therapy must achieve results equivalent to those of conventional breast-conserving therapy in terms of local control and survival in further clinical studies.

Acknowledgments This study was supported in part by a grant from Clinical Research for the Development of Preventive Medicine and New Therapeutics of Health and Labor Science Research from the Ministry of Health, Labor and Welfare, Japan.

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原著

2011.4.19受付

当院における進行・再発乳癌に対するエキセメスタンの治療成績

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Outcome of Endocrine Therapies for Metastatic Breast Cancer in our Hospital：Ookubo Y[*1,2], Yamamoto N[*1], Nakamura R[*1], Onai Y[*1], Konishi T[*1] and Miyazaki M[*2] ([*1]Division of Breast Surgery, Chiba Cancer Center Hosipital, [*2]Department of General Surgery, Chiba University Graduate School of Medicine)

Background：Third-generation aromatase inhibitors (AI) are now replacing tamoxifen as first-line postoperative adjuvant treatment for postmenopausal endocrine-responsive breast cancer. Accordingly, the number of patients with AI-resistant recurrent breast cancer is anticipated to increase. However, we often encounter difficulty in determining whether to switch to chemotherapy or perform sequential endocrine therapy in endocrine-failure patients. Therefore, we retrospectively investigated the efficacy and therapeutic effect of sequential treatment with AI, particularly the steroidal AI Exemestane.

Methods：Patients with recurrent or advanced breast cancer who had evaluable lesions, were diagnosed as having progressive disease during endocrine therapy, and subsequently given Exemestane were selected and analyzed retrospectively in relation to their medical history.

Results：Of a total of 69 cases examined, 68 were evaluable. When Exemestane was used as a 1st, 2nd, or 3rd-line treatment, the clinical benefit rate and time to failure was 41.7% (10/24) and 620 days, 65.5% (19/29) and 361 days, and 66.7% (10/15) and 490 days, respectively. Exemestane and non-steroidal AI were effective in cases previously treated with tamoxifen (TAM), with CB rates of 70 and 86%, respectively.

Conclusions：Our retrospective study suggested that Exemestane was an effective sequential treatment with AI for recurrent or advanced breast cancer in ER-positive cases.

Key words：Metastatic breast cancer, Steroidal aromatase inhibitor
Jpn J Breast Cancer 26(4)：439～444, 2011

緒 言

近年，閉経後乳癌の術後補助内分泌療法はいくつかの臨床試験[1~3]によりタモキシフェン（TAM）と比較しアロマターゼ阻害薬（AI）の有効性が示された．さらに2010年の San Antonio Breast Cancer Symposium（SABCS）において，術後内分泌療法において作用機序の異なる2剤のAI（アナストロゾールとエキセメスタン）を直接比較したMA27試験[4]においては一部，有害事象について差があるものの有効性については同等であることが確認された．また術前内分泌療法で3剤のAIを直接比較したACOSOG Z1031試験[5]で腫瘍縮小効果がそれぞれのAI間に有意差のないことが示された．これらのことより，今後はadjuvant内分泌療法で第3世代のAI剤の使用が主流となり必然的にadjuvant AI後の再発症例の増加が予想される．一方，今までの再発乳癌治療に対する臨床試験はadjuvant TAM後の再発症

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表1　当院で再発治療にエキセメスタンを使用した68症例

		症例数（%）
進行・再発	進行	11（16）
	再発	57（84）
年齢，平均（range）		55.7（29－75）
ER 陽性率，平均（range）		81（30－100）
PgR 陽性率，平均（range）		63（0－100）
Her2蛋白	陽性	5（7）
過剰発現	陰性	63（93）
DFI（Stage I-IV）		5.15y（0－28y）
前治療数	1st line	24（35）
	2nd line	29（42）
	3rd line	13（19）
	4th line	2（4）
転移部位	骨	45（66）
	肺	29（43）
	肝	9（13）
	その他	13（19）
転移臓器数	1	46（67）
	2	18（26）
	3	4（7）

表2　進行・再発乳癌のエキセメスタンのレジメ数別の治療効果

	PR（%）	CB（%）	non CB	PFS（日）（CB）
1次治療	4（16.6）	10（41.7）	14（58.3）	620（207-2248）
2次治療	2（6.9）	19（65.5）	10（34.5）	361（131-1467）
3次治療	0（0）	10（66.7）	5（33.3）	490（249-1535）

例を対象としたものが多く[6]，adjuvant AI 後の再発内分泌療法の臨床試験の報告は少ない．それ故，adjuvant AI 後の進行再発乳癌の治療として作用機序を考慮したホルモン療法剤の使用順序が重要な課題となってくる．そこで当院での AI の逐次投与の有効性と治療効果予測を steroidal AI であるエキセメスタンを中心に retrospective に検討することとした．

1．対象と方法

当院において2000年から2010年の間の ER 陽性乳癌で進行・再発治療にエキセメスタンを使用した69症例のうち，肝機能障害の発生により中止した1例を除く68症例を対象とした．それらの年齢やホルモンレセプター発現状況，HER2 Disease interval（DFI），前治療数，転移部位や転移臓器数は表1に示すとおりである．再発乳癌は57症例（adjuvant TAM；37症例，adjuvant non-steroidal AI；20症例），進行乳癌は11症例であった．エキセメスタンの選択の妥当性と治療効果予測を検討する目的で，1）再発内分泌療法の治療次数，2）前治療薬の種類と効果，3）再発1次治療エキセメスタンの無効症例の2次内分泌療法の治療効果について retrospective に検討した．

なお，治療効果予測因子の比較には χ^2 検定を使用し $p<0.05$ を有意差ありとした．

2．結　果

進行・再発治療にエキセメスタンを使用した68症例においてエキセメスタンの治療次数別

表3a 術後補助療法でTAMを使用した症例に対する再発1次内分泌療法の比較

効果	エキセメスタン（n＝10）	non-steroidal AI（n＝28）
CR	2 (20.0)	3 (10.3)
PR	3 (30.0)	5 (20.7)
Long SD	2 (20.0)	16 (55.2)
SD	0 (0.0)	0
PD	3 (30.0)	4 (13.8)
ORR	5 (50.0)	8 (31.0)
CB	7 (70.0)	24 (86.0)

CR；Complete Response, PR；Partial Response, SD；Stable Disease,
PD；Progression Disease, ORR；Objective Response Rate, CR；Clinical Benefit

表3b 術後補助療法でnon-steroidal AIを使用した症例に対する再発1次内分泌療法の比較

効果	エキセメスタン（n＝15）	Non-steroidal AI（n＝5）
CR	0 (0)	0 (0)
PR	0 (0)	1 (20.0)
Long SD	4 (26.7)	2 (40.0)
SD	1 (6.6)	0 (0)
PD	10 (66.7)	2 (40.0)
ORR	0 (0)	1 (20.0)
CB	4 (26.7)	3 (60.0)

CR；Complete Response, PR；Partial Response, SD；Stable Disease,
PD；Progression Disease, ORR；Objective Response Rate, CR；Clinical Benefit

のClinical Benefit Rate（CBR＝CR＋PR＋Long SD），time to failure（TTF）中央値は1次治療；41.7%，620日，2次治療；65.5%，361日，3次治療；66.7%，490日であった（表2）．

前治療薬との関係は，術後補助療法にTAMを使用した症例の再発1次治療ではエキセメスタンとnon-steroidal AIのCBRはそれぞれ70%と86%であった（表3a）．一方，術後補助療法にnon-steroidal AIを使用した症例の再発1次治療のsteroidal AI（エキセメスタン）とnon-steroidal AIの治療効果はそれぞれCBR：26.7%と60%であった（表3b）．前治療の効果との関係は，再発治療にnon-steroidal AIを使用してCBまたはnon CBであった症例の逐次治療エキセメスタンのCBRはそれぞれ72.2%，76.9%であり有意差は認めなかった（表4a）．なお，non-steroidal AIの前治療でCRを得た2例はエキセメスタンの逐次投与ではいずれもnon CBであり，また同様にPRを得た9例のうち3例はnon CBであった（表4b）．

そして再発1次治療としてエキセメスタンに不応症例のうち，2次治療でnon-steroidal AIまたはSERMを施行した症例のCBRはいずれも28.6%であった（表5）．またエキセメスタンの治療効果予測因子として5年以降の再発症例と原発巣で50%以上のPgR陽性症例は有意差をもってCBが得られ，転移部位や転移臓器数には有意差が認められなかった（表6）．

3．考　察

内分泌感受性進行・再発乳癌の治療は，Hortobagyiのアルゴリズム[7]が良く知られてお

表4a　前治療の non-steroidal AI の効果とエキセメスタンの治療効果の関係

		エキセメスタンの効果（n）			P value
		CB	non CB	CBR	
non-steroidal AI の前治療効果	CB	24	9	72.2%	0.66
	non CB	10	3	76.9%	

表4b　前治療の non-steroidal AI の効果とエキセメスタンの治療効果の関係

			エキセメスタンの逐次治療効果			
			CB			non CB
			CR	PR	long SD	
non-steroidal AI の前治療効果	CB	CR	0	0	0	2
		PR	0	0	6	3
		long SD	0	1	17	4
	non CB		0	2	8	3

表5　再発1次治療としてエキセメスタンに無効症例の2次内分泌療法の治療効果

	治療薬 n（%）	
	TAM（n＝7）	non-steroidal AI（n＝7）
CR	0	0
PR	0	0
Long SD	2（28.6）	2（28.6）
SD	1（14.3）	1（14.3）
PD	4（57.1）	4（57.1）
CB	2（28.6）	2（28.6）

り，non-life threatening な状況であれば長期間の治療効果を期待して可能な限り内分泌療法を選択する．内分泌療法として SERM や non-steroidal AI，steroidal AI などの治療薬があげられるが，これらの間には交叉耐性が少なく，逐次的な投与が可能とされている[8]．その中で Lønning ら[9] の phase II trail の報告では，再発1次治療の non-steroidal AI の不応症例に対するエキセメスタンの効果は CBR：24%，Time to progression（TTP）中央値は9カ月であった．また再発1，2次治療に non-steroidal AI と steroidal AI の交互使用をした試験である GONO MIG-8 Study[10] の CBR はそれぞれ45%と55%であり両薬剤間に交差耐性はないと報告された．さらに non-steroidal AI による術後療法中に再発もしくは再発治療中に増悪した症例を対象とした EFECT 試験[11] においても，エキセメスタンは non-steroidal AI に交叉耐性の少ないことが示唆された．

当院の検討でも術後補助療法に TAM を使用した症例の再発1次治療では non-steroidal AI とエキセメスタンの CBR はそれぞれ86%と70%であり同等の効果を示し AI 剤間の優劣は認めていない．また2次，3次内分泌療法においてもエキセメスタンはいずれも60%以上の高い CBR を認め，直接比較はできないもののこれまでの報告と同様に臨床的有用性が確認された．

しかしながら，adjuvant 療法に non-steroidal AI を使用した症例群の再発1次治療ではエキセメス

表6　エキセメスタンの臨床的治療効果の予測因子

		CB（n）	non CB（n）	P value
ER（%）	50>	28	20	
	50<	1	1	
	不明	13	5	
PgR（%）	50>	17	5	0.01*
	50<	12	17	
	不明	10	7	
HER2	+	2	3	0.29
	−	40	23	
DFS（Stage IV を除く）	5y<	21	5	0.02*
	5y>	15	14	
転移臓器数	1	35	13	
	2	10	6	0.13
	3	1	3	
転移部位	骨	24	20	
	肺	18	9	0.58
	肝	5	4	

* χ^2検定：$p < 0.05$

タンのCBRは26.7%であった．さらに再発1次治療としてエキセメスタンに不応症例のうち，2次治療（non-steroidal AIまたはSERM）を施行した症例群のCBRも低かった．以上の結果よりエキセメスタンの再発1次治療が2，3次治療に比べCBRが低い原因として，①再発初回治療時にnon-life threateningな症例も多く含まれていた可能性が高いこと，一方，②1次内分泌療法に奏効した症例は2，3次治療でも効果が望め薬剤間の交叉耐性は認められないこと[8~11]，の2つの要因が考えられた．

それ故，再発1次治療ではnon-life threateningな症例や内分泌療法に不能症例の鑑別は難しい場合も多く，内分泌療法の選択は慎重に判断する必要がある．また，術後補助療法でnon-Steroidal AIを使用して再発した症例では，これらの再発1次治療はAI抵抗性の2次治療と位置付け治療に望むことも重要と思われる．そのため，化学療法への移行を考慮するためにnon-life threateningな判断以外の内分泌療法の治療効果予測も重要となってくる．

今回の検討から原発巣でPgR：50%以下のproportion群やDFIの5年以下の再発症例群でエキセメスタンの治療効果が劣ることが示唆された．近年，乳癌の術後補助療法では2009年のSt. Gallen consensus meeting[12]において内分泌高度感受性かつKi-67低値である増殖能の低い乳癌の術後治療は化学療法よりも内分泌療法が推奨された．このことは，再発治療においても内分泌療法の治療効果を判断する一助となり，再発巣のER，PgRのproportionやKi-67 labeling indexの測定は化学療法への移行を検討する有効な手段となると思われる．

なお，今回の検討はretrospective studyであり，また症例数も少なく今後は計画された臨床試験を行うなどさらなる検討が必要と思われる．しかしながら，エキセメスタンは各治療次数で内分泌療法の効果が得られ，薬剤間の交叉耐性のない症例も多く認めることが確認された．

結　語

内分泌感受性進行・再発乳癌患者に対するAI

の逐次的使用の中で，エキセメスタンの臨床的治療効果は十分高いと考えられた．

本要旨は，千葉乳がん薬物療法セミナー（2011年3月4日開催）にて報告した．

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症　例

乳癌術後再発例における中心静脈ポート留置による左内頸静脈血栓症の1例

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症例は60歳，女性．2002年右乳癌に対し術前化学療法後，右乳房切除術を施行．2004年骨転移のため化学療法を開始．2005年左鎖骨下静脈より中心静脈ポート（以下CVポート）を留置．その後，同ポートに感染を認め抜去し2008年6月左上腕静脈に再留置．2009年5月左頸部の腫脹，疼痛が出現し精査にて左内頸静脈内に広範な血栓を認めた．CVポートによる血栓形成と考え同日緊急入院．肺塞栓予防目的でヘパリナイゼーション後，CVポートを抜去．その後ワルファリン内服開始し症状は軽快した．

当院における2007年1月～2009年6月までのポート留置症例の血栓形成に関する合併症は6/276（2.1%）であった．担癌患者のCVポート留置症例に対しては血栓形成の有無を画像にて定期的に確認することが重要である．

索引用語：中心静脈ポート，合併症，血栓症

緒　言

皮下埋め込み型中心静脈ポートは各種癌の術後治療を行うための必要な医療器具であり使用頻度が高まっている[1)~3)]．その一方で留置に伴う合併症も増加している[4)5)]．

今回，CVポート留置症例において比較的稀な血栓性静脈炎を経験したので当院における血栓形成に関連した合併症も含め報告する．

症　例

症例：60歳，女性．

主訴：左頸部腫脹，疼痛．

既往歴：2002年右乳癌に対して術前化学療法後（EC7クール），右乳房切除術，右腋窩リンパ節郭清施行．術後はタモキシフェンを内服し経過観察されていた．2004年骨転移を認め化学療法（3wDocetaxel＋Trastuzumabを約4年間）を施行．2005年左鎖骨下静脈よりCVポート留置するも感染にて抜去．2008年6月左上腕静脈にX線透視下でCVポート再留置（カテーテル先端は上大静脈内に留置できず，左腕頭静脈内に留置となった）．

現病歴：2009年5月左頸部の腫脹，疼痛を主訴に内科受診．リンパ節炎の診断により経口抗菌薬とNSAIDsで経過観察となった．数日後，腫脹は増大傾向でありリンパ節転移疑いのもと当科受診となった．

入院時現症：身長154cm，体重56kg，BMI 23.6Kg/m^2．

入院時検査所見：WBC 2,700/μl，CRP 3.9mg/dl，その他の血算，生化学，凝固系（FDP），腫瘍マーカー（CEA，CA15-3）値はいずれも正常範囲内であった．

頸部超音波所見（Fig. 1）：左内頸静脈は血栓により閉塞していた．

頸部CT所見：左内頸静脈は血栓により造影効果は認めず，広範囲に血栓形成を認めた．3D構築画像を示す（**Fig. 2**）．

入院後経過：CVポートによる血栓形成と考え同日緊急入院．肺塞栓予防目的でヘパリナイゼーション後，CVポートを抜去した（**Table 1**）．その後ワルファリン内服開始し問題なく経過し退院となった．なお入院時WBCは化学療法の影響により軽度減少していたが，入院中は発熱などの感染徴候はなかったため抗菌薬は使用せず経過観察し，退院後WBCは回復した．

考　察

当院にて2007年1月～2009年6月までの間に悪性腫

2010年12月6日受付　2010年12月24日採用
〈所属施設住所〉
〒260-8717　千葉市中央区仁戸名町666—2

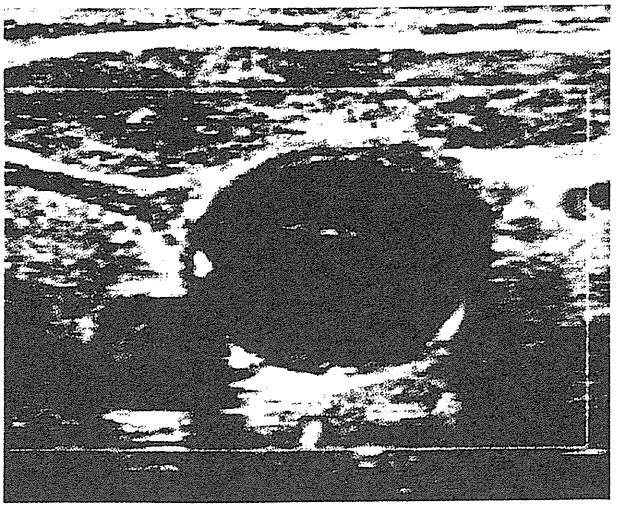

Fig. 1 Color doppler ultrasound revealed a left internal jugular vein thrombus.

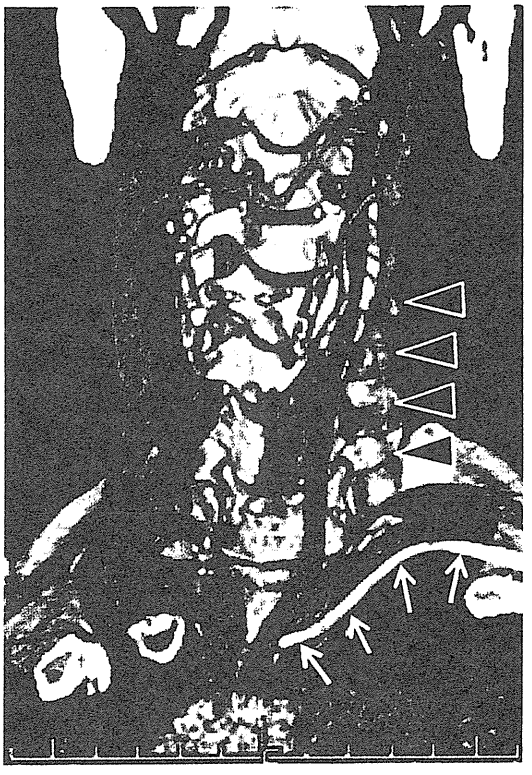

Fig. 2 3-D CT also showed a left internal jugular vein thrombus (△).
The catheter tip is positioned in the left brachiocephalic vein (→).

瘍治療目的に CV ポートを留置した276症例のうち合併症は34症例（12%）で一般的な報告の5.7〜19.47%[5)〜10)]と同等の成績であった．そのうち血栓形成に関連した合併症は血栓付着 4 症例（1.4%）と血栓性静脈炎 2 症例（0.7%）の計 6 症例であった（**Table 2**）．

Table 1　Anticoagulant therapy

	Heparin (U/day)	Warfarin (mg)
Day1 (admission)	15,000	0
Day2 (port removal)	10,000	0
Day3	4,000	3
Day4	2,000	3
Day5	0	2

Table 2　Complications after central venous port implantation in our hospital

Complications	Number (Percent)
Bacteremia	10 (3.6)
Catheter malposition	6 (2.1)
System breakage	6 (2.1)
Skin erosion	4 (1.4)
Catheter tip thrombus	4 (1.4)
Thrombophlebitis	2 (0.7)
System occlusion	2 (0.7)

静脈血栓症の発生頻度は1.5〜8.46%[6)〜10)]と報告され，その症状は留置側の腕や頸部の浮腫，腫脹，疼痛である[1)2)6)7)10)11)]．血栓症の発見には超音波検査，患側末梢静脈からの造影検査，造影 CT 検査が有効である[1)2)6)7)10)〜14)]．

血栓形成の危険因子は①担癌患者②カテーテル挿入部位および留置位置③血管内膜損傷④治療薬が考えられる．Ambrus らの報告では担癌患者の約15%が有症候性の静脈性血栓塞栓症が生じ，剖検例では約50%が無症候性の静脈性血栓塞栓症が生じるとされる[15)]．またカテーテル挿入部位は左側からの挿入でリスクが高く，カテーテル先端位置が腕頭静脈内や上大静脈上部にある場合に血栓性静脈炎を起こす可能性があると報告されている[10)]．また頻回の穿刺による血管内膜損傷部位へのフィブリンの沈着が血栓形成を促すと報告されている[10)12)]．治療薬においては分子標的薬を含む進行大腸癌の化学療法での血栓症[1)14)]やタモキシフェン内服での血栓症[16)]に注意が必要である．

今回の症例では左鎖骨下静脈に穿刺歴があり，さらにはカテーテル先端が上大静脈ではなく左腕頭静脈内に留置されていたことが血栓形成の一因と考えられた．発症時タモキシフェンは内服しておらず，病状の進行のため2008年 7 月より Vinorelbine＋Trastuzumab へ変更しているが血栓形成との因果関係は不明である．上大静脈内への挿入が困難な場合は血管損傷の危険もあるため無理をせずに血管外科医や放射線

科医へのコンサルテーションが必要と考えられた．

カテーテルへの血栓付着症例はCT画像により偶発的に診断されることが多く，そのほとんどは無症状である．画像上はカテーテル先端に血栓形成を認め血管内の陰影欠損としてとらえられる（**Fig. 3**）．カテーテル先端におけるフィブリン付着や血管壁損傷によるフィブリン形成により血栓が生じるとされている[17]．

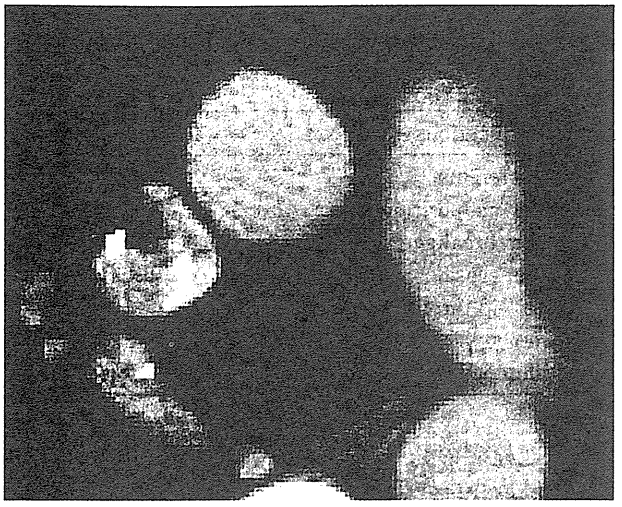

Fig. 3　Enhanced CT showed the catheter tip thrombus.

血栓形成時の対処法は，抗血小板薬，抗凝固薬，血栓溶解薬の投与，CVポート抜去が一般的である[1)2)6)~11)13)14)18)]．広範な血栓形成症例では抜去に伴う肺塞栓症の危険性もあり抜去の是非について慎重を要す[2)10)11)]．坪井らは血栓が大きい場合はカテーテルを抜去せずに抗血小板薬を投与し保存的に治療を行い，それでも改善がみられない場合は抜去すると報告している[11)]．当院で経験した血栓形成症例の対処法も各々の症例で異なっていた（**Table 3**）．

本症例を経験し担癌患者のCVポート留置例においては症状の有無に関わらず血栓形成を念頭におき，原疾患の経過観察のために定期的に撮影する造影CTなどの画像検査施行時には，病勢のみならずカテーテルの状態（留置位置，血栓形成の有無など）も確認する必要があり，血栓形成時には症例ごとに応じた対処が必要であると考えた．

結　語

CVポート留置患者において血栓性静脈炎は比較的稀な合併症であるが無症状の血栓形成患者はより多く存在する．このためCT検査や超音波検査施行時にはカテーテルの状態や留置血管内における血栓形成の有

Table 3　Six patients with central venous port-related venous thrombosis in our hospital

Age/Sex	Disease	Retention period	Site	Material	Chemotherapy	Treatment
①62/M	Colorectal Cancer	5.5 months	left subclavian	silicone rubber	FOLFOX＋BV	port removal
②61/F	Colorectal Cancer	3 years	left subclavian	silicone rubber	sLV5FU2	port removal
③60/M	Colorectal Cancer	5 months	right subclavian	silicone rubber	FOLFOX	port removal
④36/M	Colorectal Cancer	3 months	right subclavian	silicone rubber	FOLFOX	Warfarin
⑤35/F	Colorectal Cancer	8 months	left subclavian	silicone rubber	sLV5FU2	Chemotherapy change
⑥60/F	Breast cancer	11 months	left upper arm	silicone rubber	VNB＋Trastuzumab	port removal ＋Warfarin

①~④: Catheter tip thrombus
⑤~⑥: Thrombophlebitis (⑥: our case)
M: male, F: female
BV: Bevacizumab
VNB: Vinorelbine

無を確認する必要があり，血栓形成時には症例ごとに応じた対処が望まれる．

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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.

Clinical Breast Cancer, Vol. xx, No. x, xxx
Keywords: Breast cancer, HER2, Primary systemic therapy, Trastuzumab

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Submitted: Jul 11, 2011; Revised: Oct 12, 2011; Accepted: Oct 17, 2011

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1526-8209/$ - see frontmatter
doi: 10.1016/j.clbc.2011.10.002

Primary Systemic Therapy in HER2 Positive Breast Cancer

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

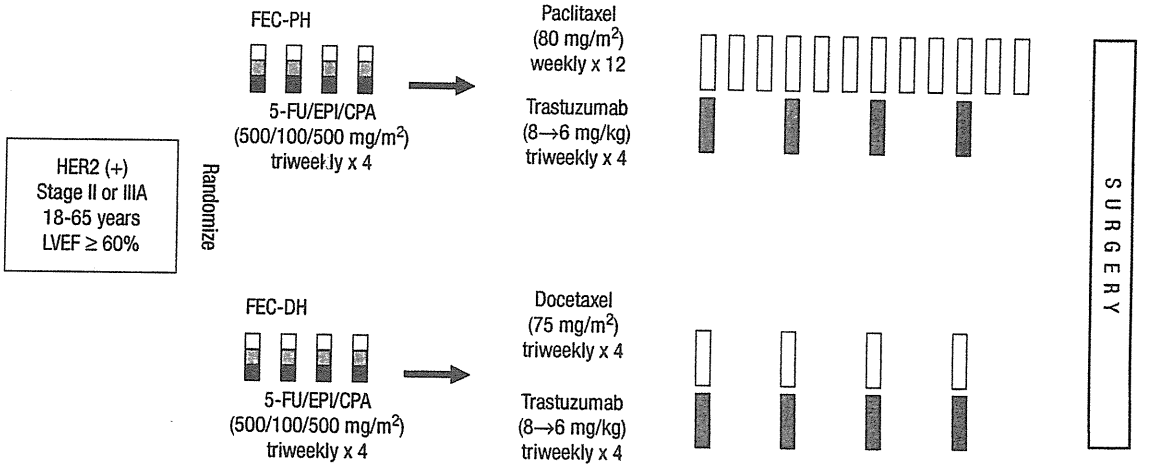
Patients were randomly assigned to receive either FEC followed by the combination of paclitaxel and trastuzumab (FEC-PH) or FEC followed by the combination of docetaxel and trastuzumab (FEC-DH). The dose and schedule of FEC and docetaxel were selected based on efficacy and safety data from our previously 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

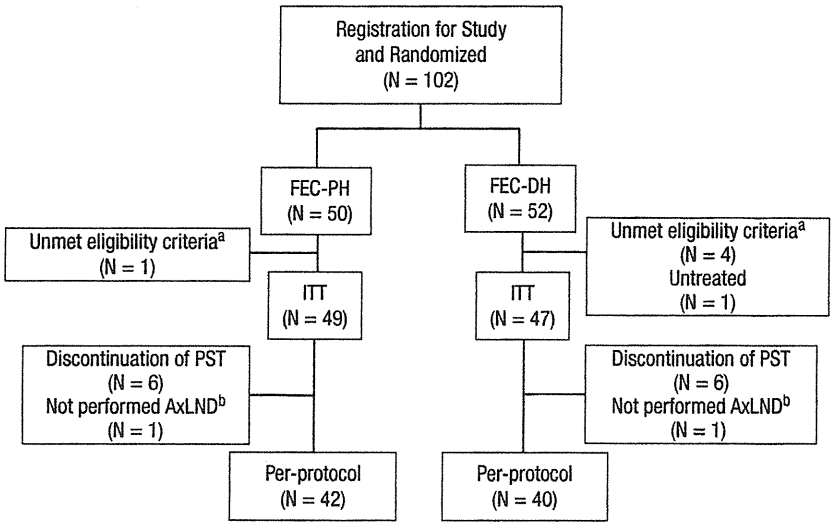
Patient Characteristics

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.

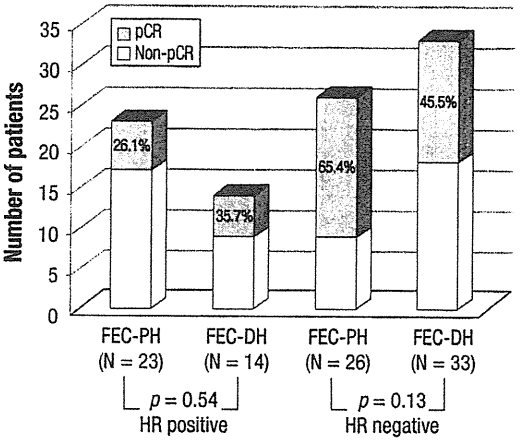
Cardiac events were observed in 4 patients. Two patients who received PH and 1 patient who received DH experienced grade 1 supraventricular arrhythmia. One patient developed grade 3 left ventricular systolic dysfunction with shortness of breath on exertion immediately after completion of 4 cycles of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

Table 1 Patient Characteristics

	FEC-PH (n = 49)	FEC-DH (n = 47)
Median Age (Range), y	51 (34-65)	53 (28-63)
Clinical Stage, No. (%) Patients		
IIA[a]	21 (42.9)	16 (34.0)
IIB	19 (38.8)	22 (46.8)
IIIA	9 (18.4)	9 (19.1)
Tumor, No. (%) Patients		
T1	1 (2.0)	1 (2.1)
T2	38 (77.6)	34 (72.3)
T3	10 (20.4)	12 (25.6)
Axillary Lymph Node-Positive Determination, No. (%) Patients		
Ultrasonography	27 (55.1)	33 (70.2)
SLNB	5 (10.2)	2 (4.3)
HER2 Status, No. (%) Patients		
IHC 3+	43 (87.8)	43 (91.5)
IHC 2+/FISH +	6 (12.2)	4 (8.5)
Hormone Receptor Status No. (%) Patients		
ER+/PgR+	12 (24.5)	4 (8.5)
ER+/PgR−	1 (20.4)	10 (21.3)
ER−/PgR+	1 (2.0)	0 (0)
ER−/PgR−	26 (53.1)	33 (70.2)

Abbreviations: DH = docetaxel; ER = estrogen receptor; FEC = 5-fluorouracil/epirubicin/cyclophosphamide; FISH = fluorescence in situ hybridization; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry; PgR = progesterone receptor; PH = paclitaxel; SLNB = sentinel lymph node biopsy.
[a] Including patients with tumor 2 cm in greatest dimension (T1c) and N0.

Figure 3 Pathologic Results According to Hormone Receptor (HR) Status. The Left Side Shows Pathologic Complete Response (pCR) in Patients With HR^+ Disease and the Right Side Shows pCR in Those With HR^- Disease



therapy for left ventricular systolic dysfunction. After 2 months, her symptoms had resolved with treatment, and she underwent BCT. Her LVEF had recovered to 58% one year after completion of PST. Four patients with adverse events were hospitalized during the trastuzumab plus taxane phase (1 patient received PH and 3 received DH). All remaining 84 patients who completed PST underwent surgery.

Twenty-nine (31.9%) of 91 patients who received trastuzumab plus taxane experienced infusion reactions during the first cycle of trastuzumab (14 patients with PH and 15 with DH). Among patients with infusion reactions, rigors and/or chills, fever, and pain were commonly observed; all events were grade 1 or 2. Eight (27.6%; 8.8% of all patients receiving trastuzumab plus taxane) of 29 patients who experienced infusion reactions during the first cycle of trastuzumab experienced a further infusion reaction during a later cycle.

Discussion

This study showed high pCR rates (46.9% with FEC-PH and 42.6% with FEC-DH) and that 62 (73.8%) of 84 patients undergoing surgery were able to receive BCT. The results of this study are consistent with the high pCR rates reported in previous trials that evaluated the combination of chemotherapy and trastuzumab as PST.[13-20,27] However, there was no significant difference in pCR rates between the 2 treatment groups. There was a trend to a higher rate of BCT with FEC-PH compared with FEC-DH, but the difference was not statistically significant. The small sample size may explain the lack of significant difference between the regimens.

The pCR rates were significantly higher in HR^- tumors than in HR^+ tumors with both treatments. This result is consistent with findings from several other studies of trastuzumab combined with anthracycline- and nonanthracyline-based regimens, including NOAH (concurrent anthracycline/taxane)[14] NeoSphere (docetaxel),[28] and NeoALTTO (paclitaxel).[29] Analysis of the data from these studies suggests that patients with $HER2^+$ and HR^- disease will obtain greatest benefit from a trastuzumab-containing chemotherapeutic regimen. Although other findings, reported by Peintinger et al[30] and Buzdar et al[13] contrast with results from NOAH, NeoSphere, NeoALTTO and the present study, the larger studies have demonstrated higher pCR rates in HR^- than HR^+ breast cancer after trastuzumab-based regimens. Moreover, after the initial conclusions from Buzdar[13] and Peintinger,[30] additional data from the M.D. Anderson group demonstrated a statistically higher pCR rate in HR^- than HR^+ breast cancer (61.1% vs. 38.9%, respectively). Recently, von Minckwitz et al[31] presented data from a meta-analysis of 7 trials (n = 6377) of neoadjuvant therapy, including anthracyclines and taxanes with or without trastuzumab, that showed that pCR is a surrogate for survival in patients with $HER2+$ HR^- breast cancer but not in those with HR^+ disease. It is also relevant to note that, in large trials of adjuvant therapy, prognosis is not different between HR^- and HR^- tumors.[8-10] Therefore, longer follow-up is required in the setting of PST before definitive conclusions can be made about the importance of HR status and therapeutic outcomes. Further clinical and translational

Table 2 Clinical and Pathologic Response Rates

	FEC-PH (n = 49)		FEC-DH (n = 47)	
	No. Patients	%	No. Patients	%
Completion of PST	43	87.8	41	87.2
Clinical Response by Palpation[a]	39	79.6	36	76.6
CR	30	–	28	–
PR	9	–	8	–
SD	0	–	2	–
PD	1	–	1	–
Breast Surgery	43	87.8	41	87.2
Mastectomy	8	–	14	–
BCT	35	71.4	27	57.4
AxLND	36	–	36	–
Lymph Nodes (Pathologic)				
Negative	32	–	28	–
Positive	4	–	8	–
SLNB Without AxLND[b]	6	–	4	–
Pathologic CR[c] ITT	23	46.9	20	42.6
Per protocol	23/43	53.5	20/40	50.0
DCIS in Breast	10	–	14	–

Abbreviations: AxLND = axillary lymph node dissection; BCT = breast conserving therapy; CR = complete response; DCIS = ductal carcinoma in situ; DH = docetaxel; FEC = 5-fluorouracil/epirubicin/cyclophosphamide; PD = progressive disease; PH = paclitaxel; PR = partial response; PST = preoperative systemic therapy; SD = stable disease; SLNB = sentinel lymph node biopsy.

[a] Including 7 patients not evaluable for response (4 in the FEC-PH group and 3 in the FEC-DH group).

[b] SLNB was performed before PST.

[c] Including one patient not evaluable for pathologic response in the FEC-DH group.

research on the interaction between HR status, HER2 status, and pCR is warranted.

In the NOAH trial, the addition of trastuzumab to preoperative chemotherapy and postoperative trastuzumab for 52 weeks improved disease-free survival relative to chemotherapy alone (71% vs. 56% at 3 years; $P = .006$).[14] It remains to be determined whether the addition of postoperative trastuzumab will further improve disease-free and overall survival in patients who have achieved a pCR with sequential anthracycline and taxane plus trastuzumab. However, longer survival has been demonstrated in patients achieving pCR compared with those not achieving pCR, even in the $HER2^+$ subgroup,[21,22] although it may be different in patients with HR^- and HR^+ breast cancer, and needs to be viewed cautiously.

In studies with trastuzumab and nonanthracycline-containing regimens (eg, combination of taxane and platinum), pCR rates have ranged from 17% to 76%.[16–20] Studies of preoperative concurrent anthracycline and taxane with trastuzumab (for 12-24 weeks) have shown pCR rates of 38%-66%.[13–15] Results of these studies suggest that concurrent anthracycline and trastuzumab has a considerable antitumor effect, although, cardiotoxicity remains a concern with this regimen. A review of the medical literature provides reassurance that the cardiac toxicity of concurrent trastuzumab and anthracycline is acceptable and manageable.[13–15] The dose of anthracycline is an important factor in cardiac safety. In the current study, the dose of anthracycline (epirubicin 100 mg/m^2 for 4 cycles was higher than in previous studies that used doxorubicin (60 mg/m^2 for 3 cycles) or epirubicin (75 mg/m^2 for 4 cycles). Therefore, cardiotoxicity may be avoided by reducing the dose of anthracycline when used in combination with trastuzumab. Sequential administration of trastuzumab after anthracycline, as used in the present study, is also an appropriate approach to reduce the risk of cardiotoxicity. However, it might relate to an administration order of anthracycline and taxane, not concurrent administration of anthracycline and trastuzumab, because concurrent administration of anthracycline and trastuzumab has less cardiotoxicity in the report by Buzder et al.[13] Longer follow-up is required to further evaluate the cardiac safety profile of anthracyline-trastuzumab PST to determine a preferable method; dose reduction or sequential administration, including an administration order of anthracycline and taxane.

Twelve (12.5%) of 96 patients in our study did not complete PST. The major reasons for discontinuation of PST were chemotherapy-related adverse events. One patient in the FEC-PH group experienced grade 3 left ventricular systolic dysfunction. A limitation of this study was the evaluation of LVEF by echocardiogram only at study entry and completion of surgery if patients showed no symptoms of left ventricular failure. Experience of cardiotoxicity in this study suggests that LVEF by echocardiogram should be monitored at completion of FEC and again at completion of trastuzumab plus taxane therapy. Long-term follow-up of cardiotoxicity is required for patients in this study who received preoperative and adjuvant trastuzumab.

Because FEC-PH and FEC-DH demonstrated similar efficacy overall, differences in safety profile are important in determining the most appropriate PST regimen to offer to candidates for BCT. Paclitaxel was associated with an increased incidence of peripheral neuropathy, whereas use of docetaxel produced greater neutropenia, febrile neutropenia, peripheral edema, and mucositis. The choice of PST, therefore, should be individualized according to patient characteristics and preferences. Although analysis of data suggested a possible advantage for paclitaxel in terms of higher pCR in the subgroup of patients with HR^- disease and a higher rate of BCS, the differences were not statistically significant.

Conclusion

FEC, followed by concurrent trastuzumab with taxane (weekly paclitaxel or 3-weekly docetaxel), seems active and feasible as PST for $HER2^+$ breast cancer. There was no significant difference in pCR rate between FEC-PH and FEC-DH, although there was a trend to a higher rate of pCR with the paclitaxel-containing regimen in patients with HR^- breast cancer. Whether this trend is clinically significant is not yet known. Long-term follow-up of patients in this study treated with preoperative and adjuvant trastuzumab will provide further information on cardiac safety and disease-free survival.

Randomized comparisons of PST regimens, comprising various permutations of anthracyclines, taxanes, and platinum administered with concurrent and/or sequential trastuzumab, together with long-term follow-up of cardiac safety and disease-free

Table 3 Adverse Events During Primary Systemic Therapy (NCI CTCAE version 3.0 grading)

Toxicity	FEC-PH (grade, %)				FEC-DH (grade, %)			
	FEC (n = 49)		PH (n = 46)		FEC (n = 47)		DH (n = 45)	
	All	3/4	All	3/4	All	3/4	All	3/4
Hematologic								
Neutropenia	46.9	28.6	39.1	2.2	36.2	27.7	15.6	8.9
Febrile neutropenia	12.2	12.2	0	0	10.6	10.6	6.7	6.7
Anemia	44.9	2.0	54.3	0	44.7	0	55.6	2.2
Thrombocytopenia	4.1	0	0	0	8.5	0	2.2	0
Nonhematologic								
Anorexia	46.9	2.0	8.7	0	40.4	0	17.8	0
Nausea/vomiting	87.8	2.0	21.7	0	91.5	0	24.4	0
Vomiting	44.9	4.1	15.2	0	65.9	6.4	15.6	0
Diarrhea	12.2	0	30.4	0	19.1	0	35.6	0
Mucositis and/or stomatitis	53.1	0	19.6	0	61.7	0	57.8	0
Taste alteration	38.8	–	41.3	–	44.7	–	53.3	–
Fatigue	49.0	0	50.0	0	68.1	2.1	64.4	0
Peripheral neurotoxicity	4.1	0	95.7	4.3	8.5	0	51.1	0
Arthralgia and/or myalgia	0	0	39.1	0	0	0	42.2	0
Peripheral edema	6.1	0	39.1	0	12.8	0	62.2	2.2
Infection	6.1	0	6.5	0	8.5	0	13.3	0
Elevated AST, ALT	38.8	2.0	47.8	0	25.5	0	31.1	0
Arrhythmia	0	0	4.3	0	2.1	0	2.2	0
Left ventricular dysfunction	0	0	2.2	2.2	0	0	0	0
Hyperglycemia	0	0	0	0	0	0	2.2	2.2
Nail changes	63.3	–	73.9	–	51.1	–	60.0	–
Skin rash	16.3	0	21.7	0	4.3	0	26.7	0
Infusion reaction	–	–	30.4	0	–	–	33.3	0

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; FEC = 5-fluorouracil/epirubicin/cyclophosphamide; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PD = progressive disease; PH = paclitaxel.

survival are required before definitive recommendations can be made for patients with HER2$^+$ breast cancer.

Clinical Practice Points

- PST is a standard management option for patients with operable breast cancer and can facilitate breast conservation.
- The addition of trastuzumab to primary systemic chemotherapy achieves a high rate of pCR in patients with HER2$^+$ breast cancer, but the optimal treatment regimen has not yet been defined.
- Concurrent use of trastuzumab and anthracycline-based therapy must be used with caution because of the potential risk for cardiac toxicity.
- Preoperative treatment regimens comprising FEC followed by either trastuzumab and paclitaxel or trastuzumab and docetaxel were similarly effective in patients with HER2$^+$ breast cancer and both achieved high rates of pCR.
- The pCR rates were higher in patients with HR$^-$ tumors than in those with HR$^+$ disease.
- The paclitaxel-containing regimen showed a trend to a higher pCR rate in patients with HR$^-$ tumors and a higher rate of breast conserving surgery compared with the docetaxel-containing regimen.
- Sequential use of trastuzumab-taxane after FEC was generally well tolerated, although cardiac safety remains an important consideration. It is important that LVEF is monitored at study entry, at the completion of FEC, and again at the completion of trastuzumab-taxane combination therapy.

Acknowledgments

This study was presented in part at the 45th annual meeting of the American Society of Clinical Oncology, Orlando, Florida, June 1, 2009. Trastuzumab was provided as an investigational drug by Chugai Pharmaceutical Co, Ltd, Tokyo, Japan. This study was supported by Health and Labour Sciences Research Grants (Clinical Cancer Research) of the Ministry of Health, Labor, and Welfare (MHLW). The study was performed as a

registration-directed trial in accordance with the Good Clinical Practice guideline (Enforcement Regulation No. 106 of the MHLW (revised GCP) dated May 15, 2003), which is laid down by the revised Pharmaceutical Affairs Act in Japan (No. 96 of the MHLW dated on 31 July 31, 2002).

Disclosure

The authors have stated that they have no conflicts of interest.

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Breast Cancer Res Treat (2011) 126:443–451
DOI 10.1007/s10549-010-1332-y

CLINICAL TRIAL

Monthly versus 3-monthly goserelin acetate treatment in pre-menopausal patients with estrogen receptor-positive early breast cancer

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Received: 10 August 2010 / Accepted: 23 December 2010 / Published online: 8 January 2011

Abstract This study compared the efficacy and safety of a 3-monthly 10.8-mg depot goserelin (Zoladex^{TM}) injection with the current 3.6 mg monthly dose in pre-menopausal Japanese women with estrogen receptor-positive (ER+) early breast cancer. This was a multicenter, open-label, randomized study. Primary endpoint was a non-inferiority analysis (10.8/3.6 mg) of the area under the concentration–time curve (AUC) of estradiol (E_2) over the first 24 weeks. Secondary endpoints included E_2 and follicle-stimulating hormone (FSH) concentrations, menstruation, and safety and tolerability. In total, 170 patients were randomized to receive goserelin 10.8 mg every 3 months ($n = 86$) or 3.6 mg every month ($n = 84$). Mean AUCs for E_2 were similar between treatment groups (18.32 and 18.95 pg/ml·week for goserelin 10.8 and 3.6 mg, respectively). AUC ratio was 0.974 (95% confidence interval, 0.80, 1.19), indicating non-inferiority for goserelin 10.8 mg. Serum E_2 and FSH remained suppressed throughout the study and no patient experienced menses after week 16. No clinically important differences in safety and tolerability were observed between the two groups. In terms of E_2 suppression, 3-monthly goserelin 10.8 mg was non-inferior to monthly goserelin 3.6 mg in pre-menopausal women with ER+ breast cancer.

Keywords Early breast cancer · Goserelin acetate · Estrogen suppression · Pre-menopausal · Zoladex^{TM}

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Introduction

Estradiol (E_2), the predominant estrogen in pre-menopausal women, promotes the growth of E_2-dependent tumors in women with breast cancer [1, 2]. Thus, E_2 deprivation is an important strategy for controlling disease in these patients. As E_2 is produced primarily in the ovaries, E_2 deprivation can be achieved by oophorectomy. However, a possibly more attractive alternative is reversible treatment with luteinizing hormone-releasing hormone (LHRH) agonists. Goserelin acetate (Zoladex^{TM}, AstraZeneca) is a synthetic decapeptide LHRH agonist which can occupy pituitary LHRH receptors. This leads to the eventual suppression of E_2 production to postmenopausal levels [3]. The standard monthly goserelin 3.6 mg depot injection has been shown to be efficacious in the treatment of women with