III. 子宮体癌

子宮体癌の治療
化学療法—概論—

Recent outline to chemotherapy for uterine endometrial cancer

渡部　洋
星合　昊

Key words　endometrial cancer, chemotherapy, clinical trial

はじめに

子宮体癌に対する化学療法は，骨盤・傍大動脈リンパ節転移陽性例や腹腔洗浄細胞診陽性例などのextra uterine spreadが認められる症例，あるいは脈管侵襲や深部筋層浸潤を有する進行例，更に再発例といった全身疾患ととらえられるべき病態を有する症例に対して予後改善が期待されている．

しかし，これまで進行体癌におけるadjuvant therapyの主体は放射線療法と考えられており，実際にNational Comprehensive Cancer Network (NCCN) practice guidelineでは，完全手術が遂行されたFIGO stage I, II例に対するadjuvant therapyの適応は摘出組織の組織分化度にもよるが放射線治療が推奨されており，化学療法はFIGO stage IIIa以上の症例に対する選択肢としてchemotherapy(±radiation therapy)と記載されているにすぎない．

体癌の大部分がchemosensitiveと考えられる類内膜腺癌であるのにもかかわらず化学療法が治療optionの一策にとどまっている原因には，歴史的に放射線治療への信頼性が高いこと，あるいは体癌化学療法に関する臨床試験が単剤phase II studyを中心に行われてきたため，卵巣癌において展開されてきた系統的な大規模phase III studyによる新規regimenの検証や移行が行われてこなかったことなどがある．現実的に我が国においても体癌に保険適応を有する薬剤が少ないため，体癌化学療法は各種regimenの有効性の比較検証が行われないまま卵巣癌化学療法の変遷に準じた治療regimenが適応されてきた感は否めない．しかし近年国内外において体癌化学療法に対するregimen検証の気運が高まっており，特に卵巣癌に対して良好な治療成績を有するタキサン系抗癌剤を中心とした効果的な新規薬剤の出現によって，我が国においても新たな臨床試験が進行してきている．

そこで本稿においては近年に至る体癌化学療法の動向と現況および今後の方向性について概説する．

1. Single-agent chemotherapy

体癌に対してはphase II studyからanthracycline系薬剤特にadriamycin(doxorubicin)の有効性が報告されており，国内外においてadriamycin(ADM)が体癌化学療法のkey-drugとして用いられてきている．anthracycline系薬剤の単剤phase II studyではADMに37%[1]と最も高い奏効率が得られており，一方anthracyclin analogではepirubicinで26%[2]，pirarubicinでは10%とやや低率である結果が報告されてい

Yoh Watanabe, Hiroshi Hoshiai: Department of Obstetrics and Gynecology, Kinki University School of Medicine
近畿大学医学部産科婦人科

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る．また近年新規anthracycline系薬剤として注目されているpegylated liposomal doxorubicinについても既にphase II studyが行われており，paclitaxel/platinumあるいは放射線治療歴を有する進行体癌を対象としたstudyであるにもかかわらず，奏効率21%[3]と良好な成績が示されていることから，今後卵巣癌のみならず体癌に対する早期適応が期待されている．このようにADMの体癌化学療法におけるkey-drugとしての優位性は広く認知されてきたが，近年卵巣癌を中心として良好な治療成績が確認されているタキサン系抗癌剤の体癌に対する有効性検証の期待が高まってきた．paclitaxelについては，既にGynecologic Oncology Group(GOG)および欧州において単剤phase II studyが行われており，奏効率36-37%[4,5]とADMとほぼ同等の治療成績が示されている．我が国においてもpaclitaxel，docetaxelの両タキサン系抗癌剤について体癌治療に関する保険適応を望む声が多いが，2003年には既に両薬剤ともに保険収載のためのphase II studyが終了しており，有効性と安全性の解析を待って早晩保険適応が認められる見込みである．

また体癌は一般的にestrogen dependentと考えられているため，anti-estrogenic activityを有する薬剤を用いたhormonal therapyについてもphase II studyが行われている．これらの薬剤では，特にmedroxyprogesterone acetate(MPA)に良好な奏効性が認められているが，他の薬剤には有効な奏効性は認められていない．したがってhormonal therapyはsteroid hormone receptorの発現レベルによって有効性が異なる可能性を有することや，多剤併用療法への適応においてsynergic effectsを発現させる薬理学的根拠が得難いことなどから，現時点ではtumor dormancyによるlong-term no change(long NC)を目的としたsalvage therapyへの応用が主と考えられている．

表1に主な薬剤の体癌に対するphase II studyの成績を示したが，現在のところ単剤で30%を越す奏効率が得られている薬剤はADMとpaclitaxelのみであり，併用化学療法への移行における認容性を考慮すると体癌化学療法のkey-drugは将来的にADMからタキサン系抗癌剤へ移行していくものと考えられる．

表1 体癌に対する単剤化学療法の直接効果

agent	response rate (%)
doxorubicin	37
epirubicin	26
pirarubicin	10
pegylated liposomal doxorubicin	21
cisplatin	20
carboplatin	24
cyclophosphamide	14
ifosfamide	15
vincristine	18
vinblastine	8
etoposide(oral)	14
topotecan	20
medroxyprogesterone acetate	25
tamoxifen	10
danazol	0(SD: 27)
leuprolide	0(SD: 32)
paclitaxel	36-37

2. Combination chemotherapy

体癌に対する多剤併用化学療法では前述のごとくADMがkey-drugと考えられており，更に多癌種における化学療法の中心的薬剤であるcisplatin(CDDP)が単剤で20%[6]の奏効率が得られていることから，主にADMとCDDPを含むregimenあるいはADMの認容性が考慮されたADMとcyclophosphamide(CPA)の併用regimen(AC)の検討が行われてきた．ただし実際に使用されるregimenは，欧米ではAP(ADM+CDDP)が広く用いられているが，我が国においては卵巣癌化学療法において経験の多いCAP(CPA+ADM+CDDP)が一般的に用いられている．

これらADM-base併用regimenの治療成績は，APで奏効率33-81%[7]，ACで31-46%[8]，一方CAPでは31-56%[9]と報告されているが，ADM単剤(60 mg/m^2)とのphase III studyによる比較

表2 体癌に対する併用化学療法の直接効果

regimen	response rate (%)
ADM-base	
doxorubicin+cisplatin (AP)	33-81
doxorubicin+cyclophosphamide (AC)	31-46
doxorubicin+cyclophosphamide+cisplatin (CAP)	31-56
taxane-base	
paclitaxel+doxorubicin (TA)	43
paclitaxel+doxorubicin+cisplatin (TAP)	57
paclitaxel+cisplatin (TP)	67
paclitaxel+carboplatin (TJ)	78
others	
vinorelbine+cisplatin (VP)	57
etoposide+5-FU+cisplatin	41
methotrexate+5-FU+carboplatin+MPA	74
methotrexate+vinblastine+doxorubicin+cisplatin	67
doxorubicin+5-FU+etoposide+cisplatin	45

試験ではAC (A; 60 mg/m^2+CPA; 500 mg/m^2)[10], AP (A; 60 mg/m^2+CDDP; 50 mg/m^2: GOG 107) いずれのregimenにおいても併用療法に奏効率あるいは生存期間がやや良好である結果が得られているものの，併用化学療法に明らかな統計学的優位性は証明されてはこなかった．更に近年The European Organization of Research and Treatment of Cancer (EORTC) からも化学療法感受性の進行・再発体癌を対象としたADM単剤とAPのcomparative phase III study (EORTC 55872) の結果が報告されたが[11]，これまでの報告と同様にAPはADM単剤に比較して有意に奏効率が高率であるが，生存については有意差を認めなかったとされている．

またAPについては1993年に米国GOGのphase II studyからcircadian-timed chemotherapyの有効性が報告され注目されたが，近年のphase III study (GOG 139) によってそのbenefitについては否定[12]されている．

このようにADM-baseの併用化学療法が生存においてADM単剤化学療法を凌駕できない現状から，現在は単剤化学療法と同様にタキサン系抗癌剤をbaseとした新規regimenの設定と検証が望まれている．既に，paclitaxelを用いた併用化学療法の有効性については幾つかのphase II，III studyが進行しており，近年のphase II studyではpaclitaxel 175 mg/m^2+CDDP 75 mg/m^{2}の併用 (TP) で奏効率67%[13]，一方paclitaxel 175 mg/m^2+carboplatin AUC=5-7の併用 (TJ) では奏効率78%[14]という驚異的な成績が報告されている．

またphase III studyでは1996年にGOGにおいてAP (A; 60 mg/m^2+CDDP 50 mg/m^2) とADM+paclitaxel (A; 50 mg/m^2+paclitaxel 150 mg/m^2, 24 h) の比較試験 (GOG 163) が行われたが，奏効率および生存期間のいずれについても両群間に有意差が認められなかった．更に1998年から同様にGOGにおいて，ADM+paclitaxel+CDDP (A; 45 mg/m^2+paclitaxel 160 mg/m^2, 3 h+CDDP 50 mg/m^2: TAP) とAP (A; 60 mg/m^2+CDDP 50 mg/m^2) の比較試験 (GOG 177) が行われ，奏効率はAP 33.3%，TAP 56.7%とTAPが勝ったもののtoxicityによるoff treatmentがAPにおいては9.8%であったのに対してTAPでは23.9%に認められたため，現時点では認容性の面からTAPの臨床適応性を疑問視する意見が多い．なお，APとTAPの比較については現在EORTCにおいてもGOGと同様のcomparative phase III study (EORTC 55984) が進行しており，体癌に対するTAPの有効性および認容性の再

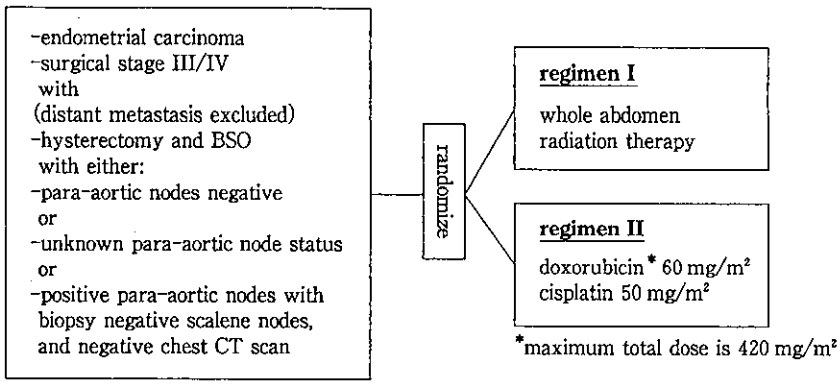

図1 GOG 122

検証結果が待たれる.

表2に体癌に対する主な併用化学療法の奏効率を示した. 各regimenの成績をみると, 現在のところ併用regimenではpaclitaxel+platinumの有効性が期待されるが, 将来的にAP, CAPなどのADM-base併用regimenあるいはTAPとのcomparative phase III studyによる有効性の検証が必要となるであろう.

また体癌に対するtaxanes-based併用regimenの有効性の検討については, 我が国でも2003年末より婦人科悪性腫瘍化学療法研究機構(Japan Gynecologic Oncology Group: JGOG)によって, 進行・再発体癌を対象としたpaclitaxel+carboplatin(paclitaxel 180 mg/m²+carboplatin AUC=6: TJ), docetaxel+carboplatin(docetaxel 60 mg/m²+carboplatin AUC=6: DJ), docetaxel+CDDP(docetaxel 70 mg/m²+CDDP 60 mg/m²: DP)の3-arm randomized comparative phase II study(JGOG 2041)がactivateされている. 本試験は体癌に対して, 複数のタキサン系抗癌剤と複数の白金錯体系抗癌剤を用いた各regimenの有効性を検証するものであり, 我が国から体癌に対する新たな治療regimenの発信が期待される興味深いstudyである.

3. Adjuvant chemotherapy

近年, 進行体癌に対するadjuvant chemotherapyの有効性について放射線療法との比較から検証したphase III studyがGOGによって行われ(GOG 122, 図1), 既に389人の症例集積が完了しAmerican Society of Clinical Oncology(ASCO)のannual meetingにおいて早期解析結果が報告された. 本試験はstage III/IVの進行体癌に対する術後adjuvant therapyとしてのchemotherapy(doxorubicin 60 mg/m²+CDDP 50 mg/m²: AP)とradiation therapy(whole abdominal irradiation: WAI)の有効性を比較検証した興味深いclinical trialであり, 現時点ではAPがWAIをprogression free survival, overall survivalともに勝るとする報告が行われたため注目を浴びている.

GOG statistical reportによると, hematologic toxicityがAPに高いことやWAIにおいて肺・脳・脊椎への再発の多い傾向などが報告されている. ただし, 治療関連死が9人(AP: 5, WAI: 4)に認められたため, GOGでは現在本試験の最終解析を行うとともに, platinum-agentをEORTCの単剤phase II studyから24%[15]の奏効率が得られているcarboplatinへ変更の可能性についても検討を行っている模様である. いずれにせよ本試験は進行体癌治療における化学療法の優位性が証明される可能性のある興味深いstudyであり, EORTCの試験結果を含めた最終解析結果が待たれる.

また頸癌については米国National Cancer InstituteからCDDP concurrent chemoradiationの有効性についてclinical announcementが行われ, 我が国においても実地臨床に応用され始めて

いるが，体癌についてはまだphase IIを含めてclinical trialは行われていない．化学療法と放射線療法のいずれもが体癌治療の標準的治療として広く応用されてきたことを考慮すると，併用薬剤の検討を含めたconcurrent chemoradiationの有効性の検討は，体癌に対するadjuvant therapyの一法として将来的な検証が必要となるかもしれない．

おわりに

NCCN practice guidelineでは体癌のsalvage chemotherapyの項に，推奨される薬剤の記載に加えて'strongly encourage clinical trial'と記載されており，現時点における体癌化学療法は効果的な新規薬剤の開発と系統的なregimenの検証が望まれる未知の分野といえる．

癌化学療法には，奏効率および生存率の改善を含む高い治療効果の達成，有害事象の抑制による認容性の改善，および2剤あるいは3剤併用を原則としたよりsimpleなregimenの設定が求められる．これらの諸点を考慮し，これまでの体癌に対するclinical trialの成績をみると，今後体癌化学療法はtaxanes+platinumの併用regimenを中心とした検証が進行するものと考えられる．

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II. 子宮頸癌

子宮頸癌の治療
血中ヘモグロビン値と再発率

Hemoglobin level and recurrent rate of uterine cervical cancer

上田晴彦
渡部　洋
星合　昊

Key words　子宮頸癌，血中ヘモグロビン値，tumor hypoxia

はじめに

子宮頸癌の予後因子についてはこれまでに数多くの検討が行われ，臨床進行期をはじめとした年齢などの患者因子，組織型・腫瘍体積・リンパ管侵襲あるいはリンパ節転移などの病理組織学的因子，血清腫瘍マーカー・血管新生因子活性などの生理学的因子，更にはp53，c-erb B2などの遺伝子学的因子など種々の予後因子の有用性が報告されてきた．更に近年では，腫瘍の低酸素状態(tumor hypoxia)が固形癌における腫瘍進展や治療抵抗性と関連する新たな予後因子として注目されており，子宮頸癌においてもtumor hypoxiaの予後因子としての有用性[2-4]が精力的に検討されてきている．特に患者血中ヘモグロビン値はtumor hypoxiaを簡便に反映する臨床的因子[1]であるとされ，治療前あるいは治療中に生じる血中ヘモグロビン値の低下は治療反応性および長期予後の改善の視点から綿密な管理が必要とされている．

そこで本稿では，子宮頸癌患者における血中ヘモグロビン値の予後因子としての意義について基礎・臨床の両面から，教室の成績および文献的考察を交えて解説する．

1. 腫瘍低酸素状態(tumor hypoxia)と腫瘍増殖・進展

近年の研究によると低酸素状態におかれた腫瘍は，hypoxia-inducible factor(HIF)-1 alphaあるいはHIF-2 alphaといった生理活性因子の発現を生じ，特にHIF-1 alphaはvascular endothelial cell growth factor(VEGF)，platelet-derived endothelial cell growth factor(PDECGF)などの血管新生因子(angiogenetic factors)発現の促進[2,3]や腫瘍細胞のapoptosisの抑制[4]を惹起するため，腫瘍発育や進展と有意な関連性を有することが報告されている．また実験動物を用いた研究から，慢性貧血によってHIF-1 alphaの発現が誘導されることやHIF-1 alphaの過剰発現がerythropoietin geneの発現や組織への酸素運搬および酸素低下に対する組織適合性に関連する遺伝子の発現を抑制することが確認されており，血中ヘモグロビン値の低下はtumor hypoxiaによるHIF-1 alphaの過剰発現を介して腫瘍増殖に間接的に関与するものと推定されている．

2. 放射線治療と血中ヘモグロビン値

tumor hypoxiaは子宮頸癌に対する放射線治療の治療抵抗性因子[5,6]としても報告されており，

Haruhiko Ueda, Yoh Watanabe, Hiroshi Hoshiai: Department of Obstetrics and Gynecology, Kinki University School of Medicine　近畿大学医学部産科婦人科

0047-1852/04/¥50/頁/JCLS

腫瘍内酸素濃度の直接測定を行って放射線の治療効果と比較検討した研究によると，%P_{O_2} <5 mmHgを示す頸癌では放射線治療後の予後が有意に不良であると報告されており，tumor hypoxiaの有効な管理の必要性が示唆されている．

前述のごとく血中ヘモグロビン値の低下はtumor hypoxiaを簡便に反映する因子とされており，Grinskiら[7]によると放射線治療が行われた進行子宮頸癌を対象とした検討成績では，血中ヘモグロビン値10 g/dlを境界値として予後と相関し，更に放射線治療中に輸血によって予後の改善が認められたと報告している．またThomasら[8]も同様の検討から，血中ヘモグロビン値12 g/dlを境界値として予後との相関性が認められ，更に治療前の血中ヘモグロビン値(base line hemoglobin value)よりも治療週ごとの平均最低ヘモグロビン値(average weekly hemoglobin nadir)がより有意な関連性を有すると報告している．

このように放射線治療を行う進行頸癌における血中ヘモグロビン値は簡便な治療効果推定因子と考えられていたが，実際的な放射線治療中の血中ヘモグロビン値の有効な管理法については不明であった．しかし近年recombinant erythropoietin(r-HuEPO)により放射線治療中の血中ヘモグロビン値が効果的に改善するとの報告[11]が行われ，臨床的な有用性が注目されている．更に報告では200 U/kg/dayのr-HuEPO投与群は非投与群に比較して有意に血中ヘモグロビン値の改善とともに治療効果，局所再発率，生存率のいずれもが良好であるとされており，現在Gynecologic Oncology Group(GOG)においてもcisplatin concurrent chemoradiationを行う進行頸癌に対するr-HuEPOを用いた血中ヘモグロビン値の管理について生存への寄与効果をphase III randomized comparative study (GOG 191)で検証が行われている．

3. 放射線治療における血中ヘモグロビン値と再発率

教室において放射線単独療法が行われた子宮頸癌における血中ヘモグロビン値と再発率について，stage IIIb扁平上皮癌22例を対象にretrospectiveに検討を行った．この結果，治療前の平均血中ヘモグロビン値(base line hemoglobin value)では10 g/dlを境界値として再発率(57.1 % vs 33.3 %)に有意差($p<0.001$)が認められ，また治療中の血中ヘモグロビン最低値(nadir hemoglobin)との関連性では9 g/dlを境界値として再発率(60.0 % vs 35.3 %)に有意差($p<0.001$)が認められた．一方，最も予後との関連性が深いとされる，治療週における最低ヘモグロビン値(average weekly hemoglobin nadir)での検討では再発率に一定の関連性は認められなかった(**表1**)．更に再発症例における再発までの期間(time to relapse)と血中ヘモグロビン値の関連性についても検討を行ったが，base line hemoglobin value，nadir hemoglobin，average weekly hemoglobin nadirのいずれの因子を用いた検討でも再発までの期間との有意な関連性は認められなかった．本検討はretrospective studyであり症例数の関係からmultivariate analysisが行えなかったため，血中ヘモグロビン値の放射線治療頸癌における再発推定因子としての有用性を論ずるにはまだ不十分ではあるが，血中ヘモグロビン値は進行頸癌における新たな予後因子である可能性が推察された．

表1 血中ヘモグロビン値と再発率

factor	recurrent rate	p value
base line Hb value		
<10.0 g/dl	57.1 %(4/ 7)	p<0.001
10.0 g/dl ≦	33.3 %(5/15)	
nadir Hb		
<9.0 g/dl	60.0 %(3/ 5)	p<0.001
9.0 g/dl ≦	35.3 %(6/17)	
average weekly Hb nadir		
<10.0 g/dl	42.9 %(3/ 7)	NSD
10.0 g/dl ≦	40.0 %(6/15)	
<9.0 g/dl	50.0 %(1/ 2)	NSD
9.0 g/dl ≦	40.0 %(8/20)	

Hb: hemoglobin

おわりに

子宮頸癌の予後因子としての血中ヘモグロビン値の有用性および臨床応用についてはまだ明らかとはいえないが，教室における検討結果や諸報告における成績をみると，少なくとも子宮頸癌においては積極的に血中ヘモグロビン値の管理を行うことが必要であると考えられる．近年tumor hypoxiaを画像診断を用いて診断する試みも始まっており，Cooperら[9]はgadoliniumを用いたenhanced MRIにより，Krishnaら[10]はOxo 63を用いたenhanced MRIによってtumor hypoxiaの画像診断が可能であると報告している．これらの方法はまだ実験段階の域を出ないが，今後臨床応用が可能となれば子宮頸癌の新たな予後因子の確立について有用な情報を与えるものと考えられる．

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Clinical experience with combination paclitaxel and carboplatin therapy for advanced or recurrent carcinosarcoma of the uterus

Masafumi Toyoshima,[a,*] Jun-ichi Akahira,[a] Gen Matsunaga,[b] Hitoshi Niikura,[a] Kiyoshi Ito,[a] Nobuo Yaegashi,[a] and Toru Tase[b]

[a] *Department of Obstetrics and Gynecology, Tohoku University Graduate School of Medicine, Sendai, Japan*
[b] *Division of Gynecology, Miyagi Prefecture Cancer Research Center, Miyagi, Japan*

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Abstract

Objective. The purpose of the study was to evaluate the efficacy of combination chemotherapy with paclitaxel and carboplatin in patients with advanced or recurrent carcinosarcoma of the uterus.

Methods. A retrospective review was carried out at Miyagi Prefecture Cancer Research Center Hospital. Six patients pathologically diagnosed with uterine carcinosarcoma were treated with paclitaxel (175 mg/m^2 given intravenously over 3 h) and carboplatin (dosed at AUC 6) every 3 weeks at our center between 1997 and 2003. Responses and adverse effects were assessed according to Response Evaluation Criteria in Solid Tumors and National Cancer Institute—Common Toxic Criteria, respectively.

Results. All six patients were evaluable for toxicity, and no unacceptably severe toxicities were reported. Grades 3 and 4 hematologic toxicities occurred, but all of them were overcome by adequate treatment with granulocyte colony-stimulating factor and blood transfusions. Five of six patients had measurable disease and thus were evaluable for response: Four patients had a complete response (CR) and the remaining patient had progressive disease (PD). The median progression-free interval (PFI) for all six cases was 18 months, with a median overall survival of 25 months.

Conclusions. Although the number of cases was small, the regimen evaluated in the current study demonstrated higher activity and lesser toxicity than those found in previous studies in patients with advanced or recurrent uterine carcinosarcoma. Additional phase II clinical studies are necessary to evaluate fully the benefits of this regimen.

Keywords: Uterus; Carcinosarcoma; Malignant mixed mullerian tumor; Chemotherapy; Paclitaxel; Carboplatin

Introduction

Carcinosarcoma (CS) of the uterus, also known as malignant mixed mullerian tumor, is a rare and aggressive neoplasm that contains both carcinomatous and sarcomatous histologic elements. The overall prognosis of uterine CS is extremely poor due to a high tendency to spread and associated with high relapse rate even after local therapy such as surgery, radiation, or both. Although total hysterectomy with surgical staging is regarded as a standard treatment for patients with early-stage disease, 53% of patients with clinical stage I–II uterine CS developed recurrent disease within 5 years of initial therapy [1]. Adjuvant pelvic radiotherapy seems to improve local disease control, but it has not had a significant impact on overall survival due to the propensity of the disease to recur in a distant location [2,3]. These data indicate that up to half of all patients diagnosed with uterine CS are potential candidates for chemotherapy.

Development of systemic chemotherapy against CS is an urgent issue, and some drugs have been examined as single-agent therapy with response rates as follows: 16–19% with adriamycin [4,5], 32–36% with ifosfamide [6,7], 19% with cisplatin [8], and 18% with paclitaxel [9]. Combination regimens have not proven to be more effective than therapy with the single-agent ifosfamide. Only two combination regimens have been reported to be superior to single-agent

* Corresponding author. Department of Obstetrics and Gynecology, Tohoku University Graduate School of Medicine, 1-1, Seiryo-machi, Aoba, Sendai 980-8574, Japan. Fax: +81-22-717-7258.
E-mail address: m-toyo@mail.tains.tohoku.ac.jp (M. Toyoshima).

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ifosfamide in their response rates [7,10], but adverse effects with these combinations were unacceptably severe, and these combinations have not been justified as standard treatment because of toxicity. For all of these reasons, there is a continuing need to identify other active agents and combinations that are effective against this aggressive malignancy.

Recently, convincing evidence has suggested that most cases of uterine CS are monoclonal in original rather than true collision tumors [11,12]. These data indicate that uterine CS may be metaplastic, with the implication that the sarcomatous components of CS are derived from its carcinomatous elements [13]. In this point of view, McCluggage [13] pointed out that chemotherapeutic regimens effective with aggressive high-grade endometrial carcinoma should also be effective with uterine CS. For advanced or recurrent endometrial carcinoma, the combination of doxorubicin and cisplatin is currently considered standard first-line chemotherapy [14]. In addition, Fleming et al. reported that 3-h paclitaxel plus the combination of doxorubicin and cisplatin with granulocyte colony-stimulating factor (G-CSF) produced an improvement in overall survival with the price of additional peripheral neuropathy, compared to the combination of doxorubicin and cisplatin, as reported for the Gynecologic Oncology Group (GOG) protocol #177 (ASCO, 2002). Furthermore, recent studies have reported the efficacy of single-agent paclitaxel [15], and many more cases of combination paclitaxel plus carboplatin for patients with advanced or recurrent endometrial carcinoma are reported [16–19].

With these backgrounds, we examined the efficacy of paclitaxel and carboplatin regimen in patients with advanced CS of the uterus.

Patients and methods

Records for the Department of Gynecology, Miyagi Prefecture Cancer Research Center Hospital, for the years 1997 through 2003 were retrospectively reviewed. We identified six cases with pathologically diagnosed uterine CS: each was to be treated with paclitaxel and carboplatin chemotherapy. All six patients presented advanced or recurrent disease at their first visit to our hospital, and treatments with few side effects were needed for them. Thus, we offered the combination of paclitaxel and carboplatin as first-line chemotherapy, instead of ifosfamide-based therapy.

No patients received any chemotherapy and radiation therapy before paclitaxel and carboplatin. All pathological specimens were reviewed in detail, and none had any heterologous elements. Clinical data are summarized in Table 1.

Five of the six cases were primary and the remaining one (Case 6) represented recurrent disease. Three of the five primary cases (Cases 1, 2, and 3) underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH-BSO) to reduce tumor burden. In addition, Case 2 underwent radiotherapy against bone metastases, 30 Gy for T6-L1, L4-S1, C5, and right hip bone, respectively, simultaneously with paclitaxel and carboplatin chemotherapy. However, irradiation fields were limited to relatively narrow scope; no dose adjustment were required. The remaining two primary cases (Cases 4 and 5) were initially treated with paclitaxel and carboplatin chemotherapy. Case 4 underwent TAH-BSO 2 weeks after the third course of paclitaxel and carboplatin chemotherapy. Because Case 5 refused surgery, her uterus with vaginal involvement and swollen pelvic lymph nodes were treated with external whole pelvic radiation 50 Gy without center split and 20 Gy with center split, simultaneously with paclitaxel and carboplatin chemotherapy. During whole pelvic radiation, the dose adjustments were needed over three cycles of chemotherapy, to 135 mg/m^2 of paclitaxel and AUC 4 of carboplatin. Her uterine size was continuously reduced while eight courses of paclitaxel and carboplatin were administered. The recurrent case (Case 6) had initially undergone TAH-BSO at another hospital after a diagnosis as stage IIIa disease, but she had not received any adjuvant treatments. Thirteen months after the surgery, she complained of abdominal distention and came to our center diagnosed as recurrent disease.

Table 1
Clinical characteristics, treatments, and results for all six patients

Case	Age (years)	Stage	Initial treatment before TJ	Sites of evaluation	Response (RECIST)			PFI (months)	OS (months)	Chemotherapy (courses)
					TL	NTL	OR			
1	63	IVb	surgery	lungs	CR	none	CR	32	AWN, 32	TJ × 14
2	55	IVb	surgery	lungs, liver	PD	none	PD	0	DOD, 5	TJ × 5
3	57	IIIa	surgery	none	none	none	–	6	DOD, 7	TJ × 6
4	52	IVb	none	lungs	CR	none	CR	16	AWD, 23	TJ × 10
5	58	IVb	none	lungs	CR	none	CR	20	AWD, 30	TJ × 8
6	47	IIIa[a]	none	pelvis, liver	CR	CR[b]	CR	28	AWN, 28	TJ × 10

RECIST: response evaluation criteria in solid tumors.
TL: target lesions; NTL: nontarget lesions; OR: overall response; PFI: progression-free interval; OS: overall survival.
AWN: alive with no evidence of disease; AWD: alive with disease; DOD: died of disease.
TJ: paclitaxel + carboplatin; CR: complete response; PD: progressive disease.
[a] Case 6 had recurrent disease.
[b] Nontarget lesions were ascites and peritonitis carcinomatosa.

Table 2
Adverse effects of TJ chemotherapy

Adverse effect	Grade (NCI-CTC)			
	1	2	3	4
Leukopenia	0	0	2	0
Anemia	0	3	1	1
Neutropenia	3	0	1	1
Nausea/vomiting	2	1	0	0
Peripheral neurotoxicity	3	1	1	0
Cardiotoxicity	0	1	0	0
Alopecia	0	6	–	–

NCI-CTC: National Cancer Institute—Common Toxicity Criteria. (NCI-CTC Version 2.0, Jan. 30, 1998).

Five of the six cases had measurable disease at the time paclitaxel and carboplatin chemotherapy was started. Cases 1, 4, and 5 had measurable regions in the lungs, Case 2 in the lungs and liver, and Case 6 in the pelvic cavity and liver. All regions were measured by spiral computed tomography (CT) and/or magnetic resonance imaging (MRI) before initial administration of paclitaxel and carboplatin chemotherapy.

The combination of paclitaxel (175 mg/m^2 over 3 h) and carboplatin (dosed at AUC 6, according to the Calvert formula) was given intravenously every 3 weeks. All patients received pretreatment medications designed to decrease allergic reactions to paclitaxel. The pretreatment regimen consisted of the following: (1) dexamethasone 20 mg intravenously 60 min before paclitaxel, (2) diphenhydramine 50 mg orally 60 min before paclitaxel, and (3) ranitidine 50 mg intravenously 60 min before paclitaxel.

Response was assessed according to Response Evaluation Criteria in Solid Tumors [20]. Complete response (CR) was defined as the disappearance of all target lesions with confirmation at 4 weeks. Partial response (PR) was at least 30% reduction in the sum of the longest diameter of target lesions, taking as reference the baseline study; this also was confirmed at 4 weeks. Progressive disease (PD) was defined at least 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum longest diameter recorded since treatment started or new lesions appeared. Patients who did not meet any of these criteria were considered to have stable disease (SD). Evaluation of overall response was determined by achievement with both target and nontarget lesions. Progression-free interval (PFI) was defined as the date of study entry to the date of reappearance or increased parameters of disease or to the day of last contact. Overall survival was the observed length of life from study entry to death or to the day of last contact.

Pretreatment evaluation for chemotherapy included the following: white blood count > 3000/μl, platelet count > 100,000/μl, blood urea nitrogen level < 30 mg/dl, serum creatinine < 1.5 mg/dl, creatinine clearance > 50 ml/min,

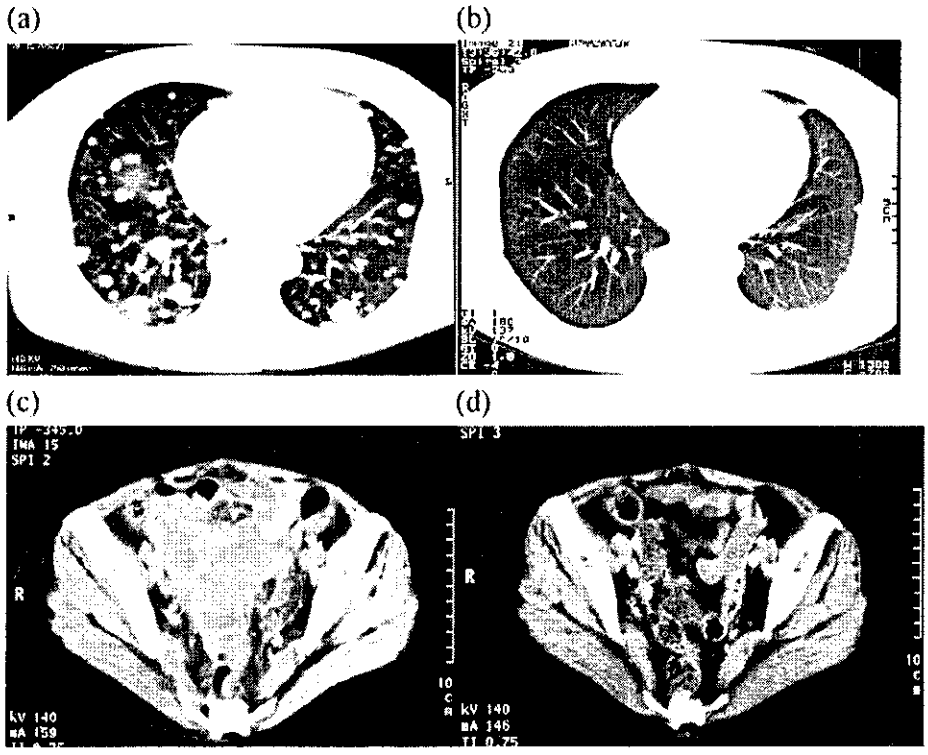

Fig. 1. (a) Pretreatment CT of the lungs and mediastinum for Case 5 shows multiple metastases. (b) CT taken after the third course of paclitaxel and carboplatin at a similar level to the scan shown in (a) shows complete disappearance of the metastatic tumors. (c) Pelvic CT for Case 6 shows 11 × 7 cm of recurrent tumor before chemotherapy began. (d) CT taken after the 10th course of paclitaxel and carboplatin at a similar level to the scan shown in (c) shows complete disappearance of the tumor.

serum bilirubin < 1.5 times normal, AST and ALT < 3 times normal, serum albumin > 3 g/dl, normal electrocardiographic pattern, normal spirometry, and a GOG performance status of 0–2. Written informed consent was obtained from all patients before initiation of treatment. Hematologic indexes were monitored weekly. Patients were removed from this study if there was clear evidence of disease progression or severe toxicity. Toxicities were evaluated according to the National Cancer Institute—Common Toxicity Criteria [21].

Results

For the total of six patients, age ranged from 47 to 63 years with a median of 56 years. The median number of chemotherapy courses administered was 9 (range, 4–14). Adverse effects for the six patients during paclitaxel and carboplatin treatment are summarized in Table 2. Grades 3 and 4 hematologic toxicities occurred in four and two patients, respectively, but all of them were overcome by adequate treatment with granulocyte colony-stimulating factor and blood transfusions. One case developed grade 3 peripheral neurotoxicity, but this adverse event did not stop the protocol. No cases developed hypersensitivity reactions. There were not any treatment delay through all period.

In the five patients with measurable disease, there were four complete responses (CR) and one progressive disease (PD) as measured by spiral CT scan and, in some cases, by MRI. Two representative CT scans are shown in Fig. 1. The overall response rate was 4/5, and the CR rate was the same.

Two patients (Case 4 and 5) experienced recurrence. Case 4 had recurrent regions in the lungs and kidneys after a 16-month progression-free interval (PFI). She was treated with docetaxel and carboplatin because of severe neurotoxicity after the 10th course of paclitaxel and carboplatin chemotherapy. However, metastatic regions grew again during chemotherapy, and docetaxel and carboplatin were stopped. She was alive with disease 7 months after the end of the second-line therapy. Case 5 had recurrent tumors in her lungs after a 20-month PFI. She was treated with radiation therapy, resulting in CR again, and she was alive without disease 10 months after the beginning of her second CR.

The median PFI of all six cases was 18 months (range, 0–32) and the median overall survival was 25 months (range, 6–32).

Discussion

To the best of our knowledge, this is the first report in which combination chemotherapy with paclitaxel and carboplatin has been used against uterine CS. Historically, numbers of chemotherapeutic agents have been utilized in uterine CS, and some of these are summarized in Table 3. In the present study, we obtained a higher overall response rate and CR rate than was observed in previous studies, although our number of cases is small for the purposes of statistical analysis, and none of six patients received prior radiation therapy.

Two prospective studies have shown higher response rates with combination chemotherapy than with single usage of ifosphamide, with the specific combinations of ifosphamide plus cisplatin, 54% in Gynecologic Oncology Group (GOG) study [7], and a combination of ifosphamide, doxorubicin, and cisplatin, 56% in the European Organization for Research ant Treatment of Cancer Gynaecological Cancer Group (EORTC) 55923 [10]. The median overall survival with measurable disease, 26 months, obtained in the EORTC study was similar to the value observed in this study, 25 months. Despite the small scale and short follow-up period of the present study, the observed 4 CR/5 patients with measurable disease and 25 months of median survival seem to be very promising. Additional phase II studies are needed to confirm and extend the results.

Table 3
Responses of chemotherapeutic trials in uterine carcinosarcoma

Author	*N*	Chemotherapeutic regimen	Response rate	CR rate
Sutton et al. [6][a]	28	IFX	32%	18%
Thigpen et al. [8][a]	63	CDDP	19%	8%
Curtin et al. [9][a]	44	Paclitaxel	18%	9%
Piver et al. [23][b]	23	CPA + VCR + ADR + DTIC	23%	12%
Hannigan et al. [24][b]	74	VCR + ACT-D + CPA	29%	13%
Currie et al. [25][a]	32	HU + DTIC + VP-16	16%	6%
van Rijswijk et al. [10][a]	32	CDDP + ADR + IFX	56%	34%
Omura et al. [4][b]	146	ADR vs. ADR + DTIC	16% vs. 24%	6% vs. 11%
Muss et al. [5][b]	52	ADR vs. ADR + CPA	19% vs. 19%	4% vs. 8%
Sutton et al. [7][a]	92	IFX vs. IFX + CDDP	36% vs. 54%	24% vs. 31%

N: number of patients with measurable disease.
CPA: cyclophosphamide; VCR: vincristine; ADR: doxorubicin; DTIC: dacarbazine.
ACT-D: actinomycin; IFX: ifosfamide; CDDP: cisplatin; HU: hydroxyurea; VP-16: etoposide.
[a] Only uterine carcinosarcoma.
[b] Uterine sarcoma.

The GOG is currently running two clinical trials related to CS of the uterus [22]. One is a phase III randomized study comparing the combination of ifosfamide and paclitaxel with single-agent ifosfamide for patients with advanced or recurrent CS of the uterus (GOG161). The other is a phase III randomized study comparing whole abdominal radiotherapy with combination chemotherapy (ifosfamide and cisplatin) in patients with optimally debulked CS of the uterus (GOG150). If the effectiveness of paclitaxel and carboplatin against uterine CS is confirmed by future studies, we can design a phase III randomized control study comparing paclitaxel and carboplatin with an advantaged therapy identified through the previously mentioned GOG studies.

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Clinical Trial Note

Feasibility Study of Neoadjuvant Chemotherapy Followed by Interval Cytoreductive Surgery for Stage III/IV Ovarian, Tubal and Peritoneal Cancers: Japan Clinical Oncology Group Study JCOG0206

Takashi Onda[1], Toshiharu Kamura[2], Naoki Ishizuka[3], Noriyuki Katsumata[4], Haruhiko Fukuda[3] and Hiroyuki Yoshikawa[5]

[1]Division of Gynecologic Oncology, National Cancer Center Hospital, Tokyo, [2]Department of Obstetrics and Gynecology, Kurume University School of Medicine, Kurume, Fukuoka, [3]Japan Clinical Oncology Group Data Center, Cancer Information and Epidemiology Division, National Cancer Center Research Institute, Tokyo, [4]Department of Medical Oncology, National Cancer Center Hospital, Tokyo and [5]Department of Obstetrics and Gynecology, Institute of Clinical Medicine, University of Tsukuba, Tsukuba, Ibaraki, Japan

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A feasibility study was started in January 2003 on neoadjuvant chemotherapy (NAC) followed by interval cytoreductive surgery (ICS) and postoperative chemotherapy for stage III/IV müllerian carcinomas such as ovarian, tubal and peritoneal carcinomas. The purpose is to assess the safety and efficacy of the treatment starting with NAC and also to know whether we can accurately diagnose these advanced carcinomas by imaging studies, cytologic findings and tumor markers without staging laparotomy or laparoscopy. Fifty-six patients with advanced müllerian carcinomas will be recruited to the study. After confirmation of diagnosis by laparoscopic inspection and biopsies, patients undergo four cycles of chemotherapy as NAC, followed by ICS and an additional four cycles of post-surgical chemotherapy. The primary endpoint is proportion of clinical complete remission after accomplishment of the protocol treatment, while the major secondary endpoint is positive predictive value of diagnosis before laparoscopy regarding tumor origin, histology and stage. Based on the results of this study, we will conduct a phase III study to compare the treatment starting with NAC and primary cytoreductive surgery followed by post-surgical chemotherapy.

Key words: ovarian neoplasms – laparoscopy – neoadjuvant therapy – interval cytoreductive surgery

INTRODUCTION

Prognosis of patients with advanced epithelial ovarian, tubal and peritoneal carcinomas is known to be poor. Even using platinum compound regimens, the 5-year survival rate of stage III/IV ovarian cancer is still around 20% (1). The current standard treatment for advanced ovarian cancer is primary cytoreductive surgery followed by post-surgical chemotherapy. However, optimal cytoreduction in primary surgery can be achieved only in 40% of stage III/IV ovarian cancer patients (2). An alternative to primary surgical cytoreduction in patients with unresectable bulky tumors or poor performance status is the use of chemotherapy in the neoadjuvant setting. Recent retrospective analyses (3–6) have revealed that progression-free and overall survival were comparable between patients treated with neoadjuvant chemotherapy (NAC) followed by interval cytoreductive surgery (ICS) and those treated by primary cytoreductive surgery, though the former group was older and had a poorer performance status. Phase II and III trials have not been performed on the role of neoadjuvant-setting treatment for advanced ovarian, tubal and peritoneal cancers. Therefore, we started a phase II study to assess the safety and efficacy of NAC followed by ICS and post-surgical chemotherapy before comparing with the current standard treatment including primary cytoreductive surgery in randomized controlled trial. Neoadjuvant setting has the advantage of earlier treatment start and lower invasiveness. However, according to the current general rules for the management of ovarian cancer, it is neces-

For reprints and all correspondence: Takashi Onda, Division of Gynecologic Oncology, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan. E-mail: taonda@ncc.go.jp

sary to confirm the origin, histology and stage before starting treatment by staging laparotomy or laparoscopy. Thus, we also determine whether we can omit the 'extra procedure' of staging laparotomy or laparoscopy before the neoadjuvant-setting treatment in the majority of patients with advanced ovarian, tubal or peritoneal cancer.

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

PROTOCOL DIGEST OF THE JCOG0206

PURPOSE

The purposes are to assess the safety and efficacy of the treatment starting with NAC with paclitaxel and CBDCA for phase III study, comparing NAC therapy with current standard procedure, and to know whether we can accurately diagnose these advanced carcinomas by imaging studies, cytologic findings and tumor markers without staging laparotomy or laparoscopy.

STUDY SETTING

A multi-institutional (26 centers) non-randomized phase II trial.

RESOURCES

Health Sciences Research Grants for Clinical Research for Evidenced Based Medicine and Grants-in Aid for Cancer Research (nos 14S-4, 14-12), from the Ministry of Health, Labor and Welfare, Japan.

ENDPOINTS

Primary endpoint is proportion of clinical complete remission (%cCR) among all stage III or IV müllerian carcinoma confirmed by laparoscopic inspection and histopathology of biopsy specimens. Clinical complete remission is defined as 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 are as follows: (i) positive predictive value (PPV) of pre-laparoscopic diagnosis concerning the origin and histology—proportion of the patients diagnosed as müllerian carcinoma by laparoscopic inspection and histopathology of biopsy specimen among those diagnosed by pre-laparoscopic findings; (ii) PPV of prelaparoscopic diagnosis concerning clinical stage—proportion of the patients diagnosed as stage III or IV by laparoscopic inspection among those diagnosed by pre-laparoscopic findings; (iii) PPV of overall pre-laparoscopic diagnosis—proportion of the patients diagnosed as stage III or IV müllerian carcinoma by laparoscopic inspection and histopathology of biopsy specimen among those diagnosed by pre-laparoscopic findings.

Other secondary endpoints are: (iv) response rate to NAC among patients whose clinical diagnosis is confirmed by laparoscopy; (v) proportion of patients who received ICS among patients whose clinical diagnosis is confirmed by laparoscopy; (vi) progression-free survival among patients whose clinical diagnosis is confirmed by laparoscopy; (vii) operative morbidity among all enrolled patients; (viii) adverse events among all enrolled patients: and (ix) overall survival among all enrolled patients.

ELIGIBILITY CRITERIA

INCLUSION CRITERIA

The study subjects are patients diagnosed as stage III or IV müllerian carcinoma by pre-laparoscopic clinical findings including imaging studies (CT, MRI or ultrasonography) and cytology of ascites, pleural effusions or fluids 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 malignancy of digestive tract origin, criteria for tumor markers are set to be CA125 >200 U/ml and CEA <20 ng/ml.

Further inclusion criteria are: (i) clinically deemed to be a candidate for debulking surgery without evidence of brain, bone, bone marrow metastases, multiple lung or multiple liver metastases; (ii) presence of at least one measurable lesion; (iii) previously untreated for these malignancies and no history of treatment with chemotherapy nor radiotherapy even for other diseases; (iv) age 20–75 years; (v) Eastern Cooperative Oncology Group (ECOG) performance status of 0–3; (vi) adequate bone marrow, hepatic, renal, cardiac and respiratory functions; and (vii) written informed consent.

EXCLUSION CRITERIA

These are: (i) synchronous or metachronous (within 5 years) malignancy other than carcinoma in situ; (ii) pregnant or nursing; (iii) severe mental disorders; (iv) systemic and continuous use of steroidal drugs; (v) active infections; (vi) uncontrolled hypertension; (vii) diabetes mellitus, uncontrolled or controlled with insulin; (viii) history of cardiac failure, unstable angina, myocardial infarction within 6 months prior to the registration; (ix) liver cirrhosis or bleeding tendency contraindicating debulking surgery; (x) intestinal occlusion necessary for surgical treatment; and (xi) hypersensitivity to alcohol.

TREATMENT METHODS

DIAGNOSTIC LAPAROSCOPY

After enrolment, diagnostic laparoscopy is performed within 2 weeks. To confirm pre-laparoscopic clinical diagnosis of origin, histology and stage, inspection of peritoneal cavity and biopsy from the main tumor or metastatic tumors are per-

formed. Resection of any organs or tumors attempting to reduce tumor volume is not allowed.

NEOADJUVANT CHEMOTHERAPY (NAC)

Four cycles of combination of paclitaxel (175 mg/m^2, day 1) and carboplatin (AUC = 6, day 1) are administered every 3 weeks. NAC is initiated within 1 week after laparoscopy.

INTERVAL CYTOREDUCTIVE SURGERY (ICS)

ICS is performed in 4–7 weeks after administration of the fourth cycle of NAC unless disease progression occurs during NAC. Standard procedures of ICS consist of total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy and maximal debulking of metastatic tumors. Systematic pelvic and/or aortic lymphadenectomies are allowed, but not included in standard procedures.

POST-SURGICAL CHEMOTHERAPY

An additional four cycles of chemotherapy (same regimen as NAC) is administered (eight cycles of chemotherapy in total). Post-surgical chemotherapy is initiated within 3 weeks after ICS.

STUDY DESIGN AND STATISTICAL METHODS

The study is planned as a single-stage safety and efficacy study. Sample size calculation was primarily based on binominal test for the primary endpoint, %cCR. Forty-four eligible patients are required when expected %cCR of 40% and an acceptable lowest %cCR of 20% with alpha error level of 0.05 and beta error level of 0.1. Additionally, PPV is to be confident enough to omit laparoscopy before NAC in the following phase III study. It is not possible to use sensitivity or specificity to evaluate accuracy of clinical diagnoses, because laparoscopy is performed only in patients diagnosed as stage III/IV müllerian carcinomas by clinical findings in this study setting. Thus, Bayesian monitoring PPV is planned, which requires 56 patients to have the 10% or lower Bayesian posterior probability that PPV is <90% in case of three false positive patients assuming prior distribution of beta (9,1). The target sample size was determined to be 56, which also can be expected sufficient for primary endpoint. The planned accrual period is 1 year and the follow-up period is set as 3 years after the completion of accrual.

STUDY MONITORING

In-house interim monitoring is performed by the JCOG Data Center to ensure data submission, patient eligibility, protocol compliance, safety and on-schedule study progress according to the JCOG standard procedures. The monitoring reports are submitted to the JCOG Data and Safety Monitoring Committee every 6 months.

PARTICIPATING INSTITUTIONS

Hokkaido University, Sapporo Medical University, Tohoku University, University of Tsukuba, Gunma Prefectural Cancer Center, Shinshu University, National Defense Medical College, Saitama Cancer Center, National Cancer Center Hospital, The Jikei University School of Medicine, Cancer Institute Hospital, University of Tokyo, Juntendo University, Nagaoka Red Cross Hospital, Aichi Cancer Center, National Nagoya Hospital, Osaka Medical Center for Cancer and Cardiovascular Diseases, Kinki University, Niigata Cancer Center, Kure National Hospital (Chugoku District Cancer Center), National Shikoku Cancer Center, National Kyushu Cancer Center, University of Kurume, Kyushu University, Saga Medical School and Kagoshima City Hospital.

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Expression of Insulin-Like Growth Factor 1 Receptor in Primary Breast Cancer: Immunohistochemical Analysis

CHIKAKO SHIMIZU, MD, TADASHI HASEGAWA, MD, PHD, YOICHI TANI, PHD, FUMIAKI TAKAHASHI, PHD, MASAHIRO TAKEUCHI, PHD, TORU WATANABE, MD, MASASHI ANDO, MD, NORIYUKI KATSUMATA, MD, AND YASUHIRO FUJIWARA, MD, PHD

Insulin-like growth factor-1 receptor (IGF-1R) has been implicated in regulation in tumor growth. The results of previous studies performed by radioimmunoassay are conflicting, and the prognostic significance of IGF-1R expression in primary breast cancer is still controversial. IGF-1R expression was evaluated in formalin-fixed, paraffin-embedded tissue of 210 primary breast cancer patients by using anti-IGF-1R antibody. The clinicopathologic variables and 5-year disease-free survival were studied, and their correlations between IGF-1R expressions were investigated. IGF-1R overexpression was observed in 43.8% of tumors. IGF-1R overexpression had no correlation with prognosis or with other clinicopathologic parameters, such as age, tumor size, nodal status, histologic grade, hormone receptor status, and human epidermal growth factor 2 status. Though its prognostic value in breast cancer is limited, immunohistochemical evaluation of IGF-1R by using this monoclonal antibody may be useful in translational research using archived material. HUM PATHOL 35:1537-1542. © 2004 Elsevier Inc. All rights reserved.

Key words: **Insulin-like growth factor 1 receptor, immunohistochemistry, primary breast cancer, prognostic marker.**

Abbreviations: **IGF-1R, insulin-like growth factor-1 receptor; IGFBPs, IGF-binding proteins; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor 2; IHC, immunohistochemistry; DFS, disease-free survival; RIA, radioimmunoassay.**

IGF-1R is a glycosylated heterotetramer composed of 2 extracellular α-subunits and β-subunits that have intrinsic tyrosine kinase activity with 70% homology to the insulin receptor.[1] IGF-1R mainly mediates the effect of insulin-like growth factors (IGFs), which are potent mitogens that regulate cell proliferation, differentiation, and protection from apoptosis.[2] The clinical and epidemiologic data suggest that the levels of IGF-1 or IGF binding proteins (IGFBPs) in the serum are related to the risk of solid tumors such as breast, prostate, endometrial, ovarian, and colon cancer.[3]

IGF-1R has been found to be significantly expressed and highly activated in breast cancer, and its prognostic and predictive value in clinical samples are of interest.[4-8] There are several methods to measure IGF-1R expression: radioimmunoassay, Western blotting, and immunohistochemistry (IHC). Immunohistochemical evaluation is the most simple and the easiest to perform. To date, there are several commercially available anti-IGF-1R antibodies, but there are no established scoring methods for IGF-1R expression in formalin-fixed, paraffin-embedded tissue. We herein report the prognostic significance of IGF-1R overexpression as determined by IHC on archive materials of consecutive primary breast cancer patients when evaluated by the intensity of membrane staining. We also investigated its correlation with various clinicopathologic factors.

MATERIALS AND METHODS

Patients

This study was performed on 276 consecutive primary breast cancer patients who underwent surgery or biopsy at National Cancer Center Hospital from January to December 1997. From the cases, 268 paraffin-embedded formalin fixed tissues were obtained. Thirteen stage IV breast cancer patients, 9 patients with malignancy of other origin, 7 metachronous bilateral breast cancer patients, 4 synchronous breast cancer patients, and cases impossible for evaluation in invasive component such as ductal carcinoma in situ were excluded from analysis. Thus immunohistochemical staining was performed on 210 invasive carcinomas.

Pathology

Tumor size, number of axillary lymph node metastasis, histologic type, and histologic grade according to Nottingham combined histologic grading were noted.

Immunohistochemistry

IHC was performed for estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor 2 (HER2), and IGF-1R on 4-μm-thick serial sections from formalin-fixed, paraffin-embedded tissue.

Monoclonal antibodies 1D5 (DAKO) and 1A6(DAKO) were used for ER and PR IHC, respectively, according to the recommended staining protocol by the manufacturer. It was scored to be positive when ≥10% of the cancer cells were

From the Departments of Medical Oncology and Pathology, National Cancer Center Hospital; Dako Cytomation, Inc.; the Department of Clinical Biostatistics, Kitasato University; and the Oncology Center, International University of Health and Welfare. Accepted for publication September 13, 2004.

Address correspondence and reprint requests to Chikako Shimizu, MD, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan.

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TABLE 1. Scoring of Insulin-Like Growth Factor-1 Receptor Expression According to Intensity of Membrane Staining

Score	Pattern of Immunohistochemical Staining in Invasive Component
0	No staining observed or staining observed in <10% of tumor cells.
1+	A faint or barely perceptible membrane staining in >10% of tumor cells. The cells are only stained in part of their membrane.
2+	A weak to moderate complete membrane staining in >10% of tumor cells.
3+	A strong complete membrane staining in >10% of tumor cells.

stained. Herceptest (DAKO) was used for HER2 assay as described elsewhere, and (2+) and (3+) was defined as overexpression.[9]

The primary antibody for IGF-1R used in this study (clone 24-31) is a mouse monoclonal antibody that is specific for α-subunit of human IGF-1R.[10] Paraffin sections were retrieved in distilled water at 95°C for 40 minutes. Then the sections were incubated with the anti-IGF1R antibody for 30 minutes and were rinsed in EnVision plus (DAKO) for 30 minutes. The reaction product was made visible after incubation in diaminobenzidine for 10 minutes.

Human normal colon mucosa and breast cancer–cultured cellblock was used as positive control. The IGF-1R expression in human colon mucosa was defined as (1+), and we scored (2+), (3+) according to the intensity of the membrane-staining within invasive component in accordance to scoring of HER2 by HercepTest (Table 1, Fig 1) at magnification of ×100 to ×200. When there was heterogeneity in IGF-1R staining within a tumor, the highest score was applied regardless of its area among the tumor.

Statistical Analysis

The results were statistically evaluated by SAS software (version 8.2; SAS Institute Inc, Cary, NC).

Disease-free survival (DFS) was calculated from the date of surgical excision of the primary tumor to the date of recurrence or last follow-up. Prognostic information was masked to the pathologists responsible for evaluation of biologic markers. DFS was calculated for all 210 cases. DFS curves were computed by the Kaplan-Meier method. Correlation between IGF-1R expression and various clinicopathologic factors were analyzed by using Fisher's exact test. Univariate analysis of DFS was performed with the use of log-rank test. *P* values of less than 0.05 were considered to be statistically significant.

RESULTS

Characteristics of the Patients

The median age of study population was 53 years (range, 25-83). The median diameter of invasion was 2.2 cm (range 0.1 to 14.0). The majority of the histologic type was invasive ductal carcinoma. About half of the cases were node negative. The number of cases with Nottingham combined histologic grade 1, 2, and 3 were 12, 37, and 137 cases, respectively.

ER and PR was positive in 154 (73.3%) and 98 (46.7%) tumors. HER2 overexpression was seen in 36 tumors (17.1%; 2+: 2.9%, 3+: 14.2%). See Table 2 for a summary of data on patient characteristics.

IGF-1R Immunohistochemistry

IGF-1R was localized to epithelial compartment including normal breast epithelium, ductal carcinoma in situ, and invasive carcinoma (Fig 1). A weak to moderate (ie, (1+) or (2+)) staining was observed in normal duct epithelium. The majority of invasive carcinoma showed both cytoplasmic and membrane staining. There was heterogeneity of staining inside the same tumor: sporadic or patchy, focal, and diffuse pattern. Heterogeneity of IGF-1R staining was observed in 61 (29%) of 210 cases. Though this intratumoral heterogeneity made scoring difficult in some cases, immunohistochemical staining of IGF-1R was stable and reproducible. The number of cases of IGF-1R score 0, 1+, 2+, 3+ was 24 (11.4%), 94 (44.8%), 25 (11.9%), and 67 (31.9%), respectively.

IGF-1R Expression in Association With Various Clinicopathologic Parameters

There was no correlation between IGF-1R expression and age, size of invasion, presence or absence of axillary lymph node metastasis, and histologic grade. ER, PR, and HER2 status also did not correlate with IGF-1R expression. See Table 3.

Univariate Analysis

The median follow-up period was 5.0 years. The 5-year DFS was significantly better among patients with positive ER expression, and negative HER2 overexpression (Table 4). The patients with invasion less than 2 cm, negative axillary lymph node and positive PR expression had a trend of better prognosis, though it did not reach statistical significance. IGF-1R expression status did not correlate with DFS (Fig 2).

DISCUSSION

We tested the prognostic significance of IGF-1R overexpression on formalin-fixed, paraffin-embedded tissue and found no correlation between IGF-1R expression in primary tumor and 5-year DFS. Because this monoclonal antibody is specific[10] and prognostic value of other known biologic markers was validated within this patient population, we conclude that IGF-1R overexpression has no impact on prognosis of breast cancer in this study. This result is concordant with the Foekins et al[4] report, in which IGF-1R was evaluated in 214 primary breast cancer by ^{125}I-IGF radioimmunoassay (RIA).

Estimates of the proportion of IGF-1R expression that have been derived from previous studies, mostly performed by RIA, vary from 39% to 93%.[5-8] This range of positivity may be due to the sensitivity of RIA, because strong membrane staining of 2+ and 3+ was seen

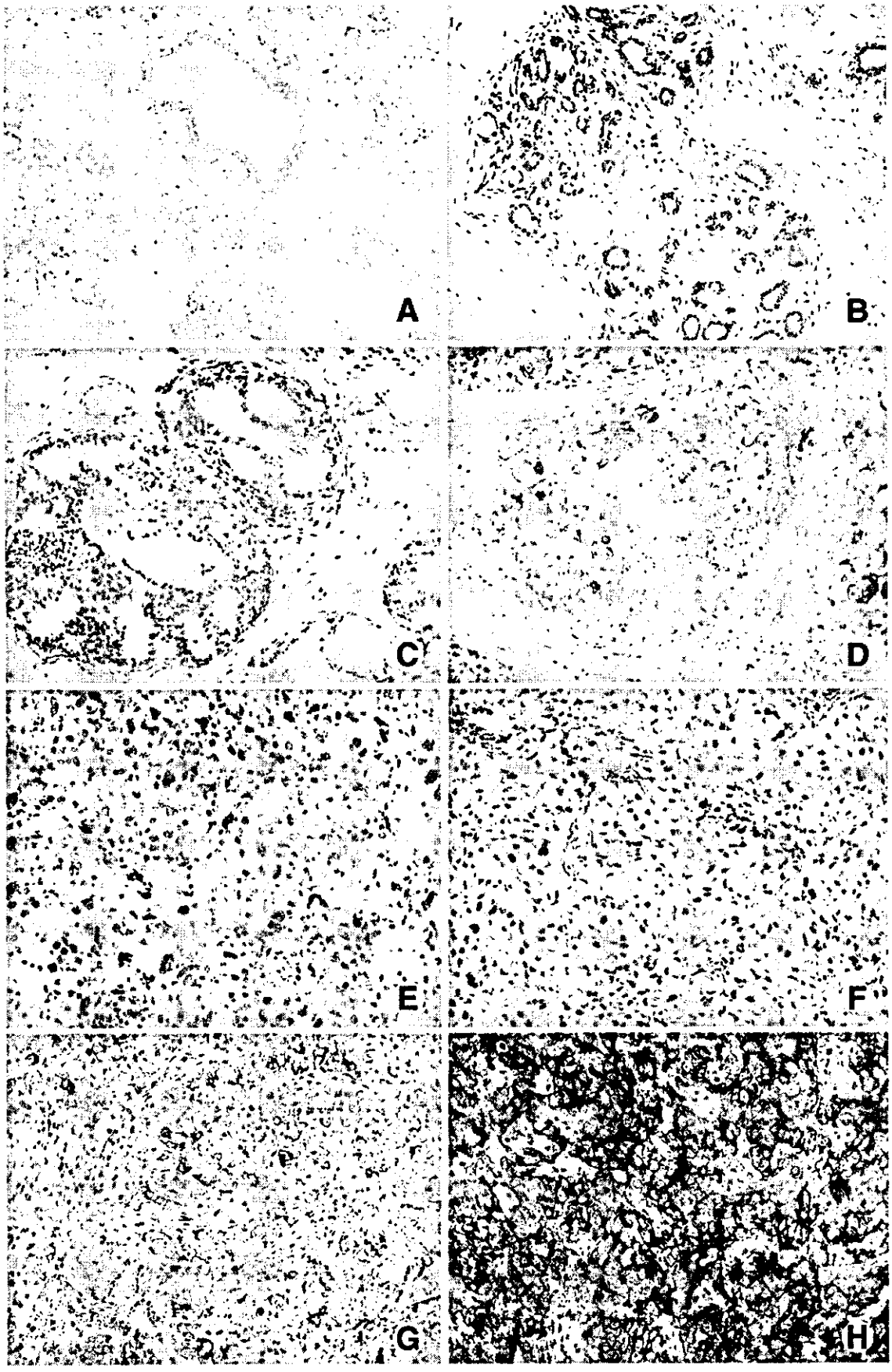

FIGURE 1. Immunohistologic staining of insulin-like growth factor-1 receptor in (A and B) normal epithelium, (C and D) ductal carcinoma in situ, and invasive ductal carcinoma (E-H). IGF-1 receptor expression was scored according to area and intensity of membrane staining (E: score = 0, F: 1+, G: 2+, H: 3+; original magnification, ×100).

TABLE 2. Characteristics of the Patients and Tumors

Parameters	Data
Total	210
Age in yr, range (median)	25-82 (51)
Size of invasion in cm, range (median)	0.1-14.0 (2.2)
Histologic type	
Invasive ductal carcinoma	19
Invasive lobular carcinoma	7
Others	6
Histologic grade	
Grade 1	10
Grade 2	80
Grade 3	120
Axillary lymph node status	
Positive	95
Negative	112
Unknown	3
ER	
Positive	154
Negative	56
PR	
Positive	98
Negative	112
HER2	
0-1	174
2	6
3	30
IGF-1R	
0	24
1	94
2	25
3	67

NOTE. Data are n unless otherwise indicated.

Abbreviations: ER, estrogen receptor, PR, progesterone receptor; HER2, human epidermal growth factor 2; IGF-1R, insulin-like growth factor-1 receptor.

in 43.8%, whereas almost 90% of invasive carcinoma showed moderate staining (scores 1, 2, and 3) in our observation. Happerfield et al[11] reported the localization of IGF-1R staining in benign and malignant fresh-frozen tissue by using monoclonal antibody α-IR3 and found high-intensity labeling in all normal mammary epithelium with an intensity that matches that of carcinomas. They observed membrane, cytoplasmic, and mixed staining patterns, which was concordant with our observation. We scored IGF-1R expression according to the intensity of membranous staining, but the role of cytoplasmic IGF-1R has yet to be clarified.

TABLE 3. Correlation Between Various Factors and IGF-1R IHC score (0/1 vs. 2/3)

Parameters	IHC Score 0/1+	IHC Score 2+/3+	Odds Ratio (95% CI)	Fisher's Exact Test (*P*)
Lymph node status			1.347 (.776-2.337)	.3268
Positive	49	46		
Negative	66	46		
Age (yr)			.932 (.536-1.620)	.8878
<50	51	41		
≥50	67	51		
ER			1.165 (.627-2.165)	.6413
Positive	85	69		
Negative	33	23		
PR			1.174 (.680-2.028)	.5800
Positive	53	45		
Negative	65	47		
HER2			1.032 (.501-2.125)	1.000
0-1	98	76		
2-3	20	16		

Abbreviations: IGF-1R, insulin-like growth factor-1 receptor; IHC, immunohistochemistry; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor 2.

TABLE 4. Univariate Analysis of DFS by Various Clinicopathologic Parameters

Parameters	5-yr DFS (%)	*P* Values
Lymph node status		0.0670
Positive	68.4	
Negative	79.5	
Age (yr)		
<50	78.3	0.6194
≥50	71.2	
Size of invasion (cm)		0.0667
<2.0	84.3	
≥2.0	66.4	
ER		0.0290
Positive	77.3	
Negative	66.1	
PR		0.1269
Positive	83.7	
Negative	66.1	
HER2		0.0483
0-1	78.4	
2-3	47.2	

Abbreviations: DFS, disease-free survival; ER, estrogen receptor, PR, progesterone receptor; HER2, human epidermal growth factor 2.

There are several other reports discussing the prognostic value of IGF-1R expression determined by RIA in primary breast cancer. Findings are contradictory: Foekins et al found no relationship between IGF-1R levels,[4] whereas Bonneterre et al[6] and 2 other groups reported IGF-1R as a favorable prognostic factor.[7,8] Because sensitivity of RIA has wide discrepancy as mentioned earlier, further studies by IHC are warranted.

Ouban et al[12] showed the overexpression of IGF-1R by using anti-IGF-1R polyclonal antibody toward the β-subunit of the human IGF-1R in variety of human carcinomas. Bhatavdekar et al[13] suggested that IGF-1R–negative tumor with concomitant hyperprolactinemia might indicate unfavorable prognosis in advanced colorectal cancer. Some data show prevalence of serum or tumor IGF-BP3 within clinical outcome in malignancy, such as breast and prostate cancer.[14,15] In Ewing sarcoma, there was a trend toward increased survival in a high IGF-BP3 to IGF-1 ratio.[16] Because biology of IGF-1R is regulated by a complex endocrine and paracrine system that involves various humoral and local factors, we should take into account those multiple factors that may affect IGF-1R in future studies.

In this study, there was no correlation between IGF-1R expression and ER, PR, or HER2 expression. In previous clinical studies in breast cancer, IGF-1R expression has been reported to have positive correlation with ER expression.[17] However, ER was not necessarily coexpressed in IGF-1R–overexpressed cells in serial sec-