G．知的財産権の出願・登録状況
（予定を含む。）

1. 特許取得

なし

2. 実用新案登録

なし

3.その他

なし

参照文献


[1] Y. Ishihama, J Chromatogr A 1067 (2005) 73.

[2] Y. Ishihama, F.Y. Wei, K. Aoshima, T. Sato, J. Kuromitsu, Y. Oda, J Proteome Res 6 (2007) 1139.

[3] M. Kokubu, Y. Ishihama, T. Sato, T. Nagasu, Y. Oda, Anal. Chem. 77 (2005) 5144.

[4] N. Sugiyama, T. Masuda, K. Shinoda, A. Nakamura, M. Tomita, Y. Ishihama, Mol Cell Proteomics 6 (2007) 1103.

[5] S.E. Ong, M. Mann, Nat Protoc 1 (2006) 2650.

[6] J. Rappsilber, M. Mann, Y. Ishihama, Nat Protoc 2 (2007) 1896.

[7] Y. Ishihama, J. Rappsilber, J.S. Andersen, M. Mann, J. Chromatogr. A 979 (2002) 233.

[8] R.X. Song, R.J. Santen, Biol Reprod 75 (2006) 9.

[9] M. Toi, Y. Iino, Breast Cancer 13 (2006) 117.

[10] R.X. Song, R.A. McPherson, L. Adam, Y. Bao, M. Shupnik, R. Kumar, R.J. Santen, Mol Endocrinol 16 (2002) 116.

厚生労働科学研究費補助金（第３次対がん総合戦略研究事業）
分担研究報告書

# バイオマーカーを導入した原発性乳癌治療の経済性に関する研究

分担研究者　近藤　正英　筑波大学大学院講師

研究要旨
バイオマーカーを導入した原発性乳癌治療の経済性の検討として，研究１：実用化段階に入りつつある代表的なバイオマーカーである 21-gene assay(Oncotype DX®)の費用効果分析，研究２：同 21-gene assay の導入が医療費に及ぼす影響に関する分析，研究３：乳癌高リスク者による tamoxifen 及び raloxifene 内服による予防の費用効果分析，の３つを行った．検査費が極めて高い 21-gene assay の臨床への導入は費用対効果に優れることが明らかとなった．また，この導入が医療費に及ぼす影響は trastuzumab の術後補助療法での使用と比較すると医療費増は小さいことが明となった．さらに，検査費が３分の１程度になれば，医療費減につながる可能性が示唆された． tamoxifen 及び raloxifene 内服乳癌予防は，異型過形成の既往，非浸潤性小葉癌の既往，５年間の発症リスク５％以上の高リスク者では，費用対効果に優れることが明らかとなった．これらの検討からは，バイオマーカーの導入ががん医療の効率化につながる可能性が示唆されたと考えられる．

## A．研究目的

近年の急速な医学の発展を背景にした医療技術の開発と，そうした技術の恩恵に対する国民の欲求が高まってきている．一方で，高度で先進的な医療に伴う費用をいかにして国民経済が負担していくかという，いわゆる‘医療費適正化’の問題も大きな社会問題となっている．このため，医療の効率的な提供の実現が，厚生労働行政の大きな課題のひとつとなっている．

がん医療においては，がんの病態における遺伝子や分子の寄与の理解の発展に基づき，腫瘍の遺伝的特性や分子的特性を評価するバイオマーカーに基づいた治療技術が，いわゆる‘テーラーメード医療’として開発されてきており，国民やがん患者から大きな期待を寄せられている．しかし，こうした治療技術が医療費としての国民負担に及ぼす影響については明らかではない．

このような問題意識から本分担研究は，「バイオマーカーを導入した原発性乳癌の集学的治療アルゴリズムの構築と意思決定過程の定式化に関する研究」の一環として，乳癌治療の経済性を評価することを目的としている．

３年計画２年目の平成１９年度には，班研究としてのアルゴリズムの構築や意思決定過程の定式化に協力しつつ，分担研究１として，乳癌治療の分野で近年開発が進み実用化段階に入りつつあり検査費が極めて高額な代表的バイオマーカーである

21-gene assay の費用効果分析に取り組み，さらに分担研究２として，その導入が医療費に及ぼす影響を評価した．これらの研究は，‘テーラーメード医療’時代のバイオマーカーの導入が医療費の国民負担に及ぼす影響を見通すうえで極めて有用な事例検討であるとともに，本研究班の３年目の成果として得られる予定の治療アルゴリズムの経済性評価の方法に関する基礎研究でもある．

さらに，原発性乳癌の予防として諸外国で導入されてきており，今後，乳癌発症リスクのバイオマーカーの開発と結びつけられ対乳癌戦略での有用性が期待される乳癌高リスク者による tamoxifen 及び raloxifene 内服による予防の費用効果分析も分担研究３として行い学会発表した．(尚，この成果に関しては国際誌に投稿中である．)

B．研究方法

研究１

21-gene assay の費用効果分析

National Surgical Adjuvant Breast and Bowel Project B-14 study の後ろ向きリスク再分類，東京都立駒込病院乳癌患者医療費調査，診療報酬点数表及び薬価基準を用いた費用推計に基づくマルコフ・モデリングによる費用効果分析．

研究２

21-gene assay 導入が医療費に及ぼす影響の評価

研究１で構築したマルコフ・モデルに基づくバジェット・インパクト分析．適応患者を絞った選択的導入とバジェット・インパクトの関係に関する分析や検査費の閾値分析．

研究３

tamoxifen 及び raloxifene 内服乳癌予防の費用効果分析

National Surgical Adjuvant Breast and Bowel Project P-1 study，同 P-2 study，日本乳癌学会全国癌登録，人口動態統計，東京都立駒込病院乳癌患者医療費調査，国民医療費等のデータを用いたマルコフ・モデリングによる費用効果分析．

C．研究結果

研究１

21-gene assay の費用効果分析

リンパ節陰性，エストロゲン受容体陽性，早期乳癌の術後補助療法での化学療法等の使用方針の決定に際して，従来から用いられてきている NCCN 分類及び St Gallen 分類ではなく，45 万円の検査費をかけて 21-gene assay を行うことに関する費用効果分析を行った結果を表１に示す．増分費用効果比として 124 万円/QALY から 300 万円/QALY が得られた．

研究２

21-gene assay 導入が医療費に及ぼす影響の評価

研究１で構築したマルコフ・モデルに基づくバジェット・インパクト分析の結果として，28 億円から 31 億円の医療費増が得られた．

適応患者を絞った選択的導入とバジェッ

表1　NCCN 分類及び St Gallen 分類対 21-gene assay 分類の費用効果分析

| | 費用 | 増分費用 | 効果 | 増分効果 | 増分費用効果比 |
|---|---|---|---|---|---|
| NCCN 分類 | 385 万円 | | 19.3QALYs | | |
| 21-gene assay 分類 | 414 万円 | 29 万円 | 19.4 QALYs | 0.097 QALYs | 300 万円/QALY |
| St Gallen 分類 | 384 万円 | | 19.2QALYs | | |
| 21-gene assay 分類 | 413 万円 | 29 万円 | 19.4QALYs | 0.237QALYs | 124 万円/QALY |

表2　適応患者を絞った選択的導入とバジェット・インパクト

| | 適応患者 | バジェット・インパクト |
|---|---|---|
| NCCN 分類 vs. 21-gene assay 分類 | 全患者検査・積極的治療 | 28 億円 |
| | 低リスク患者検査・積極的治療 | 4 億円 |
| | 低リスク患者検査・消極的治療 | 3 億円 |
| | 高リスク患者検査・積極的治療 | 25 億円 |
| St Gallen 分類 vs. 21-gene assay 分類 | 全患者検査・積極的治療 | 31 億円 |
| | 低リスク患者検査・積極的治療 | 4 億円 |
| | 中リスク患者検査・積極的治療 | 12 億円 |
| | 低中リスク患者検査・積極的治療 | 16 億円 |
| | 高リスク患者検査・積極的治療 | 17 億円 |
| | 低高リスク患者検査・積極的治療 | 20 億円 |
| | 中高リスク患者検査・積極的治療 | 29 億円 |

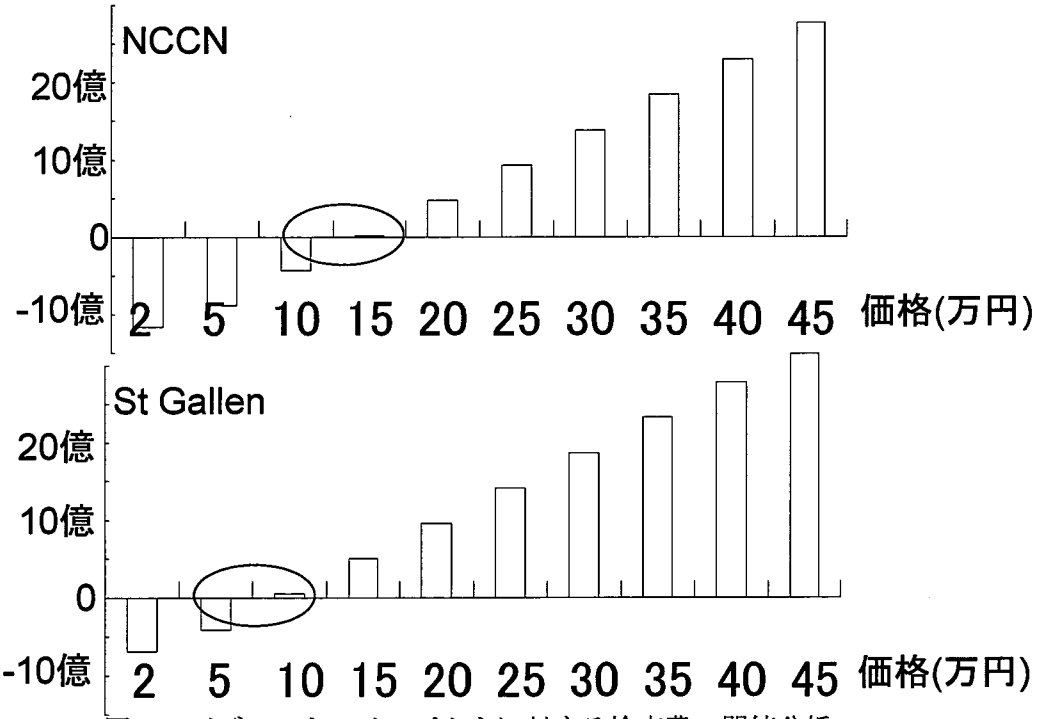

図1　バジェット・インパクトに対する検査費の閾値分析

ト・インパクトの関係に関する分析の結果を表２に示す．NCCN 分類及び St Gallen 分類にしたがって検査対象を絞り，21-gene assay の結果再発リスクが高く及び化学療法有効可能性が高いと判断される患者にのみ化学療法を行うことが消極的治療であり，中等度と判断されるものにも化学療法を行うことが積極的治療である．適応患者を絞ることによっては，医療費減にはつながらないことが明らかとなった．

バジェット・インパクトに対する検査費の閾値分析の結果を図１に示す．NCCN 分類からの導入ではおよそ15万円，St Gallen 分類からの導入ではおよそ 10 万円まで検査費が下がると，医療費減につながる可能性があることが明らかとなった．

研究３

tamoxifen 及び raloxifene 内服乳癌予防の費用効果分析

乳癌高リスク者が tamoxifen あるいは raloxifene を予防的に内服した場合の費用効果分析を行った結果を表４に示す．異型過形成の既往，非浸潤性小葉癌の既往，５年間の発症リスク５％以上の高リスク者では，両剤で優位になり得ることが示され，開始年齢が低いほど，大きな費用節減と効果増加が見込めることが明らかとなった．異型過形成の既往がある者では，60 歳から内服開始しても増分費用効果比は費用対効果に優れる範囲に入ることも明らかとなった．逆に，５年間の発症リスクが 5.00%以

表４　tamoxifen 及び raloxifene 内服乳癌予防の費用効果分析

| リスク分類 | 開始年齢 | 増分費用効果比 | |
|---|---|---|---|
| | | tamoxifen | raloxifene |
| ５年間の発症リスク 1.66%以上 | 35 | 劣位 | 劣位 |
| | 50 | 劣位 | 劣位 |
| | 60 | 劣位 | 劣位 |
| ５年間の発症リスク 3.01-5.00% | 35 | 劣位 | 419 万円/QALY |
| | 50 | 劣位 | 劣位 |
| | 60 | 劣位 | 劣位 |
| ５年間の発症リスク 5.01%以上 | 35 | 優位 | 優位 |
| | 50 | 優位 | 優位 |
| | 60 | 1,038 万円/QALY | 656 万円/QALY |
| 非浸潤性小葉癌の既往 | 35 | 優位 | 優位 |
| | 50 | 優位 | 63 万円/QALY |
| | 60 | 劣位 | 1098 万円/QALY |
| 異型過形成の既往 | 35 | 優位 | 優位 |
| | 50 | 優位 | 優位 |
| | 60 | 348 万円/QALY | 377 万円/QALY |

下の者では劣位になりうることが明らかとなった.

D．考察

研究1では,21-gene assayの導入の費用対効果を，NCCN分類とSt Gallen分類が併用される日本の現状と，導入後の予測を利用可能な最善のエビデンスに基づいて検討した．結果，導入は「高かろう，良かろう」ということになるが，増分費用効果比をみると，1QALYを獲得するために600万円を下回ることとなった．これは，費用効果分析の結果の一般的な解釈としては，21-gene assayは導入すべきであるということである．但し，今回のモデルはアメリカでのバリデーション研究の結果に基づいたものであり，これから得られる日本でバリデーション研究や，アメリカでの臨床試験の結果を待ってから再検討すれば結論が変わる可能性は孕んでいる．また，リンパ節陰性，エストロゲン受容体陽性，早期乳癌の術後補助療法以外の適応については別に検討する必要があることには変わりない.

研究2では，さらに，21-gene assayの導入が医療費減につながるかどうかを検討した．これは，‘テーラーメード医療’時代には，現行の費用効果分析の一般的な解釈である，「1QALYを獲得するために600万円程度までは社会は支払う用意がある」という前提が成り立ち続けるとは限らないという観点からの分析である．まず,「高かろう」に対応する医療費増をバジェット・インパクトとして評価し，28～31億円が得られた．この多寡を解釈する一般的な基準は存在しないが，乳癌領域で今まさに導入されようとしているtrastuzumabの術後補助療法での使用の160～320億円と比較するとかなり小さいと言うことができよう．さらに，例えば21-gene assayが化学療法の有効性を予測できることを利用して，無駄な化学療法を避けることに集中して使うためにNCCN分類やSt Gallen分類で高リスクとされる人にのみ適応とするような導入戦略のパターンを考えてバジェット・インパクトを検討した．この結果は，いくつかのパターンでは数億円にまで減ることが明となったが，医療費減にはつながらないことも明らかとなった．そこで，このようなバジェット・インパクトの規定因子としては，検査費が大きな役割を果たしていることに鑑み，検査費の閾値分析を行ったところ，15万円を下回ると医療費減につながる可能性があることが明らかとなった.

研究1と研究2の検討から,いわゆる「無効で無駄な」治療を避けることができるバイオマーカーの臨床への導入は，医療費減へつながる可能性があるが，容易に想像できるように，その価格設定が大きな影響をもっていることが分かった.

研究3の結果からは，tamoxifenとraloxifeneは極めてリスクの高い女性においては，乳癌予防の効果があり，かつ費用節約的であることが明となった.tamoxifenよりもraloxifeneのほうが効果が大きいことと，後者の適応が閉経後女性であることを鑑みると，わが国でも，高リスクの閉経全女性には，tamoxifenを，閉経後女性には，raloxifeneを使用可能とする努力が望まれると考えられる.

E．結論

検査費が極めて高い21-gene assayの臨

床への導入は費用対効果に優れることが明らかとなった．また，この導入が医療費に及ぼす影響はtrastuzumabの術後補助療法での使用と比較すると医療費増は小さいことが明となった．さらに，検査費が３分の１程度になれば，医療費減につながる可能性が示唆された．tamoxifen及びraloxifene内服乳癌予防は，異型過形成の既往，非浸潤性小葉癌の既往，５年間の発症リスク５％以上の高リスク者では，費用対効果に優れることが明らかとなった．これらの検討からは，バイオマーカーの導入ががん医療の効率化につながる可能性が示唆されたと考えられる．

F．健康危険情報

特になし．

G．研究発表

1. 論文発表

Kondo M, Hoshi SL, Ishiguro H, Yoshibayashi H, Toi M. Economic evaluation of 21-gene reverse transcriptase-polymerase chain reaction assay in lymph-node-negative, estrogen-receptor-positive, early-stage breast cancer in Japan. Breast Cancer Res Treat. 2007 Dec 13; [Epub ahead of print]

2. 学会発表

近藤正英，星淑玲，戸井雅和．乳癌高リスク者によるホルモン療法剤予防内服の費用効果分析．日本公衆衛生雑誌．54(10S);421:2007.

H．知的財産権の出願・登録状況

特になし．

I．研究協力者

星　淑玲
筑波大学大学院
人間総合科学研究科
ヒューマン・ケア科学専攻
保健医療政策学分野

石黒洋
京都大学
大学院医学研究科
探索臨床腫瘍学講座

芳林浩史
京都大学
医学部付属病院
外科（乳腺外科）

研究成果の刊行に関する一覧表　　別添４

書籍　　無

雑誌

| 発表者氏名 | 論文タイトル名 | 発表誌名 | 巻号 | ページ | 出版年 |
|---|---|---|---|---|---|
| Toi M. | Long-term outcomes of aromatase inhibition for breast cancer. | Lancet Oncol. | Jan;9(1) | 8-10 | 2008 |
| Toi M, Nakamura S, Kuroi K, Iwata H, Ohno S, Masuda N, Kusama M, Yamazaki K, Hisamatsu K, Sato Y, Kashiwaba M, Kaise H, Kurosumi M, Tsuda H, Akiyama F, Ohashi Y, Takatsuka Y; for Japan Breast Cancer Research Group (JBCRG). | Phase II study of preoperative sequential FEC and docetaxel predicts of pathological response and disease free survival. | Breast Cancer Res Treat. | Sep 19 [Epub ahead of print] | | 2007 |
| Suzuki E, Toi M. | Improving the efficacy of trastuzumab in breast cancer. | Cancer Sci. | Jun;98(6) | 767-71 | 2007 |
| Olofsson MH, Ueno T, Pan Y, Xu R, Cai F, van der Kuip H, Muerdter TE, Sonnenberg M, Aulitzky WE, Schwarz S, Andersson E, Shoshan MC, Havelka AM, Toi M, Linder S. | Cytokeratin-18 is a useful serum biomarker for early determination of response of breast carcinomas to chemotherapy. | Clin Cancer Res. | 1;13(11) | 3198-20 | 2007 |
| Suzuki E, Niwa R, Saji S, Muta M, Hirose M, Iida S, Shiotsu Y, Satoh M, Shitara K, Kondo M, Toi M. | A nonfucosylated anti-HER2 antibody augments antibody-dependent cellular | Clin Cancer Res. | 15;13(6) | 1875-82 | 2007 |
| 戸井雅和 | 乳癌のホルモン療法―最新動向 | 医学のあゆみ | V221(2) | 133 | 2007 |
| 戸井雅和 | がん分子標的治療の最先端<br>抗VEGF療法（乳腺）－原発性乳癌に対する治療応用が視野に－<br>Anti VEGF therapy | 医学のあゆみ（土曜特集） | V224(1) | 11-15 | 2007 |

| | | | | | |
|---|---|---|---|---|---|
| 戸井雅和 | Anti-HER therapy | がん分子標的治療(HER familyをターゲットとした分子標的治療) | V5(1) | | 2007 |
| 上野貴之、戸井雅和 | 分子プロファイリングに関する進歩「Breast and Endocrine Tumor」乳癌（原発性乳癌） | 癌と化学療法 | 34(13) | 2218-22 | 2007 |
| 上野貴之、戸井雅和 | バイオマーカーと乳癌治療 | 細胞工学 | 26(9) | 1026-10 | 2007 |
| 加藤大典、戸井雅和 | 2007年の乳癌術後補助化学療法(がん診療の最前線) | 最新医学 | 62 | 1282-12 | 2007 |
| Suzuki T, Miki Y, Moriya T, Akahira JI, Ishida T, Hirakawa H, Yamaguchi Y, Hayashi Si, Sasano H. | 5alpha-reductase type 1 and aromatase in breast carcinoma as regulators of in situ androgen production. | International Journal of Cancer | 120 | 285-291 | 2007 |
| Miki Y, Suzuki T, Tazawa C, Yamaguchi Y, Kitada K, Honma S, Moriya T, Hirakawa H, Evans DB, Hayashi S, Ohuchi N, Sasano H. | Aromatase localization in human breast cancer tissues: possible interactions between intratumoral stromal and parenchymal cells. 3945-3954 | Cancer Research | 67 | 3945-3954 | 2007 |
| Miki Y, Suzuki T, Sasano H. | Controversies of aromatase localization in human breast cancer-Stromal Versus parenchymal cells. | J Steroid Biochem Mol Biol. | 106 | 97-101 | 2007 |
| Usami S, Moriya T, Amari M, Suzuki A, Ishida T, Sasano H, Ohuchi N. | Reliability of prognostic factors in breast carcinoma determined by core needle biopsy. | Jpn J Clin Oncol. | 37 | 250-255 | 2007 |
| Sakuma M, Akahira J, Ito K, Niikura H, Moriya T, Okamura K, Sasano H, Yaegashi N. | Promoter methylation status of the Cyclin D2 gene is associated with poor prognosis in human epithelial ovarian cancer. | Cancer science | 98 | 380-386 | 2007 |
| Miki Y, Suzuki T, Hatori M, Igarashi K, Aisaki KI, Kanno J, Nakamura Y, Uzuki M, Sawai T, Sasano H. | Effects of aromatase inhibitors on human osteoblast and osteoblast-like | Bone | 40 | 876-87 | 2007 |

| | | | | | |
|---|---|---|---|---|---|
| Akahira JI, Tokunaga H, Toyoshima M, Takano T, Nagase S, Yoshinaga K, Tase T, Wada Y, Ito K, Niikura H, Yamada H, Sato A, Sasano H, Yaegashi N. | Prognoses and Prognostic Factors of Carcinosarcoma, Endometrial Stromal Sarcoma and Uterine Leiomyosarcoma: A Comparison with Uterine Endometrial Adenocarcinoma. | Oncology. | 71 | 333-340 | 2007 |
| Suzuki T, Miki Y, Moriya T, Akahira J, Hirakawa H, Ohuchi N, Sasano H. | In situ production of sex steroids in human breast carcinoma. | Med Mol Morphol. | 40 | 121-127 | 2007 |
| Sasano H, Suzuki T, Moriya T. | Analysis of surrogate markers for target-specific therapy in breast Carcinomas using archival materials. | Biomed Pharmacother. | 61 | 543-547 | 2007 |
| Miki Y, Suzuki T, Sasano H. | Aromatase inhibitor and bone. | Biomed Pharmacother. | 61 | 540-542 | 2007 |
| Sasano H, Suzuki T, Miki Y, Moriya T. | Intracrinology of estrogens and androgens in breast carcinoma. | J Steroid Biochem Mol Biol. | 108 | 181-185 | 2007 |
| Ito M, Moriya T, Ishida T, Usami S, Kasajima A, Sasano H, Ohuchi N. | Significance of pathological evaluation for lymphatic vessel invasion in invasive breast cancer. | Breast Cancer. | 14 | 381-387 | 2007 |
| Suzuki T, Urano T, Miki Y, Moriya T, Akahira J, Ishida T, Horie K, Inoue S, Sasano H | Nuclear cyclin B1 in human breast carcinoma as a potent prognostic factor. | Cancer Sci | 98 | 644-51 | 2007 |
| Suzuki T, Inoue A, Miki Y, Moriya T, Ishida T, Hirakawa H, Yamaguchi Y, Hayashi S, Sasano H. | Early growth responsive gene 3 (EGR3) in human breast carcinoma: a regulator of estrogen-mediated invasion and a potent prognostic factor. | Endocrine-Related Cancer | 14 | 279-292 | 2007 |
| Mita K, Zhang Z, Ando Y, Toyama T, Hamaguchi M, Kobayashi S, Hayashi S, Fujii Y, Iwase H, Yamashita H. | Prognostic significance of insulin-like growth factor binding protein (IGFBP)-4 and IGFBP-5 expression in breast cancer. | Jan J Clin Onco | 37(8) | 575-582 | 2007 |
| 林　慎一 | ホルモン療法奏効メカニズムと効果予測　ーエストロゲンシグナルを標的にー | 医学のあゆみ | 221 (2) | 140-143 | 2007 |

| | | | | | |
|---|---|---|---|---|---|
| 林　慎一 | 乳癌　－基礎・臨床研究のアップデート－　内分泌療法感受性予測因子 | 日本臨床 | 65 | 148-153 | 2007 |
| 松本光代、畠山　篤、坂本宙子、山口ゆり、笹野公伸、八重樫伸生、林　慎一 | 3次元マイクロアレイー乳癌の診断と治療効果予測への臨床応用を目指して一 | 東北大学医学部保健学科紀要 | 16(1) | 19－25 | 2007 |
| Kondo M, Hoshi SL, Ishiguro H, Yoshibayashi H, Toi M. | Economic evaluation of 21-gene reverse transcriptase-polymerase chain reaction assay in lymph-node-negative, estrogen-receptor-positive, early-stage breast cancer in Japan. | Breast Cancer Res Treat. | Dec 13; [Epub ahead of print] | | 2007 |
| 近藤正英、星淑玲、戸井雅和 | 乳癌高リスク者によるホルモン療法剤予防内服の費用効果分析 | 日本公衆衛生雑誌 | 54(10S) | 421 | 2007 |

学会

| 発表者氏名 | 演題タイトル | 学会名 | 発表年 |
|---|---|---|---|
| 近藤正英、星淑玲、戸井雅和 | 乳癌高リスク者によるホルモン療法剤予防内服の費用効果分析 | 第６６回日本公衆衛生学会 | 2007年10月 |
| Ishihama Y | Signaling Proteome of Breast Cancer by High-Accuracy Mass Spectrometry. | 第２７回キャピラリー電気泳動シンポジウム (SCE2007) | 2007年11月 |
| 石濱　泰 | シグナル伝達とリン酸化プロテオミクス | rganization for Oncology and Translational Research 4th Annual Conference. | 2007年11月 |
| Imami, K.; Sugiyama, N.; Kyono, Y.; Tomita, M.; Ishihama, Y. | Phosphoproteome Analysis for Breast Cancer Cells by Two-Dimensional NanoLC-MS using a Calcined Titania/C18 Biphasic Column. | 22nd International Symposium on Microscale Bioseparations & Methods for Systems Biology. | 2008年3月 |

Therefore, is EGFR targeting in pancreatic cancer a futile research area, especially when monoclonal antibodies are used for targeting? In my opinion the answer to this question is probably no. Research on the identification of predictive biomarkers is underway, and, therefore, EGFR blockade with monoclonal antibodies will probably be revisited in the near future when these studies are successfully completed. Moreover, given the redundancies of signalling pathways, EGFR inhibitors might have greater benefits when combined with other targeted treatments. Preclinical models of pancreatic cancer should guide our study of targeted combinations in clinical trials and help refine the identification of biomarkers. Finally, EGFR blockade might have greater benefit when used alone or in combination with different cytotoxic drugs, because gemcitabine alone offers only a small clinical benefit to patients.

The tradition of randomly combining drugs in the hope of achieving a better outcome in an unselected patient population or patients selected on unproven scientific grounds should be replaced by individualised treatments that have a solid scientific rationale. An exploration of predictive biomarkers should start before and continue alongside properly designed clinical trials. In this way, futile and costly exercises are avoided and patients with advanced pancreatic cancer might have the active treatments they so desperately need.

*Philip A Philip*
Karmanos Cancer Institute, Detroit, MI, USA
philipp@karmanos.org

The author declared no conflicts of interest.

1 Welch SA, Moore MJ. Combination chemotherapy in advanced pancreatic cancer: time to raise the white flag? *J Clin Oncol* 2007; **25**: 2159–61.
2 Cascinu S, Berardi R, Labianca R, et al. Cetuximab plus gemcitabine and cisplatin compared with gemcitabine and cisplatin alone in patients with advanced pancreatic cancer: a randomised, multicentre, phase II trial. *Lancet Oncol* 2007; **9**: 39–44.
3 Philip PA, Benedetti J, Fenoglio-Preiser C, et al. Phase III study of gemcitabine [G] plus cetuximab [C] versus gemcitabine in patients [pts] with locally advanced or metastatic pancreatic adenocarcinoma [PC]: SWOG S0205 study. *Proc Am Soc Clin Oncol* 2007; **25**: (abstr 4509).
4 Moore MJ, Goldstein D, Hamm J, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol* 2007; **25**: 1960–66.
5 Xiong HQ, Rosenberg A, LoBuglio A, et al. Cetuximab, a monoclonal antibody targeting the epidermal growth factor receptor, in combination with gemcitabine for advanced pancreatic cancer: a multicenter phase II trial. *J Clin Oncol* 2004; **22**: 2610–16.
6 Burtness BA, Powell M, Berlin J, et al. Phase II trial of irinotecan/docetaxel for advanced pancreatic cancer with randomization between irinotecan/docetaxel and irinotecan/docetaxel plus C225, a monoclonal antibody to the epidermal growth factor receptor (EGF-r) : Eastern Cooperative Oncology. *Proc Am Soc Clin Oncol* 2007; **25**: (abstr 4519).
7 Xiong HQ, Abbruzzese JL. Epidermal growth factor receptor-targeted therapy for pancreatic cancer. *Semin Oncol* 2002; **29** (5 Suppl 14): 31–37.
8 Khambata-Ford S, Garrett CR, Meropol NJ, et al. Expression of epiregulin and amphiregulin and K-ras mutation status predict disease control in metastatic colorectal cancer patients treated with cetuximab. *J Clin Oncol* 2007; **25**: 3230–37.
9 Amado RG, Wolf M, Freeman D, et al. Analysis of KRAS mutations in patients with metastatic colorectal cancer receiving panitumumab monotherapy. 14th European Cancer Conference. Barcelona, Spain. Sept 23–27, 2007. Abstract 0007.
10 Moore MJ, da Cunha Santos G, Kamel-Reid S, et al. The relationship of K-ras mutations and EGFR gene copy number to outcome in patients treated with erlotinib on National Cancer Institute of Canada Clinical Trials Group trial study PA.3 *Proc Am Soc Clin Oncol* 2007; **25**: (abstr 4521).

# Long-term outcomes of aromatase inhibition for breast cancer

See Articles page 45

Hormone manipulation is an essential treatment option for breast cancer. Oestrogen depletion decreases disease occurrence and suppresses disease progression, especially hormone-dependent growth and metastasis. Recent accumulated data from postoperative adjuvant trials that compared use of third-generation steroidal or non-steroidal aromatase inhibitors with tamoxifen (a selective oestrogen-receptor modulator) have suggested that aromatase inhibitors are better than tamoxifen at decreasing disease recurrence and occurrence of contralateral breast cancer, as a class effect.[1–3]

Major guidelines and consensus meetings recommend 5-years of adjuvant treatment with aromatase inhibitors or 2–3 years of tamoxifen followed by 2–3 years of aromatase inhibitors as a standard treatment for women with breast cancer who are hormone-receptor-positive and postmenopausal.[4,5] However, the long-term therapeutic effect of treatment with aromatase inhibitors, especially disease control, after cessation of the treatment and adverse effects on bone and the cardiovascular system, have yet to be clarified.

In this issue of *The Lancet Oncology*, the Arimidex, Tamoxifen, Alone or in Combination (ATAC) Trialists' Group report findings of an analysis of 100-month follow-up data.[6] In the overall intention-to-treat and hormone-receptor-positive populations, disease-free survival, time to recurrence, time to distant recurrence, and incidence of new contralateral breast cancer improved significantly in women assigned anastrozole compared with women assigned tamoxifen. This improvement in disease control with anastrozole treatment was maintained for more than 8 years, suggesting that the therapeutic effect of 5 years'

treatment with aromatase inhibitors can be prolonged for over 3 years after treatment cessation. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) showed that disease control by use of 5 years' treatment with tamoxifen is maintained after cessation of treatment for 5–10 years.[7] Therefore, given the long-term findings from the ATAC trial reported in this issue,[6] anastrozole might have a larger carryover effect after cessation of treatment than tamoxifen, which should be taken into consideration in clinical-practice decisions. Likewise, a lower number of recurrences and of new contralateral breast cancers after anastrozole compared with tamoxifen was also maintained in the latest findings from the ATAC trial.

Despite the findings mentioned above, no significant survival advantage for anastrozole over tamoxifen was shown in this trial.[1,6] Deaths after recurrence were fewer in women assigned anastrozole than in those assigned tamoxifen (350 *vs* 382); however, deaths without recurrence were more frequent with anastrozole treatment than for tamoxifen (279 *vs* 242). The researchers did not note any significant difference in the incidence of deaths due to cardiovascular or cerebrovascular disease, but deaths due to second primary non-breast cancers and deaths due to other causes were more frequent in patients assigned anastrozole. Endometrial cancers, ovarian cancers, and melanomas were less frequent in those assigned anastrozole; however, colorectal cancers, lung cancers, and head and neck cancers were more frequent in women assigned anastrozole. With the exception of endometrial cancers, no statistically significant difference was noted for the occurrences of these cancers.

According to epidemiological studies, hormone-replacement treatment probably decreases the risk of developing colorectal cancer.[9] Additionally, oestrogen receptors α and β have been shown to inhibit the development of adenomatous polyposis coli (*APC*)-dependent colon cancer in mice.[10] By contrast, aromatase seems to enhance disease progression in lung cancers,[11] suggesting that the role of oestradiol in tumour progression or tumour regression could be diverse and dependent on cancer type. Since oestrogen receptor β is widely expressed in many organs, the effects of hormone manipulation on non-breast malignant disease occurrence needs to be assessed further.

Furthermore, in two trials that studied treatment with tamoxifen followed by aromatase inhibitors (such as exemestane and anastrozole), despite relatively short follow-up, incidence of second primary non-breast cancer was lower in patients assigned an aromatase inhibitor than in those assigned tamoxifen alone.[2,8] Therefore, we might not need to worry at present about the increased numbers of colorectal, lung, and head and neck cancers noted in the long-term ATAC findings for patients assigned anastrozole, but we need to continue collecting data on the incidence of these second primary non-breast cancers.

Fracture incidence is one of the adverse effects of aromatase inhibition that has caused most concern for oncologists and patients. Previous findings from both the ATAC group and others have shown that during the treatment period, patients assigned to an aromatase inhibitor have a higher incidence of bone fracture than those assigned to tamoxifen.[6,12] However, in the post-treatment period, the incidence of fractures decreased in both groups of patients,[6] and the difference in fractures between the two treatment groups was no longer apparent.[6] These findings lend support to a working hypothesis that bone damage by aromatase inhibition is reversible and potentially manageable, although the mechanisms of action of the bone damage by aromatase inhibitors and subsequent apparent recovery are still unclear.[13]

Oestrogen blockade is a core concept in the management of hormone-receptor-positive breast cancers. The ATAC trial has elucidated that aromatase inhibition can achieve a larger carryover effect in long-term disease control compared with tamoxifen treatment. However, we still need to pay attention to long-term follow-up findings, not only of this trial, but also of other trials containing aromatase inhibitors because an advantage in terms of overall survival has not yet been confirmed.

*Masakazu Toi*
Breast Surgery, Graduate School of Medicine, Kyoto University, Kyoto, Japan
toi@kuhp.kyoto-u.ac.jp

The author declared no conflicts of interest.

1 Howell A, Cuzick J, Baum M, et al. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. *Lancet* 2005; **365**: 60–62.
2 Coombes RC, Hall E, Gibson LJ, et al. A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. *N Engl J Med* 2004; **350**: 1081–92.
3 Breast International Group (BIG) 1-98 Collaborative Group. A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer. *New Engl J Med* 2005; **353**: 2747–57.
4 Winer EP, Hudis C, Burstein HJ, et al. American Society of Clinical Oncology technology assessment on the use of aromatase inhibitors as adjuvant therapy for women with hormone receptor-positive breast cancer: status report 2002. *J Clin Oncol* 2002; **20**: 3317–27.

If you would like to respond to an article published in *The Lancet Oncology*, please submit your correspondence online at: http://ees.elsevier.com/thelancetoncology


5 Goldhirsch A, Wood WC, Gelber RD, et al. Progress and promise: highlights of the international expert consensus on the primary therapy of early breast cancer 2007. *Ann Oncol* 2007; **18**: 1133–44.

6 Arimidex, Tamoxifen, Alone or in Combination (ATAC) Trialists' Group.Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 100-month analysis of the ATAC trial. *Lancet Oncol* 2008; **8**: 45–53.

7 Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005; **365**: 1687–717.

8 Kaufmann M, Jonat W, Hilfrich J, et al. Improved overall survival in postmenopausal women with early breast cancer after anastrozole initiated after treatment with tamoxifen compared with continued tamoxifen: the ARNO 95 study. *J Clin Oncol* 2007; **25**: 2664–70.

9 Humphries KH, Gill S. Risks and benefits of hormone replacement therapy: the evidence speaks. *CMAJ* 2003; **168**: 1001–10.

10 Cho NL, Javid SH, Carothers AM, et al. Estrogen receptors alpha and beta are inhibitory modifiers of Apc-dependent tumorigenesis in the proximal colon of Min/+ mice. *Cancer Res* 2007; **67**: 2366–72.

11 Mah V, Seligson DB, Li A, et al. Aromatase expression predicts survival in women with early-stage non-small cell lung cancer. *Cancer Res* 2007; **67**: 10484–90.

12 Coleman L, Banks S, Girgis L, et al. Skeletal effects of exemestane on bone-mineral density, bone biomarkers, and fracture incidence in postmenopausal women with early breast cancer participating in the Intergroup Exemestane Study (IES): a randomised controlled study. *Lancet Oncol* 2007; **8**: 119–127.

13 Geisler J, Lonning PE, Krag LE, et al. Changes in bone and lipid metabolism in postmenopausal women with early breast cancer after terminating 2-year treatment with exemestane: a randomised, placebo-controlled study. *Eur J Cancer* 2006; **42**: 2968–75.


# Call for papers: lung cancer, Storyboard, and From the Archives

To submit a paper go to http://ees.elsevier.com/thelancetoncology

For Information for Authors see http://www.thelancet.com/authors/oncology/authorinfo

In 2007 *The Lancet Oncology* published themed issues on paediatric oncology and on breast cancer. We will be continuing this concept into 2008 with a themed issue on lung cancer. Despite many advances in treatment over recent years, lung cancer is still the number one cause of death due to cancer in the world[1] and mean relative 5-year survival is only 12·6% in Europe[2]. *The Lancet Oncology* is therefore issuing a call for papers that report on major advances in the management of lung cancer. In particular, we are interested in the results of phase III randomised clinical trials. Accepted papers will be published in *The Lancet Oncology* to coincide with the International Lung Cancer Conference ([ILCC] Liverpool, UK, July 9–12, 2008). We are especially interested in research that will be presented at this conference, but we will also consider other suitable articles. If your study describes, in part or wholly, a study accepted for presentation at the ILCC, please let us know the precise details of the type of presentation (such as poster or oral presentation), including dates and times, so that publication in *The Lancet Oncology* can be scheduled to comply with ILCC's embargo policies. Articles should be submitted via *The Lancet Oncology*'s online submission service, and all authors must clearly state in the covering letter that their submission is in response to the "Lung Cancer Call for Papers". The deadline for submissions is May 2, 2008.

Second, *The Lancet Oncology* is introducing two new sections: Storyboard and From the Archives. Storyboard will provide an educational and entertaining opportunity to present new oncological techniques in pictorial form and will allow the progressive accumulation of knowledge by leading a reader from panel-to-panel. From the Archives will be a short report based on a reference of historical importance in oncology that has contributed to a substantial change in thinking in the era originally published. Please see our Information for Authors for full details of these new sections.

*Lidia Siemaszkiewicz*
*The Lancet Oncology*, London NW1 7BY, UK


1 Parkin DM, Bray F, Ferlay J, Pisani B. Global Cancer Statistics, 2002. *CA Cancer J Clin* 2005; **55**: 74-108

2 Berrino F, De Angelis R, Sant M et al. Survival for eight major cancers and all cancers combined for European adults diagnosed in 1995–99: results of the EUROCARE-4 study. *Lancet Oncol* 2007; **8**: 773–783


## Erratum

Bueno-de-Mesquita J, van Harten W H, Retel V P, et al. *Use of 70-gene signature to predict prognosis of patients with node-negative breast cancer: a prospective community-based feasibility study (RASTER).* Lancet Oncol 2007; **8**: 1079–87. The last two sentences of the Summary's Findings should have read 'St Gallen guidelines identified 353 (83%) patients with poor prognosis and discordance with the signature in 168 (39%) patients. Nottingham Prognostic Index recorded 179 (42%) patients with poor prognosis and discordance with the signature in 117 (27%) patients.'

Breast Cancer Res Treat
DOI 10.1007/s10549-007-9744-z

CLINICAL TRIAL

# Phase II study of preoperative sequential FEC and docetaxel predicts of pathological response and disease free survival

**Masakazu Toi · Seigo Nakamura · Katsumasa Kuroi · Hiroji Iwata · Shinji Ohno · Norikazu Masuda · Mikihiro Kusama · Kosuke Yamazaki · Kazuhumi Hisamatsu · Yasuyuki Sato · Masahiro Kashiwaba · Hiroshi Kaise · Masafumi Kurosumi · Hitoshi Tsuda · Futoshi Akiyama · Yasuo Ohashi · Yuichi Takatsuka · for Japan Breast Cancer Research Group (JBCRG)**

Received: 23 August 2007 / Accepted: 23 August 2007


**Abstract** *Purpose* This multicenter phase II study examined the impact of pathological effect on survival after preoperative chemotherapy in Japanese women with early stage breast cancer. *Patients and methods* Prior to surgery, patients received four cycles of FEC (fluorouracil 500 mg/m$^2$, epirubicin 100 mg/m$^2$, cyclophosphamide 500 mg/m$^2$ q3w) followed by four cycles of docetaxel (75 mg/m$^2$ q3w). Primary endpoint was 3 year disease free survival (DFS) stratified by the absence or presence of Quasi-pCR (QpCR; absence of invasive tumor or only focal residual tumor cells). Secondary endpoints were predictors for QpCR, clinical response, breast conservation rate, and safety. *Results* Between June 2002 and June 2004, 202 women were enrolled. Among 191 assessable patients, 25% achieved QpCR. With 40 months median follow-up, 3 year DFS was estimated at 91% for all patients. 3 year DFS for patients with QpCR was 98% vs. 89% without QpCR (hazard ratio 0.38 [95% Confidence Interval 0.09–0.84], $P = 0.0134$). HER2 status and response to FEC were independent predictors of QpCR. The overall clinical

M. Toi (✉)
Department of Surgery (Breast Surgery), Graduate School of Faculty of Medicine, Kyoto University, 54 Shogoin-Kawara-cho, Sakyo-ku, Kyoto 606-8507, Japan
e-mail: maktoi77@wa2.so-net.ne.jp

S. Nakamura
Breast Surgical Oncology, St. Luke's International Hospital, Tokyo, Japan

K. Kuroi
Division of Clinical Trials and Research and Department of Surgery, Tokyo Metropolitan Komagome Hospital, Tokyo, Japan

H. Iwata
Department of Breast Oncology, Aichi Cancer Center Hospital, Aichi, Japan

S. Ohno
Division of Breast Oncology, National Kyushu Cancer Center, Fukuoka, Japan

N. Masuda
Department of Surgery, National Hospital Organization Osaka National Hospital, Osaka, Japan

M. Kusama
Shinjyuku Breast Center Kusama Clinic, Tokyo, Japan

K. Yamazaki
Sapporo Kotoni Breast Clinic, Hokkaido, Japan

K. Hisamatsu
Department of Surgery, Hiroshima City Asa Hospital, Hiroshima, Japan

Y. Sato
Department of Breast and Endocrine Surgery, Nagoya Medical Center, Nagoya National Hospital, Aichi, Japan

M. Kashiwaba
Department of Surgery, Iwate Medical University, Iwate, Japan

H. Kaise
Department of Breast Oncology, Tokyo Medical University Hospital, Tokyo, Japan

M. Kurosumi
Department of Pathology, Saitama Cancer Center, Saitama, Japan

H. Tsuda
Department of Basic Pathology, National Defense Medical College, Saitama, Japan

response was 75%; 85% of patients achieved breast conservation. Grade 3/4 neutropenia was the most common adverse event, observed in 44% and 35% of patients during FEC and docetaxel, respectively. Treatment related side effects were manageable; there were no treatment related fatalities. *Conclusion* FEC followed by docetaxel is an active and manageable preoperative regimen for women with early stage breast cancer. QpCR following preoperative chemotherapy predicts favorable DFS. HER2 overexpression and clinical response to FEC predict QpCR.

**Keywords** Clinical trial · Docetaxel · Early stage breast cancer · FEC · Preoperative chemotherapy · Phase II

## Introduction

Preoperative systemic chemotherapy has been widely used for patients with operable breast cancer to increase the chance for breast conservation [1–3]. Furthermore, response to preoperative treatment can provide information on long-term survival outcomes. Pathological complete response (pCR) in the breast and axillary lymph nodes predicts a favorable prognosis, whereas non-pCR of the breast or node-positive status does not, which can facilitate tailoring of subsequent treatment [1, 3]. In addition, correlative studies of tumor samples before and after treatment may provide information on markers that could predict response or resistance to treatment [4].

Results from the National Surgical Adjuvant Breast and Bowel Project (NSABP) study B-18 demonstrated the impact of preoperative chemotherapy in patients with operable early stage breast cancer [5]. The protocol-specified anthracycline-containing regimen of four cycles of doxorubicin and cyclophosphamide (AC), resulted in an increased chance of breast-conserving surgery (BCS) compared to no preoperative chemotherapy. The study established pCR as a prognostic marker for long-term disease-free survival and demonstrated that there was no difference in survival whether chemotherapy was administered before or after surgery. Subsequently, studies such as the Aberdeen trial have demonstrated the benefit of the sequential addition of taxanes to preoperative anthracycline regimens [6, 7]. NSABP Protocol B-27 demonstrated that compared to preoperative AC alone, the addition of sequential docetaxel doubled the pCR rate, increased the clinical complete response (cCR) rate, and increased the proportion of patients with negative axillary nodes [3, 7]. Although NSABP B-27 did not show that the addition of docetaxel to AC significantly improved disease free survival (DFS) and overall survival (OS) compared to AC alone, other studies, mainly of patients with node-positive disease, have shown favorable DFS and OS by including a taxane with an anthracycline, either in sequence or combination [8–12]. Multiple neoadjuvant studies demonstrated that patients with pathological complete response to chemotherapy had a good prognosis [1, 2].

Here we conducted a multicenter prospective neoadjuvant trial with four cycles of fluorouracil, epirubicin, and cyclophosphamide (FEC) followed by four cycles of docetaxel in Japanese patients with operable breast cancer to investigate the relationship between pathological effect and survival. The pathological effect was determined using the definitions of Quasi-pCR (QpCR: complete disappearance of invasive carcinoma in the breast or only focal tumor cells remaining in the stroma in the removed breast) [13]. The primary endpoint was to examine 3 year DFS stratified by pathological response (QpCR versus non-QpCR). We also performed a logistic regression analysis to examine which features were associated with QpCR with this regimen. Clinical response, the rate of BCS, and safety were also evaluated.

## Methods

### Study design and ethics

This multicenter, open-label, single-arm, phase II clinical study was conducted at 13 institutions throughout Japan. This study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. The protocol was reviewed and approved by the institutional review board of each participating institution and written informed consent was obtained from all patients prior to the study.

### Patients

Women aged 20–59 years of age with histologically proven early stage breast cancer (T1c-3 N0 M0/T1-3 N1 M0)

F. Akiyama
Department of Breast Pathology, The Cancer Institute of Japanese Foundation for Cancer Research, Tokyo, Japan

Y. Ohashi
Department of Biostatistics/Epidemiology and Preventive Health Science, School of Health Science and Nursing, University of Tokyo, Tokyo, Japan

Y. Takatsuka
Department of Breast Surgery, Kansai Rosai Hospital, Hyogo, Japan

for Japan Breast Cancer Research Group (JBCRG)
c/o Tokyo Metropolitan Cancer and Infectious Disease Center, Komagome Hospital, 3-18-22, Honkomagome, Bunkyo, Tokyo 113-8677, Japan

were enrolled. No prior chemotherapy, radiotherapy, hormonal therapy, or immunotherapy was allowed. Other inclusion criteria were the following: Eastern Cooperative Oncology Group performance status of 0–1; white blood cell count between 4000/mm$^3$ and 12000/mm$^3$; neutrophil count ≥2000/mm$^3$; platelet count ≥100000/mm$^3$; hemoglobin ≥9.5 g/dl; serum bilirubin <1.25 times upper normal limit (UNL), creatinine <1.5 times UNL, or AST and ALT <1.5 times UNL. Patients with congestive heart failure or left ventricular ejection fraction ≤60% were excluded. Patients were also excluded if they had confirmed infection; serious concomitant illness such as severe cardiovascular disease, uncontrolled diabetes, malignant hypertension and hemorrhagic disease; active concomitant malignancy; brain metastasis; interstitial pneumonia or lung fibrosis confirmed by chest X-ray or computed tomography; pleural or peritoneal effusion that required treatment; pericardial effusion; motor paralysis, peripheral neuropathy or edema history of severe drug allergy; or had previously received long-term corticosteroid therapy. Pregnant or lactating women were also excluded.

## Treatment procedures

Four cycles of FEC (fluorouracil 500 mg/m$^2$, epirubicin 100 mg/m$^2$, and cyclophosphamide 500 mg/m$^2$) administered intravenously (i.v.) on day 1 every 21 days were followed by four cycles of docetaxel i.v. (75 mg/m$^2$) every 21 days, prior to surgery. The doses of docetaxel and epirubicin selected at the time of this study were higher than the approved doses in Japan (60 mg/m$^2$ each). Premedication consisted of a 5-HT$_3$ antagonist and dexamethasone i.v. on day 1 with oral dexamethasone on days 2 and 3 with each cycle of FEC and dexamethasone i.v. with or without 5-HT$_3$ antagonist on day 1 with each cycle of docetaxel. Administration of recombinant human granulocyte colony-stimulating factor (rh G-CSF) and antibiotics was left to the judgment of each investigator. If patients prematurely discontinued FEC treatment, they were expected to proceed to four cycles of docetaxel.

Treatment could be postponed for a maximum of 2 weeks for severe toxicity. If toxicity did not improve during this period, chemotherapy was discontinued and surgery was recommended. Dose reductions of epirubicin from 100 mg/m$^2$ to 75 mg/m$^2$ and for docetaxel from 75 mg/m$^2$ to 60 mg/m$^2$ were permitted in case of febrile neutropenia and grade 3 or 4 non-hematological toxicities except for nausea, vomiting, and fatigue. Following chemotherapy and clinical assessment of response, patients underwent surgery. If the tumor was too large or invasive for breast-conserving surgery, modified radical mastectomy was recommended. Sentinel lymph node biopsy (SNB) was performed to confirm disease stage. Most patients with negative biopsies did not undergo surgical clearance of axillary nodes. Autologous or heterologous reconstructive surgery was performed as needed. All patients who underwent breast-conserving surgery were given standard radiotherapy to the remaining ipsilateral breast tissue after surgical recovery. For patients with node-negative status in the sentinel nodes not requiring axillary dissection, radiotherapy to the axilla was allowed but not required. No recommendations were made for post-study hormone therapy in the protocol.

## Assessment

### *Hormone receptor and HER2 overexpression*

Estrogen receptor (ER) status and progesterone receptor (PgR) status were determined by immunohistochemistry at each institute. In general, tumors with >10% positively stained tumor cells were classified positive for ER and PgR. HER2 status was also determined at each institute by immunohistochemistry or by fluorescence in situ hybridization (FISH) analysis. HER2 positive tumors were defined as 3+ on immunohistochemistry staining or as positive by FISH.

### *Central pathological assessment*

Haematoxylin and eosin (H&E) and keratin stained slides were prepared as 5 mm tissue sections from the primary tumor. Pathological breast tumor response was assessed by a central review committee consisting of three pathologists using modified criteria of the Japanese Breast Cancer Society [14]. A blinded central review committee evaluated the pathologic response independently to the local pathologists. In this study, the response of stromal invasion and intraductal component was assessed separately. Cytokeratin immunostaining was performed to confirm residual cancer cells in required cases.

### *Toxicity and clinical assessment*

Toxicity was evaluated according to the National Cancer Institute Common Toxicity Criteria (version 2). Tumor response was assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines in patients who had measurable lesions. Tumor and toxicity assessments were performed within 4 weeks prior to FEC treatment, after completion of FEC treatment, and before surgery.

### Statistical methods

The primary endpoint was to examine 3 year DFS stratified by pathological response (QpCR versus non-QpCR). Secondary endpoints included predictors for QpCR, clinical response, the rate of BCS, and safety.

For the primary efficacy analysis, we assumed that approximately 25% of patients would achieve QpCR and that the 3 year DFS rate in patients with non-QpCR would be 70%. To demonstrate a 20–25% reduction in the hazard of DFS between patients achieving QpCR compared with those without QpCR, we planned to enroll 200 patients. Using the log rank test this would provide $\alpha = 0.05$ and $\beta = 0.2$.

Kaplan–Meier analysis was used to estimate the values of DFS. DFS was compared using a log-rank test stratified for QpCR and non-QpCR. Events for the calculation of DFS include all local, regional, or distant recurrence, all clinically inoperable and residual disease at surgery, all second cancers, contralateral breast cancers, and all deaths.

In the logistic regression analyses, adjustments were made for the stratification variables of menopausal status, tumor size, estrogen receptor status, progesterone receptor status, HER2 status, clinical response to FEC treatment and clinical response to docetaxel following FEC treatment. Analyses were performed with JMP (version 6, SAS Institute Inc.). Analyses of endpoint data reported here are based on information received as of July 2007.

## Results

### Patient characteristics

Between June 2002 and June 2004, 202 patients were prospectively enrolled. As two patients were ineligible and two patients withdrew consent, 198 patients were assessed for safety. One patient was removed from the study after planned chemotherapy but before surgery because of a protocol violation (non-protocol chemotherapy), four patients elected to not have surgery and withdrew from the study, and two were lost to follow-up, leaving 191 evaluable for clinical, pathologic assessment and DFS.

The median age of the assessable 198 patients was 46 years, and 72% of patients were pre-menopausal. The majority of the patients had T2 tumors (74%), with 20% of the patients having T3 tumors and 6% with T1 tumors (Table 1). Distribution with regard to hormone receptor or HER2 overexpression was representative of that seen in common practice in Japan [15].

**Table 1** Patients characteristics ($n = 198$)

| | No. of patients | % |
|---|---|---|
| *Age (years)* | | |
| Median | 46 | |
| Range | 25–60 | |
| *Menopausal status* | | |
| Pre | 142 | 72 |
| Post | 56 | 28 |
| *Tumor stage* | | |
| T1 | 12 | 6 |
| T2 | 146 | 74 |
| T3 | 40 | 20 |
| *Nodal stage* | | |
| N0 | 80 | 40 |
| N1 | 117 | 59 |
| N2 | 1 | 1 |
| *Hormone receptor status* | | |
| ER | | |
| Positive | 133 | 67 |
| Negative | 62 | 31 |
| Unknown | 3 | 2 |
| PgR | | |
| Positive | 100 | 51 |
| Negative | 95 | 48 |
| Unknown | 3 | 2 |
| *HER2 (IHC)* | | |
| 0 | 60 | 30 |
| 1+ | 54 | 27 |
| 2+ | 42 | 21 |
| 3+ | 38 | 19 |
| Unknown | 4 | 2 |

*ER* estrogen receptor, *PgR* progesterone receptor, *IHC* immunohistochemistry

Percentages may not add up to 100% because of rounding

### Compliance to chemotherapy and toxicity

Dose reduction due to toxicities was made in 18% of the patients during FEC treatment; febrile neutropenia (19), grade 3–4 neutropenia without fever (10), suspicion of febrile neutropenia (4), vomiting, and deterioration in liver function (1 each) and 14% of patients during docetaxel therapy, febrile neutropenia (5), grade 3–4 neutropenia without fever (5), neutropathy (2), deterioration in liver function (2), myalgia (2) allergy (1) previous reduction of FEC (8), and unknown (2).

Six patients (3%) discontinued FEC treatment due to toxicities (3: two patients with febrile neutropenia and one with vomiting), progression of disease (2), and mental disorder (1). Ten (please refer toxicity section) patients (5%) discontinued docetaxel treatment due to toxicity (3:

one patient each with rash, febrile neutropenia, and phototoxicity), progression of disease (3), and patients' requests for early surgery (2) changing hospital (1), patient's request (1).

Percentage of treatment cycles requiring dose reduction for FEC, docetaxel and all were 11.1, 11.6 and 11.3%. Percentage of treatment cycles (FEC, docetaxel and all) including rh G-CSF were 10.5, 8.2 and 9.4%, respectively.

The safety profile is summarized in Table 2. Four patients didn't receive docetaxel treatment at patients' request. For toxicity 198 and 194 patients were evaluable for FEC treatment and docetaxel treatment, respectively. The most common adverse event was grade 3 or 4 neutropenia, which was observed in 44% of patients during FEC treatment and 35% of patients during docetaxel treatment. Fever, including febrile neutropenia, was seen in 20% and 7% during treatment with FEC and docetaxel, respectively. The only grade 3–4 non-hematologic toxicities reported were; nausea (12 patients), vomiting (11) and fatigue (3). No fatal events were observed.

## Response to treatment

The overall clinical response was 74% (95% CI, 67–80%) with 22% CR and 52% PR. Thirty-eight (51%) of 75 FEC non-responders had a response to docetaxel treatment. One hundred and six of 118 FEC responders maintained their response or had a continued decrease in tumor size with docetaxel (Table 3). QpCR were seen in 25% of patients (including 16% complete disappearance of invasive carcinoma in the breast). One patient was removed from assessable for BCS because of a protocol violation. BCS was achieved in 85% of all the assessable patients. Ninety-two percent of patients who had original tumor size 3 cm or less underwent BCS; those with larger tumors had an 80% rate of BCS. As of July 11, 2007, with a median follow up of 40 months, the estimated 3-year DFS was 91% for all patients. Patients who achieved QpCR had significantly improved DFS compared to those without QpCR (QpCR (98%) and non-QpCR (89%), log rank test, $P = 0.0333$, Fig. 1). HR 0.38 [95% CI 0.09–0.84], $P = 0.0134$).

## Predictive factors of pathological response

A multiple logistic regression analysis was performed to examine which factors among menopausal status, tumor size, estrogen receptor status, progesterone receptor status, HER2 status and clinical response to FEC were associated with QpCR (Table 4). HER2 status and response to the initial FEC treatment and response to docetaxel were independent predictive factors for QpCR. The QpCR rates stratified by HER2 and ER are shown in Fig. 2. QpCR rate was 67, 33, 35 and 13% in HER2 positive/ER negative, HER2 positive/ER positive, HER2 negative/ER negative, HER2 negative/ER positive, respectively.

**Table 2** Treatment related toxicities

| | FEC ($n$ = 198) | | Docetaxel ($n$ = 194) | |
|---|---|---|---|---|
| | All grades $n$ (%) | Grade 3, 4 $n$ (%) | All grades $n$ (%) | Grade3, 4 $n$ (%) |
| *Non-hematologic toxicities* | | | | |
| Fatigue | 83 (42%) | 2 (1%) | 83 (42%) | 1 (1%) |
| Diarrhea | 17 (9%) | 1 (1%) | 31 (16%) | 0 |
| Nausea | 162 (82%) | 11 (6%) | 81 (42%) | 1 (1%) |
| Vomiting | 98 (50%) | 10 (5%) | 38 (20%) | 1 (1%) |
| Neurotoxicity | 6 (3%) | 0 | 85 (44%) | 2 (1%) |
| Constipation | 67 (34%) | 0 | 50 (26%) | 1 (1%) |
| Arthralgia/myalgia | 12 (6%) | 0 | 60 (30%) | 1 (1%) |
| *Hematologic toxicities* | | | | |
| Hemoglobin | 119 (60%) | 1 (1%) | 101 (52%) | 0 |
| Platelets | 26 (13%) | 1 (1%) | 3 (2%) | 1 (1%) |
| AST/ALT | 81 (41%) | 3 (2%) | 70 (36%) | 1 (1%) |
| Leukocytes | 131 (66%) | 68 (35%) | 92 (47%) | 57 (30%) |
| Neutrophils | 137 (69%) | 85 (44%) | 85 (44%) | 67 (35%) |
| Febrile neutropenia | – | 40 (20%) | – | 14 (7%) |

*FEC* fluorouracil, epirubicin, cyclophosphamide