の4コースのレジメンは術前化学療法として有用な治療と考えられる。

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CLINICAL TRIAL

Study of time-course changes in annual recurrence rates for breast cancer: data analysis of 2,209 patients for 10 years post-surgery

Morihiko Kimura · Yasuhiro Yanagita · Tomomi Fujisawa · Tokihiro Koida

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Abstract Annual recurrence rates (ARR) are used to assess changes in the risk of breast cancer recurrence following surgery. In this retrospective study, ARR were calculated from the clinical records of 2,209 breast cancer patients who had undergone surgery. The time-course changes of ARR associated with prognostic/predictive factors were calculated. Overall, ARR decreased for 5 years following surgery and then remained almost constant. In hormone receptor (HR)-negative patients, ARR peaked after 2 years and peaked again at 6–7 years. In HR-positive patients, ARR peaked at 2 years. ARR increased in relation to the number of lymph-node metastases for 5 years, and peaked after 2 years in the absence and presence of venous invasion. The log-rank test demonstrated significant differences in recurrence between HR-negative and HR-positive cancer up to 5 years post-surgery. The presence of venous invasion had a significant effect on recurrence in the first 5 years, and the presence of lymph-node metastasis had a significant effect on recurrence up to and after 5 years. In conclusion, prognostic/predictive factors affected breast cancer recurrence in the first 5 years but had a lesser effect on recurrence more than 5 years post-surgery.

Keywords Aromatase inhibitor · Breast cancer · Chemotherapy · Hormone receptor · Hormone therapy · Lymph node · Risk · Recurrence · Surgery · Venous invasion

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Introduction

A number of comparative studies of post-operative adjuvant therapy for breast cancer have been reported. Meta-analyses of these studies have served as the basis for therapeutic guidelines for patients with breast cancer [1], so that all patients are treated under the principle of evidence-based medicine.

The purpose of post-operative adjuvant therapy is to reduce the risk of breast cancer recurrence. Annual recurrence rates (ARR) are used to assess changes in the risk of recurrence. ARR are defined as the 'percentage of patients developing recurrent cancer in 1 year among those without recurrence, at a certain time after surgery'. This definition is based on the hypothesis that ARR are constant, regardless of the time elapsed after surgery. ARR are widely used as an index for simulation of recurrence-free survival curves and to calculate the risk reduction: the odds of non-recurrence X years after surgery in patients with ARR of 15% are calculated as $(1–0.15)^X$. For evaluation of the therapeutic effect, reduction of ARR is also used to assess decreases in risk of recurrence after post-operative adjuvant therapy.

However, it is questionable whether the above hypothesis is realistic. A total of 70% of recurrences occur within 3 years post-surgery [2], and based on an integral analysis of data from the Eastern Cooperative Oncology Group (ECOG), it has been reported that the risk for breast cancer recurrence reaches a peak 1–2 years after surgery and then decreases [3]. According to the results of a meta-analysis carried out by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG), the optimal administration period for tamoxifen is 5 years [4, 5]; however, there is insufficient evidence available to determine the optimal treatment period of other hormone therapies. Moreover, chemotherapy is generally recommended for short periods in patients with hormone receptor (HR)-negative breast cancer. In the present study, we investigate time-course changes of ARR associated with HR-expression status, number of lymph-node metastases and the presence or absence of venous invasion. These prognostic/predictive factors are considered to be key determinants affecting recurrence after surgery. We also discuss therapeutic strategies, including post-operative adjuvant therapy, taking ARR into consideration.

Methods

This was an exploratory retrospective study. The study was approved by the ethics committee of Gumma Cancer Centre, and performed in accordance with the Declaration of Helsinki. ARR were calculated from the clinical records of breast cancer patients who had undergone surgery between April 1972 and March 2003 at the Gunma Cancer Centre. Time-course changes of ARR and differences in time-course changes in ARR between patients with different prognostic/predictive factors were investigated.

ARR were defined as 'the percentage of patients with recurrence between X years after surgery and $X + 1$ years after surgery among patients without recurrence X years after surgery'. ARR were calculated for the whole study population and were assessed according to HR-expression status, number of lymph-node metastases and the presence or absence of venous invasion. The specific time when ARR tended to change was also determined. Recurrence rates before and after that time were compared using 95% confidence intervals and log-rank tests. Since the study was exploratory, no adjustment was made for multiplicity, and the level of statistical significance was set at 5%.

Results

Patient characteristics

The ARR of 2,209 patients were calculated. The clinical characteristics of the study population, including prognostic/predictive factors, are summarised in Table 1.

Changes in ARR

The overall ARR peaked at 2 years post-surgery, gradually decreased up to 5 years post-surgery and then remained relatively constant (Fig. 1).

Time-course changes in ARR differed according to HR-expression status. In HR-negative patients, ARR peaked within 2 years post-surgery and then reached another peak 6–7 years post-surgery. In HR-positive patients, ARR peaked 2 years post-surgery and then remained almost constant (Fig. 2). ARR increased in relation to the number of lymph-node metastases up to 5 years post-surgery, peaking at 2 years, but remained relatively constant between 5 and 10 years (Fig. 3). ARR varied greatly depending on the presence or absence of venous invasion up to 5 years post-surgery with a peak at 2 years, and thereafter remained almost constant (Fig. 4).

Comparison of recurrence up to 5 years post-surgery with more than 5 years post-surgery

There were differences in time-course changes of recurrence rates between up to 5 years post-surgery and after more than 5 years post-surgery. Table 2 shows recurrence rates and confidence intervals in the first 5 years post-surgery and after more than 5 years post-surgery, according to prognostic/predictive factors. Confidence intervals for recurrence rates up to 5 years post-surgery in patients distributed by HR-expression status, number of lymph-node metastases and the presence or absence of venous invasion, did not overlap, whereas confidence intervals for recurrence rates 5–10 years post-surgery did overlap.

When evaluated using the log-rank test, there were significant differences in recurrence between patients with HR-negative cancer and those with HR-positive cancer for up to 5 years post-surgery (Table 3). There were also significant differences in recurrence depending on the presence or absence of venous invasion in the first 5 years. When assessed by HR-expression status and the presence or absence of venous invasion, there were no significant differences in recurrence 5–10 years post-surgery. The presence of

Table 1 Clinical characteristics of the study population

Total number of patients (*N*)	2,209
Age, years	
Median	51
Range	20–92
Menopause status, *n*	
Premenopause	961
Postmenopause	1,084
Unknown	164
Hormone receptor-expression status, *n*	
Positive	1,211 (54.8%)
Negative	526 (23.8%)
Unknown	472 (21.4%)
Lymph-node metastasis, *n*	
0	1,237 (56.0%)
1–3	505 (22.9%)
4–6	403 (13.2%)
≥7	63 (2.9%)
Unknown	1 (0.0%)
Venous invasion status, *n*	
Presence	1,105 (50.0%)
Absence	1,009 (45.7%)
Unknown	95 (4.3%)
Histological classification, *n*	
Infiltrating mammary duct carcinoma	1,923 (87.1%)
Infiltrating lobular carcinoma	76 (3.4%)
Other/unknown	210 (9.5%)

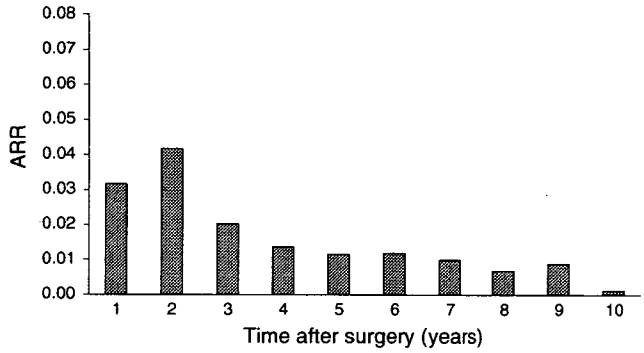

Fig. 1 Time-course changes of the overall annual recurrence rates (ARR)

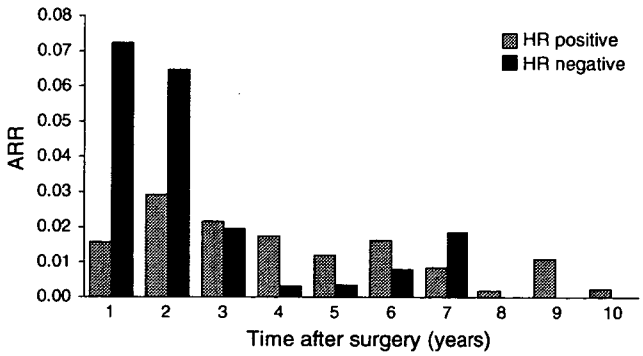

Fig. 2 Time-course changes of annual recurrence rates (ARR) in hormone receptor-positive and -negative patients

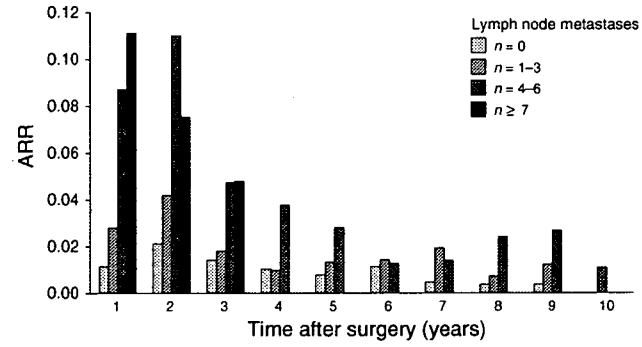

Fig. 3 Time-course changes of annual recurrence rates (ARR) according to number of lymph-node metastases

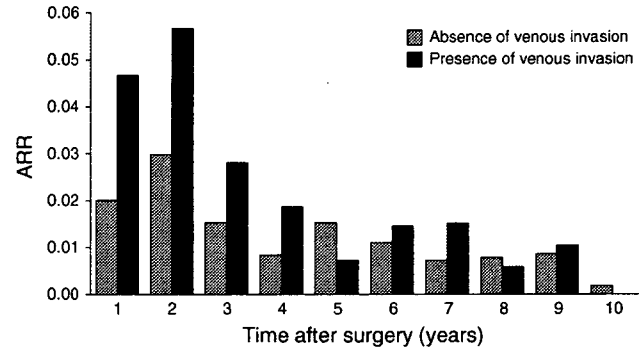

Fig. 4 Time-course changes of annual recurrence rates (ARR) in patients according to the absence or presence of venous invasion

lymph-node metastasis had a significant effect on recurrence up to 5 years post-surgery and 5–10 years post-surgery.

Discussion

In the present study, the ARR up to 5 years post-surgery reached a peak at 2 years and then gradually decreased, while the ARR more than 5 years post-surgery remained almost constant. Time-course changes in ARR in the first 5 years post-surgery were different from those more than 5 years post-surgery. Annual hazard rates of recurrence (AHRR) have been calculated previously based on the results of seven clinical studies carried out by the ECOG [3]. The time-course changes of AHRR in all patients and for patients distributed according to HR-expression status and the presence or absence of lymph-node metastasis tended to be similar to the results of the present study. The results of the meta-analysis done by the EBCTCG also showed that the AHRR more than 5 years post-surgery was lower than in the first 5 years post-surgery

Table 2 Recurrence rates up to 5 years and 5–10 years post-surgery according to prognostic/predictive factors

	Up to 5 years post-surgery		5–10 years post-surgery	
	Recurrence rates	95% CI	Recurrence rates	95% CI
All patients	224/2,209 (10.1%)	8.9–11.5	42/1,247 (3.4%)	2.4–4.5
HR+	96/1,211 (7.9%)	6.5–9.6	23/677 (3.4%)	2.2–5.1
HR-	75/526 (14.3%)	11.4–17.5	6/251 (2.4%)	0.9–5.1
Absence of lymph-node metastasis	67/1,237 (5.4%)	4.2–6.8	15/723 (2.1%)	1.2–3.4
Presence of lymph-node metastasis	157/971 (16.2%)	13.9–18.6	27/523 (5.2%)	3.4–7.4
No. of lymph-node metastases (1–3)	51/505 (10.1%)	7.6–13.1	16/357 (4.5%)	2.6–7.2
No. of lymph-node metastases (4–6)	95/403 (23.6%)	19.5–28.0	11/158 (7.0%)	3.5–12.1
No. of lymph-node metastases (≥7)	11/63 (17.5%)	9.1–29.1	0/8 (0.0%)	0.0–31.2
Presence of venous invasion	134/1,009 (13.3%)	11.2–15.5	18/482 (3.7%)	2.2–5.8
Absence of venous invasion	85/1,105 (7.7%)	6.2–9.4	24/731 (3.3%)	2.1–4.8

CI, confidence intervals; HR+/–, hormone receptor-positive/-negative

Table 3 Log-rank test for recurrence up to 5 years post-surgery and 5–10 years post-surgery according to prognostic/predictive factors

Prognostic/ predictive factor		Recurrence up to 5 years post-surgery		Log-rank test	Recurrence 5–10 years post-surgery		Log-rank test
		Presence *n*	Absence *n*		Presence *n*	Absence *n*	
HR	HR+	96 (7.9%)	1,115 (92.1%)	$P < 0.0001$	23 (3.4%)	654 (96.6%)	$P = 0.4454$
	HR–	75 (14.3%)	451 (85.7%)		6 (2.4%)	245 (97.6%)	
Lymph-node metastasis	n+	157 (16.2%)	814 (83.8%)	$P < 0.0001$	27 (5.2%)	496 (94.8%)	$P = 0.0025$
	n–	67 (5.4%)	1,170 (94.6%)		15 (2.1%)	708 (97.9%)	
Venous invasion	v+	134 (13.3%)	875 (86.7%)	$P < 0.0001$	18 (3.7%)	464 (96.3%)	$P = 0.3343$
	v–	85 (7.7%)	1,020 (92.3%)		24 (3.3%)	707 (96.7%)	

HR+/–, hormone receptor-positive/-negative; n+/–, presence/absence of lymph-node metastasis; v+/–, presence/absence of venous invasion

[4, 5], suggesting that time-course changes in ARR up to 5 years post-surgery were different from those more than 5 years post-surgery.

We found that all the prognostic/predictive factors (HR-expression, lymph-node metastasis and venous invasion) affected the ARR up to 5 years post-surgery, as previously reported. In particular, venous invasion was included in the risk category at the International Consensus Conference on Primary Treatment of Breast Cancer in 2005 [1]. The results of the present study also suggested that venous invasion affected ARR, with a higher ARR in the first 5 years post-surgery than that more than 5 years post-surgery, and the recurrence risk was increased by the occurrence of venous invasion. It is important to discuss therapeutic strategies, including use of post-operative adjuvant therapy, for the prevention of recurrence within 5 years and particularly within 3 years of surgery.

In HR-negative patients, recurrence was observed mainly within 2 years, so it appears reasonable to initiate potent chemotherapy immediately after surgery. Interestingly, ARR again increased 6–7 years after surgery. This suggests that closer observation of HR-negative patients is required, and there should be further discussion about therapeutic strategies, including the possibility of administering extra courses of chemotherapy if necessary.

The pattern of ARR in HR-positive patients was quite different from HR-negative patients. In HR-positive patients, the ARR were almost constant and barely decreased beyond 5 years post-surgery, with a small peak at 2 years. In addition, there was no difference in ARR between premenopausal and postmenopausal patients (data not shown). This correlates with previously published results [3]. The meta-analysis done by the EBCTCG concluded that the optimal treatment period with tamoxifen should be 5 years. Recently, the use of aromatase inhibitors after 2–3 years of tamoxifen has also resulted in improvement in disease-free survival [6, 7]. However, it was reported that aromatase inhibitors, which are becoming first-choice drugs for postmenopausal HR-positive patients with breast cancer, were effective when administered beyond the 5-year treatment period of tamoxifen [8, 9]. This suggests that hormone therapy for more than 5 years post-surgery may be effective. The present study also confirmed that the recurrence rates more than 5 years post-surgery were higher in

HR-positive patients than in HR-negative patients. Further investigation of the usefulness of hormone therapy beyond 5 years post-surgery is required, with a focus on the use of aromatase inhibitors.

As long-term data on ARR accumulate and more clinical studies are conducted, the optimal therapeutic methods for use in breast cancer beyond 5 years post-surgery should become clearer.

Conclusion

In the present study, ARR were not constant and differed between up to 5 years post-surgery and more than 5 years post-surgery. Prognostic/predictive factors affected recurrence up to 5 years post-surgery but had a lesser effect on recurrence more than 5 years post-surgery. The results of this study suggest that recurrence-free survival rates can be improved by preventing recurrence up to 5 years, especially 3 years, after surgery. The use of post-operative adjuvant therapy for more than 5 years after surgery should be considered, depending on the HR-expression status of the patient.

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●原 著●

乳癌周術期化学療法の現状およびSupportive Careの工夫
—JBCRG01試験アンケートより—

Japan Breast Cancer Research Group (JBCRG)

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Summary

We carried out a survey of supportive care at institutions that participated in the JBCRG01 study (FEC followed by docetaxel) as neoadjuvant therapy for operable breast cancer. The purpose was to share the information of supportive care for the treatment effect of perioperative intensive chemotherapy among institutions.

Appropriate supportive care for nausea, vomiting, edema and febrile neutropenia (FN) is important with respect to the safety of chemotherapy. According to the results of the questionnaire, support from the family and the relationships with doctors, nurses and pharmacists familiar with the chemotherapy were important. The equipment and service for outpatients' cancer chemotherapy center are also important.

This multicenter study enhances the exchange of information among institutes. The results of this survey suggest that adequate supportive care makes anthracycline and taxane chemotherapy manageable in the outpatient setting.

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要旨 乳癌周術期のintensiveな化学療法施行の際に，治療効果を最大限に期するための工夫が各施設にて行われている。FEC＋docetaxelの術前化学療法の臨床試験（JBCRG01）参加施設のsupportive careの工夫を施設間で共有することを目的にアンケート調査を実施した。化学療法を安全に遂行するには悪心・嘔吐や浮腫，発熱性好中球減少症などの有害事象に対する適切なsupportive careが重要である。それには医師のみでなく，癌薬物療法に詳しい看護師や薬剤師をはじめとする医療スタッフのかかわり，外来化学療法センターなどのハード面の整備，家族の支えなどが重要なポイントであることがアンケート調査から判明した。本グループのように多施設臨床試験を遂行することで施設間の情報交換も進む。今回のアンケートで得られた工夫が十分に行われていれば，anthracycline系ならびにtaxane系薬物療法は，外来ベースで管理可能な薬物療法であると考えられた。

はじめに

近年，乳癌の治癒をめざし，エビデンスやガイドラインに準拠した化学療法レジメンの遂行が重要視されている。よりよい成果を得るためには，適格なレジメンの選択と同時に，予定されている投与サイクル，投与量を計画的に実施することがポイントである。化学療法には悪心・嘔吐，全身倦怠感などをはじめ数々の副作用を伴うことから，その予防と管理が重要である[1,2]。

Japan Breast Cancer Research Group（JBCRG）では，2002～2004年にFEC（5-FU 500 mg/m^2，epirubicin 100 mg/m^2，cyclophosphamide 500 mg/m^2）を4コース後，docetaxel（DOC）75 mg/m^{2}を4コース行う術前化学療法の臨床試験（JBCRG01）を実施した。79例の中間解析では，完遂率はFEC 97.5%，DOCで92.3%とコンプライアンスは良好であり，臨床的効果は71%であった[3]。

今回われわれはintensiveな化学療法施行の際に，治療効果を最大限に期するための工夫を施設間で共有することを目的に，JBCRG01試験参加施設を対象に周術期化学療法の現状および各有害事象に対するsupportive careの現状についてアンケート調査を行い検討した。

Ⅰ．対象と方法

2005年6月に，JBCRG01試験に参加した13施設を対象に，周術期化学療法の現状ならびに各有害事象に対するsupportive careの現状に関するアンケート調査（図1）を，eメールもしくはFAXによる回答形式で実施した。回収率は100%であった。

本調査参加施設は，国立病院機構大阪医療センター，東京都立駒込病院，関西労災病院，聖路加国際病院，愛知県がんセンター中央病院，国立病院機構九州がんセンター，広島市立安佐市民病院，旭川医科大学，東京医科大学病院，国立病院機構名古屋医療センター，昭和大学附属豊洲病院，岩手医科大学，熊本大学の13施設である。

Ⅱ．調査結果

1．JBCRG参加施設における周術期化学療法の現状

周術期化学療法の各施設の現状を，1）原発乳癌症例数，基本レジメンについて，2）術前・術後化学療法の初回コース治療開始状況，3）外来化学療法システムの整備，4）クリニカルパスの導入，5）informed consent（IC）の工夫，としてまとめた。

1）原発乳癌症例数，基本レジメンについて

1年間の乳癌初発症例数（2004年度）は，中央値で160（20～500）例であった。術前化学療法施行数は，中央値で16（3～150）例，13施設での平均施行率は15.8（4～40）%であった。その際，通常よく使用する術前化学療法レジメンとして，表1に示すレジメンが列挙されたが，多くはanthracycline系とtaxane系の逐次併用レジメンであった。

2）術前・術後化学療法の初回コース治療開始状況

6施設が全コース外来実施を基本としていた。しかし，このうち5施設においては，JBCRG01試験参加前には1コース目の化学療法は入院にて行っていた。

外来実施が可能な主な理由として，①治療内容，目的，起こり得る副作用とその対策についての十分な説明をチーム医療で行っている，②緊急時の対応が可能（検査・入院体制），③看護師をはじめスタッフが有害事象に関してもよく理解し慣れている，などがあげられた。

一方，7施設が1コース目は入院，2コース目以降は外来で行う体制をとっていた。1コース目に入院にて治療を行うメリットは，①十分な説明と理解のための時間の確保ができる（患者への対応や教育の充実），②不安解消・副作用出現時の対策をとりやすい，③個人差の掌握が可能，④病床稼働率・平均入院日数減少への貢献，などをほぼ共通してあげていた。デメリットは，医療費の高騰，患者負担の増加（生活制限・入院費），ベッドコントロールの煩雑さがあげられた。

周術期化学療法に関するアンケート

周術期化学療法の現状についてお答えください。再発例の場合は除いてお考えください。

- 施設と症例数・基本治療レジメについて
  - ① 1年間(2004年)の乳癌患者数(新患原発例)
  - ② 術前化学療法施行症例数(2004年)と代表的レジメ(3つ)
- 患者さんの治療形態について
  - ① 術前ないし術後の化学療法の施行場所について
    全コース外来を基本 or 1コース目は入院で2コース目以降は外来 or 施行毎に入院 or その他
  - ② 全コース外来を基本とされている施設への質問
    ◆昔、FEC やタキサン系治療を最初にはじめられたときでも、入院治療の経験はありませんか？
    最初は入院治療で経過をみたり、WBC などを測定したり、[ ]などの経験を踏んだ上で、今は外来治療スタートが可能となった or 最初から、外来治療で安心と考え、入院での治療経験はない
    ◆全コース外来治療が可能な理由
  - ③ 入院治療を行う施設の先生方へ質問。その理由をお聞かせください。
  - ④ 入院治療を行うメリット・デメリットは何でしょうか？
- 外来通院型化療療法施行の際の工夫について

1. ハード面の整備として外来化学療法センターの整備はありますか？
   有りのご施設は以下の①～⑦の質問にお答えください。無しのご施設は2. 以降の質問にお答えください。
   - ① 外来化学療法センターの開設時期
   - ② ホームページや外来等で化学療法室について紹介していますか？
   - ③ スタッフについて:専任医師_____名・専任薬剤師_____名・専任看護師_____名
   - ④ 設備について
     ベッド/救急カート/EKG モニター/ナースコール/リクライニングチェア/トイレ/洗面台/ テレビ/DVD プレイヤー/冷蔵庫/図書/BGM /プライベート空間確保のためのカーテンなど
   - ⑤ 稼働日・稼動時間について
   - ⑥ 業務について:ルート確保及び薬剤の調合は誰が行いますか？
2. 化学療法に関し、クリニカルパスは導入していますか？
   導入している場合各レジメ毎に作成？何種類あるか？
   導入していない場合他に何か工夫をしていますか？
3. 化学療法に関する患者さん向け文書を利用しているか？
4. ソフト面での工夫(一般的に使用するレジメを想定してお書きください)
   - ① 治療効果をあげる目的では、治療の完遂が大切かと思います。そのために工夫されているICのポイントなどを列記してください。
   - ② 患者を支える家族へのアプローチには何か工夫がありますか？
   - ③ 悪心・嘔吐対策・予防
   - ④ 口内炎などの粘膜障害への対策・予防
   - ⑤ 血管炎、血管痛対策・予防
   - ⑥ 血管外漏出に対する予防⇒実際に起きたときを想定してマニュアルを作成していますか？
   - ⑦ FN(好中球減少性発熱)への対策・予防(予防的抗生物質を処方する場合にはその使用基準もお示しください)
     ⇒実際に熱がどのようになれば、救急受診など含めて来院するように指導していますか？
     ⇒実際に、クール途中で、好中球などを測定しますか？その理由も。
     ⇒あるクールで、FNを確認した場合、次クールでの対策は？
     ⇒G-CSF について、その使用基準をお教えください。
     ⇒FN の際に、使用する抗菌剤・抗生物質について、使用薬剤・投与期間・使用基準・抗菌剤使用の有無
   - ⑧ 爪の変形・色素沈着などの皮膚障害への対策・予防
   - ⑨ 神経毒性(しびれ、感覚異常など)への対策・予防
   - ⑩ 関節痛・筋肉痛への対策・予防
   - ⑪ 浮腫対策・予防
   - ⑫ 脱毛対策・予防

それでは具体的に・・・今回の術前化学療法における貴施設の基本的な支持療法をお教えください。

JBCRG 01(FEC→Doc) 試験の supportive care に関するアンケート

副作用対策としてレジメごとに工夫されている支持療法を具体的にご記入ください。

- FEC 時
  化学療法投与前の投薬:薬剤名・投与経路・投与期間・総投与量・投与時期・使用理由
  化学療法投与後の投薬:薬剤名・投与経路・投与期間・総投与量・投与時期・使用理由
- Doc 時
  化学療法投与前の投薬:薬剤名・投与経路・投与期間・総投与量・投与時期・使用理由
  化学療法投与後の投薬:薬剤名・投与経路・投与期間・総投与量・投与時期・使用理由

図 1 JBCRG01 アンケート概要

表 1 JBCRG 参加施設で施行されている術前化学療法レジメン（施設数）

FEC100×4 コース＋docetaxel×4 コース（n＝13）
AC（adriamycin＋cyclophosphamide）×4 コース＋weekly paclitaxel×12 コース（n＝3）
FEC100×4 コース＋weekly paclitaxel×12 コース（n＝2）
AC×6 コース（n＝2）
ET（epirubicin＋docetaxel）×6 コース（n＝1）
weekly paclitaxel×12 コース（n＝1） など

各施設より主な 3 レジメンが列挙された

表 2 周術期化学療法における IC の工夫

①乳癌について現実を理解してもらう
全身病の性格，具体的な数字を示し再発したら助からないことを理解する
②化学療法のメリットを理解してもらう
治療の目的・目標（治療完遂の重要性），スケジュールを明確にし，治療意欲を惹気する
特に術前化学療法の場合は，
治療効果の確認，pCR の意義，温存術成功の可能性などメリットを明言
オーダーメード医療の一環，translational research への貢献も説明
③化学療法の副作用を理解してもらう
副作用の十分な説明とともに，supportive care を示し，不安を解消する
予防できることできないこと（脱毛など）を明確にする
④緊急時の連絡先，対応などを明示
電話相談，メール相談
⑤精神的なサポート（安心感を与える）
カウンセラー，患者中心の精神サポートグループへの参加を提案
同じ治療を受ける患者間での情報交換，患者どうしの支えあいもポイント
⑥説明時の工夫
説明パンフレットの利用，家族の同席，同意を急がない，生活様式の調整を図る
医療相談室へ紹介し，早期から経済支援方法の検討を提案する
家族のみとの話し合いにより患者の精神的サポートをお願いする

3）外来化学療法システムの整備

整備された外来化学療法センターは 9 施設で稼動している。開設時期は早い施設で 1994 年，1999 年に開設されているが，その他は 2002 年以降であった。9 施設のうち 7 施設が外来やホームページで外来化学療法センターの開設について紹介していた。7 施設が月～金の朝から夕方まで平日はほぼ全日稼動していた。各施設の規模は異なるもののほぼ共通して，ベッド，リクライニングチェア（3～25 床），救急カート，ECG モニター，ナースコール，カーテンなどのプライベート空間確保，洗面台，トイレの設備がされていた。これらの設備に加え，BGM，図書，テレビ，DVD プレーヤー，冷蔵庫など患者が心地よく過ごせるためのアメニティも工夫され，癒しの環境づくりに力を入れている施設があった。

9 施設とも外来化学療法センターの専任医師，専任薬剤師，専任看護師のいずれかが常駐しており，5 施設では専任医師・専任薬剤師・専任看護師すべてが常駐していた。外来化学療法センターの整備に伴い，業務の分担も明確になってきている。13 施設中，調剤は薬剤師が担当するのが 8 施設，点滴ルートの確保も一定の資格を有した看護師が実施する施設は 3 施設あった。

4）クリニカルパスの導入

5 施設で化学療法用のクリニカルパスが導入され，基本レジメン以外に複数のクリニカルパスが作成されていた。一方，未導入の 8 施設でも電子カルテのレジメン登録機能の活用，レジメンの固定，チェック機能の強化，医療スタッフの固定，患者情報を共有するなど工夫を行い，常に同じレベルで患者への対応や指導説明ができる体制をとっていた。

5）Informed consent（IC）の工夫

適格な治療を選択し完遂率を高め，ひいては治癒率を向上させるために informed consent（IC）は大変重要である。各施設の IC の工夫をまとめた結果を表 2 に示す。周術期化学療法に際しては告知はもちろんのこと，具体的に再発リスクを示すなど治療への意欲を引きだす工夫がなされている。患者説明用パンフレットの活用は 12 施設で実施されており，11 施設では製薬メーカーの冊子を応用するだけでなく，院内で独自に作成していた。

2．JBCRG01 試験参加施設における supportive care

各施設で基本的なレジメンを行う上で，各有害事象に対する supportive care の現状を調査した。図 2 は

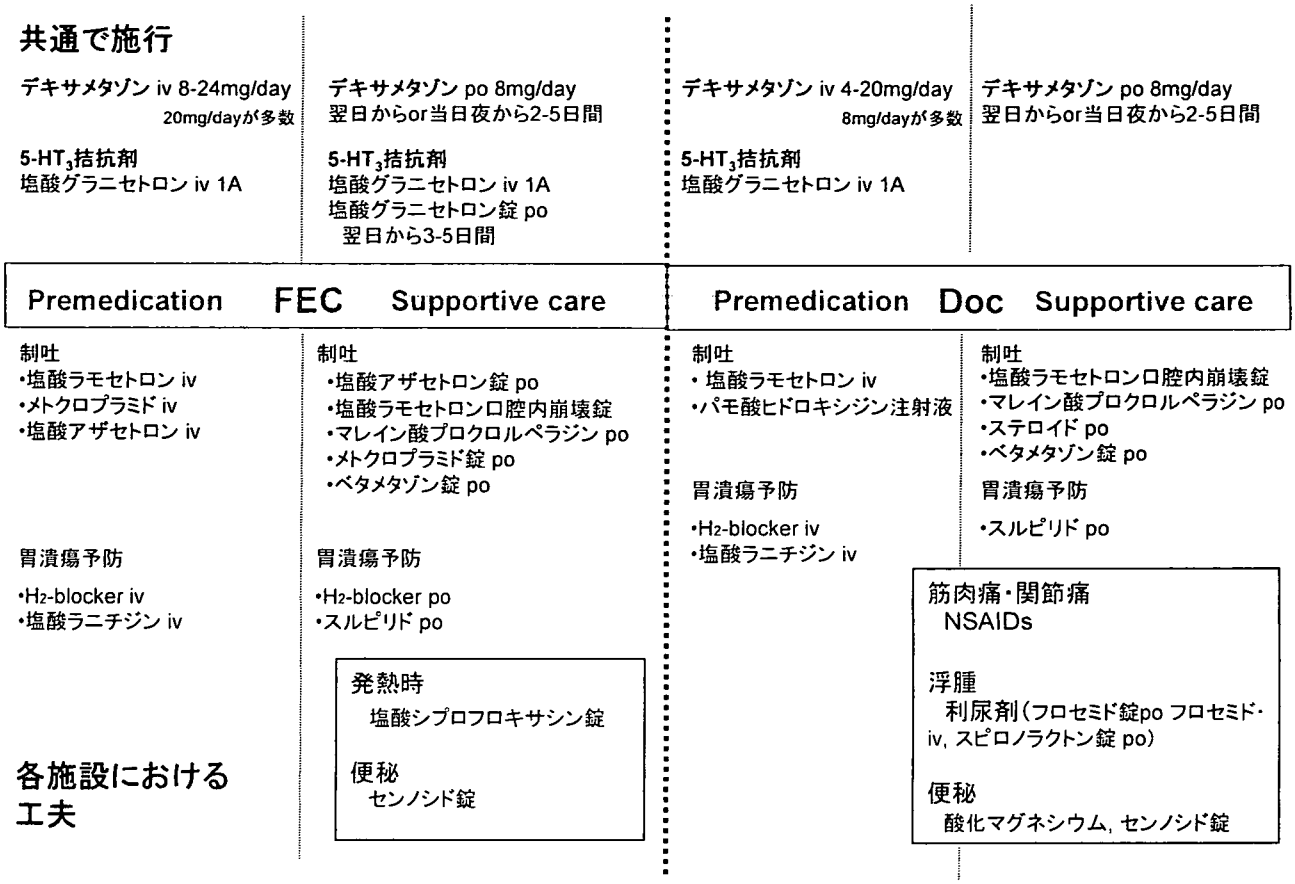

図 2 JBCRG01 試験における supportive care の工夫
上段は各施設でほぼ共通して行われており，下段は各施設で試行されている工夫を示している。

JBCRG01（FEC-DOC 術前化学療法）時の premedication と supportive care を示す。以下，有害事象別の予防と対策のポイントであった。

1）悪心・嘔吐，便秘

悪心・嘔吐，倦怠感に対しては，図2に示すステロイドと 5-HT_3拮抗剤の前投薬が全施設で共通しており，化学療法後の supportive care も内容の細部は異なるものの，各施設で制吐剤が中心であった。注射剤の 5-HT_3拮抗剤の前投薬以外に，投与の翌日以降から3〜5日間経口 5-HT_3拮抗剤を併用するなどの工夫がされていた。予測性嘔吐に対してマイナートランキライザーをあらかじめ内服させる施設もあった。制吐剤によるコントロール以外に，急性期嘔吐と遅発性嘔吐を管理できるように症状経過の予測をあらかじめ説明したり，開始前の外来受診時に化学療法室（治療現場）を見学することで予測性嘔吐を予防したり，食事の工夫，患者との信頼関係の構築，排便コントロールの重要性を啓発するなどの工夫がなされていた。

5-HT_3拮抗剤の使用の影響などで便秘傾向になる場合もあるが，長期間の便秘は悪心・嘔吐の遷延の原因にもなり得る。便秘に対しては，センノシド錠，酸化マグネシウムなどの緩下剤をあらかじめ処方する，水分コントロール・食事の工夫を考え指導する，などがなされていた。

2）口内炎など粘膜障害

予防として，うがいの励行，治療開始前の齲歯治療・口腔内の保清の指導がされていた。化学療法中にエレースアイスボールなど氷片を含み，発現時にはステロイド外用薬（デキサルチン軟膏，プロピオン酸ベクロメタゾン）が処方されていた。

3）血管炎，血管痛

繰り返し同じ血管を用いない，点滴時間を速くし化学療法終了後，生理食塩水によりフラッシュする，点滴中は加温（ホットパックなど），終了後冷庵する，FEC の epirubicin で RTU（水溶液）を用いる時はステロイドとの併用で pH を調整するなど予防の工夫がされていた[4]。実際に血管炎が起きた場合には，ステロイド軟膏を処方する，重症例では一期的に CV ポートを留置するなどされていた。

4）血管外漏出

予防として，確実なルートを確保するために太い血管を選ぶ，関節近傍の血管には挿入しない，採血用のルートと点滴用の血管を変える，抜針前生理食塩水のフラッシュを徹底する，実際に起きた場合はステロイド軟膏・

ステロイド局注を行い，生理食塩水ガーゼで冷罨がされていた。8施設では実際に起こったことを想定してマニュアルを作成し，皮膚科紹介などがされていた。

5）発熱性好中球減少症（FN）

あらかじめニューキノロン系薬剤（ciprofloxacin, ofloxacin）やセフェム系抗生物質などを処方し発熱時の対応を指導する，経口の抗生物質を使用しても遷延（抗菌剤を服用しても熱が下がらない場合，熱が3日以上継続する時）や高熱を認める場合には救急受診するように指導されていた。

3施設で，個人差把握の目的で実際にコース途中で好中球数を測定していた。10施設では発熱時以外，好中球数は測定していなかった。

G-CSFの投与のタイミングは，発熱後すぐ開始（3施設），FNが続く時のみ使用する（7施設），原則使用しない（1施設），FNがなくても遅延などによるdose intensity低下を防ぐ目的で使用（2施設）と回答が分かれた。経口抗生物質でコントロール可能なFNであった場合，次コース以降の対応は，25%減量し投与するのが7施設，再度減量せず投与するのが4施設，G-CSFを使用しながらdose intensityを維持するのが2施設との回答であった。G-CSFの投与はガイドラインに基づき行われていた[5,6]。

6）爪の変形・色素沈着などの皮膚障害

ビタミンB_6，ケラチナミン軟膏，尿素軟膏，デキサルチン軟膏などの処方がされていた。投与中に冷却パックで冷庵する，爪に対してマニキュアで爪を保護するという施設もあった。

7）神経毒性（しびれ・感覚異常など）

発現時にビタミンB_{12}・B_6剤内服，漢方薬（牛車腎気丸，芍薬甘草湯），胃炎・潰瘍治療剤，非ステロイド性抗炎症薬（NSAIDs）などの処方がされていたが，標準的治療はなかった。

8）関節痛・筋肉痛

ビタミンB_{12}剤内服，漢方薬（牛車腎気丸，芍薬甘草湯），NSAIDsなど鎮痛剤の処方が行われていた。

9）浮　腫

ステロイド剤の予防投与，心・腎機能が正常ならば出現時には早期から利尿剤の処方，治療前から浮腫傾向がある患者には漢方薬として柴苓湯や五苓散が処方されていた。サポーターや弾性包帯の使用，マッサージ，減塩食の指導などの工夫もされていた。

10）脱　毛

予防はできないため，脱毛は抗癌剤使用中に限られる点の理解を得，かつらや帽子，バンダナの紹介を行っていた。

Ⅲ．考　察

JBCRG参加施設における周術期化学療法のレジメンは基本的にanthracycline系とtaxane系の逐次併用療法であり，これらのintensiveな治療を確実に行うためには，外来化学療法センターの設備（アメニティ）などのハード面の工夫と，看護師・薬剤師とのチーム医療の実践，そして有害事象のマネージメントがポイントとしてあげられる。外来での化学療法により，患者はQOLを維持しながら通常の生活を継続することが可能になる。また，化学療法の入院治療から外来治療への移行は，今後，diagnosis-procedure combination（DPC）の採用に伴いますます加速するものと思われる[7]。JBCRGに参加している施設は，初回コースの治療開始状況は外来治療と入院治療に分かれていたが，2コース目以降は全施設で外来治療が行われていた。外来治療でも緊急時に対応できる体制として，専門スタッフの固定，レジメンの固定，クリニカルパスの導入などがされており，外来化学療法にはチーム医療による治療管理体制の構築が重要と思われた。また，患者に化学療法への能動的な気持ちを惹起するために，ICの際に家族のみとの話合いを行い患者の精神的サポートの協力を依頼したりするなど，家族の協力や患者間での情報交換支援が重要なポイントと思われた。

有害事象がいったん生じると患者の化学療法継続への意欲低下，ひいては治癒率の低下に結び付くため，予防に重点をおくことが大切である。JBCRG01試験の中間解析時では，前半のFEC時にはgrade 1，2の悪心・嘔吐が半数以上の患者で発現し，grade 3も認められた。嘔吐は約半数で発現しているが，後半のDOCでは発現頻度は低下していた[3]。基本は予防であり，ガイドラインに従い5-HT_3拮抗剤とステロイドの投与は全施設で実施されていた[8-10]。悪心・嘔吐を理由に治療継続を断念した例はなかったことから，悪心・嘔吐に対するpremedicationやsupportive careにより管理可能と考えられた。ただし，FEC療法中の悪心の発現率は高く，さらに予測性の悪心・嘔吐対策にも心がける必要があると思われた。また，5-HT_3拮抗剤の使用の影響などで便秘傾向になり，長期間の便秘は悪心・嘔吐の遷延の原因にもなり得るので，FEC療法での便秘への対策も必須と考えられた。

また，中間解析の結果では，DOC療法はFEC療法に対し浮腫や筋肉痛・関節痛の発現頻度が高かったがいずれもgrade 1，2であり，重篤なものはなかった。浮腫に対してはステロイドの予防投与や早期からの利尿剤の処方，筋肉痛・関節痛が発現した際にはNSAIDsを服用す

るよう指導がされており，早期のsupportive careにより重篤な副作用が避けられると思われた。FNはDOCに対しFEC療法で発現頻度が高かったが（19% vs 3.8%）[3]，多くの施設で発熱時以外には好中球を測定しておらず，発熱時に抗菌剤を服用するように指導されていた。副作用の発現時の服用を指示する以外に，外来化学療法の施行時には感染予防のためのセルフケア支援なども重要と考えられた[11]。

今回のアンケート調査の結果から，各施設の様々なアイデアを得ることができ，グループ内で共有することができた。本グループのように多施設臨床試験の遂行により，施設間の情報交換が進む。副作用対策に関してもガイドラインに準拠する以外に，今回のアンケートのように施設間で情報交換し，すぐに実践するような姿勢が，高い完遂率と良好な治療成績に結び付くものと思われた。今回の調査で得ることができた様々な化学療法時のsupportive careが十分に行われていれば，FEC療法やtaxane系薬剤による化学療法は，外来ベースで管理可能な薬物療法であると考えられた。

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CLINICAL TRIAL

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

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

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

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

Introduction

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

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

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

Methods

Study design and ethics

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

Patients

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

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

Treatment procedures

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

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

Assessment

Hormone receptor and HER2 overexpression

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

Central pathological assessment

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

Toxicity and clinical assessment

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

Statistical methods

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

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

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

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

Results

Patient characteristics

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

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

Table 1 Patients characteristics ($n = 198$)

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

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

Percentages may not add up to 100% because of rounding

Compliance to chemotherapy and toxicity

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

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

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

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

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

Response to treatment

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

Predictive factors of pathological response

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

Table 2 Treatment related toxicities

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

FEC fluorouracil, epirubicin, cyclophosphamide

Table 3 Clinical response after FEC and after docetaxel following FEC treatment (n = 194)

Clinical response, N (%)	Overall	
	Responder	Non-responder
FEC		
Responder	106 (90%)	13 (10%)
Non-responder	38 (51%)	37 (49%)

cCR + cPR responder, *cSD + cPD* non-responder, *FEC* fluorouracil, epirubicin, cyclophosphamide, *CI* confidence interval

Discussion

We have presented results from the largest study to date that enrolled Japanese women undergoing preoperative chemotherapy for early stage breast cancer. Our findings demonstrated that four cycles of preoperative FEC followed by four cycles of docetaxel conferred a high rate of BCS, even among patients with primary tumors larger than 3 cm. We found a significant improvement in DFS when QpCR could be achieved, compared to the absence of QpCR. HER2 overexpression, response to FEC and response to docetaxel were significant predictors of QpCR with this regimen.

Regarding toxicity, there were no fatal events and no significant differences in the types and severity of toxicity as compared to other recent studies using similar regimens outside of Japan [6, 8, 9, 16–18]. Compared with overseas studies that also did not allow rh G-CSF the incidence of fever was the same in this study [8, 19]. In another studies which showed lower incidence of febrile neutropenia (13.5%) all patients were treated with rh G-CSF [16].

One of the merits of neoadjuvant chemotherapy for operable breast cancer is to decrease the size of the primary tumor in order to allow for BCS. The study protocol did not provide guidelines for breast conservation; therefore, the BCS rate that we observed reflected the biases that may occur in real-life clinical practice in Japan. Nevertheless, the BCS rate of 80% that we observed was favorable compared with other neoadjuvant studies performed overseas [3, 16].

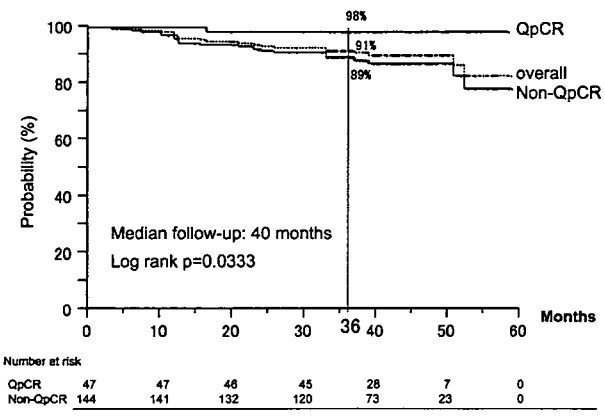

Fig. 1 Relationship of QpCR and non-QpCR to disease free survival

The PACS 01 trial which compared six cycles of adjuvant FEC with a sequential regimen of three cycles of FEC followed by three cycles of docetaxel 100 mg/m^2 (FEC-D) demonstrated an 18% risk reduction in DFS and 27% risk reduction in OS with FEC-D (adjusted P = 0.017). This study supports the conclusions that sequential adjuvant chemotherapy with FEC followed by docetaxel significantly improves DFS and OS in node-positive breast cancer patients [9]. In the current study the dose of docetaxel 75 mg/m^2 was selected based on the recommended doses for docetaxel in Japan, and we showed that the actual 3-year DFS rate of 91% was better than expected based on the results of overseas studies [7, 9, 20]. This confirms that the approved doses of 75 mg/m^2 is an appropriate does in Japanese women.

Furthermore a new definition of QpCR was defined for pathological effect in this study. When stratified between QpCR and non-QpCR, patients with QpCR had significantly favorable DFS. Indeed by adding docetaxel to FEC patients with QpCR resulted in improved survival similar to previous studies.

Even without anti-HER2 targeting therapy, a QpCR rate >60% was achievable in ER negative and HER2 positive tumors. A multivariate analysis has indicated the significant value of HER2 overexpression, which seems to suggest the importance of HER2 in the prediction of QpCR with this regimen. In this study both an anthracycline and docetaxel were used, so it is not clear which treatment was more strongly associated with HER2 as a predictive value of QpCR. Data in the metastatic and adjuvants setting suggest that docetaxel regimens may be more active than non docetaxel regimens in HER2 positive tumors [8, 21]. The value of HER2 status as a predictor of response to anthracycline-based chemotherapy is still a matter debate. On the other hand, there are several implicative data showing the predictive value of topoisomerase (Topo)-II for anthracyclines because Topo-II is a molecular target of anthracyclines [22–25]. There is evidence that HER2 amplification and Topo-II amplification usually occur in parallel and it is rare to have Topo-II amplification without HER2 amplification [23, 26]. In this study QpCR rate might clarify the difference between HER2 positive tumors and HER2 negative tumors. No patient has received trastuzumab in the adjuvant setting. Future translational studies will be necessary to explore the significance of Topo-II amplifications as well as HER2 gene amplifications in the prediction of the pathological response of this regimen. This result will be included the information in the future if

Table 4 Predictive variables for QpCR

Variables	Before treatment OR 95% CI (*P*)	After FEC treatment OR 95% CI (*P*)	After docetaxel following FEC treatment OR 95% CI (*P*)
Menopausal status	1.43	1.38	1.37
Pre (versus post)	0.94–2.15 (NS)	0.89–2.14 (NS)	0.87–2.12 (NS)
Tumor size	0.89	0.93	0.87
>3 cm (vs ≤3 cm)	0.61–1.3 (NS)	0.63–1.37 (NS)	0.59–1.28 (NS)
ER	1.4	1.44	1.35
Negative (versus Positive)	0.87–2.27 (NS)	0.88–2.36 (NS)	0.81–2.23 (NS)
PgR	1.61	1.49	1.65
Negative (versus Positive)	0.97–2.67 (NS)	0.89–2.51 (NS)	0.98–2.79 (NS)
HER2	2.02	2.24	2.11
3+ (vs <3+)	1.31–3.11 (0.0014)	1.42–3.53 (0.0005)	1.36–3.3 (0.0009)
Clinical response to FEC treatment	–	1.78	–
Response (versus non-response)	–	1.15–2.76 (0.0096)	–
Clinical response to docetaxel following FEC treatment	–	–	1.99
Response (versus non-response)	–	–	1.14–3.47 (0.0154)

QpCR quasi pathological complete response, *FEC* fluorouracil, epirubicin, cyclophosphamide, *OR* odds ratio, *ER* estrogen receptor, *PgR* progesterone receptor, *CI* confidence interval, *NS* not significant

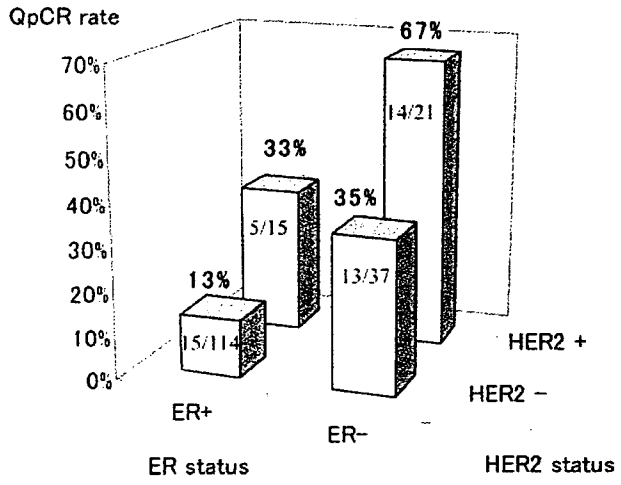

Fig. 2 Relationship between QpCR and HER2/ER status (n=187)

we use anthracycline and trastuzumab for all HER2 positive patients.

In the present study, though a multivariate analysis hasn't indicated the significant value of the status of hormone receptor, QpCR rate was higher in ER negative tumors than ER positive tumors, and QpCR rate in ER negative and HER2 positive tumors was remarkably high compared with ER positive and HER2 negative tumors. This model suggests that ER status is a dependent predictor, for QpCR possibly because it is related to HER2 expression. The sample size was perhaps too small to effectively determine the true impact of ER negative status as a predictor of QpCR. As most patients who are HER2 positive are also ER negative, it is likely that ER status will have some predictive value. However, larger studies are needed to determine this. These results are important for considering individual preoperative systemic therapy. This trend was similar to previous studies using AC followed by paclitaxel regimens, though the therapeutic situations are different [10, 12, 27, 28]. According to recent meta-analyses of post-operative adjuvant therapy, chemotherapy including cyclophosphamide/methotrexate/5FU (CMF)-type regimens, anthracycline-containing regimens and anthracycline followed by paclitaxel are more effective for hormone receptor negative tumors than for hormone receptor positive tumors [10–12, 27–32]. However, while hormone receptor negative tumors may be more responsive to preoperative regimens, a survival benefit can be observed regardless of receptor status [2]. In this study a multivariate analysis hasn't indicated the significant value of the status of hormone receptor. This may be affected by addition of docetaxel. Dose response with anthracycline is also different between hormone receptor positive tumors and hormone receptor negative tumors. For ER negative tumors, higher anthracycline doses may be required for improved prognosis, however, for ER positive tumors it might not be necessary [29].

In this study, most tumors responded to docetaxel even if they did not respond to FEC. However, some tumors showed a response to the initial therapy but a lesser response to the second therapy. This underscores the need to include non-cross resistant treatments in the