Asian and recent trials.

Stratification factors

Among the 67 trials, 40 (60%) used stratification factors (Table 4). The median number of factors was 3, with an observed range of 1–5. The most common stratification factor was PS, followed by institution and previous gastrectomy. More recent trials used one or more stratification factors than older trials (47 vs. 75%, $P = 0.03$, Table 4).

Table 3 Patient characteristics ($n = 12,656$) in AGC trials included in this analysis

Patient characteristic	Entire patient population (median)	Median per trial	Range	Reported year			Area of trial[a]		
				Before 2004 (median)	After 2004 (median)	P value[†]	Non-Asian (median)	Asian (median)	P value[†]
Median age (years)	–	59	52–72	58	59	ns	59	58	Ns
Male gender (%)	73	72	58–83	70	74	ns	72	69	ns
PS0–1 (%)	84	83	18–100	69	94	≤0.01	78	89	ns
PS2 or more (%)	16	17	0–82	31	6	≤0.01	22	11	ns
Diffuse histology (%)	42	38	1–66	44	34	ns	34	53	≤0.01
One metastatic organ (%)	33	30	9–51	26	32	ns	27	35	ns
Locally advanced disease (%)	15	14	0–43	27	4	≤0.01	15	3	0.04
Liver metastasis (%)	44	42	18–79	42	42	ns	43	31	0.02
Peritoneal metastasis (%)	23	24	3–62	23	29	ns	20	29	ns
With measurable disease (%)	88	99	33–100	96	100	ns	100	96	ns
Previous gastrectomy (%)	33	39	8–83	38	40	ns	41	33	ns
Previous adjuvant chemotherapy (%)	5	5	1–31	–	5	–	4	9	0.02
Previous radiotherapy (%)	1	1	0–3	2	1	ns	1	1	ns
Second-line chemotherapy (%)	40	41	14–83	18	40	≤0.01	36	57	0.01

ns not significant, *PS* performance status

[a] Excluded two global studies

[†] Statistical analyses were performed using the Mann–Whitney test, with the level of significance set at $P < 0.05$ (underlined)

Table 4 Stratification factors in the 67 clinical trials analyzed in the present study

Stratification factor	N of studies (%)	Reported year			Area of trial[a]		
		Before 2004 (%)	After 2004 (%)	P value[†]	Non-Asian (%)	Asian (%)	P value[†]
No factor	27 (47)	19 (53)	8 (26)	0.03	22 (43)	5 (36)	ns
1 or 2 factors	12 (21)	5 (14)	7 (23)		7 (14)	4 (29)	
3 or more factors	28 (49)	12 (33)	16 (52)		22 (43)	5 (36)	
PS	24 (42)	9 (25)	15 (48)	ns	16 (31)	7 (50)	ns
Previous gastrectomy	18 (32)	9 (25)	9 (29)	ns	14 (27)	4 (29)	ns
Institution	18 (32)	5 (14)	7 (23)	0.35	16 (31)	2 (14)	ns
Measurable disease	12 (21)	6 (17)	6 (19)	ns	10 (20)	1 (7)	ns
Metastatic sites	8 (14)	2 (6)	6 (19)	0.08	8 (16)	0 (0)	ns
Disease extension	8 (14)	4 (11)	4 (13)	ns	7 (14)	1 (7)	ns
Age	6 (11)	5 (14)	1 (3)	ns	5 (10)	1 (7)	ns
Gender	5 (9)	5 (14)	0 (0)	0.03	5 (10)	0 (0)	ns
Adjuvant chemotherapy	5 (9)	1 (3)	4 (13)	ns	3 (6)	2 (14)	ns
Disease status	3 (5)	0 (0)	3 (10)	ns	0 (0)	2 (14)	≤0.01
Location of primary tumor	3 (5)	1 (3)	2 (6)	ns	2 (4)	0 (0)	ns

ns not significant, *PS* performance status

[a] Excluded two global studies

[†] Statistical analyses were performed using the χ^2 test or Fisher's exact test, with the level of significance set at $P < 0.05$ (underlined)

Gender was more commonly used in older trials (14 vs. 0%). No significant difference of stratification factors was observed between Asian and non-Asian trials, other than the frequency of use of disease status (0 vs. 14%).

Discussion

To our knowledge, this represents the first study to review the reporting of patient characteristics in published

randomized trials for AGC. Our results showed considerable inconsistency in the reporting of patient characteristics and the use of stratification factors in clinical trials for AGC. A similar finding was reported by Sorbye et al. [16], who analyzed metastatic colorectal cancer (MCRC) clinical trials and advocated that an urgent need exists for an international consensus on the reporting of patient characteristics and stratification in MCRC trials. Our data also revealed several differences in patient characteristics between trials conducted before and after 2004, and between Asian and non-Asian trials. It is possible that these differences may have contributed to the observed heterogeneity in the survival outcomes of each trial.

Several prognostic factors have been identified for patients with AGC who have undergone chemotherapy [10–14]. As described in the "Introduction", the GASTRIC project confirmed the impact of ECOG PS, disease status, number of metastatic organs, location of metastasis, and prior surgery on the survival of AGC patients, as determined by individual patient data analysis of previous randomized studies [10]. Notably, this project, which may have included the largest AGC patient set to date, identified that PS1 and PS2 were significantly associated with poor survival, with hazard ratios (HRs) of death of 1.36 and 2.17, respectively [10]. In the GASTRIC analysis, although most trials included PS among the reported patient characteristics, a number of studies classified PS0 and PS1 separately, and several studies used KPS rather than the ECOG scale. In addition, local recurrence and metastatic disease were reported to be associated with worse outcomes than locally advanced disease [10]. In our present analysis, approximately 50% of trials reported disease extension (locally advanced or metastatic disease), and only 30% of trials indicated disease status (advanced or recurrent disease).

Although the GASTRIC analysis did not evaluate the importance of specific metastatic organs on outcomes, another large prognostic analysis, by Chau et al. [11, 12], reported the impact of liver and peritoneal metastasis on AGC patient survival. Affected metastatic organs were reported in 64% of the trials in our analysis, but the number of metastatic organs, which has significant impact on survival according to the GASTRIC analysis, was only reported with a frequency of 39%. Although histology was not identified as prognostic in the GASTRIC analysis, several recent trials suggest that an interaction exists between histology and drug response [6, 7, 17, 18]. For example, a subset analysis of the First-line Advanced Gastric Cancer Study (FLAGS) trial has indicated that the oral fluoropyrimidine S-1 appears to be superior to fluorouracil in the treatment of diffuse-type gastric cancer [6]. This finding is consistent with the results of a subset analysis of the Japan Clinical Oncology Group (JCOG) 9912 study that also indicated S-1 is better than fluorouracil in patients with diffuse-type AGC or gastric cancer associated with high dihydropyrimidine dehydrogenase (DPD) activity, which is more commonly associated with diffuse-type than intestinal-type tumors [17]. This result was not unexpected, because S-1 is a potent competitive inhibitor of DPD. In contrast to DPD, human epidermal growth factor receptor 2 (HER2)-positive AGC, for which the anti-HER2 agent trastuzumab is effective [7], is reported to be higher among intestinal-type tumors [18]. The prognostic factors and tumor characteristics identified in these studies should be reported in all clinical trials of AGC, as they are necessary to adequately interpret trial data and treatment outcomes.

Our analysis also revealed that the types of second-line chemotherapy and proportions of patients who received such treatment were not routinely reported in AGC trials. As several recent reports have suggested that second-line chemotherapy has a significant impact on OS [19–21], we propose that second-line therapies should be diligently reported in future clinical trials of first-line AGC treatment, because second-line chemotherapy might influence the OS as the primary endpoint, as suggested by our previous analysis [22].

Additionally, the numerous prognostic factors identified for AGC may be important for the stratification of patients with respect to risk and treatment arms in randomized trials. To adequately analyze treatment effects on clinical outcomes, efforts should be undertaken to maximally decrease imbalance of prognostic factors between treatment arms in a clinical trial [23]. Although there is no definite consensus on the optimal method for stratification, stratification is recommended for superiority trials with fewer than 400 patients [24] and for non-inferiority trials with any number of patients [25]. In our analysis, stratification was conducted in only 60% of the examined trials, and was performed with quite variable stratifying factors. Based only on the present analysis, it is difficult to suggest a standardization approach for stratification factors in AGC trials, and further analysis and discussion are necessary.

In recent years, a trend of increased median OS in AGC patients has been observed concurrent with the development of new chemotherapeutic agents [2, 4, 7, 26]. It is also possible that second-line chemotherapy may have contributed to the improvement in OS [19–21]; however, our crude comparison of trials conducted prior to and after 2004 also showed significant differences in PS and disease extension. These differences may have also contributed to the improved survival reported in more recent trials, as well as survival differences between Asian and non-Asian trials. The exact impact of chemotherapy and patient characteristics on survival would be best addressed in well-designed randomized studies and meta-analyses of individual patient data.

In conclusion, our analyses of published clinical trials for AGC revealed inconsistencies in the reporting of

patient characteristics and use of stratification factors. An international consensus on the reported characteristics and stratification in AGC trials is necessary to improve the analysis of future clinical trials.

Conflict of interest None.

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PHASE II STUDIES

Phase II study of combination chemotherapy with biweekly cetuximab and irinotecan for wild-type *KRAS* metastatic colorectal cancer refractory to irinotecan, oxaliplatin, and fluoropyrimidines

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Summary The aim of this study is to prospectively evaluate the efficacy of combination chemotherapy with every second week cetuximab and irinotecan in patients with pretreated metastatic colorectal cancer harboring wild-type *KRAS*. Patients with wild-type *KRAS* metastatic colorectal cancer that had progressed after chemotherapy with irinotecan, oxaliplatin, and fluoropyrimidine were included. Cetuximab was administered at 500 mg/m^2 biweekly with irinotecan. The primary endpoint was response rate. The pharmacokinetics of cetuximab was also evaluated in 5 patients. From May 2009 to February 2010, a total of 31 patients were enrolled from five institutions. One patient was not eligible. Among the 30 patients who were treated with biweekly cetuximab plus irinotecan, partial response was observed in 9 patients. The objective response rate was 30.0% (95% confidence interval [CI], 14.7%–49.4%) and the disease control rate (complete response, partial response, or stable disease) was 76.7% (95% CI, 57.7%–90.0%). The median progression-free survival was 5.3 months and median overall survival was 10.8 months. Grade 3 skin toxicity was observed in 3 patients (10.0%) and one treatment related death due to pneumonia was observed. Combination chemotherapy with biweekly cetuximab and irinotecan was effective for

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pretreated metastatic colorectal cancer with wild-type *KRAS*.

Keywords Colorectal cancer · Chemotherapy · Cetuximab · Biweekly · Irinotecan

Introduction

Cetuximab, a recombinant, human/mouse chimeric monoclonal IgG1 antibody that specifically targets epidermal growth factor receptor (EGFR), has been shown to significantly improve the prognosis for metastatic colorectal cancer (MCRC) compared to best-supportive care alone in the third-line setting [1]. Furthermore, combining cetuximab with irinotecan results in a higher response rate than cetuximab alone, even in patients with irinotecan-refractory disease [2], suggesting that cetuximab may restore chemosensitivity in these patients. Because of these results, cetuximab plus irinotecan has become the standard chemotherapy in MCRC after failure with 5-fluorouracil (5-FU), oxaliplatin, and irinotecan. Following these two pivotal studies, several retrospective reports suggested that cetuximab is not efficacious in patients with cancers harboring *KRAS* mutations [3–7]. Therefore, the indications for cetuximab are considered to be limited to cancers bearing wild-type *KRAS* based on these retrospective studies [8]. We conducted a phase II study employing weekly cetuximab plus biweekly irinotecan for wild-type *KRAS* MCRC [9]. Objective response rate of 30.0% and disease control rate of 80.0% was shown in our previous study [10].

Based on past pivotal studies, the standard schedule for cetuximab is weekly administration [1, 2]. In principal, cetuximab is administered weekly with an initial intravenous infusion of 400 mg/m^2 on day 1 infused over 120 min, with subsequent weekly doses of 250 mg/m^2 infused over 60 min. This regimen was used in a Japanese phase II study [10] and in our prior study [9] with acceptable toxicity. However, in Japan, irinotecan has been commonly administered biweekly to patients with metastatic colorectal cancer. Therefore, if we could achieve similar efficacy and safety with biweekly administration of cetuximab, it would be more convenient both for the patient and for the treating institution. There are a few reports that evaluated efficacy and feasibility of biweekly administration of cetuximab [11–13]. Tabernero et al. conducted a phase I study of biweekly cetuximab. In their study, cetuximab could be safely administered biweekly at doses between 400 and 700 mg/m^2 [11]. They concluded that 500 mg/m^2 was the most convenient and feasible dose. Other two studies using biweekly cetuximab 500 mg/m^2 plus irinotecan showed a response rate of 22.5%–25% in pretreated MCRC with a similar toxicity compared with weekly cetuximab [12, 13]. However, to the best of our knowledge, no study using biweekly cetuximab evaluated *KRAS* status prospectively [11–13]. Therefore, we have planned a phase II study of combination chemotherapy with biweekly cetuximab and irinotecan for pretreated MCRC harboring wild-type *KRAS*.

Patients and methods

Purpose

The aim of this study was to explore the effectiveness and safety of combination chemotherapy with biweekly cetuximab plus irinotecan for the treatment of patients with MCRC that had progressed after irinotecan-, oxaliplatin-, and fluoropyrimidine-based chemotherapy.

Study setting

A multi-institutional prospective phase II trial, where participating institutions included 5 specialized centers.

Endpoints

The primary endpoint was response rate. The tumor response was assessed objectively once every two weeks after each course according to the Response Evaluation Criteria in Solid Tumors (RECIST ver. 1.0), and the best overall response rate was taken as the antitumor effect for that patient. The secondary endpoints included adverse events defined by Common Terminology Criteria for Adverse Events (CTCAE) version 3.0, progression-free survival time, and overall survival time. A pharmacokinetic (PK) study of cetuximab was evaluated in 5 patients.

Patients

Prior to enrollment in the study, patients must fulfill all of the following criteria: (i) Patients with histopathologically proven metastatic colorectal adenocarcinoma with wild-type *KRAS* were eligible for this study. EGFR positive staining was not required. *KRAS* status was evaluated in each institution using one of the following methods: cycleave PCR (Aichi Cancer Center Hospital) [14, 15] or direct sequence methods (BML, Tokyo, Japan). Wild-type *KRAS* meant patients without *KRAS* mutations in codons 12 and 13 regardless of the *KRAS* testing method. The remaining criteria were as follows: (ii) Eastern Cooperative Oncology Group performance status (PS) 0–2; (iii) presence of measurable metastatic disease as defined by the

RECIST criteria; (iii) presence of radiographically confirmed disease progression during previous chemotherapy using irinotecan or within 3 months after the last chemotherapy dose; (iv) treatment failure (defined as disease progression/discontinuation due to toxicity) within 6 months of the last dose of fluoropyrimidine- and oxaliplatin-based chemotherapy; (v) adequate bone marrow reserve (neutrophil count >1,000/mm^3, platelet count >100,000/mm^3); (vi) adequate hepatic function (aspartate aminotransferase and alanine aminotransferase <2.5 times the institutional upper normal limit [<5 times in patients with liver metastases] and total bilirubin <1.5 times the upper normal limit); and (vii) adequate renal function (serum creatinine <2.0 times the upper normal limit).

Patients were excluded if they met any of the following criteria: (i) uncontrollable ascites or pleural effusion and (ii) serious comorbidities, such as pulmonary fibrosis or interstitial pneumonia, uncontrollable diabetes mellitus, severe heart disease, other active malignancy, active inflammation, or other serious medical conditions.

The institutional review board of each participating center approved the study. This study was registered in the UMIN clinical trial registry (UMIN000001951). Written informed consent was obtained from each patient prior to treatment administration.

Treatment methods

The treatment schedule was based on the results of prior studies [10–12]. Cetuximab was administered initially at a dose of 500 mg/m^2 as a 2-hour infusion followed by biweekly administration of 500 mg/m^2 as a 1-hour infusion. Irinotecan was administered biweekly. The dose of irinotecan (100–150 mg/m^2) was selected by each physician according to each individual patient, based on prior toxicities experienced with irinotecan. Patients received premedication with antihistamine (e.g., 50 mg diphenhydramine hydrochloride intravenously [IV]) to minimize the risk of infusion-related reactions associated with cetuximab. The following anti-emetic treatments were administered on demand: dexamethasone 4 mg prior to cetuximab, and dexamethasone 8–16 mg plus granisetron 1 mg IV prior to irinotecan. Toxicity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE, version 3.0). Grade 3–4 hypersensitivity necessitated cetuximab discontinuation; infusion was slowed to 50% of the prior infusion rate for grade 1–2 allergic/hypersensitivity reactions. Cetuximab was withheld for grade 3 skin toxicity until resolution to ≤grade 2. Dose modification and treatment alterations were also performed for irinotecan-associated toxicities. For grade 4 thrombocytopenia or grade 3–4 neuropathy, irinotecan was discontinued. The irinotecan dose was reduced by 20 mg/m^2 in the case of grade 4 neutropenia, grade 2–3 thrombocytopenia, or grade 3–4 non-hematological toxicity. Other dose adjustments were made on an individual patient basis. Treatment was discontinued if the tumor progressed, severe toxicity occurred, or at the patient's request. There was no set maximum number of courses.

Evaluation of treatment and follow-up

Medical history, physical examination, and safety evaluation were performed prior to starting treatment and biweekly thereafter. Laboratory tests were also obtained biweekly or more frequent in the case of severe toxicities, and always prior to each irinotecan infusion. Toxicity was evaluated by CTCAE ver. 3.0. Tumor marker analysis (carcinoembryonic antigen [CEA]) was also performed every 4 weeks. Responses were evaluated using RECIST criteria every 8 weeks, or earlier if there were indications of treatment failure due to toxicity. All eligible subjects were included in the assessment of efficacy and safety. Non-evaluable subjects were only added into the efficacy assessment data set as "not evaluable." The following dates were recorded: (i) date of starting treatment, (ii) date achieving best tumor response, (iii) date of disease progression, (iv) final date assessing survival, and (v) date of death.

Statistical analysis

A 1-stage design employing binomial probability was used to determine sample size. A patient receiving at least 1 chemotherapy study dose was considered evaluable for response. The response rate threshold was defined as 5%, and the expected response rate was set at 25%, since the response rate in the BOND-1 study was 22.9% [2]. The sample size of this trial was 25 patients (α- and β-error probabilities, 0.05 and 0.2, respectively). Considering an approximately 10% dropout rate, 30 patients were required for this study. Progression-free survival was measured from the date of entry into the trial to the time when progression or death without evidence of progression occurred. The median survival time was estimated from the date of study entry to the date of death or last follow-up visit using Kaplan-Meier methodology.

Cetuximab pharmacokinetics (PK) analysis

Blood samples for PK analysis were taken in 5 patients at day 1 (end of infusion), day 15 (predose and end of infusion), and day 29 (predose). PK parameters were