PERGAMON

European Journal of Cancer 36 (2000) S4–S10

European Journal of Cancer

www.ejconline.com

Review

The impact of chemotherapy dose density and dose intensity on breast cancer outcome: what have we learned?

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Abstract

Optimising chemotherapy dose density and dose intensity are strategies aimed at improving outcomes in adjuvant therapy for patients with breast cancer. There are, in theory, at least five models allowing the delivery of a higher overall drug dose intensity. These are reviewed in this article and vary according to three main variables: the dose per course, the interval between doses and the total cumulative dose. Cyclophosphamide, anthracyclines and taxanes are among the most active agents for the treatment of breast cancer and, as such, they have been or are currently the focus of prospective, randomised clinical trials testing some of these dose-intensity models in the adjuvant setting. The results of recent trials suggest that anthracyclines, but not cyclophosphamide, are associated with better outcomes if used at higher doses per course and at higher cumulative doses. However, care has to be taken with premenopausal women where an increased dose of anthracycline per course but a reduced cumulative dose appears to produce a worse outcome. Moreover, decreasing the interval between doses, for anthracyclines and cyclophosphamide, does not seem to provide, so far, additional benefits for women with locally advanced breast cancer. This approach is not feasible with docetaxel, since an increase in dose density induces unwanted side-effects. These results represent our current state of knowledge, but clinical trials are being performed to evaluate further the effect of dose intensity, dose density and cumulative dose of key therapeutic agents on patient outcomes.

Keywords: Dose density; Dose intensity; Cumulative dose; Breast cancer; Anthracycline; Cyclophosphamide; Taxanes

1. Introduction

The use of adjuvant chemotherapy in breast cancer has been a successful addition to locoregional treatment, with the demonstration of a modest but sustained and significant impact on survival [1–3]. As a result, large numbers of women now receive adjuvant chemotherapy. However, it is still unclear which dosing strategy will achieve the best results. Several laboratory models, as well as retrospective analyses of clinical studies, have strongly suggested that intensified or higher-dose chemotherapy regimens could favourably influence the outcome of breast cancer treatment [4–8]. In this review five therapeutic models are described, that allow the delivery of a higher overall drug dose intensity (dose intensification — Table 1 [9]). These vary according to three main variables, including the dose per course, the interval between courses and the total cumulative dose. Each of these variables may indeed contribute to the treatment results.

Dose intensification refers to the amount of drug delivered per unit of time and is expressed in mg/m^2/week, whilst the cumulative dose delivered is a function of the total number of courses of chemotherapy given, as well as of the total dose per course. Dose densification is achieved by decreasing the intervals between doses.

The models fall into two broad categories. Models I–III allow the dose per course to be increased whilst the interval between courses is held constant. The difference between these models is the cumulative dose, which can be increased, decreased or remain unchanged. In models IV and V, the key variable is the interval between courses which is shortened. Hence, courses are administered on an accelerated schedule with a standard or reduced dose per course and, usually, a maintained cumulative dose.

It is important to establish which treatment model is effective for a particular chemotherapeutic drug, as escalating the dose and intensity inappropriately may not only fail to benefit the patient, but also cause additional

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0959-8049/00/$ - see front matter
PII: S0959-8049(99)00256-7

Table 1
Five therapeutic models to describe dose intensification, dose densification and changes in cumulative doses in the adjuvant chemotherapeutic treatment of breast cancer [9]

Model	Variable		
	Dose per course	Interval between doses	Cumulative dose
I	↑	–	–
II	↑	–	↑
III	↑	–	↓
IV	↓	↓	–
V	–	↓	–

toxicity and excessive costs. Cyclophosphamide, anthracyclines and taxanes are at present among the best chemotherapy options in the adjuvant setting. In the present review, the results of prospective, randomised clinical trials testing these drugs as adjuvant chemotherapy, in four of the five proposed models for dose intensification, are summarised and briefly discussed. These clinical trials (outlined in Table 2) evaluate the role of dose intensity, dose density and cumulative dose of key agents such as cyclophosphamide, doxorubicin and the taxanes (paclitaxel and docetaxel).

High-dose chemotherapy with stem cell support is currently being investigated and the results of several large studies in this area are awaited. In the meantime, high-dose chemotherapy and stem cell transplantation have no indication in breast cancer outside the setting of randomised, controlled clinical trials and are not discussed further in this paper.

2. Model I: increased dose per course with constant interval and unchanged cumulative dose

Four studies have been published assessing the effectiveness of this model in the adjuvant setting [10–13]. The only variable is the dose per course as the interval between doses and the cumulative dose both remain unchanged (Table 1).

2.1. Cyclophosphamide

Only one randomised trial has assessed the effect of cyclophosphamide as adjuvant therapy in this model (NSABP-22) [10]. A total of 2306 women, who were diagnosed with axillary node-positive breast cancer, were randomised to one of three treatment groups. They received an adjuvant chemotherapy regimen combining doxorubicin and cyclophosphamide. This consisted of four courses of doxorubicin (60 mg/m^2) combined with either cyclophosphamide 600 mg/m^2 on each occasion (group 1), or cyclophosphamide 1200 mg/m^2 on two occasions (group 2), or cyclophosphamide 1200 mg/m^2 on each occasion (group 3). Courses were administered every 3 weeks.

The cumulative doses administered in groups 1 and 2 were identical and, thus, the comparison between these two groups fits model I. A comparison between group 1 and group 3 fulfils the criteria for model II. At a 5-year follow-up there were no differences observed in disease-free and overall survival rates between groups 1 and 2 of this trial. Furthermore, the numbers of patients who developed acute myeloid leukaemia and myelodysplastic syndrome were similar (4 versus 6). This indicates that cyclophosphamide does not provide any additional benefit to the patient when its use fulfils the criteria for model I.

2.2. Anthracyclines

A clinical trial published in 1994 by the Cancer and Leukemia Group B (CALGB) randomised 1572 women with node-positive breast cancer to a CAF (cyclophosphamide, doxorubicin and 5-fluorouracil) regimen of either high-, intermediate- or low-dose intensity [11]. Identical cumulative doses of 5-fluorouracil, anthracycline and cyclophosphamide were administered in the high- and intermediate-dose intensity treatment groups. However, the low-dose intensity treatment group received only half of the total dose given to the other two groups. Importantly, the dose intensities for doxorubicin were

Table 2
Prospective randomised clinical trials testing adjuvant chemotherapy dose intensity models

Model tested	Drug under investigation		
	Cyclophosphamide (C)	Anthracyclines (A)	Taxanes (T) (±anthracyclines)
I	NSABP-22 groups 1 versus 2 [10]	CALGB 3-group CAF trial [11] SWOG combination versus sequential trial [13]	BIG combination versus sequential docetaxel trial
II	NSABP-22 groups 1 versus 3 [10]	Belgian 'EC' versus CMF trial [16] Bonneterre French 'FEC' trial [17] US Intergroup AC (followed or not by T) with three A dose levels [18]	
III		Brémond French trial [19]	
V		EORTC-NCIC-SAKK LABC trial [20] MIG-1 Italian trial [21]	US Intergroup 2×2 trial of 2- or 3-weekly AC×4→T×4 or A×3→T×3→C×3 (T = paclitaxel)

15, 10 and 7.5 mg/m^2/wk for the high-, intermediate- and low-dose intensity treatment groups, respectively.

At a median follow-up of 3.4 years, the women treated at a high- or intermediate-dose intensity had a significantly longer disease-free survival ($P < 0.001$) and overall survival ($P = 0.004$) than those treated at a low-dose intensity. Overall and disease-free survival rates in the high-dose intensity treatment group were higher than those in the intermediate group, but this difference did not reach statistical significance. This result is maintained at a median follow-up of 9 years [12]. Hence, changes in anthracycline dose intensity within this dose range do not seem to significantly affect treatment outcome unless the dose given falls below a minimum value. The important message from this trial is that it is detrimental to give adjuvant chemotherapy with suboptimal doses or low cumulative doses of anthracycline. Hence, there is a critical level of dosing which must be administered in order to improve patient survival.

Interestingly, the primary tumour blocks have been recovered from almost two-thirds of the patients who entered this trial and assessed for their expression of c-erbB-2. A retrospective analysis has identified that any additional survival benefits seen with high-dose anthracycline appear to be confined to patients who overexpress c-erbB-2, which is indicative of a biologically aggressive tumour [13]. This finding may have important implications for future treatment strategies; however, more studies are required to confirm this interesting observation.

The Southwest Oncology Group (SWOG) has recently completed an elegant clinical trial that compared two different strategies in the administration of adjuvant chemotherapy [14]. The more traditional concomitant delivery of anthracycline plus cyclophosphamide was compared with the sequential administration of both drugs (anthracycline followed by cyclophosphamide). Sequential treatment does offer some theoretical advantages over combination regimens or regimens that deliver only single courses of high-dose chemotherapy and an initial pilot trial demonstrated the feasibility of using this approach [14]. Patients with high-risk, node-negative breast cancer, or with up to three involved nodes, were randomised to either six courses of concurrent therapy with anthracycline plus cyclophosphamide or to four courses of anthracycline therapy followed sequentially by three high-dose cyclophosphamide courses. Importantly, the cumulative doses of both drugs (324 mg/m^2 anthracycline and 7200 mg/m^2 cyclophosphamide) and the treatment duration were identical for both groups, with the only variable being dose intensity.

The full results of this trial should be available within 2 years and may shed some light on the fundamental issue of sequential versus combination drug regimens in the treatment of breast cancer.

2.3. Taxanes

In a small-scale trial, patients with node-positive breast cancer were randomised to one of two treatment groups [15]. One group received adjuvant therapy with doxorubicin followed sequentially by docetaxel, whereas a second group received doxorubicin combined with docetaxel. The cumulative doses of both drugs were nearly identical between the two treatment groups and the only variable was dose intensity. This trial did not assess efficacy but determined the feasibility of these two dosing regimens (sequential or combined). The data suggested that when patients received sequential treatment rather than combination treatment there was a higher incidence of single drug-related side-effects and a lower incidence of neutropenic fever. However, the authors concluded that both treatment strategies are feasible in the adjuvant treatment of breast cancer.

The promising results of this preliminary trial have led to the development of the BIG 2-98 docetaxel trial. This has been undertaken to compare the efficacy of these two dosing regimens in patients with node-positive breast cancer, as well as the impact of docetaxel on outcome. The methodology proposed for this trial fits the criteria for model I. A total of 2300 patients will be enrolled over a period of 3 years and the study will compare the sequential dosing strategy and combination dosing strategy with two control groups. The trial will also administer cyclophosphamide, methotrexate and 5-fluorouracil to all groups (Fig. 1). It is planned that patients entering the sequential treatment group will have a higher dose intensity of docetaxel than in the combination group; however, the cumulative dose of the drug will be exactly the same between the two groups. As can be seen in Fig. 1, there are small differences in anthracycline dose-intensity and cumulative dose that may favour the 'control' arms over the experimental taxane-containing arms. The randomisation for this trial is unbalanced and patients have a 66% chance of entering the docetaxel-based treatment groups, compared with a 33% chance of entering one of the two control groups. Recruitment for this trial was initiated in June 1998 and it is hoped that the first results will be available in approximately 5 years.

3. Model II: increased dose per course and increased cumulative dose with constant course interval

Four studies have been published assessing the effectiveness of this model in the adjuvant setting [10,16–18]. Model II proposes two variables, with the dose per course being increased as well as the cumulative dose. However, the interval between doses remains unchanged (Table 1).

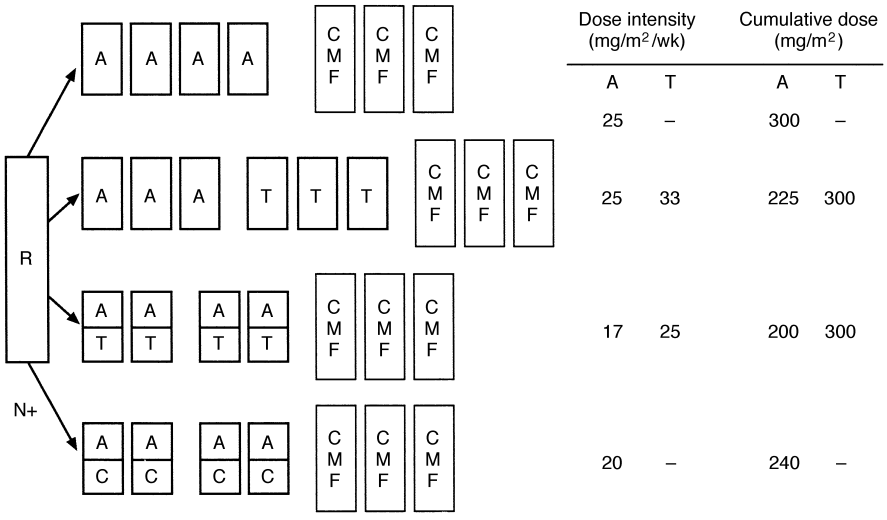

Fig. 1. Adjuvant treatment for breast cancer. Concurrent or sequential drug administration: the BIG 2-98 docetaxel trial. A, doxorubicin; T, docetaxel; C, cyclophosphamide; M, methotrexate; F, 5-fluorouracil.

3.1. Cyclophosphamide

As previously discussed, a comparison of the first and third treatment groups of the NSABP-22 clinical trial fits the criteria for this model [10]. Hence, the dose per course and the cumulative doses of cyclophosphamide are different between these two groups. At a median follow-up of 5-years, there were no differences observed in disease-free and overall survival between groups 1 and 3 of this trial.

3.2. Anthracyclines

A three-arm multicentre Belgian trial randomised 807 node-positive patients to receive either a standard-dose regimen of cyclophosphamide, methotrexate and 5-fluorouracil for six courses (the classical Bonadonna CMF regimen) or a standard-dose regimen of epirubicin plus cyclophosphamide for eight courses (EC; E = 60 mg/m^2, C = 500 mg/m^2 every 3 weeks) or a higher dose EC regimen for eight courses (E = 100 mg/m^2, C = 830 mg/m^2 every 3 weeks) [16]. Hence, the dose per course and the cumulative dose are increased. The trial was completed approximately 2 years ago and safety data at a median follow-up of 50 months are available.

During treatment, a higher incidence of cardiotoxicity was observed in patients who received a higher dose of epirubicin per course and an increased cumulative dose of anthracycline. Premature discontinuation of therapy, due to a decrease in left ventricular ejection fraction, occurred in 13% of these (EC higher-dose group) patients compared with 6% for patients in the standard-dose EC group. The incidence of clinical congestive heart failure was also more frequent in the group receiving higher-dose EC (2 versus 0.4%). Moreover, during follow-up, three cases of acute myeloid leukaemia have been reported in the higher-dose EC group. Efficacy data will be available within the next 6 months and it is hoped that a higher efficacy will counterbalance the increased toxicity of the high-dose EC group.

Evidence for improved outcomes with a higher dose of epirubicin has been presented in a recent French trial [17]. A total of 565 pre- and postmenopausal high-risk patients, having more than 4 involved axillary lymph nodes, or 1–3 positive nodes and either grade 2–3 tumours or a negative hormonal receptor status, were randomised to receive epirubicin 50 or 100 mg/m^2 in association with 5-fluorouracil (500 mg/m^2) and cyclophosphamide (500 mg/m^2), for six courses every 3 weeks (FEC50 versus FEC100). A total of 534 patients were available for analysis, and at a median follow-up of 5 years significant differences are emerging between the FEC50 and FEC100 treatment groups in disease-free survival and overall survival (Table 3).

In contrast to the promising results discussed above, the preliminary findings of a recent clinical trial suggest that no additional benefit is gained by increasing the dose of doxorubicin above 60 mg/m^2 [18]. A total of 3170 patients with node-positive breast cancer were randomised to receive cyclophosphamide (600 mg/m^2) plus doxorubicin 60, 75 or 90 mg/m^2. The treatments were given for four courses at 3-week intervals. After this initial treatment patients were randomised again to receive either no paclitaxel or paclitaxel 175 mg/m^2 for

Table 3
Survival rates of 534 patients receiving anthracycline at two different dose intensities [17]

Results at median 5-year follow up	FEC 50	FEC 100	*P*
Disease-free survival (%)	58	70	0.01
Overall survival (%)	70	80	0.002

four further courses. At a median follow-up of 22 months, no differences in the rates of disease-free survival or overall survival were seen in relation to the dose of doxorubicin, according to an interim analysis with 450 'events'. Statistical projection indicates that this result is extremely unlikely to change over a longer follow-up period. Interestingly, paclitaxel provided an additional benefit to patients and a multivariate analysis indicated a reduced rate of recurrence (22%) and death (26%) when compared with cyclophosphamide and doxorubicin alone.

3.3. Taxanes

To the best of our knowledge, no randomised clinical trials with taxanes which fulfil the criteria for model II have been reported so far.

4. Model III: increased dose per course, constant course interval, reduced cumulative dose

Only one trial has been published assessing the effectiveness of this model in the adjuvant setting [19]. Model III proposes that the dose per course is increased but the cumulative dose is decreased. However, the interval between doses remains unchanged (Table 1).

4.1. Anthracyclines

Brémond and colleagues randomised 595 premenopausal women with node-positive breast cancer to receive one of these regimens: (A) six courses of FEC50 (5-fluorouracil 500 mg/m^2 plus epirubicin 50 mg/m^2 plus cyclophosphamide 500 mg/m^2); (B) three courses of FEC50; or (C) three courses of FEC75 (epirubicin 75 mg/m^2 plus 5-fluorouracil and cyclophosphamide at the same doses as in the FEC50 group) [19]. The interval between courses remained unchanged (3 weeks). A comparison between groups C and A reveals that the dose intensity of epirubicin is increased by 50% in group C whilst the cumulative dose of the drug is reduced by 25%. This fits the criteria for model III. At a median follow-up of 5 years, no differences were found in disease-free survival or in overall survival (64.2% and 82.6% for A; 55.6% and 74.9% for B; 55.2% and 79.5% for C). However, in a multivariate analysis the planned number of courses was found to be a significant factor. Indeed, disease-free survival was positively influenced by treatment duration (64 versus 55 months for six and three treatment courses, respectively; $P = 0.031$). The authors concluded that FEC50 given for six courses was the best treatment option, but it is worth noting that the clinical trial may be open to criticism and the results have only been published in abstract form.

5. Model IV: reduced dose per course, shortened course interval, constant cumulative dose

Model IV proposes that the dose per course is reduced whilst the cumulative dose remains unchanged. In contrast to the previous models, dose densification is performed by decreasing the interval between doses (Table 1). Few, if any, clinical trials have been published which fulfil the criteria for this model. Moreover, with the availability of haematopoietic growth factors, it is usually possible to shorten the interval between doses without having to decrease the dose per course. Hence, model IV is not further discussed in this review.

6. Model V: constant dose per course, shortened course interval, constant cumulative dose

Model V proposes that both the dose per course and the cumulative dose are kept constant. However, dose densification is performed by decreasing the interval between doses (Table 1). Two clinical studies [20,21] have been reported, which assess the effectiveness of this model in the adjuvant setting.

6.1. Cyclophosphamide and anthracycline

The European Organization for the Research and Treatment of Cancer, the National Cancer Institute of Canada Clinical Trials Group and the Swiss Group for Clinical Cancer Research have joined forces to run a phase III trial in locally advanced breast cancer [20]. A total of 448 patients were randomised to receive either (A) intravenous epirubicin 60 mg/m^2 on days 1 and 8, oral cyclophosphamide 75 mg/m^2 on days 1–14 and intravenous 5-fluorouracil 500 mg/m^2 on days 1 and 8 for six courses (the known 'Canadian CEF' regimen); or (B) intravenous epirubicin 120 mg/m^2 on day 1, intravenous cyclophosphamide 830 mg/m^2 on day 1 and subcutaneous recombinant granulocyte colony-stimulating factor (G-CSF) 5 μg/kg/day on days 2–13 for six courses (EC + G-CSF). Courses were administered every 4 weeks for group A and every 2 weeks for group B. Hence, the duration of treatment was much shorter in group B (3 months versus 6 months). The primary outcome for this trial was progression-free survival; however, other important secondary outcomes included overall survival, response, toxicity, quality of life and cost-effectiveness.

During treatment 61% of patients in the EC + G-CSF group tolerated a full dose, delivered according to protocol, compared with only 29% in the CEF group. Moreover, the planned 2:1 dose intensity ratio for epirubicin and cyclophosphamide in the EC + G-CSF group was achieved. Therefore, dose densification using G-CSF is feasible and much easier to deliver than 'Canadian CEF' therapy. Moreover, there were fewer serious adverse events in the EC + G-CSF group.

Efficacy results are available at a relatively short median follow-up of 30 months. No differences in progression-free survival or overall survival are seen between the two treatment groups. Therefore, it can be concluded that dose densification with G-CSF is both safe and effective, but the efficacy achieved has so far not been demonstrated to be greater than with standard therapy. The cost-effectiveness of this intense treatment approach is currently being analysed and most likely will determine the place of this regimen in clinical practice.

Of note, this trial was performed in a subset of breast cancer patients who had locally advanced disease and, hence, the results may not provide a final answer to the relative merits of dose intensification/densification compared with standard treatments. It is conceivable that this strategy may produce better results in patients with early breast cancer. A trial performed in Italy has recently attempted to address this question [21]. A total of 1214 patients were randomised to receive a CEF regimen (cyclophosphamide 600 mg/m^2, epirubicin 60 mg/m^2 and 5-fluorouracil 600 mg/m^2) over a period of either 3 weeks or 2 weeks with the support of recombinant G-CSF. The only dose intensity variable affected by this trial was the dose density, which was increased by 50% in the accelerated treatment regimen. The use of an equivalent dose of 5-fluorouracil in both treatment groups may offer some advantages over the previous trial design, but it is unfortunate that a relatively low dose of epirubicin was selected. Efficacy results for this trial should be available within 2 years.

6.2. Taxanes

To date, no full-scale studies have been performed with any taxanes that fulfil the criteria for this model. However, a pilot feasibility trial in breast cancer patients, prior to the BIG 2-98 docetaxel trial, administered the same doses of doxorubicin and docetaxel sequentially, either every 3 weeks or 2 weeks with recombinant G-CSF support. Interestingly, an unacceptable rate of premature withdrawals, due to toxic drug effects, was observed in patients receiving accelerated treatment. As a result, the accelerated treatment regimen was abandoned and not incorporated in the design of the BIG 2-98 docetaxel trial.

The effect of dose densification on adjuvant chemotherapy outcome is going to be assessed by the CALGB. The next US Intergroup 2×2 trial has two dosing regimens which will be administered either every 3 weeks or every 2 weeks with recombinant G-CSF support. Patients will receive doxorubicin in combination with cyclophosphamide for four courses. This will be followed by paclitaxel for another four courses. Alternatively, patients will receive the sequential administration of three courses each of doxorubicin, paclitaxel and cyclophosphamide. It is hoped that this trial will provide important information about the suitability of dose densification during adjuvant chemotherapy with paclitaxel, doxorubicin and cyclophosphamide.

7. Conclusions

From the results of the randomised clinical trials discussed in this review, a number of conclusions and recommendations can be made that may help optimise adjuvant therapy for patients with breast cancer:

- Suboptimal doses of chemotherapy are associated with reduced survival. Lower doses per course of anthracycline are associated with a low overall survival [11]. However, higher doses of cyclophosphamide per course (model I) and higher cumulative doses (model II) do not appear to benefit the patient [10].
- Increased doses of anthracycline may benefit patients with biologically aggressive tumours [11,15]. A retrospective analysis has suggested that any additional survival benefits seen with high-dose anthracycline are restricted to patients who overexpress c-*erbB*-2.
- Larger doses of epirubicin may be more beneficial in high-risk patients [17]. The results from one trial suggest that a higher dose of epirubicin per course, with an increased cumulative dose, increase patient survival (model II).
- The duration of adjuvant chemotherapy may be important in premenopausal women [19]. Care should be taken when increasing the dose per course if it is planned to decrease the number of courses. A worse outcome may be obtained with small increases in dose per course and a reduced cumulative dose (model III).
- Dose densification with epirubicin and cyclophosphamide does not appear to significantly improve patient survival in locally advanced breast cancer, according to the early results of one randomised Intergroup trial [20]. However, toxicity can be improved with recombinant G-CSF (model V).
- Dose densification with docetaxel leads to reduced tolerability and unwanted side-effects. However, a planned dose densification clinical trial with paclitaxel may help to determine its suitability in this treatment regimen.

Finally, in optimising chemotherapy with cyclophosphamide, anthracyclines and taxanes for breast cancer there are still several important pieces of information that are, as yet, unknown. These include the long-term impact of anthracycline dose intensification, dose densification or increased cumulative dose on outcome of

early breast cancer; the long-term impact of paclitaxel dose densification or cumulative dose on outcome of early breast cancer, and the impact of the selection of an appropriate patient subset (for example, HER-2/neu+) on the therapeutic index of chemotherapy dose intensification. It is hoped that some of these questions will be answered within the next 2 or 3 years.

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