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症　例

乳房温存術後にPaget病を発症した1例

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今回われわれは乳房温存術後にPaget病をきたした症例を経験したので報告する．症例は64歳，女性．他院で乳癌と診断され（TisN0M0 pStage 0）左乳房部分切除術＋センチネルリンパ節生検が施行された．術後に温存乳房に対し放射線照射が行われた．術後1年半より患側乳頭部にびらんが出現し，皮膚炎として経過観察されていた．術後5年になりびらんの範囲が拡大し皮膚生検を施行したところ，Paget病と診断され当院を紹介受診した．乳房温存手術後のPaget病型再発と診断し左乳房切除術を施行した．このようなPaget病の発症は比較的まれであるが長期にわたり経過観察されることが多く常に念頭におく必要がある．

索引用語：Paget病，乳房内再発，センチネルリンパ節生検

緒　言

近年，乳癌手術は縮小傾向にあり，乳房温存術（BCS）＋sentinel lymph node biopsy（SLNB）症例が増加している．それに伴い，温存乳房内再発の発見とその再発治療は問題となってくる．温存乳房に対する定期的検査のエビデンスはないが，温存乳房内再発は乳房腫瘤や炎症性乳がん再発などによる皮膚の発赤を伴う結節が主であり，その発見には自覚症状や視触診が重要である．しかしながらBCS後は放射線照射を施行するため，放射線皮膚炎をはじめとして乳房浮腫や乳房の色素沈着が出現することがあり，皮膚所見はさまざまに変化する．また，Paget病でも浸潤巣を有することも多く，再発手術時にリンパ節郭清を考慮する必要もある．今回われわれは，乳房温存術1.5年後に乳頭乳輪の色調変化が出現し，術後5年目にPaget病と診断した1例を経験した．今までBCS＋腋窩リンパ節郭清後にPaget病を発症した報告は散見されるが，BCS＋SLNB後にPaget病の発症に対する術式に言及した報告はない．BCS＋SLNB後のPaget病の診断と治療，術式は重要な課題と考える．

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症　例

患者：64歳，女性．

主訴：左乳房皮膚びらん．

既往歴：高血圧，虫垂炎．

現病歴：他院にて左乳癌に対し左乳房温存術＋SLNBを施行し，術後に温存乳房に放射線照射（50Gy）を施行した．術後1年6カ月（放射線終了後1年）で患側乳頭にびらん・浸出液を認めたが経過観察をしていた．次第に浸出液は消失しびらん部は乾燥していった．術後3年で乳頭乳輪のびらんは改善しないため前医で皮膚科を受診したが放射線皮膚炎と診断され経過観察となった．その後も改善せず乳頭は次第に陥没していった．術後5年にびらんの範囲が拡大していたため，前医皮膚科にて皮膚生検を施行しPaget病と診断され当院を紹介受診した．

初回手術：病理所見．

左D領域に径15mmの病変を認めた．病理組織像は乳管内に異型上皮の充実性・乳頭状の増殖を認め，high-grade ductal carcinoma in situ（DCIS），comedo typeと診断された．切除断端は陰性でリンパ節転移も陰性であった．ホルモンレセプターはER・PgRともに陰性であった（**Fig. 1**）．

局所写真：左乳輪から外側にびらん面を認めた．3年目から5年目にかけてびらんは拡大しており，3年目ではわずかに乳頭を認めるが，5年目には乳頭の構

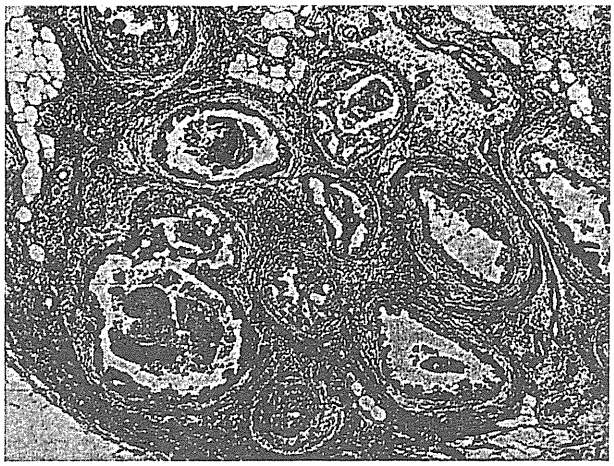

Fig. 1　初回病理所見（H.E. 染色　弱拡大）
乳管内に異型上皮の充実性・乳頭状の増殖を認め，内部に壊死を伴う．high-grade DCIS（comedo type）と診断した．

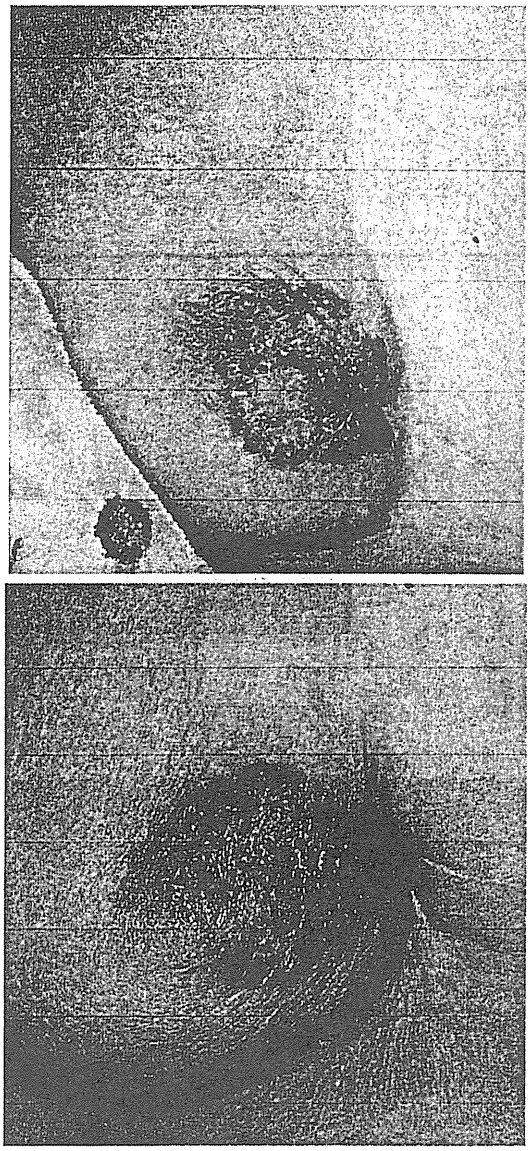

Fig. 2A　術後 3 年目　左乳輪から外側にびらん面を認める．わずかに乳頭を認める．
B　術後 5 年目　術後の瘢痕収縮の進行とびらんの拡大傾向を認める．乳頭の構造は消失している．
A/B

造は消失している（**Fig. 2A, B**）．

マンモグラフィ：左 BCS 後，異常所見を認めない（カテゴリー 1）（**Fig. 3**）．

胸部造影 CT：左乳房 CD 領域に初回手術による瘢痕を認め，周囲の皮膚には肥厚と造影効果を認める．乳房内に腫瘤性病変は認めなかった（**Fig. 4**）．

胸部造影 MRI：左乳房の中央から外側にかけて皮膚の肥厚と造影効果を認める．病変の境界は不明瞭であった．乳房内に腫瘤性病変は認めなかった（**Fig. 5**）．

手術：以上より，Paget 病単独病変と診断し，左乳房切除術を施行した．

病理結果：びらんを形成した乳頭周囲に，明るい細胞質を持つ大型の異型細胞が表皮内に伸展しており，Paget 病と診断した．乳腺内には他病変を認めず，乳頭直下の乳管内にも異型細胞を認めなかった（**Fig. 6**）．

考　察

乳房 Paget 病は全乳癌の0.5-2％を占め，比較的まれな疾患である．そして乳房 Paget 病の94-98％は乳房内に DCIS や浸潤性乳管癌を伴うと報告され Paget 病単独発症は非常に少ない[1)~3)]．さらに温存乳房内の Paget 病発症の報告は 1％以下と報告され，非常にまれな疾患である[4)]．その中でも，乳房温存術後の Paget 病型再発（真の再発）と異時性発症の Paget 病（新出病変）との鑑別は言及されていない．また乳房温存後の乳房内再発に関する報告においても新出病変と真の再発を鑑別する標準化された基準はないが，Huang ら[5)]や Komoike ら[6)]は新出病変を以下の如く定義している．①温存乳房術後から発症時間が長い②初発巣と異なった部位（3 cm 以上）に発症③組織学的なサブタイプが異なる④切除断端の評価（陰性），などの臨床的および病理学的因子を複合し分類し，真の再発は予後不良であり，その鑑別が重要と述べている．

本疾患は① Paget 病発症までに1.6年と短く，②原発巣と再発乳頭は比較的近い部位にあり，また③原発巣および Paget 病巣ともに DCIS で内分泌感受性がなく，同様のサブタイプであった．そして④初回手術

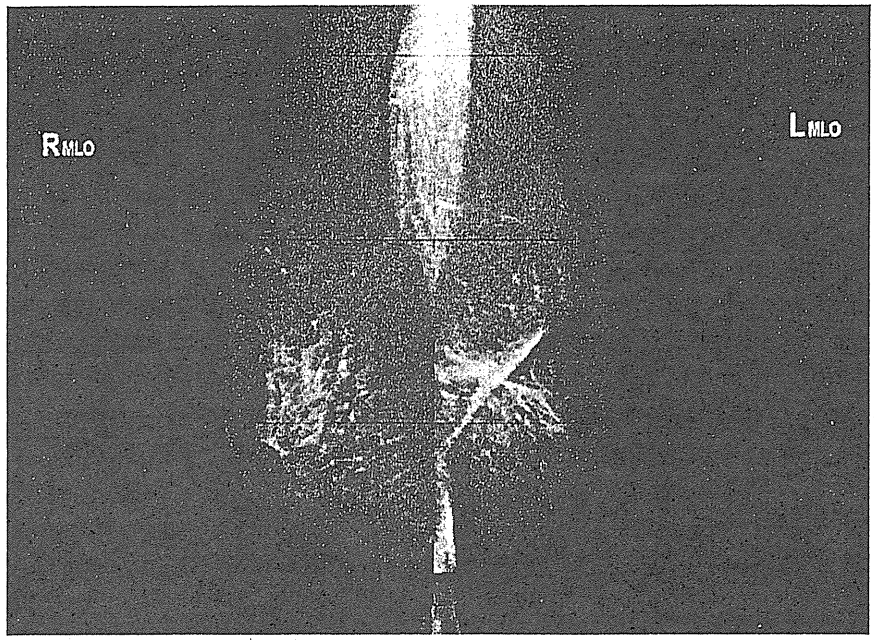

Fig. 3　マンモグラフィ(術後5年目)　左乳房温存術後，異常所見を認めない(カテゴリー1)．

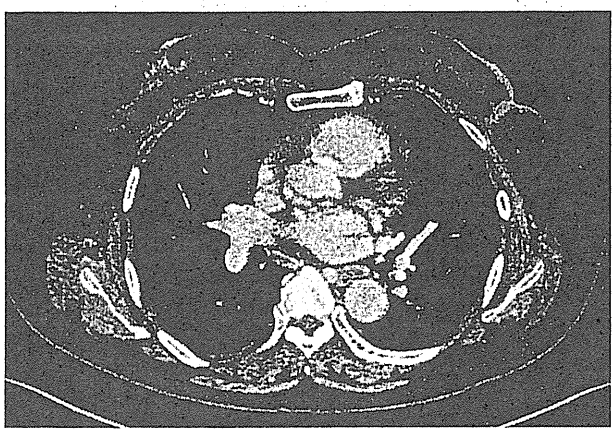

Fig. 4　胸部造影CT：左乳房CD領域に温存手術による瘢痕を認める．周囲の皮膚には肥厚と造影効果を認める．

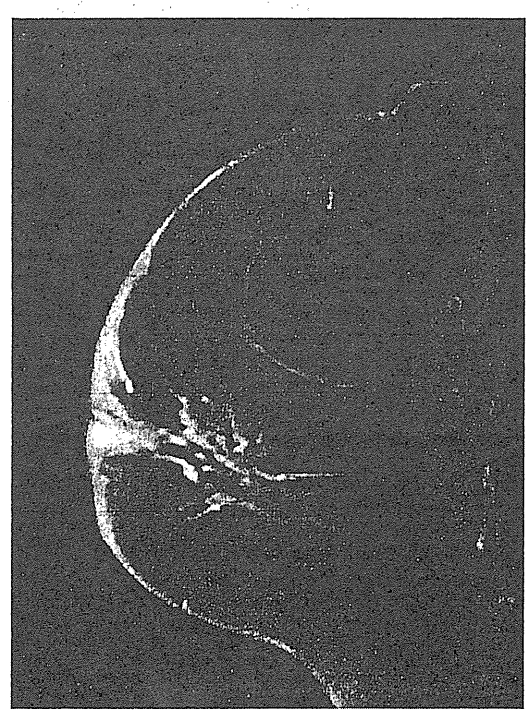

Fig. 5　乳房造影MRI：左乳房の中央から外側にかけて皮膚の肥厚と造影効果を認める．

の切除断端は陰性で，再手術の病理学的検査では乳頭直下の乳管内には異型細胞を認めず，病巣は乳頭乳輪に限局していた．そのため，切除断端評価以外は上述した真の乳房内再発の基準を満たしていた．

さらに，Paget病においては切除断端評価と乳房内再発の因果関係に関しては議論の余地がある．Laronga ら[7]の皮下乳腺全摘を施行した検討では，初回手術で乳腺の切除断端が陰性であった286例のうち，5.6%に術後の病理診断で乳頭乳輪への浸潤を認めたと報告している．また Luttges[8]らは乳房切除を施行した166例のうち21%に多中心性病変を認め，その63%は乳頭乳輪への病変を認めたと報告し切除断端陰性は Paget病の異時性発症の根拠とはならない．

以上より本症例は臨床的には Paget病型再発の可能性が高い．しかしながら詳細な病理学的な比較にお

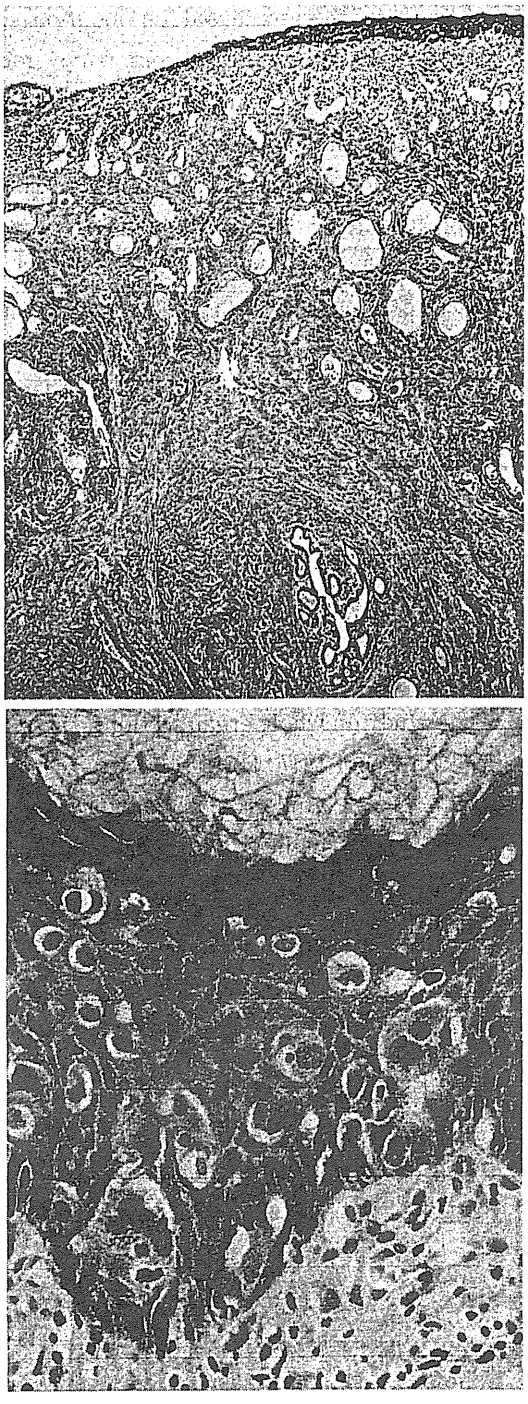

Fig. 6A　H.E. 染色　弱拡大　表皮内に Paget 細胞が進展している．乳頭直下の乳管内には進展を認めない．

B　H.E. 染色　強拡大　大型の明るい細胞質をもつ Paget 細胞を認める．　A/B

いては今回の Paget 病巣には壊死組織や石灰化は認めず，原発巣と完全には一致せず，臨床的にまれであるが乳頭乳輪のみに限局して病巣のある新出病変の可能性もあり得る．そのため，最終的には本症例の Paget 病巣は真の再発と新出病変の鑑別は困難であり，予後に関しても不明であり，経過観察が必要である．

一方，原発 Paget 病の予後は乳房内病変に依存していることが諸家の報告で知られている．Chen らによると15年生存率は Paget 病単独で88%，Paget 病＋DCIS で94%，Paget 病＋浸潤癌で61%と報告しており浸潤癌を伴わなければ予後は良好である[9]．また Paget 病に浸潤癌を伴うとリンパ節転移は45-66%と高率に認める[10)~13)]．

Paget 病と診断されるまでの期間と浸潤癌を併存する可能性の相関関係は不明であるが併存する浸潤癌の可能性を考えると早期診断が望まれる．いくつかの報告では Paget 病の発症から診断までの所要時間については比較的時間を要している．Rosen によると Paget 病と診断に至るまでに 6 -12カ月を要することが多く，その診断を遅らせる要因として皮膚の湿疹などの良性疾患として見逃されることが多い[2]．Menzies ら[14]は温存術後の Paget 型再発 3 例でそれぞれ診断までに14カ月，15カ月，27カ月を要し放射線照射による乳房の色素沈着，硬結や浮腫の変化を認め放射線皮膚炎との鑑別に難渋すると考察している．本症例は術後 1 年 6 カ月の時点で発症していた可能性がある．この時点では乳頭のびらんと浸出液を認め次第にこれが乾燥し約 5 年後に乳頭の構造自体が消失した．病理学的には，乳頭が存在していた部位の直下は正常な乳腺構造を認めており Paget 細胞が表皮内進展することで乳頭の隆起が消失したと考えられる．本症例では浸潤癌の併存は認めていないものの診断までに要した時間は長く乳房の色調変化や乳頭陥凹を認めた時点で Paget 病を疑い生検をしていれば診断できたと反省される．

術式に関しては術前 Paget 病と診断された症例で乳房全摘術；62%，乳房温存手術；38%と報告されており，リンパ節に関しては，まとまった報告がない[3]．一般的に非浸潤癌であれば腋窩リンパ節転移をきたさず，SLNB の必要性もない．しかしながら術前診断が非浸潤癌の診断であっても術後の病理学的評価で浸潤癌と診断されることも多く，Sukumvanich ら[15]は，術前に乳房 Paget 病単独と診断し乳房切除をした19例について，術後の検索で27%に浸潤癌を認め11%にセンチネルリンパ節（SLN）の転移を認めたと報告している．そのため温存再発巣に浸潤巣の併存が疑われた場合は乳房全摘術＋腋窩リンパ節郭清が妥当であると

考える．しかし，浸潤巣を有さないPaget病再発の場合のリンパ節郭清は過剰治療となる．このためPaget病の乳房内病変の術前画像評価は重要である．本症例は術前画像診断のマンモグラフィ・乳腺超音波検査・CT・MRIにて乳頭の陥凹と乳輪皮膚の肥厚を認めたものの腫瘍性病変や皮膚直下の脂肪織浸潤を疑う所見は認めずPaget病単独と診断し，腋窩リンパ節郭清を回避し単純乳房切除術を施行した．本症例は術後に浸潤癌が検出された場合に2期的な腋窩郭清を考慮していたが結果的には乳房Paget病のみであり追加治療の必要性はないと判断した．なお，近年，乳房温存術＋SLNB後の温存乳房内再発に対して再度SLNBを施行した報告がなされてきているが[16)17)]，症例数の問題や観察期間の短さなどの問題がありSLNBの再試行を標準術式とするのは今後の課題と考えられる[18)]．

結　語

乳房温存術後の乳房は放射線照射の影響もあり，皮膚の色調や硬結びらんが出現するためPaget病の早期発見には厳重な視触診が重要である．またセンチネルリンパ節生検後のPaget病発症の外科的治療は画像診断が重要であり浸潤癌再発が疑われなければ腋窩郭清を回避した単純乳房切除を第一選択にすべきと考える．

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A CASE OF PAGET'S DISEASE OF THE NIPPLE AFTER BREAST-CONSERVING TREATMENT

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We report a case of Paget's disease of the nipple after breast-conserving surgery. The case involved a 64-year-old postmenopausal woman who had undergone breast-conserving surgery and sentinel lymph node biopsy with radiation therapy for ductal carcinoma in situ of the left breast (pTis pN0 M0 Stage 0) at another hospital in 2002. She noticed skin erosion of the left nipple and areola about 1.5 years after the breast-conserving treatment (BCT). She had been followed at the hospital with a diagnosis of dermatitis. Erosion of the nipple and areola had expanded in about 5 years after the BCT. Skin biopsy of the areola confirmed Paget's disease after BCT. She was referred to our hospital and left total mastectomy was performed for Paget's disease after BCT. Such a recurrence as Paget's disease of the nipple occurs after BCT like in this case is comparatively rare, but its clinical course can be observed during long-term follow-up period. Paget's disease of the nipple should be suspected whenever nipple changes appear after BCT for early diagnosis of recurrence.

Key words : Paget's disease, sentinel lymph node biopsy, ipsilateral breast tumor recurrence

TOPICS 第19回日本乳癌学会学術総会より

乳がん診療地域連携パスの運用と実際
—診療所の立場から—

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はじめに

当院では2008年から現在までに約160名余の乳がん地域連携パスの患者の診療を行っている．その経験から，パスの受け手である診療所でのパスの運用について，および患者に行ったアンケートをもとに患者からの反応について報告する．

パスの運用

2008年3月に千葉県乳がん診療地域連携協議会（現在は研究会）が発足した．千葉県がんセンター，千葉労災病院を拠点病院として，地域の乳癌診療を行っている病院やクリニックの有志でパスを作成した．このパスは連携先で投薬および定期検査も行い，拠点病院にはバリアンス時などに紹介される形式となっている．経過観察の内容は2007年のザンクトガレンで定められたリスク分類[1]に応じて，ガイドライン[2]を参考に決定した．（表1）

連携パスに患者が登録されると診療情報提供書とパスが連携先に郵送される．当院では来院前に電子カルテと紙のファイルも個人ごとに作成し，来院時には紙のファイル（パス）も活用している．初診時には看護師が時間をかけてオリエンテーションを行い初対面の患者とのコミュニケーションを図っている．診察や検査，結果説明を通じて患者と接し，安心感を持ってもらうのが医師の仕事だが，時間は限られてしまう．看護師は，患者と共にパスを確認しながら検査や投薬の予定を立て，内分泌治療の副作用チェック，リンパ浮腫に対するセルフケアの説明，術後の下着の相談，乳房再建についての情報提供を行なうなど，多岐にわたって患者のサポートに当たっている．このように当院では連携パス運用に看護師が重要な役割を果たしている．

現在，千葉県がんセンターからの連携パス患者は163名でリスク別には表2に示すようにintermediate risk，内分泌療法有りの患者が多い．経過観察中に10例にバリアンスが発生し，千葉県がんセンターに紹介となっている．バリアンスの内訳は放射線肺臓炎，内分泌治療の副作用，定期検査で発見された局所再発，遠隔再発である．バリアンス例については研究会の場などでオープンに解析し，今後の経過観察に活かしていくことが必要と考える．

患者アンケートより（図1）

当院に通院中のパスの患者にアンケートによる満足度調査を行った．調査項目は年齢，当院への通院回数，通院のしやすさ，待ち時間について，医師や看護師の説明について，相談のしやすさについて，当院に望む情報提供について，地域連携のシステムに満足しているか，である．90名に配布し匿名，郵送で60名から回答を得た．

回答者の年齢は40代，50代を中心に幅広い．通院については，当院が郊外のショッピングモールにあるため車で来院する人には便利な反面，公共の交通機関利用者にはやや不便となっている．待ち時間はなるべく短くなるように検査予定を患者

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表1　経過観察（パス）の内容

5年目まで
半年ごとの視触診，採血，乳腺エコー
1年ごとのマンモグラフィ，胸部レントゲン
骨シンチ（リスクに応じて）
腹部エコー（リスクに応じて）
6年目以降
視触診，乳腺エコー，マンモグラフィ，胸部レントゲン
パスの目標（アウトカム）
内分泌治療が5年間継続できる
転移，再発がない
パスからの逸脱（バリアンス）
内分泌療法の副作用による中断など
転移，再発の所見，または疑い

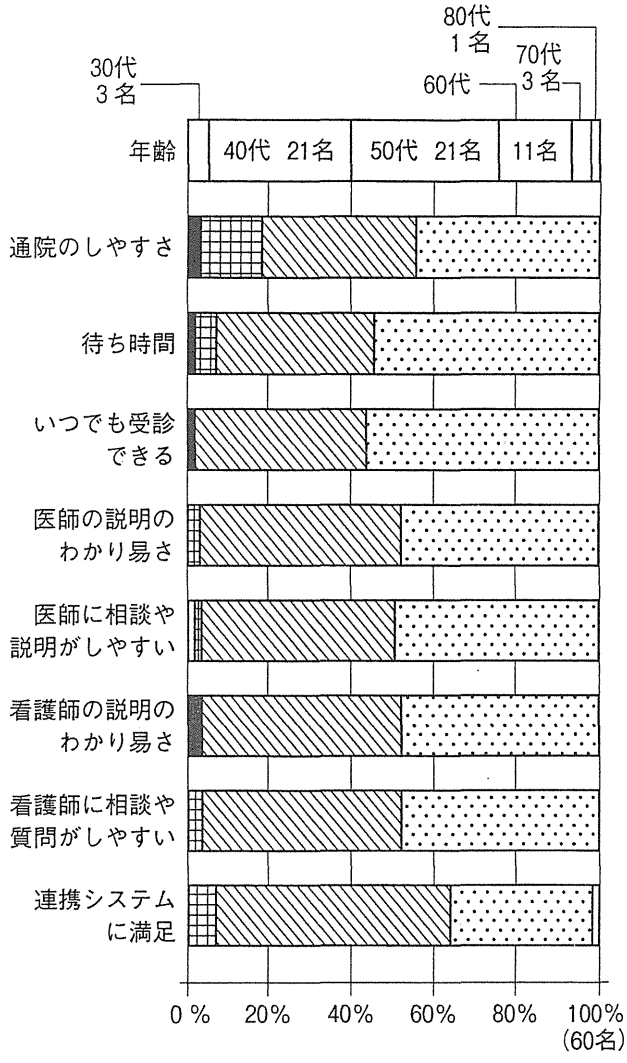
表2　連携患者の内訳

紹介患者数	163名（2011年5月31日現在）
リスク別	
Low risk	48名
Intermediate risk	96名
High risk	19名
内分泌療法	
あり	114名
なし	49名
10例にバリアンスあり．がん拠点病院に紹介	
再発疑い，放射線治療による肺炎，内分泌治療副作用	
44名が当院からの紹介患者	

と相談して予約制としているため，比較的良好な結果であった．また，定期受診以外でも気になることや感冒症状などでも受診できる点は評価された．医師や看護師の説明や相談のしやすさについてもおおむね良いと回答された．連携システムに満足しているか，という項目にも良いという評価だった．この結果はアンケートに協力してくださった患者からの意見というバイアスがあることは考慮する点である．情報提供を望むこととしては，患者会について，リンパ浮腫について，術後用の下着について，などの要望が寄せられた．

結　語

今後の課題としては，標準治療の変化に対してパスを柔軟に対応させること，検査精度の維持，向上を図ること，他の専門科（婦人科，メンタルケア，整形外科など）との連携を行うこと，連携パスで起こった問題点やバリアンスを検討し，患者がより安心して経過観察を受けられる環境を作ることなどである．



情報提供を望むこと
- 術後用の下着の試着会の案内や，開催
- 乳房再建の相談
- 患者会を作ってほしい
- 既存の患者会を紹介してほしい
- 乳がんの情報誌の案内
- リンパ浮腫の相談
- 相談室を設置してほしい
- いろいろな情報をクリニックのHPにのせてほしい

図1　調査結果

文　献

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TOPICS

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ORIGINAL ARTICLE

A phase III open-label study to assess safety and efficacy of palonosetron for preventing chemotherapy-induced nausea and vomiting (CINV) in repeated cycles of emetogenic chemotherapy

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Abstract
Purpose Prevention of chemotherapy-induced nausea and vomiting (CINV) is of great importance for the completion of multiple cycles of cancer chemotherapy. Palonosetron is a second-generation 5-HT_3 receptor antagonist with proven efficacy for both acute and delayed CINV. This study was designed to assess the safety and efficacy of 0.75 mg palonosetron in repeated cycles of highly emetogenic chemotherapy or anthracycline–cyclophosphamide combination (AC/EC).
Methods We gave 0.75 mg palonosetron to 538 patients 30 min prior to ≥50 mg/m^2 cisplatin or AC/EC on day 1. Prophylactic dexamethasone was administered on days 1–3. The primary endpoint was the incidence rate of adverse events (AEs). The secondary endpoint was complete response rate (CR, defined as no emesis and no rescue medication) throughout the study period.
Results Treatment-related AEs were seen in 44% (237 of 538 patients). Serious AEs were seen in 4% (23 of 538 patients), all considered unrelated or unlikely to be related to palonosetron. Only one patient discontinued the study due to a treatment-related AE. No trend toward worsening of AEs was observed in subsequent cycles of chemotherapy.

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Complete response rates were maintained throughout repeated cycles.
Conclusion The extraordinary safety profile and maintenance of efficacy of 0.75 mg palonosetron combined with dexamethasone were demonstrated throughout repeated chemotherapy cycles.

Keywords Palonosetron · 5-HT_3 receptor antagonist · Antiemetic · Chemotherapy-induced nausea and vomiting · Highly emetogenic chemotherapy

Introduction

Cancer chemotherapy plays a key role in cancer treatment, and it is essential to continue multiple cycles aimed at stabilizing cancer growth and to cure the disease in various clinical settings. Chemotherapy-induced nausea and vomiting (CINV) are among the most problematic adverse events (AEs) in cancer chemotherapy [1–3].

Palonosetron is a second-generation 5-HT_3 receptor antagonist, which has been reported to be effective in the prevention of acute and delayed CINV compared to previous 5-HT_3 receptor antagonists, dolasetron, and ondansetron in moderately emetogenic chemotherapy [4, 5].

Two phase II studies performed in Japan reported a tendency toward better efficacy with the 0.75-mg dose than with 0.25- and 0.075-mg doses of palonosetron, and the excellent safety profile of all these doses suggested that 0.75 mg palonosetron could be the recommended dose for use in a trial [6, 7]. A phase III trial showed non-inferiority of palonosetron to granisetron in the acute phase, superiority of palonosetron to granisetron in the delayed phase in prevention of CINV, and similar safety profiles of palonosetron and granisetron in patients receiving cisplatin or anthracycline–cyclophosphamide combination therapy (AC/EC) [8].

A study has reported the safety and efficacy profile of 0.75 mg palonosetron in repeated cycles of chemotherapy [9].

The goal of this trial was to confirm the safety and efficacy profile of 0.75 mg palonosetron, combined with dexamethasone in patients receiving repeated cycles of highly emetogenic chemotherapy or AC/EC.

Methods

Patients

The patients enrolled in this open-label study on repeated chemotherapy cycles were selected from among patients who had previously completed the randomized phase III trial of palonosetron compared to granisetron [8] and were scheduled to receive the same chemotherapy regimen as in the randomized phase III study (≥50 mg/m^2 cisplatin or AC/EC). All patients provided written informed consent prior to enrollment. Eligible patients were men and women ≥20 years of age with a confirmed diagnosis of malignant disease. Patients were required to have an ECOG performance status of 0–2, adequate bone marrow function (WBC≥3,000/mm^3), hepatic function (AST and ALT <100 U/L or grade ≤3 according to the Common Terminology Criteria for Adverse Events v3.0 (CTCAE) for patients with liver metastasis), and renal function (creatinine clearance ≥60 mL/min).

The exclusion criteria included severe, uncontrolled, concurrent illness other than neoplasia; asymptomatic metastases to the brain; seizure disorders requiring anticonvulsants, unless clinically stable; gastric outlet or intestinal obstruction; any vomiting, retching, or grade ≥2 nausea according to CTCAE v3.0; a known hypersensitivity to palonosetron or other 5-HT_3 receptor antagonists or dexamethasone ingredients; participation in another drug study or receipt of any investigational agents other than palonosetron within a month of enrollment in the study; pregnant or breast-feeding women; and all subjects (men or women) who planned conception during the study period.

Study design

This phase III, multicenter, open-label trial was conducted between July 2006 and August 2007 in Japan. Eligible patients received 0.75 mg palonosetron 30 min before cisplatin or AC/EC initiation on day 1 in each cycle. Administration of 16 mg prophylactic dexamethasone i.v. within 45 min before palonosetron on day 1 was also required. Additionally, 8 mg dexamethasone i.v. for patients receiving cisplatin or 4 mg p.o. for patients receiving AC/EC was administered on day 2 (24–26 h after chemotherapy) and day 3 (48–50 h after chemotherapy). For patients receiving irinotecan on day 8 or after, palonosetron was administered 30 min before the administration of irinotecan (e.g., day 8 and day 15 in combination chemotherapy of cisplatin and irinotecan for lung cancer). The interval between administrations of palonosetron had to be 7 days or more. Administration of dexamethasone was permitted before irinotecan at the discretion of each investigator. More than one factor influenced the choice of dexamethasone dose and schedule in this trial, including international antiemetic guidelines [10–12], the results of Japanese clinical studies on antiemetic agents [13, 14], and the findings of a survey on antiemetic treatments conducted in the trial sites. Patients repeatedly received up to four cycles of the study treatment, including treatment received during the first cycle, described as the treatment administered in the previous randomized phase III trial in which the patients participated before entering this

trial. Patients were confirmed for eligibility to continue study treatment before the start of each cycle according to the following discontinuation criteria: not meeting the eligibility criteria; receiving an antiemetic drug within 24 h before the start of a cycle; or vomiting, retching, or grade 2 or higher nausea within 24 h before the start of a cycle.

Efficacy was assessed every 24 h for 5 days, only after administration of cisplatin or AC/EC. The safety profile of palonosetron was assessed from its first administration, until 8 days after its last administration.

The study was conducted according to the Declaration of Helsinki, and written approval was obtained from the Institutional Review Boards at each site before study commencement.

Study visits and assessment procedures

The 12 lead-ECG and laboratory assessments were conducted within 8 days before the beginning of the first cycle, and once each during days 2–4 and 8–10 of each cycle. In patients receiving irinotecan, these assessments were also carried out 7–9 days after every administration of palonosetron. AEs and concomitant medications were recorded.

The investigators judged the causal relationship between AE and palonosetron according to five categories (none, unlikely, possible, probable, and definite). Any AE judged by the investigator to be possibly, probably, or definitely related to palonosetron was regarded as a treatment-related AE.

Study endpoints

The primary endpoint was the rate of AEs in the study. The secondary endpoints were the type, severity, and causal relationship of the AEs, the proportion of patients with a complete response (CR; defined as no emetic episodes and no rescue medication use), and severity of nausea. Severity of nausea was indicated as none, mild, moderate, or severe, according to a Likert scale, based on subjective evaluation by each patient. Patient diaries were used for recording of emetic episodes, nausea, or rescue anti-emetics at daily (24-h) intervals.

Statistical analysis

The safety analysis cohort included all patients who received the study drug. This safety analysis cohort was divided into three subset cohorts: patients receiving irinotecan combined with cisplatin (irinotecan cohort), patients receiving cisplatin combined with other treatment excluding irinotecan (cisplatin cohort), and patients receiving AC/EC (AC/EC cohort). The modified intent-to-treat (ITT) cohort included all patients who received the study drug and chemotherapy (cisplatin or AC/EC). This modified ITT cohort was used for efficacy analysis.

The data for the patients who received palonosetron in the randomized phase III trial [8] have been considered as both "first cycle" efficacy and safety data; thereafter, the first cycle of this open-label study was counted as the second cycle of chemotherapy.

Safety data were listed and summarized descriptively (data on file). Toxicity grades were generated for hematology and blood chemistry parameters, according to CTCAE v.3.0 adapted toxicity grades, and treatment-related AE were tabulated. New adverse events (NAE) and worsened adverse events (WAE) were listed to identify the safety profile of palonosetron on repeated administration. An NAE was defined as an AE not observed in the first cycle and observed only in the second or subsequent cycles. A WAE was defined as an AE that could be seen in the first cycle but worsened in grade only from the second cycle or later compared to the grade observed in the first cycle.

To evaluate the influence of palonosetron on cardiovascular abnormality, the proportion of patients with QTc prolonged to more than 60 ms from baseline or more than 500 ms was examined in the safety analysis cohort by chemotherapy (cisplatin or AC/EC).

A sample size of 300 patients was needed to find AEs observed in 1% or more of patients after repeating the administration of palonosetron two or more times, including the safety data of palonosetron in the randomized phase III study.

The proportions of patients with CR or no nausea were assessed during the acute phase (0–24 h post-chemotherapy), the delayed phase (24–120 h post-chemotherapy), and the overall phase (0–120 h post-chemotherapy) in each cycle.

All statistical analyses were performed using SAS software (version 8.2; SAS Institute, Cary, NC, USA).

Results

We enrolled 546 patients to receive a single i.v. dose of palonosetron, but eight of these patients did not receive the study treatment since three patients met discontinuation criteria for this study and five patients were withdrawn from this study at the discretion of the investigators. Therefore, 538 patients were evaluated for safety. These 538 patients were also included in the modified intention-to-treat (ITT) cohort for efficacy analysis.

Demographic data for the safety analysis cohort are presented in Table 1. Of the 538 patients in the safety analysis cohort, 304 (57%) women and 358 (67%) patients overall were aged ≥55 years. The most common types of malignant disease were non-small cell lung carcinoma (249 patients [46%]) and breast carcinoma (224 patients [42%]).

Table 1 Patient demographics and baseline characteristics

		N=538	
		N	%
Age categories (years)	Mean, SD	57.8, 10.4	
	≥55	358	66.5
	<55	180	33.5
Height (cm)	Mean, SD	160.00, 8.25	
Weight (kg)	Mean, SD	57.89, 10.07	
Sex	Women	304	56.5
	Men	234	43.5
PS	0	388	72.1
	1	147	27.3
	2	3	0.6
Previous surgery	No	257	47.8
	Yes	281	52.2
Previous radiation	No	486	90.3
	Yes	52	9.7
Alcohol consumption within 180 days of enrollment	No	236	43.9
	Rarely	72	13.4
	Sometimes	60	11.2
	Everyday	170	31.6
Tumor type	Non-small cell lung carcinoma	249	46.3
	Small cell lung carcinoma	45	8.4
	Breast carcinoma	224	41.6
	Others	20	3.7
Chemotherapy	Cisplatin with treatment excluding irinotecan	277	51.5
	Cisplatin with irinotecan	37	6.9
	AC/EC	224	41.6

Regarding chemotherapy regimen, 277 of 538 patients (51%) were given cisplatin combined with other treatment excluding irinotecan, 224 of 538 patients (42%) received AC/EC, and 37 of 538 patients (7%) were given irinotecan. Furthermore, vinorelbine (95 of 277 patients [34%]) and gemcitabine (89 of 277 patients [32%]) were agents commonly combined with cisplatin; fluorouracil (92 of 224 patients [41%]) was associated with AC/EC.

The numbers of patients receiving palonosetron in each cycle are shown in Table 2. Over 50% of the patients received palonosetron through cycle 3. The minimum, median, and maximum numbers of administrations of palonosetron throughout the study period were 1, 3, and 10, respectively.

Of the 538 patients in the safety analysis cohort, 536 patients (99.6%) experienced at least one AE. In the subcohort of the safety analysis, patients reported to have at least one AE, 99% (275 of 277) of patients were in the cisplatin cohort, 100% (224 of 224) in the AC/EC cohort, and 100% (37 of 37) in the irinotecan cohort. Treatment-related AEs judged by the investigators to be possibly, probably, or definitely related to palonosetron were reported in a total of 44% (237 of 538) of the safety analysis cohort, including 35% (97 of 277) of the cisplatin cohort, 55% (123 of 224) of the AC/EC cohort, and 46% (17 of 37) of the irinotecan cohort.

Table 3 shows the main treatment-related AEs that occurred in at least 2% of patients in the safety analysis

Table 2 Number of patients in each cycle in the safety analysis cohort

N = total number of patients in a cohort

n = number of patients for each cycle

Cohort	N	Cycle 1		Cycle 2		Cycle 3		Cycle 4	
		n	%	n	%	n	%	n	%
Cisplatin	277	277	100.0	230	83.0	153	55.2	66	23.8
Irinotecan	37	37	100.0	36	97.3	25	67.6	7	18.9
AC/EC	224	224	100.0	220	98.2	211	94.2	98	43.8

Table 3 Treatment-related adverse events

Cohort	Cisplatin (*N*=277)			AC/EC (*N*=224)			Irinotecan (*N*=37)			Total (*N*=538)		
	G1, *n* (%)	G2, *n* (%)	G3, *n* (%)	G1, *n* (%)	G2, *n* (%)	G3, *n* (%)	G1, *n* (%)	G2, *n* (%)	G3, *n* (%)	G1, *n* (%)	G2, *n* (%)	G3, *n* (%)
Constipation	3i (11.2)	12 (4.3)	1 (0.4)	57 (25.4)	19 (8.5)	2 (0.9)	5 (13.5)	2 (5.4)	0 (0.0)	93 (17.3)	33 (6.1)	3 (0.6)
Electrocardiogram QTc prolonged	6 (2.2)	2 (0.7)	1 (0.4)	14 (6.3)	16 (7.1)	0 (0.0)	0 (0.0)	2 (5.4)	0 (0.0)	20 (3.7)	20 (3.7)	1 (0.2)
Angiopathy	19 (6.9)	1 (0.4)	0 (0.0)	16 (7.1)	0 (0.0)	0 (0.0)	2 (5.4)	0 (0.0)	0 (0.0)	37 (6.9)	1 (0.2)	0 (0.0)
Alanine aminotransferase increased	12 (4.3)	6 (2.2)	3 (1.1)	4 (1.8)	2 (0.9)	0 (0.0)	0 (0.0)	1 (2.7)	1 (2.7)	16 (3.0)	9 (1.7)	4 (0.7)
Aspartate aminotransferase increased	11 (4.0)	5 (1.8)	4 (1.4)	2 (0.9)	2 (0.9)	0 (0.0)	0 (0.0)	2 (5.4)	0 (0.0)	13 (2.4)	9 (1.7)	4 (0.7)
Headache	9 (3.2)	0 (0.0)	0 (0.0)	12 (5.4)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	21 (3.9)	1 (0.2)	0 (0.0)
Gamma-glutamyl-transferase increased	5 (1.8)	2 (0.7)	1 (0.4)	2 (0.9)	0 (0.0)	1 (0.4)	1 (2.7)	0 (0.0)	1 (2.7)	8 (1.5)	2 (0.4)	3 (0.6)

Possibly, probably, or definitely related to study product and over 2% incidence of patients in the safety analysis cohort

N = total number of patients in a cohort

G1, G2, G3 = Grade of adverse event as per CTCAE v.3

n = number of patients with at least one treatment-related AE

cohort. The incidences of constipation and electrocardiographic QTc variation were higher in patients receiving AC/EC than in those receiving cisplatin.

The proportions of patients who experienced an increase in QTc value more than 60 ms (QT1) from baseline or more than 500 ms (QT2) are summarized in Table 4. There was no clinically significant difference in the proportion of patients who experienced increase in QTc value between the patients receiving cisplatin and those receiving AC/EC, and the proportion was low (less than 3%) in both treatments, with no QTc variation reported to be symptomatic.

The incidence of NAE, defined as AEs observed only from the second cycle, was very low (less than 1%). In addition, the incidence of WAE, defined as AEs worsened by grade, starting from the second cycle compared to their grade in the first cycle, was very low (less than 0.5%). Among NAEs and WAEs, only one case of angiopathy was judged to be definitely related to palonosetron. This patient recovered within a day without treatment.

Serious AEs were reported in 4% of patients (23 of 538). All of these events were judged to be unrelated or unlikely to be related to palonosetron by the investigators.

Three patients withdrew from the study. Only one withdrawal, due to atrial fibrillation, was judged to be possibly related to palonosetron. The atrial fibrillation was not serious and resolved in 8 days with medical treatment. Two other patients withdrew from the study due to AEs judged to be related to chemotherapy or treatment for concomitant disease.

The proportion of patients with complete response to each of the four chemotherapy cycles considered in this study ranged from 72% to 77% in the acute phase, from 56% to 63% in the delayed phase, and from 52% to 56% in the overall phase (Fig. 1a). Similarly, the proportion of patients with no nausea in each cycle ranged from 55% to 61% in the acute phase, from 35% to 41% in the delayed phase, and from 33% to 39% in the overall phase (Fig. 1b). There were no major differences in the efficacy parameters

Table 4 Number of patients (percent) with QTc variations in cisplatin and AC/EC cohort in each cycle

Chemotherapy		Cycle 1	%	Cycle 2	%	Cycle 3	%	Cycle 4	%
Cisplatin	Evaluable patients (*N*)	314		266		178		73	
	QT1 (*n*)	3	1.0	5	1.9	1	0.6	2	2.7
	QT2 (*n*)	1	0.3	2	0.8	0	0.0	0	0.0
AC/EC	Evaluable patients (*N*)	223		220		211		98	
	QT1 (*n*)	4	1.8	3	1.4	4	1.9	1	1.0
	QT2 (*n*)	0	0.0	1	0.5	0	0.0	0	0.0

QT1 more than 60 ms from baseline, *QT2* more than 500 ms (absolute QTc value)

N = total number of evaluable patients in a cohort for each cycle

n = number of patients with QT1 or QT2 for each cycle

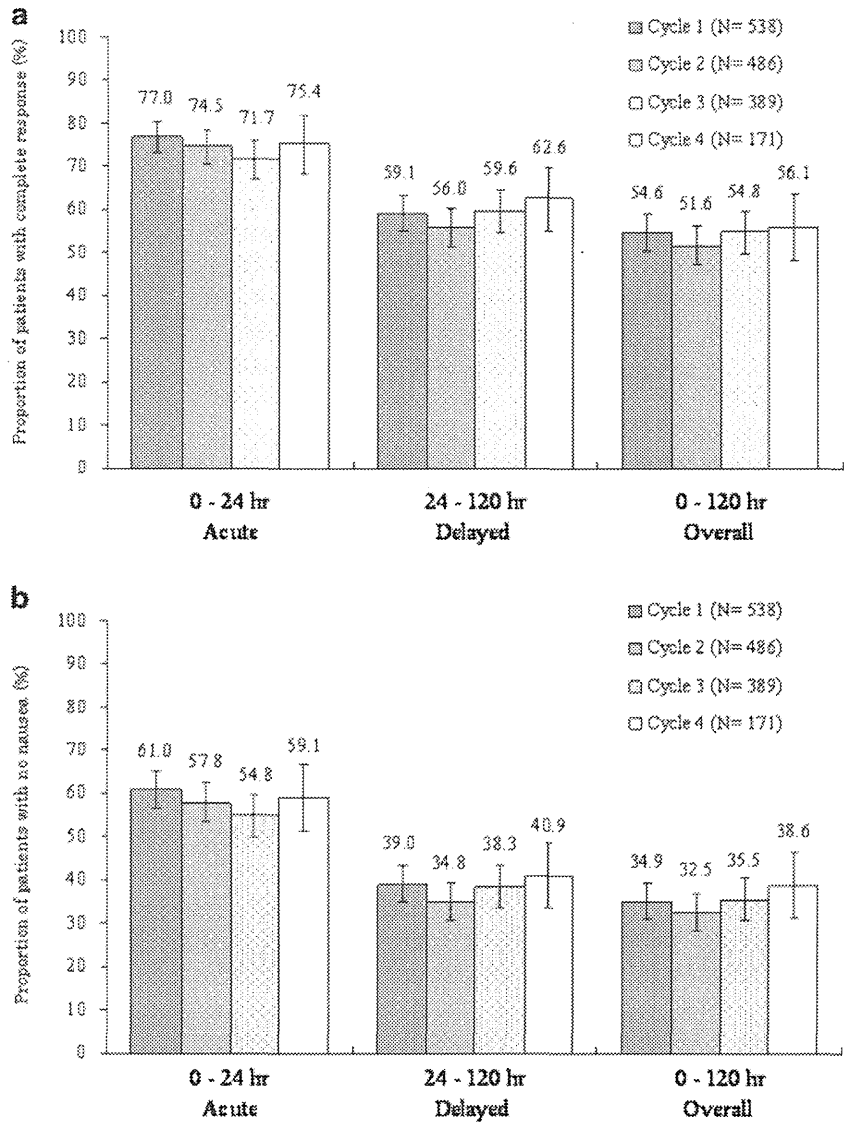

Fig. 1 **a** Proportion of patients with complete response for each study cycle. **b** Proportion of patients with no nausea for each study cycle. *Error bars* indicate 95% confidence intervals

among cycles within the acute (0–24 h), delayed (24–120 h), or overall (0–120 h) phases.

Discussion

In this phase III trial for patients receiving cisplatin or AC/EC in repeated chemotherapy cycles, an excellent palonosetron safety profile was observed.

Many women were enrolled in this trial because AC/EC was the treatment for breast cancer. Although the population of this study consisted of patients receiving highly emetogenic chemotherapy or AC/EC, they did not receive three-drug antiemetic regimens including a 5-HT_3 receptor antagonist, dexamethasone, and aprepitant. This is because aprepitant was not available in Japan at the time when this study was conducted. The dose of palonosetron, approved by the Ministry of Health, Labor and Welfare (MHLW) in Japan, was higher than that recommended by the international guidelines [12]. Both 0.75- and 0.25-mg doses of palonosetron exhibited superiority to ondansetron or dolasetron in the delayed phase in two comparative phase III studies for moderately emetogenic chemotherapy [4, 5]. Additionally, 0.75 mg palonosetron was superior to granisetron in the delayed phase in a phase III study for highly emetogenic chemotherapy [8]. The 0.75-mg i.v. dose of palonosetron is the dose approved in Japan by the MHLW, driven by results of the phase III comparative study [8] and two phase II dose-ranging studies for use in combination with dexamethasone [6, 7]. These dose-ranging phase II and comparative phase III studies showed no difference in safety between the two doses of 0.75 and 0.25 mg palonosetron.

The safety profile of this study showed that AEs related to palonosetron were similar to those identified in the safety profile described in a single chemotherapy cycle studies,

with a single administration of palonosetron [8]. Also, in a small population treated with palonosetron in each irinotecan cycle, almost weekly, the safety profile was similar to that described in single palonosetron dose studies.

NAE and WAE were reported in a very small number of patients and were mainly judged not to be related to palonosetron but to antineoplastic treatment or to the primary disease. No worsening trend in AEs was observed in the subsequent cycles of chemotherapy. Therefore, the results of this study did not arouse any special concern related to the administration of palonosetron in repeated cycles of chemotherapy.

Interactions of some 5-HT_3 receptor antagonists with human cardiac ion channels are known and have been reported [15], and recently, the effect of palonosetron on QTc prolongation has been studied in an European double-blind, randomized, placebo-controlled trial, which showed no significant effect on any ECG interval, including QTc duration, with intravenous palonosetron administered up to 2.25 mg, three times the study dose [16]. In the double-blind, randomized phase III study, the incidences of QTc prolongation in the palonosetron group and in the granisetron group were comparable [8]. In the present study, we carefully evaluated ECG because the effect of palonosetron on ECG interval was not known at the start of this study. The incidence of QTc prolongation was higher in those patients receiving AC/EC than in those receiving cisplatin; however, the proportion of patients with an increase in QTc (more than 500 ms as an absolute value or more than 60 ms difference from the baseline value) was very low, both in the patients receiving cisplatin and those receiving AC/EC. Therefore, the influence of palonosetron on QTc interval was not found to be clinically significant, as reported in previous studies [8, 16].

Maintenance of the efficacy of palonosetron was also shown during its administration throughout repeated chemotherapy cycles. De Wit et al. [17] reported that the antiemetic effect of granisetron plus dexamethasone was not maintained over multiple cycles of highly emetogenic chemotherapy because failure in its protection against delayed emesis negatively influenced the antiemetic effect against acute emesis in the subsequent cycles. We considered that efficacy of palonosetron in the delayed phase might contribute to the maintenance of antiemetic effect throughout repeated chemotherapy cycles. It is of great importance to assure maintenance of efficacy, as well as to provide a very good safety profile to assure patient compliance with chemotherapy, especially when administered in multiple cycle regimens.

In conclusion, in this multiple cycle study conducted with palonosetron, the analysis of AEs did not raise any safety concerns; the type and intensity of treatment-related AEs were consistent with previous reports for palonosetron and for 5-HT_3 receptor antagonists; they did not change after repeated administration of the study drug. Both the excellent safety profile and the sustained efficacy of 0.75 mg palonosetron were shown throughout repeated chemotherapy cycles in this study, and also even when it was administered more frequently (at least 7-day intervals) in patients receiving irinotecan-containing regimens.

Further research is warranted to assess this maintenance of efficacy and the excellent safety profile of palonosetron in multiple cycles of emetogenic chemotherapy as well as in combination with other antiemetic class agents.

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Randomized Phase II Study of Primary Systemic Chemotherapy and Trastuzumab for Operable HER2 Positive Breast Cancer

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Abstract

Primary systemic therapy for patients with HER2$^+$ (human epidermal growth factor receptor 2 positive) breast cancer may be improved by adding trastuzumab to chemotherapy. This randomized phase II trial compared 2 chemotherapy regimens comprising FEC (5-fluorouracil/epirubicin/cyclophosphamide), trastuzumab and either PH (paclitaxel) or DH (docetaxel) in 102 patients. FEC-PH and FEC-DH achieved high pathologic complete response rates. Breast conserving surgery was possible in more patients in the paclitaxel arm.

Background: In primary systemic therapy in patients with human epidermal growth factor receptor 2 positive (HER2$^+$) breast cancer, improvements in pathologic complete response (pCR) rate have been achieved by administering trastuzumab. **Patients and Methods:** Patients with stage II or IIIA HER2$^+$ operable breast cancer were randomly assigned to receive four 3-weekly cycles of FEC (5-fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2, cyclophosphamide 500 mg/m^2) followed by 4 cycles of 3-weekly trastuzumab (8 mg/kg week 1 and then 6 mg/kg) with either 12 weekly doses of paclitaxel 80 mg/m^2 (FEC-PH) or 4 cycles of 3-weekly docetaxel 75 mg/m^2 (FEC-DH). **Results:** Between March 2007 and June 2008, 102 patients were enrolled. Forty-nine patients receiving FEC-PH and 47 receiving FEC-DH were assessable for efficacy and safety. Eighty-four patients completed treatment and underwent surgery. There was no significant difference in the pCR rate between the 2 groups (46.9% [95% CI, 33.7%-60.6%] with FEC-PH vs. 42.6% [95% CI, 29.5%-56.8%] with FEC-DH; $P = .67$). Analysis by hormone receptor (HR) status showed pCR rates of 54.2% (32/59) in HR$^-$ tumors and 29.7% (11/37) in HR$^+$ tumors ($P = .02$). Among HR$^-$ tumors, the pCR rates were 65.4% and 45.5% in patients treated with FEC-PH and FEC-DH, respectively ($P = .13$). **Conclusions:** There was no significant difference in pCR rate between FEC-PH and FEC-DH. Both regimens achieved higher pCR rates in HR$^-$ than HR$^+$ breast cancer, and there was a trend toward higher pCR in HR$^-$ tumors with FEC-PH compared with FEC-DH. Further investigation is warranted to explore the relationship between efficacy and HR status.

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Keywords: Breast cancer, HER2, Primary systemic therapy, Trastuzumab

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Introduction

Primary systemic therapy (PST) is regarded as one of the standard therapies for locally advanced breast cancer and selected patients with operable disease to facilitate breast conservation.[1-4] Patients achieving pathologic complete response (pCR) in the primary lesion and with no residual tumor in axillary nodes after PST have longer recurrence-free survival than those without pCR.[4-6] Consequently, pCR is commonly used as a surrogate for long-term outcome when evaluating novel chemotherapy regimens. Currently, sequential regimens, including an anthracycline followed by either weekly paclitaxel or 3-weekly docetaxel are commonly used to achieve high pCR rates.[3,7]

Trastuzumab plays an important role in therapy for human epidermal growth factor receptor 2 (HER2) positive ($HER2^+$) breast cancer, and its efficacy has been proven in both the adjuvant[8-10] and the metastatic[11,12] settings. In the neoadjuvant setting, improvements in the pCR rate have been achieved by administering trastuzumab with PST in patients with $HER2^+$ breast cancer. In a randomized trial that compared chemotherapy with or without trastuzumab, the trastuzumab-containing regimen improved the pCR rate (65.2% vs. 26.3%; $P = .002$).[13] A second randomized trial, the neoadjuvant herceptin (NOAH), showed a higher pCR rate with the combination of chemotherapy and trastuzumab than chemotherapy alone (39% vs. 20%; $P = .002$).[14] In addition, single-arm trials that evaluated the combination of chemotherapy and trastuzumab as PST showed high pCR rates.[15-20] Recently, it was reported that patients who achieve pCR have longer survival compared with those who do not achieve pCR, even in a $HER2^+$ population.[21,22] It is possible, therefore, that pCR could be considered to be a surrogate marker for the efficacy of PST, even in patients with $HER2^+$ breast cancer, although definitive evidence is required to confirm this proposition. Based on these data, we conducted a randomized phase II trial to compare pCR rates achieved with FEC (5-fluorouracil/epirubicin/cyclophosphamide) followed by weekly paclitaxel plus trastuzumab and FEC followed by 3-weekly docetaxel plus trastuzumab as PST for $HER2^+$ breast cancer.

Patients and Methods

Patient Eligibility

Eligible patients had previously untreated, unilateral, histologically confirmed, invasive, noninflammatory breast carcinoma. Histologic confirmation of invasive cancer was performed by core needle biopsy (CNB). $HER2^+$ was defined as a score of 3+ by immunohistochemistry or a HER2 gene copy-chromosome 17 ratio of ≥ 2.0 by fluorescence in situ hybridization. Patients with a tumor ≥ 2 cm at the largest dimension by ultrasonography or <2 cm with axillary lymph node metastasis clinically diagnosed as positive were eligible (clinical stage II and IIIA). Patients with axillary nodes enlarged by >1 cm at the largest dimension according to ultrasonography were considered node positive without the need for confirmatory biopsy. Patients with T4N3 (supraclavicular lymph node), or distant metastatic disease (M1) were excluded from the study.

Other requirements were age between 18 and 65 years, ECOG (Eastern Cooperative Oncology Group) performance status 0 to 2, adequate bone marrow function (absolute granulocyte count $\geq 1500/mm^3$ and platelet count $\geq 100,000/mm^3$), liver function (total bilirubin level ≤ 1.5 mg/dL and liver transaminase levels [aspartate aminotransferase and alanine aminotransferase] ≤ 60 IU/L), and renal function (serum creatinine level ≤ 1.5 mg/dL). Patients with a history of ischemic cardiac disease and cardiomyopathy or a left ventricular ejection fraction (LVEF) $<60\%$ according to echocardiogram were excluded. Patients with clinically negative axillary lymph nodes had the option of undergoing pretreatment sentinel lymph node biopsy (SLNB). The study was approved by institutional review boards and was conducted in accordance with the Declaration of Helsinki. All the patients provided written informed consent.

Study Design and Preoperative Systemic Therapy

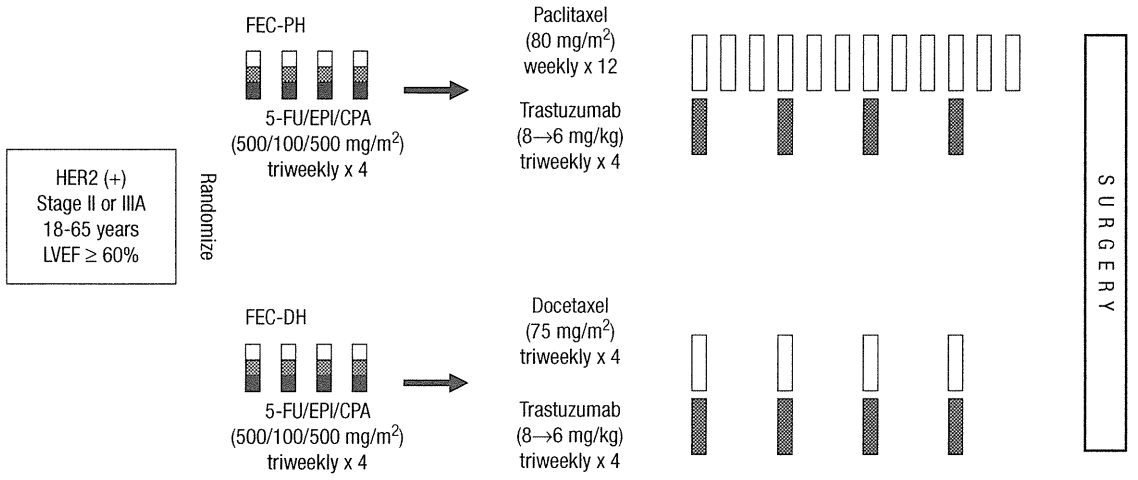
Patients were randomly assigned to receive either FEC followed by the combination of paclitaxel and trastuzumab (FEC-PH) or FEC followed by the combination of docetaxel and trastuzumab (FEC-DH). The dose and schedule of FEC and docetaxel were selected based on efficacy and safety data from our previously reported study of PST.[23,24] FEC consisted of 5-fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2, and cyclophosphamide 500 mg/m^2 administered by intravenous (I.V.) infusion on day 1 every 3 weeks for 4 cycles (Figure 1). Paclitaxel was administered at 80 mg/m^2 I.V. over 1 hour on days 1, 8, and 15 every 3 weeks for 4 cycles. Docetaxel was administered at 75 mg/m^2 I.V. over 1 hour on day 1 every 3 weeks for 4 cycles. In both arms, trastuzumab was administered at a dose of 8 mg/kg I.V. over 90 minutes on day 1 of the first cycle and subsequent doses were administered at a dose of 6 mg/kg over 30 minutes every 3 weeks for a total of 4 cycles.

If a patient developed grade ≥ 3 febrile neutropenia, thrombocytopenia $<25,000/mm^3$, or grade ≥ 3 nonhematologic toxicity, then the doses of epirubicin and docetaxel were reduced by 25% and 20%, respectively, in subsequent cycles. The dose of paclitaxel was reduced by 25% in subsequent cycles if a patient developed grade 3 neurotoxicity. Before administration of the following cycle of FEC or docetaxel, the patients were required to have a granulocyte count $\geq 1500/mm^3$, platelet count $\geq 75,000/mm^3$, and no nonhematologic toxicity of grade >2 (excluding alopecia). Before administration of the next cycle of paclitaxel, the patients were required to have a granulocyte count $\geq 1000/mm^3$, platelet count $\geq 75,000/mm^3$, and no nonhematologic toxicity of grade >2 (excluding alopecia). If toxicity did not improve within 2 weeks, then chemotherapy and trastuzumab were discontinued and surgery was recommended.

Therapy After Preoperative Chemotherapy

Patients who were considered candidates for breast-conserving therapy (BCT) were offered lumpectomy. Patients who refused or were considered inappropriate for BCT received total mastectomy. Axillary lymph node dissection (AxLND) was mandatory, except in the patients diagnosed with nonmetastatic disease by SLNB before PST. Surgery was performed within 8 weeks after completion of preoperative chemotherapy. All the patients who underwent BCT received whole-breast irradiation. After completion of preoperative chemotherapy and surgery, the patients with hormone receptor (HR) positive (HR^+) disease received adjuvant endocrine therapy. After completion of local therapy, adjuvant trastuzumab was administered every 3 weeks for up to 1 year. The patients with HR^+ breast cancer received adjuvant trastuzumab in combination with endocrine therapy.

Figure 1 Study Regimen



Study Evaluation and Criteria

The HER2 status of a CNB was determined by immunohistochemistry and/or fluorescence in situ hybridization performed in each institution (no central review) before study enrollment. After completion of PST, resected specimens and CNB specimens were evaluated centrally by 3 breast pathologists (H.T., F.A. and M.K.). The pCR was defined as the absence of viable invasive tumor in both the breast and the axillary nodes. Patients with residual ductal carcinoma in situ (DCIS) in breast tissue and no viable invasive tumor in the axillary nodes also were classified as having pCR. Clinical response was evaluated by palpation after each cycle by using the response evaluation criteria in solid tumors.[25]

All adverse events were evaluated according to the CTCAE (Common Terminology Criteria for Adverse Events) v3.0.[26] Infusion reactions were defined by the occurrence of the following symptoms during infusion or within 24 hours after starting trastuzumab: pyrexia, chills, nausea, vomiting, pain, headache, cough, dyspnea, dizziness, rash, pruritus, general malaise, skin eruption, and decrease in blood pressure.

Endpoints and Statistical Analysis

The primary endpoint was the pCR rate. The secondary endpoints were disease-free survival, clinical response rate, breast conservation rate, and safety. In this report, disease-free survival is not reported because of the short follow-up. Analyses of efficacy and safety were performed in the intent-to-treat (ITT) population. The ITT population comprised subjects fulfilling the study inclusion criteria who had received at least one dose of study chemotherapy. The per-protocol population comprised ITT subjects who had undergone surgery in this study without serious violations of the inclusion criteria. As sensitivity analysis, the pCR rates among the per-protocol population were calculated. By assuming a difference in the pCR rate between the 2 groups of 10% and an expected baseline pCR rate of 30%, a sample size of 49 patients in each treatment group was necessary to demonstrate a higher pCR rate with a probability of 85%. The target number of patients was considered to be 100 patients to allow for patient dropout. The pCR was compared between 2 groups by using the χ^2 test. P values $<.05$ were considered statistically significant.

Results

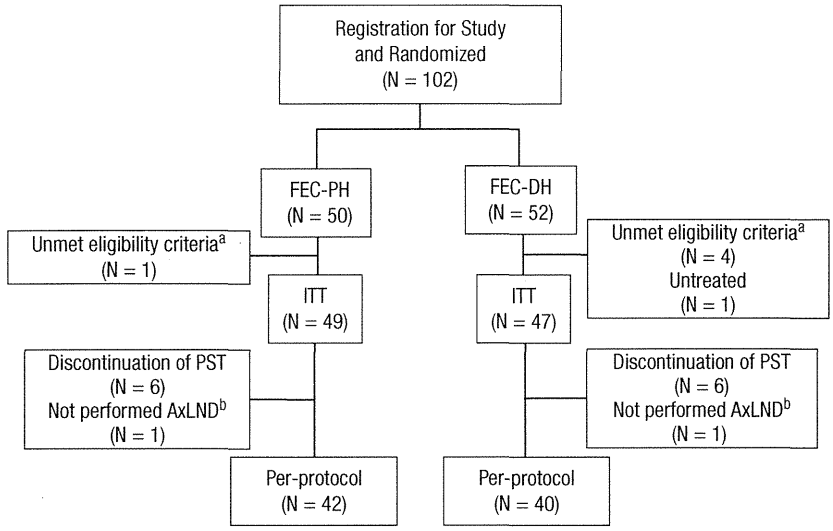
Patient Characteristics

Between March 2007 and June 2008, 102 patients were enrolled in this study. Of these, 49 patients receiving FEC-PH and 47 receiving FEC-DH were evaluable in the ITT population. According to central review, 4 patients were considered ineligible (2 patients not $HER2^+$, 1 not evaluable for HER2 status, 1 with noninvasive carcinoma in the CNB specimen). One patient had an aneurysm of the thoracic aorta immediately after the first cycle of FEC, discontinued FEC, and, therefore, was considered ineligible. One patient did not receive PST because of persistent hypertension (Figure 2).

The characteristics of the ITT population are shown in Table 1. Distribution of tumor size was similar in the 2 treatment groups. The proportion of patients with clinically diagnosed axillary node-positive tumors was higher in the FEC-DH arm. Approximately two-thirds of patients had HR^- tumors, with a slightly higher representation in the FEC-DH than in the FEC-PH arm.

One patient in the FEC-DH arm was considered not evaluable for pathologic response by central review because she had not undergone AxLND or SNLB before PST and had DCIS in the breast after surgery. Eighty-four patients received surgery after completion of PST. The HR and HER2 status of the breast tumors were not reassessed after surgery. Twelve of 72 patients who received AxLND had lymph-node metastases. Two patients did not undergo either AxLND or SLNB before PST. Therefore, 82

Figure 2 Consort Diagram



[a]Three Cases Were Human Epidermal Growth Factor Receptor 2 Negative (HER2$^-$) by Central Review. [b]Axillary Node Dissection.

patients (42 in the FEC-PH arm and 40 in the FEC-DH arm) were evaluated in the per-protocol population (Figure 2).

Treatment Exposure

Ninety-one (94.8%) of 96 patients completed 4 cycles of FEC. Four patients discontinued FEC due to adverse events, and one patient discontinued due to disease progression after 2 cycles of FEC. Among patients who completed 4 cycles of FEC, 3 discontinued PH (grade 3 neurotoxicity in 2 patients; suicide in 1 patient) and 4 discontinued DH (adverse events in 2 patients; disease progression after 1 cycle in 1 patient; refusal in one patient). Thus, 43 of 49 patients (87.8%) in the FEC-PH arm and 41 (87.2%) of 47 patients in the FEC-DH arm completed PST.

Efficacy

In the ITT population, 23 (46.9%) of 49 patients receiving FEC-PH and 21 (44.7%) of 47 patients receiving FEC-DH achieved a pCR according to central pathologic review. The difference between FEC-PH and FEC-DH is 2.3% (95% confidence interval [CI], −17.7% to 22.2%; $P = .82$). The pCR rates were 54.8% with FEC-PH and 50.0% with FEC-DH in the per-protocol population. The difference is 4.8% (95% CI, −16.8% to 26.4%; $P = .67$). The difference between the 2 arms were <10%. The pCR rate included 24 patients with DCIS in the breast (10 in the FEC-PH arm and 14 in the FEC-DH arm). No patients with pCR in the breast had persistent nodal carcinoma. The pCR rates according to institutional review were 44.9% (22/49) in the FEC-PH arm and 36.2% (17/47) in the FEC-DH arm; 4 patients who were diagnosed with residual invasive carcinoma in the breast by institutional review were assessed as pCR with DCIS by central review.

Subpopulation analysis according to HR status showed pCR rates of 54.2% (32/59) in HR$^-$ tumors and 29.7% (11/37) in HR$^+$ tumors ($P = .02$). The pCR rates in patients with HR$^+$ tumors were 26.1% with FEC-PH and 35.7% with FEC-DH ($P = .54$) (Figure 3). In patients with HR$^-$ tumors, the pCR rates for FEC-PH and FEC-DH were 65.4% and 45.5%, respectively ($P = .13$) (Figure 3). The clinical response rates by palpation were 79.6% in the FEC-PH arm and 76.6% in the FEC-DH arm, respectively (Table 2). Eighty-four patients received surgery. Seventy-two of these 84 patients received adjuvant trastuzumab. BCT was possible in 35 patients (71.4%) in the FEC-PH arm and 27 (57.4%) in the FEC-DH arm.

Safety

Grade 3/4 neutropenia was observed in 28.1% of 96 patients who received FEC, and 11 patients (11.5%) developed febrile neutropenia (Table 3). Adverse events that lead to hospitalization were reported in a total of 8 patients during FEC; 3 of these discontinued FEC. During the taxane phase, peripheral neurotoxicity was more common with PH than DH, whereas grade 3/4 neutropenia, febrile neutropenia, peripheral edema, and grade 1/2 mucositis and/or stomatitis were more common with DH than with PH. One patient developed grade 3 peripheral edema after 2 cycles of DH and stopped chemotherapy.

Cardiac events were observed in 4 patients. Two patients who received PH and 1 patient who received DH experienced grade 1 supraventricular arrhythmia. One patient developed grade 3 left ventricular systolic dysfunction with shortness of breath on exertion immediately after completion of 4 cycles of PH, accompanied by a decrease in LVEF to 39%. She had no history of cardiovascular disease but had received diuretic and beta-blocker