卵巣癌症例に対する second line chemotherapy としての CPT-11、cisplatin 併用療法（CPT-P 療法）の治療成績 第 46 回日本癌治療学会総会、11 月 1 日、2008、名古屋.

H. 知的財産権の出願・登録状況（予定含）

1．特許取得

なし

2．実用新案登録

なし

3．その他

なし

厚生労働科学研究費補助金（がん臨床研究事業）
分担研究報告書

婦人科腫瘍における細胞接着分子をターゲットとした新規治療の開発と治療戦略の個別化

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研究要旨
in vitro において婦人科癌細胞での細胞間コミュニケーションによるバイスタンダー効果を証明した。さらに性ステロイドホルモンやレチノイドなどを用いてより細胞間コミュニケーションを促進させることによりバイスタンダー効果が増強されるか検証を行なった。今後は in vivo での実験を通じて生体内でのバイスタンダー効果の変動と最終的には新しい治療法の開発を到達点として研究を進める。

A. 研究目的

近年、本邦において婦人科腫瘍の中でもとりわけ子宮体癌と卵巣癌の罹患率が上昇している。これら子宮体癌と卵巣癌の進行期とその治療戦略は主に手術所見に基づいて決定されるが、進行期決定のためには後腹膜リンパ節転移の有無を郭清および生検によって確認する必要があり、またリンパ転移の有無が予後や補助療法などの治療方針決定に大きな影響を及ぼしていることは議論の余地がない。

しかし、リンパ浮腫をはじめとする術後合併症による治療後の QOL 低下も見逃すことはできず、症例による縮小手術は体癌・卵巣癌の治療戦略上の検討課題となっている。

また、手術後の放射線療法についても、放射線腸炎や膀胱炎などの合併症が問題となる。しかし、これらの問題を解決するには従来の病理組織学的因子に加え、種々のバイオマーカーによる多面的解析によって治療の個別化を図る必要がある。また、進行あるいは再発癌の補助療法として放射線療法や化学療法が行われているが、これらの治療が充分癌を制御しているとは言えず、新しい治療法の開発が待たれている。

B. 研究方法

近年、悪性腫瘍に対する遺伝子治療の有効性が数多く報告されその臨床応用が期待されたが、ベクターの毒性や腫瘍に対する特異性などの問題が未だ解決されたとはいえない。遺伝子治療においては、通常は目的遺伝子が組み込まれた細胞のみが障害を受けるのであるが、時にこの組み込まれた周辺の細胞にも障害をおよぼすことがある。このことをバイスタンダー効果と言うが、このメカニズムの一つにギャップ結合を介した細胞間コミュニケーション(GJIC)が関与していることが知られている(文献 4, 5, 6)。本研究ではこのメカニズムの癌治療への応用を目指す。このことによって、①少量のベクターで済むので副作用を最小限に抑えることが可能になる、②GJIC は同種の細胞(癌細胞)にしか及ばないと言う性質があるので投与の仕方で治療の特異性を高めることが可能になる、などの問題が解決される可能性がある。本研究の具体目標

としては、①子宮体癌および卵巣癌細胞を用いて実際にGJICがバイスタンダー効果に寄与しているかを確認する、②まだコネキシンの発現などが検討されていない卵巣癌についてこれを行う、我々のこれまでの研究では性ステロイドがGJICを制御することを報告してきたが(文献 6)③レチノイドや性ステロイドなどを用いて in vitro および in vivo で GJIC あるいはバイスタンダー効果を増強する方法の検討を行う、④ヌードマウスモデルを用いて実際に本研究の有効性を検証する、を到達点として研究を進める。

（倫理面への配慮）

参加患者の安全性確保については、正確な診断、有用性の高い治療等に配慮がなされており、試験参加による不利益は最小化される。また、「臨床研究に関する倫理指針」およびヘルシンキ宣言等の国際的倫理原則に従い以下を遵守する。

1) 研究実施計画書（プロトコール）の IRB 承認が得られた施設からしか患者登録を行わない。

2) すべての患者について登録前に充分な説明と理解に基づく自発的同意を本人より文書で得る。

C. 研究結果

ヌードマウスにHSV-tk遺伝子を導入した RL-952-HSV-tk 細胞を接種し腫瘍を形成させ、このマウスに GCV を投与し、腫瘍の縮小効果を観察した。これをコントロールとし、RL-952-HSV-tk 細胞と wild-type- RL-952 細胞を 1:9 で混合し腫瘍を形成させ、コントロールと同様の実験を行ったところ、これにより in vivo にて in vitro と同様にバイスタンダー効果が起こることが明らかになった。

ヌードマウスに形成された腫瘍におけるレチノイドのコネキシン発言に与える影響についても、ヌードマウスに形成された子宮体癌腫瘍のコネキシンの発現がレチノイドを投与することにより、増強することがRT-PCR法およびウエスタンブロット法にて確認された。

D. 考察

婦人科癌においてもHSV-tk遺伝子を用いたバイスタンダー効果が有効に働いていることが本研究で明らかになった。また、このバイスタンダー効果はレチノイドによって増強することが明らかな胃なった。

E. 結論

本研究ではこれらの知見を元に①治療を行う前にこれらの遺伝子の解析を行って治療戦略の個別化を図る、②われわれが癌組織で解析してきた遺伝子をターゲットとした新しい治療法が期待される。

F. 健康危険情報

特記すべき事項なし

G. 研究発表

1. 論文発表

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2. 学会発表

なし

H. 知的財産権の出願・登録状況（予定含）

1．特許取得

なし

2．実用新案登録

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厚生労働科学研究費補助金（がん臨床研究事業）
分担研究報告書

進行卵巣癌に対するNeoadjuvant Chemotherapy(NAC)の後方視的研究

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研究要旨
進行卵巣癌の治療は初回手術時に腫瘍の縮小を図り(Primary Debulking Surgery;PDS)、次に効果的な化学療法が長期予後に有用であるが、全ての腫瘍が必ずしも切除されるとは限らず、suboptimalに終わる症例もあり、予後不良である。腫瘍の摘出が困難と判断された場合には、Neoadjuvant Chemotherapy(NAC)とInterval Debulking Surgery(IDS)の組み合わせによる予後改善の可能性がある。当施設での進行卵巣癌III期における5年生存率はNAC群：51.2%、PDS群：64.8%であり(p=0.16)、NAC群は今後期待される治療法と思われる。現在、多施設でのProspective Radomized Study(Japan Clinical Oncology Group; JCOG0602)が進行中であり、その結果が期待される。

A. 研究目的

卵巣癌は早期発見が困難であり、しかも症状が出現して発見される場合が多く、進行症例がほとんどである。進行卵巣癌の治療は初回手術時に腫瘍の縮小を図り(Primary Debulking Surgery;PDS)、次に効果的な化学療法が長期予後に有用であるが、全ての腫瘍が必ずしも切除されるとは限らず、suboptimalに終わる症例もあり、予後不良である。腫瘍の摘出が困難と判断された場合には、Neoadjuvant Chemotherapy(NAC)とInterval Debulking Surgery(IDS)の組み合わせによる予後改善の可能性があるとされている[1]。卵巣癌においては、Performans Status(PS)が不良な開腹不能例や、腹水穿刺、胸水穿刺、針生検、CTで開腹せずに卵巣癌と推定され、Stage XとしてNACを行う場合がある[2]。できれば腹腔鏡よる原発巣の確定や病変の拡がりを検索する方が望ましいが、やむを得ない場合は別として開腹手術による確定診断を行った上で治療方針を決定することが原則である。術前に進行卵巣癌と推定された症例において試験開腹により、他臓器の悪性腫瘍のこともあり、転移部位を含めて卵巣の生検が必須で、腹腔内病変をくまなく検索して臨床進行期を確定する必要がある。

本研究では、NAC群は試験開腹+生検による化学療法/IDSを基本とし、PDS群との予後を後方視的に比較検討した。

B. 研究方法

対象は1993-2006年の間に国立病院機構四国がんセンターにおいて文書による同意を得て治療した卵巣癌III期-79例(PDS群：36例、NAC群：43例)である。平均年齢はPDS群：54(25-75)歳、NAC群：58(33-76)歳で、PDS群、NAC群の組織型は、それぞれ漿液性腺癌：18例(50.0%)、22例(51.2%)、類内膜腺癌：12例(33.3%)、14例(32.5%)、粘液性腺癌：3例(8.3%)、3例(7.0%)、明細胞腺癌：2例(5.6%)、4例(9.3%)、混合型上皮性腫瘍：1例(2.8%)、0例(0%)である。両群間に年齢、

組織型において有意差は認められていない。生存率(Kaplan-Meier 法)は logrank 検定で長期予後を検討し，$p<0.05$ を統計学的に有意差ありとした。

NAC 群は、初回手術時に試験開腹のみに終わった症例で卵巣の生検ができ、他の病変からも少なくとも数カ所の生検を施行して組織学的に上皮性卵巣癌の確定診断と病変の拡がりを検索し、臨床進行期が確定されることが条件である。骨盤腔内が腫瘍で一塊となって固着し、腹腔内全体にも腫瘍病変が拡がって手術の遂行が困難とされる場合がその適応になる。PDS 群、NAC 群ともに白金製剤を含む併用化学療法として 1997 年以前では CEP(CPA/EPI/CDDP)療法、1998 年以降には TP(PTX/CDDP)療法、TC(PTX/CBDCA)療法を施行した。NAC 群には、3 コース施行し、薬剤耐性を作らないためにも内診、CT、腫瘍マーカーなどを参考にして IDS を早めに行うことを原則とした。IDS による基本術式は PDS 群と同様に単純子宮全摘術、両側附属器摘出術、大網切除術、骨盤・傍大動脈リンパ節郭清を原則とし、また、腸管への浸潤があればその合併切除を考慮した。

(倫理面への配慮)

本治療を受けなくても不利益を受けないこと、いつでも治療は希望により中止できることなどの倫理面への配慮を行った。

C. 研究結果

卵巣癌 III 期-79 例での PDS 群(n=36)、NAC 群(n=43)における 5 年全生存率を検討した。PDS 群、NAC 群の 5 年全生存率はそれぞれ 64.8%、51.2%であり、両群間において統計学的有意差はみられなかった(表 1、p=0.16)。また、粘液性腺癌症例での suboptimal 症例は optimal 症例に比し、その予後は極めて不良であった。

D. 考察

卵巣癌の治療は初回開腹時にできるだけ腫瘍の縮小を図り[3]、続いて効果的な化学療法を施行することである。腫瘍の縮小が十分にできないと判断されれば、無理な手術による合併症の併発や化学療法の遅延を来すよりは生検による試験開腹にとどめ、NAC による治療効果と IDS による減量手術に期待する考え方がある[2]。しかも、初回手術時に腫瘍残存症例(>2cm)と試験開腹例では、化学療法の効果は同じで生存率も変わらないとされ[4]、PDS 群と試験開腹群との間に明らかな生存率の差はみられていない[5]。試験開腹に終わった症例では適切な化学療法がなされるべきで NAC が奏効した後に、IDS を期待して生存率の改善に努める必要がある。

PDS 後の IDS の予後改善に関しては、van der Burg et al[7]は、FIGOⅡb～Ⅳ期、1cm 以上の残存腫瘍径を有する症例に対して CP 療法 3 コース施行後、IDS 群(n=140、IDS 後に 3 コース追加)、非 IDS 群(n=138、さらに 3 コース追加)を前方視的に検討して IDS により 1cm 以下にできれば、有意に生存期間の延長に貢献できると報告している。

しかしながら、Rose et al[7]は、1cm 以上の残存腫瘍径を有する症例に対して TP 療法 3 コース施行後、IDS 群と非 IDS 群との検討では、IDS の有用性はみられていない。薬剤の種類にもよるが、IDS の有用性は PDS 後の残存腫瘍径の大きさが関与していると考えられる。

本研究での PDS 群(n=36)、NAC 群(n=43)の 5 年全生存率はそれぞれ 64.8%、51.2%であり、両群間において統計学的有意差はみられなかった(p=0.16)。当施設での試験開腹後の NAC は少数例であるが、NAC 後の IDS によって腫瘍の縮小が得られた症例は予後良好の傾向はみられている。ただし、化学療法が奏効しにくい粘液性腺癌や明細胞腺癌などではできるだけ腫瘍切除をした後で抗癌剤を慎重

に選択する必要がある。

試験開腹例での予後改善策は、患者の年齢、進行期、PS、 組織学的分化度、腹腔内腫瘍の進展度、腹水や胸水の合併、化学療法の内容および回数、薬剤耐性、術者の技量、 IDS の時期を含めて多くの課題が残されている。今後、新規抗癌剤の開発がなされていくことを考慮すると、本治療において薬剤の投与を統一した多施設での Prospective Randomized Study が望まれる。この点に関しては、JCOG0602 が進行中であり、その結果が期待される。

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E. 結論

進行卵巣癌における NAC の意義はまだこれからの課題であるが、切除不能な症例に対して無理な手術は結果的に optimal に至らず、種々な合併症の併発や化学療法の遅延を招く危険性がある。むしろ NAC と IDS の適切な組み合わせによって optimal にすることによってある程度の予後改善が得られ、進行卵巣癌の治療の選択肢として今後十分に期待される。最終的には、PDS と NAC の有用性についてはランダム化比較試験によって得られたエビデンスが必要である。

F. 健康危険情報

特記すべき事項なし

G. 研究発表

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H. 知的財産権の出願・登録状況(予定含)

1．特許取得

なし

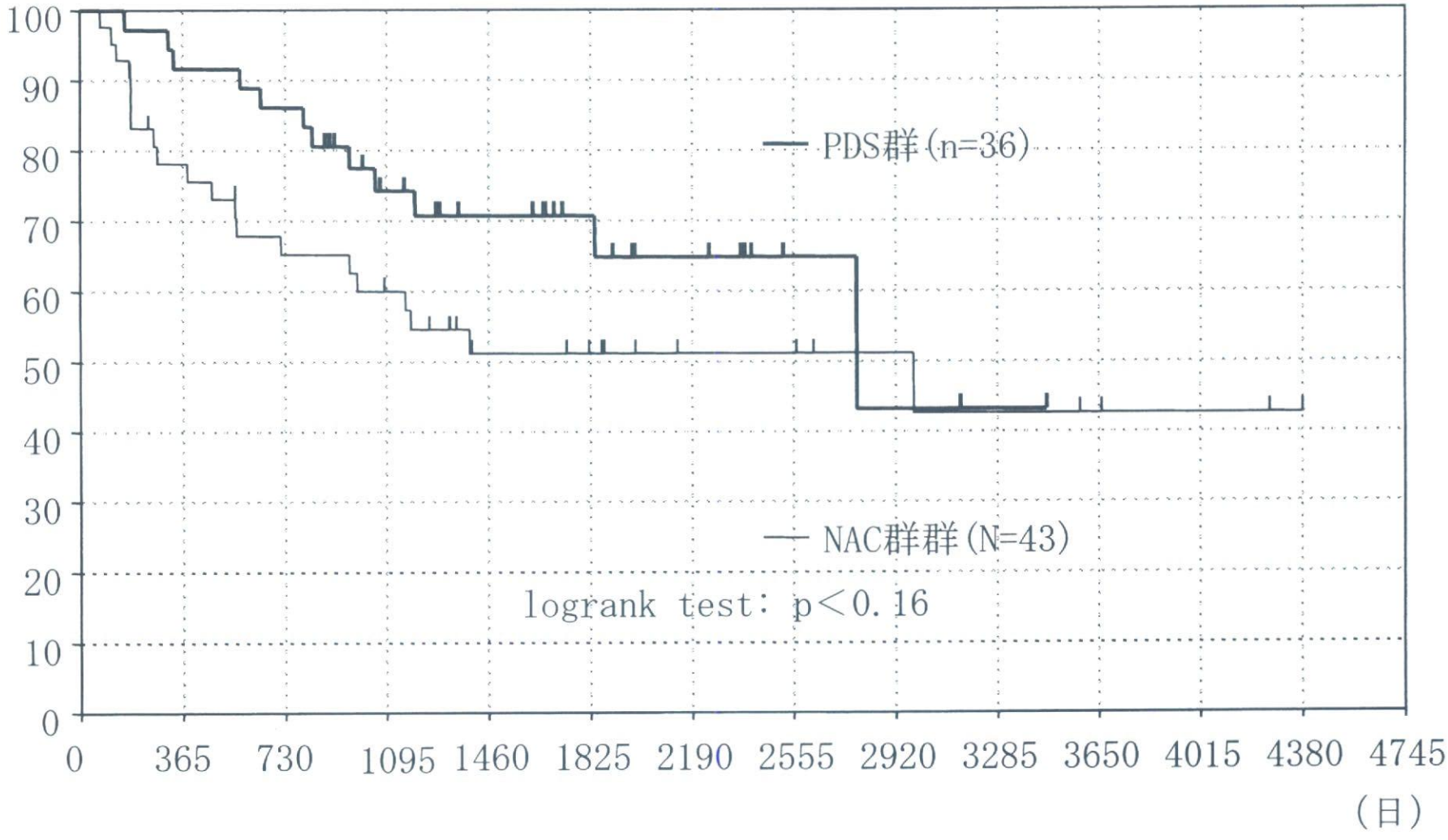
2．実用新案登録

なし

3．その他

なし

PDS群およびPDS群における5年全生存率



厚生労働科学研究費補助金（がん臨床研究事業）
分担研究報告書

再発卵巣癌の診断における効率的サーベイランスに関する研究

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研究要旨
卵巣癌の治療戦略においては、再発の早期診断が重要なカギとなるが、初回治療後のフォローアップ間隔や診察・検査項目についての明確な指針はない。本研究では、再発卵巣癌を診断するための効率的なサーベイランス方法について検討した。その結果、「II 期以上かつ 2 年以内」の症例と、それ以外の症例とで取り扱いを分けることが適切であると考えられた。CT 等画像検査の間隔および撮像部位、CA125 値による再発診断の有用性についても検証していく予定である。

A. 研究目的

卵巣癌の治療戦略においては、再発の早期診断が重要なカギとなるが、2007 年に発刊された卵巣がん治療ガイドラインにおいても初回治療後のフォローアップ間隔や診察・検査項目についてエビデンスレベルの高い記載はない。本研究では、再発卵巣癌を診断するための効率的なサーベイランス方法について検討した。

B. 研究方法

卵巣癌初回化学療法にタキサン製剤を導入した 1997 年以降の卵巣癌症例 220 例を対象とした。各種臨床病理学的因子別に再発率、再発時期、再発部位、診断方法(CT・超音波等画像検査、細胞診、腫瘍マーカー)等について解析を行った。

（倫理面への配慮）

本研究は文部科学省・厚生労働省「疫学研究の倫理指針」に従って実施されたものであり、既存資料のみを用いた観察研究である。対象患者のプライバシーは保護されており、氏名、生年月日、カルテ番号等、個人を特定する情報は公表されない。

C. 研究結果

2 年および 5 年累積再発率は、I 期：5%および 15%、II 期以上：47%および 68%であった(P＜0.05)。II 期以上の再発症例についてみると、再発時期は治療後 1 年未満：36%、1-2 年：44%、3-5 年：18%、5 年以降：2%であった。

治療前 CA-125 値、組織型、分化度別には累積再発率に有意差をみとめなかった。再発部位は 54%が腹腔内、25%がリンパ節、20%が遠隔臓器であった。

D. 考察

再発率には I 期と II 期以上、再発時期には 2 年以内とそれ以降で明らかに差があり、検診間隔はこれらをカテゴリー化し、重み付けをする必要があると考えられる。また、遠隔臓器への再発率 20%については、胸～骨盤部の CT 検査をルーティンとして 6-12 ヶ月毎に撮像している状況下での再発率であり、従来ガイドラインに記載されている腹部 CT と胸部 X 線検査の組み合わせであっても同程度の再発率であるかどうかは、多施設の治療成績を比較し、医療コストも含めた検討が必要と考える。

E. 結論

再発頻度に応じた診察間隔の設定をすべきであり、II 期以上かつ 2 年以内の症例とそれ以外の症例で取扱いを分けることが適切である。

F. 健康危険情報

特記すべき事項なし

G. 研究発表

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H. 知的財産権の出願・登録状況 (予定含)

1. 特許取得
   なし
2. 実用新案登録
   なし
3. その他
   なし

研究成果の刊行に関する一覧表

書籍：該当なし

雑誌：

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Feasibility study of neoadjuvant chemotherapy followed by interval debulking surgery for stage III/IV ovarian, tubal, and peritoneal cancers: Japan Clinical Oncology Group Study JCOG0206☆,☆☆

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ABSTRACT

Background. To assess the safety and efficacy of neoadjuvant chemotherapy (NAC) followed by interval debulking surgery (IDS) for müllerian carcinomas, such as ovarian, tubal, and peritoneal cancers, and to determine whether we can omit diagnostic laparoscopy before treatment initiation, a feasibility study was performed.

Methods. Eligible patients had presumed stage III/IV müllerian carcinomas clinically diagnosed by imaging studies, cytology, and tumor markers. All patients underwent diagnostic laparoscopy to confirm the clinical diagnosis. Four cycles of paclitaxel and carboplatin were administered as NAC, followed by interval debulking surgery and an additional 4 cycles of chemotherapy. The primary end point was the proportion of patients achieving clinical complete remission (cCR) among all stage III/IV müllerian carcinomas confirmed by diagnostic laparoscopy. The major secondary end point was the positive predictive value (PPV) of clinical diagnosis.

Results. Fifty-six patients were enrolled into the study. The PPV of overall clinical diagnosis for the tumor origin, histology, and stage was 95% (53/56). Fifty-three patients received the protocol treatment starting with NAC. IDS was performed in 89% (47/53) of patients. Complete resection without residual tumors was achieved in 55% (29/53) and residual tumors became ≤1 cm in 17% (9/53) of patients. Twenty-two patients (42%) achieved cCR after completion of the treatment. The median overall and progression-free survival was 45 and 14 months, respectively.

Conclusion. NAC without diagnostic laparoscopy for advanced müllerian carcinomas holds sufficient promise to be compared with direct surgery in a phase III trial.

Introduction

The standard treatment for advanced müllerian cancer (MC), such as ovarian, tubal, and peritoneal cancer, is primary debulking surgery (PDS) and postoperative chemotherapy. Previous studies have demonstrated that optimal debulking at the time of primary surgery improves patient survival [1–3]. Though optimal resection rates of experienced centers on gynecologic oncology reach up to 90%, optimal debulking can be achieved in only 30–60% of stage III/IV ovarian cancers in average institutions [1,2].

Retrospective analyses [4–7] have revealed that survival of the patients who received neoadjuvant chemotherapy (NAC) is comparable to that of patients who underwent direct PDS, even though the former group was older with more advanced disease and had a poorer performance status (PS). Thus, NAC appears to be useful at least for patients with far advanced ovarian cancer. However, NAC is allowed as an alternative to the standard treatment only in MC

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☆☆ This study is registered with Clinicaltrials.gov (identification number: NCT00112086) and with UMIN-CTR [www.umin.ac.jp/ctr/] (identification number: C000000005).

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patients with apparently unresectable bulky tumors or poor PS (NCCN guidelines).

European Organization for Research and Treatment of Cancer (EORTC) started a phase III study comparing NAC with the standard treatment for advanced MC [8] and thereafter, Medical Research Council Clinical Trials Unit (CTU-MRC) started similar phase III study in 2004 [identification number in Clinicaltrials.gov: NCT00075712]. In 2002, we also planned to conduct a phase III trial to compare NAC and direct PDS. At that time, we had little experience with NAC for treatment of advanced MC, including the possibly resectable cases. Thus, we planned to conduct a feasibility study of NAC before a phase III trial. The main purpose of the study was to assess the safety and efficacy of NAC with paclitaxel and carboplatin for advanced MC. The other purpose was to determine whether omission of the diagnostic laparoscopy (DLS) before NAC for advanced MC is possible by the use of imaging studies, cytological findings, and tumor markers. According to the current treatment guidelines, DLS or laparotomy to confirm the diagnosis and stage before NAC is mandatory. However, these procedures lead to a delay in the initiation of treatment and nullify the advantage of less invasiveness of NAC. Therefore, if ethically and medically acceptable, it seems desirable to omit the diagnostic procedure in the phase III trial.

The study protocol was designed by the Gynecologic Cancer Study Group of the Japan Clinical Oncology Group (JCOG) and was approved by the Clinical Trial Review Committee of JCOG on 6 December 2002 and activated on 14 January 2003 [9].

Patients and methods

Patient selection

The study subjects were patients with presumed stage III/IV MC clinically diagnosed by imaging studies (CT [computed tomography] or MRI [magnetic resonance imaging]) and cytological examination of ascites, pleural effusions, or fluids obtained by tumor centesis. Stage IV disease was diagnosed according to the routine FIGO staging. Diagnosis of stage III disease based on retroperitoneal lymph node metastasis was allowed only when swollen nodes were suspicious for metastasis by imaging studies and >2 cm in diameter. Malignancies of other origins, such as the breast and the digestive tract, when suspected from symptoms, physical examinations, or imaging studies, were ruled out by ultrasonography, endoscopy, or opaque enema. To efficiently rule out malignancies originating from the digestive tract, the criteria for the tumor markers were set as CA125 >200 U/ml and CEA <20 ng/ml. The further inclusion criteria were as follows: clinically deemed to be a candidate for debulking surgery without evidence of brain, bone, bone marrow, or multiple lung or liver metastases; presence of at least one measurable lesion; previously untreated for these malignancies and no history of treatment with chemotherapy or radiotherapy even for other diseases; aged between 20 and 75 years; Eastern Cooperative Oncology Group (ECOG) PS of 0 to 3; adequate organ functions; and written informed consent.

The exclusion criteria include intestinal occlusion necessary for surgical treatment; hypersensitivity to alcohol; and severe medical complications. More details of eligibility criteria were described previously [9].

Treatment plan

After enrollment, DLS was performed. Inspection of peritoneal cavity and biopsy from the main tumor or metastatic tumors was performed to confirm the clinical diagnosis of the origin, histology, and stage.

Four cycles of a combination of intravenous paclitaxel [over 3 h; day 1] and carboplatin [day 1], i.e., TC, were administered every 3 weeks as NAC. Before paclitaxel was administered, standard short premedication was used to avoid anaphylactic reactions. The dose of carboplatin was calculated from the formula of Calvert [10]. The creatinine clearance by the Cockcroft–Gault [11] equation was used as the glomerular filtration rate (GFR) in the formula. The creatinine clearance, body weight, and body surface area on entry into the study were used during all 4 cycles of NAC.

Interval debulking surgery (IDS) was performed after the fourth cycle of NAC, unless there was evidence of disease progression. The standard procedures in IDS comprised total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and maximal debulking of the metastatic tumors. Systematic pelvic and/or paraaortic lymphadenectomies were allowed, but not included in the standard procedure.

After IDS, an additional 4 cycles of chemotherapy was administered as postoperative chemotherapy (8 cycles in all). The creatinine clearance, body weight, and body surface area between IDS and the first cycle of postoperative chemotherapy were used during all 4 cycles of postoperative chemotherapy.

Modification of the treatment

Four dose levels were set for both paclitaxel and carboplatin. The initial dose of paclitaxel was 175 mg/m^2 (level 0), and the dose was reduced to 130 mg/m^2 (level −3) in decrements of 15 mg/m^2. The dose of carboplatin was reduced from the starting targeted area under the curve (AUC) of 6 (level 0) to 5, 4.5, and 4 (level −3) in a step-by-step manner. Even when the toxicities disappeared, the dose level was not restored to the previous dose level. The level during NAC was carried forward to postoperative chemotherapy.

Hematological toxicities that required a dose reduction of 1 level of both agents were grade 4 neutropenia observed in an interval of >3 days in the same cycle, neutropenic fever observed in an interval of >1 day in the same cycle, and grade 3 thrombocytopenia. Neurotoxicity that required a dose reduction of 1 level of paclitaxel alone was grade 2 sensory-neuropathy.

When the toxicities that required dose reduction were observed at the lowest level, or grade 3 sensory-neuropathy was observed at any dose level, the treatment protocol was discontinued. The other discontinuation criteria were progression of the disease, delay of chemotherapy for >2 weeks, delay of surgery from the planned time period, grade 3 allergic-reaction/hypersensitivity, grade 4 non-hematological toxicities, and misdiagnosis confirmed by DLS.

End points

The primary end point was the proportion of clinical complete remission (%cCR) among all patients with stage III/IV MC, whose diagnosis was confirmed by DLS. Clinical complete remission was defined as the disappearance of all lesions on CT or MRI, no pleural effusion on chest radiography, and a serum CA125 level of <20 U/ml upon completion of the treatment.

The secondary end points were positive predictive value (PPV) of the clinical diagnosis with regard to the origin and histology, FIGO stage, and overall clinical diagnosis among all the participants. The PPV of overall clinical diagnosis was the end point to decide whether we could omit DLS in the subsequent phase III study. Because laparoscopy was performed only in patients diagnosed as stage III/IV MC by clinical findings, it was not possible to use sensitivity or specificity to evaluate the accuracy of clinical diagnoses, therefore we adopted PPV. With regard to the histology, the histological diagnosis compatible with any of the epithelial ovarian carcinomas was considered as correct diagnosis. Concerning the diagnosis of stage, surgical stage III was considered as correct even if substage was different from prelaparoscopic stage III substage. Regarding prelaparoscopic stage IV disease, the diagnosis of the stage was correct irrespective of the peritoneal findings on DLS.

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The other secondary end points were the response rate to NAC, the proportion of patients who underwent IDS, progression-free survival (PFS) among patients whose clinical diagnosis was confirmed by laparoscopy, the operative morbidity, the adverse events, and the overall survival (OS) among all the enrolled patients. The response to NAC was assessed according to the RECIST (Response Evaluation Criteria In Solid Tumor) [12]. Grading of the adverse events was performed based on NCI-CTC (National Cancer Institute-common toxicity criteria) ver. 2.0.

Study design and statistical methods

The study was planned as a single-stage safety and efficacy study. Sample size calculation was primarily based on the binominal test for the primary end point. Forty-four patients were required when expected %cCR of 40% and an acceptable lowest %cCR of 20% with a one-sided alpha error of 0.05 and a beta error of 0.1. Additionally, the PPV of overall prelaparoscopic diagnoses was to be sufficiently confident to enable the omission of laparoscopy in the subsequent phase III study. Thus, Bayesian monitoring of PPV was planned, and it required 56 patients to have a 10% or lower Bayesian posterior probability that PPV is less than 90% in case of 3 false-positive patients assuming the prior distribution of Beta (9,1). The target sample size was determined to be 56, which is also sufficient for the primary end point. The planned accrual period was 1 year, and the follow-up period was 3 years. All analyses were performed using the SAS software release 9.1 (SAS Institute, Cary, NC).

Results

Patient characteristics

Fifty-six women were entered between January 2003 and February 2004. All but one patient were eligible for the study. The ineligible patient once fulfilled the eligibility 1 week before enrollment. However, the blood examination just before enrollment showed a slightly lower WBC and ANC than the eligibility. This patient was included in the following analysis, though this patient dropped out of the study during NAC due to myelo-suppression. The PS of all 56 patients at enrollment was 0 in 28 patients, 1 in 18 patients, 2 in 7 patients, and 3 in 3 patients. The median age at enrollment was 55 (range, 33–73) years. The median follow-up period of the living patients was 39 (range, 34–46) months at the data cutoff in February 2007.

Accuracy of the clinical diagnosis

DLS was performed in all enrolled patients. Laparoscopic findings and histological findings revealed all 56 patients had MC with a histology corresponding to epithelial ovarian carcinoma. Concerning the stage of the disease, the diagnosis was stage III/IV in 53 patients by laparoscopic findings in combination with prelaparoscopic findings of the presence of distant metastases, malignant pleural effusion, and lymph node metastases. The PPV of prelaparoscopic diagnosis concerning the origin and histology was 100% (56/56), and both the PPVs of prelaparoscopic diagnosis concerning the stage and overall diagnosis were 95% (53/56). The histology of the diseases misdiagnosed in stage were endometrioid adenocarcinoma in 2 and serous adenocarcinoma in 1. Table 1 shows the prelaparoscopic and laparoscopic diagnoses of the disease.

Compliance to the treatment

The compliance to the treatment protocol is depicted in Fig. 1. Six patients successfully completed the treatment algorithm once they were off protocol due to toxicities. In one patient, after the discontinuation criteria were fulfilled during NAC, a similar treatment consisting of 3 cycles of chemotherapy as NAC, IDS and 6 cycles of postoperative chemotherapy was performed. In the other 5 patients, the same treatment was administered at a reduced dose and/or a delayed schedule.

Table 1
Prelaparoscopic and laparoscopic diagnosis of the disease

	Prelaparoscopic diagnosis		Laparoscopic diagnosis	
Origin[a]	Ovary	48	Ovary	47
	Tube	4	Tube	7
	Peritoneum	10	Peritoneum	12
Histology[b]	Adenocarcinoma (not specified)	56	Adenocarcinoma (not specified)	18
			Serous	29
			Mucinous	2
			Endometrioid	5
			Undifferentiated	2
T classification	T1c	0	T1c	1
	T2c	4	T2c	5
	T3	52	T3a	0
			T3b	12
			T3c	38
Stage	III	38	IC	1
	IV	18	IIC	2
			IIIA	0
			IIIB	4
			IIIC	31
			IV	18

[a] Selection of 2 or 3 sites from among the ovary, fallopian tube, and peritoneum was allowed in both prelaparoscopic and laparoscopic diagnosis.
[b] Histology by prelaparoscopic diagnosis has been estimated from cytological findings.

Safety of the treatment

The mean number of cycles of chemotherapy was 7.0 (range, 1–9) cycles. Dose reductions of chemotherapy were performed in 42% (22/53) of patients and 11% (39/371) of cycles. Discontinuation of treatment due to toxicities or patients' refusal in relation to toxicities occurred in 9 patients except 6 patients who continuously received the treatment by deviation. Table 2 shows the major toxicities of the chemotherapy. Grade 4 hematological toxicities, particularly neutropenia (>70%) and anemia (≥15%), were frequently observed during both neoadjuvant and postoperative chemotherapy. Concerning neutropenia, 74% (39/53) of patients and 49% (182/371) of cycles required G-CSF support. Although more than 10% of patients experienced grade 3 neutropenic fever, grade 4 was not observed. Other grade 3 non-hematological toxicities were rarely observed except for gastrointestinal toxicities. As a non-typical adverse event, grade 4 cerebral infarction was observed in 1 patient.

In 47 patients who underwent IDS, the median duration of the surgery and median blood loss were 330 (130–735) min and 1284 (280–4565) ml, respectively. Gastrointestinal resection excluding appendectomy was performed in 9% (4/47) of patients, and splenectomy was performed in 6% (3/47) of patients. Repair of the ureter or the colon because of operative injury was performed in 6% (3/47) of patients. Grade 3 or 4 toxicities observed during and/or after surgery were grade 3 hypotension in 19% (9/47), grade 3 bleeding without thrombocytopenia in 77% (36/47), and grade 3 ileus in 4% (2/47). Blood transfusion other than autotransfusion was required in 72% (34/47); only autotransfusion was performed in 4% (2/47).

There was no treatment-related mortality. There were 2 unexpected events: a primary aldosteronism and a metachronous lung cancer after the treatment protocol. Both events were judged as unlikely to be related with the treatment protocol by the Data and Safety Monitoring Committee of JCOG.

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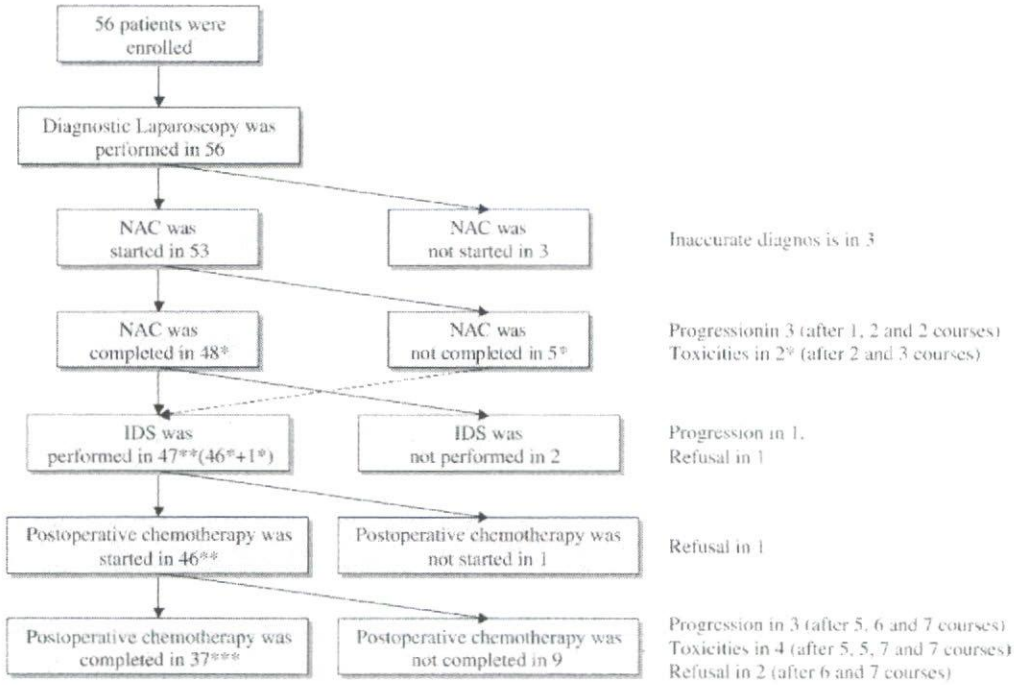

Fig. 1. Compliance of protocol treatment. Including 1 patients (*), 2 patients (**) and 6 patients (***) who deviated from the criteria for discontinuation. NAC, neoadjuvant chemotherapy; IDS, interval debulking surgery.

Efficacy of the treatment

Responses to chemotherapy after 4 cycles of NAC were evaluated in 48 patients who completed NAC. Partial response or CR was obtained in 41 patients (77% of 53 patients), SD was observed in 6 patients (11%), and PD was observed in 1 patient (2%) according to RECIST criteria.

IDS was performed in 47 patients (89% of 53 patients), including a patient who underwent IDS after 3 cycles of NAC. Complete resection of all tumors was obtained in 29 patients (55% of 53 patients), residual disease became <1 cm in 9 patients (17%) and ≥1 cm was left in 9 patients (17%).

The entire treatment protocol was completed by 37 patients and cCR was obtained in 22 patients (42% of 53 patients), including 6 and 3 patients who deviated from the discontinuation criteria. The primary end point of %cCR was 42% [95% CI: 28%–56%].

The median and 3-year PFS of 53 patients was 14 months and 19% (Fig. 2). The median and 3-year OS of 53 patients was 45 months and 60% (Fig. 3).

Discussion

The purpose of this study was to assess the safety and efficacy of NAC and to determine whether advanced MC can be accurately diagnosed on the basis of imaging studies, cytological findings, and tumor markers.

As far as the safety is concerned, treatment initiation with NAC is well known as a safe treatment [4–7,13,14]. There was no treatment-related mortality, the drug-induced toxicities were easily manageable, and surgical toxicities or severe complications were rare. In this study, the safety of NAC was reconfirmed by a prospective study.

Table 2
Drug-induced toxicities

Toxicities	Neoadjuvant chemotherapy (n=53)				Postoperative chemotherapy (n=46)			
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
Hematological								
Leukopenia	4%	34%	53%	9%	2%	17%	72%	9%
Neutropenia	0%	6%	19%	75%	2%	0%	24%	73%
Thrombocytopenia	13%	26%	23%	2%	17%	22%	43%	2%
Anemia	9%	49%	26%	15%	11%	52%	20%	17%
Non-hematological								
Neutropenic fever	–	–	15%	0%	–	–	11%	0%
Allergy/Hypersensitivity	9%	2%	0%	0%	4%	0%	0%	0%
Fatigue	42%	9%	4%	0%	41%	9%	0%	0%
Alopecia	11%	89%	–	–	11%	84%	–	–
Arthralgia	32%	11%	0%	0%	37%	2%	2%	0%
Neuropathy (sensory)	55%	9%	0%	0%	52%	15%	0%	0%
Myalgia	38%	13%	2%	0%	26%	2%	2%	0%
Nausea	43%	23%	11%	–	46%	13%	2%	–
Vomiting	13%	6%	9%	0%	9%	9%	2%	0%
Diarrhea	15%	4%	6%	0%	11%	2%	2%	0%

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Regarding the efficacy of NAC, cCR according to our definition was achieved in 22 patients (42%). It is difficult to compare our results with those of the previous studies targeting surgical stage III/IV ovarian cancer because our target was clinically diagnosed stage III/IV disease. In addition, our definition of cCR is stricter than general definition. We set the CA125 titer at <20 U/ml rather than <35 U/ml. Taking into account these differences, we set, at the beginning of the study, the expected %cCR as 40% and an acceptable lowest %cCR of 20% for the statistical analysis of the primary end point, based on the results of previous studies [15–19]. According to the calculation of the exact binominal distribution, the 95% confidence interval of the %cCR of the target population was 28%–56%. Even if we omit 3 patients with deviation from the discontinuation criteria, the 95% confidence interval of %cCR of the target population would be 23% to 50%. In either case, the null hypothesis "the true proportion of cCR is <20%" was rejected. Furthermore, the median PFS and OS of 53 patients with stage III/IV disease (14 and 45 months, respectively) in the present study also represent promising results comparable with the results of treatments consisting of PDS and postoperative chemotherapy in the previous reports [15,16,20]. Although two Gynecologic Oncology Group studies showed much better PFS and OS with PDS and postoperative intravenous chemotherapy (21 and 57 months) [21] and with PDS and postoperative intra-peritoneal chemotherapy (23 and 66 months) [22], the subjects of both studies were only patients who had undergone optimal surgery. Thus, our results may be comparable to those of the other reports. From the analysis, we confirmed that NAC for advanced MC is sufficiently effective to be compared with current standard treatment.

With regard to the accuracy of clinical diagnosis, the overall diagnosis of the tumor origin, histology, and stage was confirmed by DLS in 53/56 patients (95%). According to the Bayesian method, the Bayesian posterior probability that PPV is <90% was 9.96%, indicating that the appropriate target diseases for NAC can be diagnosed with >90% accuracy without the need for DLS. Although misdiagnosis may occur in <10% cases, the most probable misdiagnosis is the stage of disease. Misdiagnosis of the stage is acceptable rather than the misdiagnosis of the origin or histology because the treatment strategy for stage IC/IIC MC is primarily the same as that for stage III/IV MC. Thus, we concluded that we could omit the staging procedure in a phase III study. Owing to this omission, both treatment arms of the phase III trial would become more practical.

Based on our promising results, we have already started the phase III study, JCOG0602 [23], for comparing NAC followed by IDS with PDS followed by postoperative chemotherapy, on the same subjects of this study. A similar phase III study has already been conducted by EORTC and CTU-MRC. Our study and EORTC study have been designed to prove the non-inferiority of NAC as compared to the standard treatment. Because of the expected lower surgical morbidity and mortality associated with NAC, NAC should become the new standard treatment for patients with advanced MC if the non-inferior OS and lower treatment related morbidity and mortality are proven. The distinctiveness of our new study is that it omits the staging procedures, such as DLS, required in this feasibility study, implying the deletion of an extra procedure in both treatment regimens; thus, our new study highlights the advantage of NAC. Our ongoing phase III study should make it possible to compare both treatments in a more practical setting. From the results of ongoing phase III studies including our study, it is hoped that a new standard treatment regimen is established.

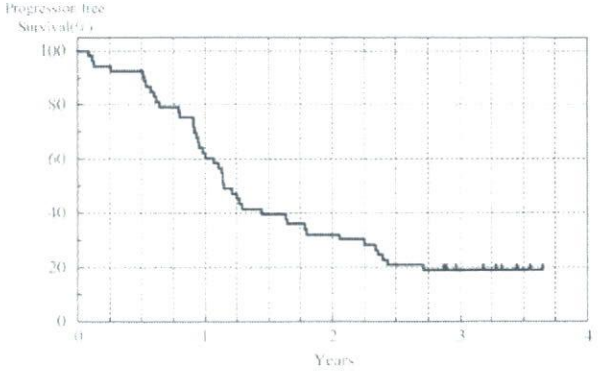

Fig. 2. Progression free survival of patients who received protocol treatment ($n=53$).

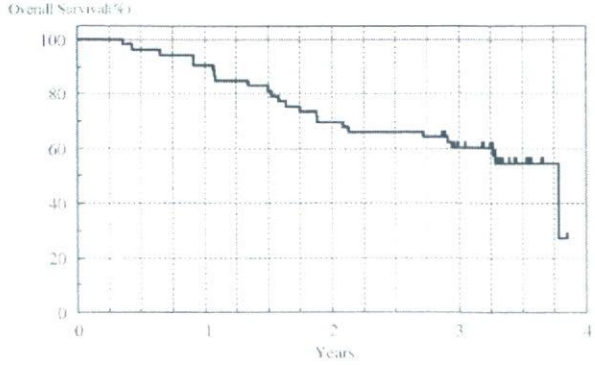

Fig. 3. Overall survival of patients who received protocol treatment ($n=53$).

Conflict of interest statement

All authors declare that there are no conflicts of interest.

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Phase III Trial of Upfront Debulking Surgery Versus Neoadjuvant Chemotherapy for Stage III/IV Ovarian, Tubal and Peritoneal Cancers: Japan Clinical Oncology Group Study JCOG0602

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On the basis of promising results of neoadjuvant chemotherapy (NAC) in our previous study (JCOG0206), we have been performing a Phase III study of treatment starting with NAC versus standard treatment starting with primary debulking surgery (PDS) for Stage III/IV müllerian carcinomas (ovarian, tubal and peritoneal carcinomas) since November 2006. The purposes are to prove the non-inferiority of the efficacy and to show the decrease in adverse effects resulting from reduced surgical invasiveness of treatment starting with NAC. Three hundred patients with advanced müllerian carcinomas will be randomized during 3 years. NAC arm patients undergo four cycles of NAC with paclitaxel plus carboplatin followed by interval debulking surgery and an additional four cycles of postsurgical chemotherapy. Standard arm patients undergo PDS and eight cycles of postsurgical chemotherapy with or without interval debulking surgery. The primary endpoint is overall survival. The major secondary endpoints are the incidence of adverse events and parameters representing surgical invasiveness.

Key words: ovarian neoplasms – neoadjuvant therapy – interval debulking surgery – primary debulking surgery

INTRODUCTION

The current standard treatment for advanced müllerian cancer is primary debulking surgery (PDS) followed by postsurgical chemotherapy. Better prognosis can be expected in cases in which optimal debulking can be achieved. Unfortunately, optimal debulking in the primary surgery can be achieved in only 30–60% of Stage III/IV müllerian cancers in average institutions (1,2), and the prognosis of patients with advanced müllerian cancers is poor. Neoadjuvant chemotherapy (NAC) has been recognized as a possible approach to improve the prognosis of these patients. In initial studies, NAC was chosen for patients with apparently unresectable bulky tumors or poor performance status as an alternative treatment to primary surgical debulking. Retrospective analyses (3–7) revealed that progression-free and overall survival were comparable between patients treated with NAC followed by interval debulking surgery (IDS) and those treated with PDS, though the former group had more advanced disease and poorer performance status. On the basis of these favorable results of NAC for patients with advanced disease or poor performance status, the target disease was extended to all cases of advanced disease, including patients without apparently unresectable tumors and good performance status in prospective studies. The European Organization for Research and Treatment of Cancer (EORTC) is conducting a Phase III study comparing neoadjuvant setting treatment with standard treatment for advanced müllerian cancers (8). We conducted a Phase II study of NAC with paclitaxel plus carboplatin followed by IDS and postsurgical chemotherapy as the study of the Japan

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Clinical Oncology Group (JCOG0206) (9). In the study, we assessed the safety and efficacy of NAC treatment, and also assessed whether we can accurately diagnose advanced müllerian cancer based on clinical findings, including imaging studies, cytologic findings and tumor markers. Although the final survival results of this Phase II study are awaited, we have started the Phase III trial on the basis of the efficacy and diagnostic accuracy shown in the study (10). Our study is basically similar to the EORTC study, with the aim of comparing NAC treatment with standard treatment for advanced müllerian cancer. One of the distinct points of our study is omitting the diagnostic surgical procedure, such as laparoscopy or laparotomy, based on the results of our above-mentioned previous study. This means the elimination of an extra procedure for the purpose of the clinical trial in both treatment arms and it has the advantage of making it possible to start NAC treatment earlier. In our study, it is possible to compare the two treatment protocols under clinically relevant conditions. Another distinct point is the number of cycles of chemotherapy. Since the study subjects are patients with evidently advanced disease according to clinical findings, we administer a total of eight cycles of chemotherapy in both treatment arms instead of the standard of six cycles.

The study protocol was designed by the Gynecologic Cancer Study Group (GCSG) of the Japan Clinical Oncology Group (JCOG), approved by the Protocol Review Committee of JCOG on 18 October 2006 and activated on 17 November 2006. This trial was registered at the UMIN Clinical Trials Registry as UMIN000000523 (http://www.umin.ac.jp/ctr/index.htm).

PROTOCOL DIGEST OF THE JCOG0602

Purpose

The purposes are to prove the non-inferiority of the efficacy and to show the decrease in adverse effects due to reduced surgical invasiveness of treatment starting with NAC with paclitaxel plus carboplatin compared with standard treatment starting with PDS for stage III/IV müllerian carcinomas.

Study Setting

A multi-institutional (30 centers) randomized Phase III trial.

Resources

Health Sciences Research Grants for the Third Term Comprehensive Control Research for Cancer (Nos. h16-035, h19-028) and Grants-in Aid for Cancer Research (Nos. 17S-1, 17S-5, 17-12), from the Ministry of Health, Labor and Welfare, Japan.

Endpoints

The primary endpoint is overall survival among all eligible patients. Secondary endpoints concerning the efficacy of the treatments are as follows: (i) proportion of clinical complete remission (%cCR) among all eligible patients, (ii) progression-free survival among all eligible patients, (iii) response rate to NAC among patients assigned to the NAC arm. Clinical complete remission is defined as the disappearance of all lesions by computed tomography (CT) or magnetic resonance imaging (MRI), no pleural effusions by chest radiography and normal serum CA125 level ($<$20 U/ml) after completion of the protocol treatment. Secondary endpoints concerning the safety and surgical invasiveness of the treatments are as follows: (i) adverse events, (ii) number of times of surgery, (iii) total duration of the surgery, (iv) total amount of blood loss, (v) amount of blood transfusion during protocol treatment, (vi) amount of blood plasma, plasma expander and albumin infusion during protocol treatment, among all treated patients.

Eligibility Criteria

Inclusion Criteria

The study subjects are patients diagnosed with Stage III or IV ovarian, tubal or peritoneal carcinoma. The diagnosis is based on both imaging studies (CT or MRI, and chest radiography) and cytology/histology of ascites, pleural effusion or fluid/tissue obtained by tumor centesis. Malignancies of other origins, such as breast and digestive tract, should be excluded by endoscopy, opaque enema, or ultrasonography when these malignancies are suspected from symptoms, physical examination or imaging diagnosis. To rule out malignancies of digestive tract origin, the criteria for tumor markers are set to be CA125 $>$200 U/ml and CEA $<$20 ng/ml.

Further inclusion criteria are (i) the patient is clinically deemed to be a candidate for debulking surgery without evidence of brain, bone or bone marrow metastases, (ii) previously untreated for these malignancies and have no history of treatment with chemotherapy or radiotherapy for other diseases, (iii) age 20–75 years, (iv) Eastern Cooperative Oncology Group (ECOG) performance status of 0–3, (v) adequate bone marrow, hepatic, renal, cardiac and respiratory functions and (vi) written informed consent.

Exclusion Criteria

Exclusion criteria are (i) synchronous or metachronous (within 5 years) malignancy other than carcinoma *in situ*, (ii) pregnant or nursing, (iii) severe mental disorder, (iv) systemic and continuous use of steroidal drugs, (v) positive for serum hepatitis B surface antigen, (vi) active infections, (vii) uncontrolled hypertension, (viii) diabetes mellitus, uncontrolled or controlled with insulin, (ix) history of cardiac failure, unstable angina, myocardial infarction within 6 months prior to registration, (x) intestinal occlusion requiring surgical treatment, (xi) hypersensitivity to polyoxyethylated castor oil and (xii) hypersensitivity to alcohol.