Adjuvant capecitabine in combination with docetaxel and cyclophosphamide plus epirubicin for breast cancer: an open-label, randomised controlled trial

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Summary

Background Standard adjuvant chemotherapy regimens for patients with moderate-to-high-risk early breast cancer typically contain a taxane, an anthracycline, and cyclophosphamide. We aimed to investigate whether integration of capecitabine into such a regimen enhances outcome.

Methods In this open-label trial, we randomly assigned (centrally by computer; stratified by node status, HER2 status, and centre) 1500 women with axillary node-positive or high-risk node-negative breast cancer to either three cycles of capecitabine and docetaxel followed by three cycles of cyclophosphamide, epirubicin, and capecitabine (capecitabine group, n=753), or to three cycles of docetaxel followed by three cycles of cyclophosphamide, epirubicin, and fluorouracil (control group, n=747). The primary endpoint was recurrence-free survival. A planned interim analysis was done after 3 years' median follow-up. Efficacy analyses were by modified intention to treat. The study is registered with ClinicalTrials.gov, number NCT00114816.

Findings Two patients in each group were excluded from efficacy analyses because of withdrawal of consent or distant metastases. After a median follow-up of 35 months (IQR 25·5–43·6), recurrence-free survival at 3 years was better with the capecitabine regimen than with control (93% *vs* 89%; hazard ratio 0·66, 95% CI 0·47–0·94; p=0·020). The capecitabine regimen was associated with more cases of grade 3 or 4 diarrhoea (46/740 [6%] *vs* 25/741 [3%]) and hand-foot syndrome (83/741 [11%] *vs* 2/741 [<1%]) and the control regimen with more occurrences of grade 3 or 4 neutropenia (368/375 [98%] *vs* 325/378 [86%]) and febrile neutropenia (65/741 [9%] *vs* 33/742 [4%]). More patients discontinued planned treatment in the capecitabine group than in the control group (178/744 [24%] *vs* 23/741 [3%]). Four patients in the capecitabine group and two in the control group died from potentially treatment-related causes.

Interpretation The capecitabine-containing chemotherapy regimen reduced breast cancer recurrence compared with a control schedule of standard agents. Capecitabine administration was frequently discontinued because of adverse effects.

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Introduction

Adjuvant chemotherapy consisting of an alkylating agent, an anthracycline, and a taxane is typically administered for early breast cancer, although the regimens used can vary considerably.[1–3] Results from a few large randomised trials and a meta-analysis suggest that addition of a taxane to adjuvant regimens containing an anthracycline improves disease-free and overall survival.[4–6] Despite such advances in chemotherapy, many women diagnosed with early breast cancer still eventually succumb to the disease.

Capecitabine is an oral prodrug of fluorouracil, which has been used in the treatment of advanced breast cancer for a few decades. After absorption, it is metabolised in the liver and in cancerous tissue. The final step of conversion to fluorouracil is catalysed by thymidine phosphorylase, which is present in high amounts in breast tumours.[7] Administration of docetaxel, paclitaxel, or cyclophosphamide boosts the concentration in tumour tissue of thymidine phosphorylase in xenograft models, suggesting that these agents might act in a synergistic manner with capecitabine.[8–10] In women treated with docetaxel, or doxorubicin or epirubicin given with cyclophosphamide before surgery for breast cancer, thymidine phosphorylase was greatly stimulated in both tumour and stromal cells.[11] Women with advanced breast cancer treated with an anthracycline had augmented survival when randomised to receive docetaxel plus capecitabine compared with those assigned to docetaxel alone.[12]

Since thymidine phosphorylase production in cancer tissue is important for capecitabine activity, in the current study (the Finland capecitabine trial [FinXX]), we administered capecitabine with agents that might enhance activity of this enzyme in tumours. Capecitabine

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was given for a total of 18 weeks to provide prolonged exposure, which might facilitate eradication of cancer cells with a slow cell-proliferation rate. Here, we report findings from the planned interim efficacy analysis of the trial.

Methods

Patients

We undertook a randomised, controlled, open-label, phase 3 trial in 15 Finnish hospitals and five Swedish hospitals. We deemed women eligible for the study if they had histologically confirmed invasive breast cancer at medium-to-high risk of recurrence, defined as either: regional node-positive disease (isolated tumour-cell clusters <0·2 mm in diameter were not judged a metastasis); or node-negative disease with primary tumour diameter greater than 20 mm and negative progesterone receptor assay (usually classified as staining of <10% of cancer cells).[13,14] Other eligibility criteria included: age 18–65 years; WHO performance score 0 or 1 (on a scale of 0–5, with a score of 5 indicating death); interval of 12 weeks or fewer between surgery and randomisation; and normal renal, cardiac, and hepatic function (serum alanine aminotransferase ≤1·5× upper limit of normal; alkaline phosphatase ≤2·5× upper limit of normal; bilirubin ≤1·0× upper limit of normal). Main exclusion criteria were: presence of distant metastases; node-negative mucinous, papillary, medullary, or tubular disease; clinically significant cardiac disease; and previous neoadjuvant chemotherapy.

For the **trial protocol** see http://ctep.cancer.gov

The trial protocol was approved by independent ethics committees and by the medical authorities. All patients provided written informed consent. Study safety was monitored by an independent data safety monitoring committee.

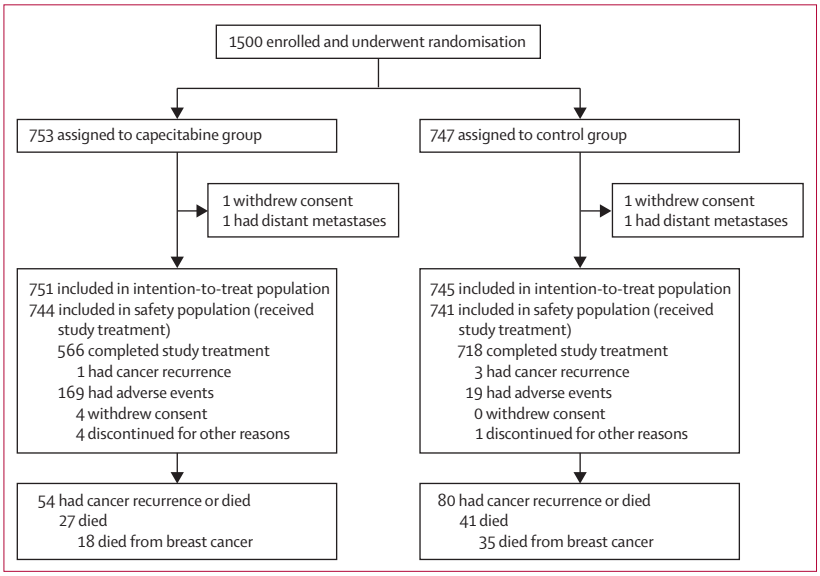

Figure 1: **Trial profile**

Randomisation and masking

We randomly assigned patients (centrally and with computer-assisted masking), in a 1:1 ratio, to receive either a capecitabine-containing chemotherapy regimen (capecitabine group) or a control schedule. A physicist otherwise uninvolved in the study generated the randomisation code (M Tenhunen, Department of Oncology, Helsinki University Central Hospital). We did randomisation with permutated blocks: block size (two, four, or six) varied at random. We stratified women at random allocation according to the number of axillary lymph nodes that contained cancer (≤3 *vs* >3), HER2 status (negative *vs* positive; ascertained by either immunohistochemistry or in-situ hybridisation), and centre. A trained study nurse communicated the randomisation result to study sites by fax.

Procedures

Patients allocated to the capecitabine group received capecitabine (900 mg/m² twice a day, days 1–15) plus docetaxel (60 mg/m² as a 1-h intravenous infusion on day 1 of every 3-week cycle), followed by cyclophosphamide (600 mg/m² on day 1), epirubicin (75 mg/m² on day 1), and capecitabine (900 mg/m² twice a day, days 1–15, every 3 weeks). Those assigned control received docetaxel (80 mg/m² as a 1-h intravenous infusion on day 1 of every 3-week cycle) followed by cyclophosphamide (600 mg/m²), epirubicin (75 mg/m²), and fluorouracil (600 mg/m²), all administered on day 1 of every 3-week cycle. In the capecitabine group, the first capecitabine dose of every cycle was given in the evening of day 1 and the last dose was administered on the morning of day 15, followed by a 7-day rest period.

We gave patients oral corticosteroids at standard doses at the time of docetaxel infusions. We permitted haemopoietic growth factor support for symptomatic neutropenia but did not allow prophylactic use. We administered treatment for six cycles (three cycles of each regimen) in both groups, unless individuals had disease recurrence or intolerable toxic effects. Patients received locoregional radiotherapy according to the institution's practice after completion of chemotherapy. Those with steroid hormone receptor-positive disease received adjuvant endocrine therapy for 5 years. We gave tamoxifen (20 mg/day) to individuals deemed premenopausal before the start of chemotherapy, whereas postmenopausal women received anastrozole (1 mg/day). Hormonal therapy was initiated within 2 months of completion of chemotherapy.

We implemented a dose-modification scheme in the event of grade 2–4 non-haematological toxic effects (graded according to the National Cancer Institute's common terminology criteria for adverse events, version 3.0). If a patient had a grade 2 event, we interrupted treatment and resumed it at the same dose once the toxic effect had resolved. If they developed a second grade 2 event, or their first grade 3 event, we

stopped chemotherapy and, after resolution to grade 0–1, resumed it at 80% of the starting dose. If a third grade 2 event arose, we continued treatment at 60% of the starting dose. For a fourth grade 2 event, the regimen was discontinued. If an individual had a second grade 3 event or any grade 4 toxic effect, we usually stopped treatment. If the investigator attributed an adverse event to one drug, then only that agent was dose-reduced. We decreased the doses of all drugs by 20% for febrile neutropenia or grade 3–4 neutropenia with infection. When scheduled treatment was discontinued for toxic effects, we replaced agents as follows: capecitabine and docetaxel by cyclophosphamide, epirubicin, and capecitabine, or cyclophosphamide, epirubicin, and fluorouracil; single-agent docetaxel by cyclophosphamide, epirubicin, and fluorouracil; and cyclophosphamide, epirubicin, and capecitabine by cyclophosphamide, epirubicin, and fluorouracil, or cyclophosphamide and epirubicin.

We regarded staging examinations (chest CT or radiography; bone scan; and abdominal CT, MRI, or ultrasound) as mandatory at screening for patients with four or more positive axillary nodes,[15,16] but these procedures were undertaken at the discretion of the investigator for all other patients. We did laboratory tests (blood-cell count and serum chemistry) within the 3 days preceding the planned start of every chemotherapy cycle. We recorded all events arising during study treatment or within 28 days of the last dose of chemotherapy. We scheduled follow-up of study participants for a minimum of 5 years after randomisation.

The primary endpoint was recurrence-free survival, defined as the time between randomisation and date of diagnosis of invasive breast cancer recurrence, or death if the patient died before cancer recurrence. Secondary endpoints were overall survival, defined as the time from randomisation to death, and treatment safety.

Statistical analysis

We estimated the recruitment period to be 3·5 years. We amended the protocol on Nov 23, 2007, to include an interim analysis to assess treatment safety and early efficacy. We expected that recurrence-free survival would rise from 83·0% to 88·5% (hazard ratio 0·65) after median follow-up of 5 years. Based on this assumption, a total of 205 events and 1500 patients were needed to achieve 80% power, assuming a 3% annual dropout rate, when α=0·028 (two-sided). To maintain a significance level of 5%, we set the significance level in interim and final analyses at 0·028.[17] The interim analysis had 80% power to detect an improvement from 89·0% to 93·5% (HR 0·58) after median follow-up of 3 years in 1500 patients (α=0·028, two-sided testing) and when about 120 recurrences had happened. We calculated sample sizes with nQuery Advisor version 6.0.

We did efficacy analyses by modified intention to treat. Exploratory subgroup analyses (by centre, [number of axillary nodes [≤3 or >3], oestrogen receptor status [positive or negative], and HER2 status) were defined in the statistical plan for the interim analysis (approved before the analysis was undertaken on Nov 6, 2008), but not in the original study protocol. The safety population included all patients who received at least one dose of any study drugs.

	Capecitabine group (N=753)	Control group (N=747)
Age (years)	52 (26–65)	53 (27–65)
Weight (kg)	70 (45–144)	69 (43–140)
Menopausal status		
Premenopausal*	331 (44%)	321 (43%)
Postmenopausal	422 (56%)	426 (57%)
WHO performance status		
0	663 (88%)	664 (89%)
1	90 (12%)	83 (11%)
Diameter of primary tumour		
≤20 mm	322 (43%)	346 (46%)
21–50 mm	389 (52%)	363 (49%)
>50 mm	40 (5%)	37 (5%)
Not available	2 (<1%)	1 (<1%)
Tumour classification†		
pT1	314 (42%)	340 (46%)
pT2	389 (52%)	351 (47%)
pT3	40 (5%)	41 (6%)
pT4	8 (1%)	14 (2%)
Not available	2 (<1%)	1 (<1%)
Positive axillary lymph nodes		
0	86 (11%)	71 (10%)
1–3	461 (61%)	466 (62%)
>3	206 (27%)	210 (28%)
Histological grade		
1	86 (11%)	80 (11%)
2	362 (48%)	351 (47%)
3	300 (40%)	312 (42%)
Not available	5 (1%)	4 (1%)
Histological type		
Ductal	569 (76%)	566 (76%)
Lobular	138 (18%)	118 (16%)
Other	46 (6%)	63 (8%)
Oestrogen receptor status		
Positive	581 (77%)	565 (76%)
Negative	172 (23%)	182 (24%)
Progesterone receptor status		
Positive	478 (63%)	456 (61%)
Negative	275 (37%)	291 (39%)
HER2 status		
Positive	146 (19%)	139 (19%)
Negative	607 (81%)	608 (81%)

Data are median (range) or number (%). *Menstrual periods within 6 months before starting chemotherapy. †Tumours with postsurgical features defined as in the 2002 International Union Against Cancer's *TNM Classification of Malignant Tumours, 6th edn*.

Table 1: **Baseline characteristics for all patients**

	Capecitabine group (N=751)	Control group (N=745)	Hazard ratio (95% CI)	p*
Any recurrence or death	54 (7%)	80 (11%)	0·66 (0·47–0·94)	0·020
Distant recurrence	43 (6%)	72 (10%)	0·64 (0·45–0·91)	0·014
Local recurrence	5 (1%)	11 (1%)	0·50 (0·16–1·61)	0·25
Death from any cause	27 (4%)	41 (6%)	0·66 (0·40–1·07)	0·089
Death from breast cancer	18 (2%)	35 (5%)	0·51 (0·29–0·90)	0·021
Death from other cause	9 (1%)†	6 (1%)‡	1·50 (0·53–4·20)	0·45

Data are number of events (%). *Calculated with unadjusted Cox proportional-hazards model. †Suicide and depression; suicide and intoxication; unknown; unknown (breast cancer unlikely); pulmonary embolus; septicaemia, colitis, and multiorgan failure; acute myocardial infarction; alcohol intoxication; cardiac and pulmonary failure. ‡Pulmonary embolus (n=2); septicaemia; septic shock; amyotrophic lateral sclerosis; subdural haemorrhage.

Table 2: **Breast cancer recurrence and survival in the modified intention-to-treat population**

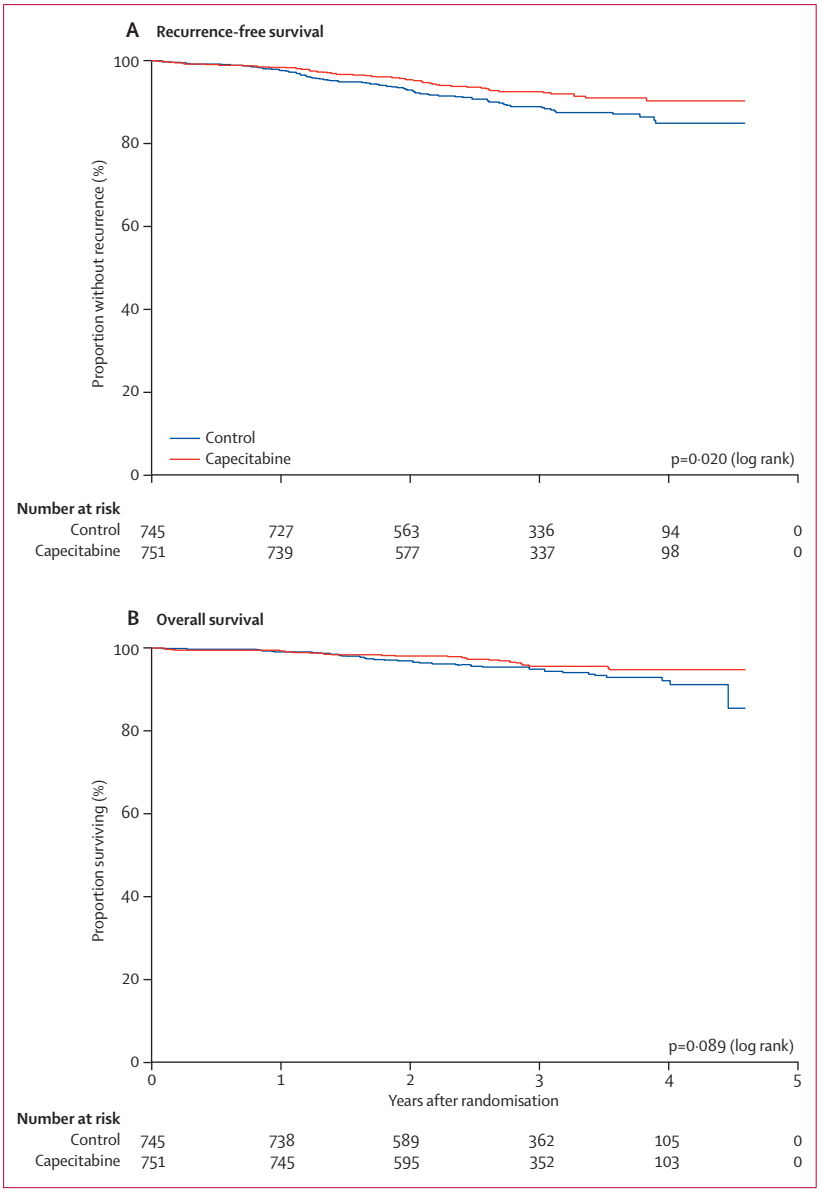

Figure 2: **Kaplan-Meier estimates of 3-year recurrence-free and overall survival in the modified intention-to-treat population**

We analysed frequency tables with Fisher's exact test or the χ^2 test, and we compared age and weight distributions with the *t* test. To compare survival between groups, we used the Kaplan-Meier life-table method and an unadjusted Cox proportional-hazards model; we implemented the log-rank test to confirm the robustness of the analysis. We undertook subgroup analyses by inclusion in the Cox model of treatment group, the subgroup variable, and their interaction. All p values are two-sided and not adjusted for multiple testing. We did statistical analyses with SAS version 8.2 for Windows. This study is registered with ClinicalTrials.gov, number NCT00114816.

Role of the funding source

The study was designed by HJ in collaboration with members of the Finnish Breast Cancer Group. The study protocol was written by the authors and Roche. The sponsors had no access to the study database. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Jan 27, 2004, and May 29, 2007, 1500 patients were recruited from 15 Finnish centres (n=1199) and five Swedish centres (n=301). Four women were excluded from the modified intention-to-treat population (two withdrew informed consent before they received study treatments, two had overt distant metastases at the time of study entry; figure 1). Baseline characteristics were balanced between groups (table 1). 90% of patients had node-positive cancer, and 19% had HER2-positive disease.

The study protocol was amended in May, 2005, to allow administration of adjuvant trastuzumab for HER2-positive disease. Subsequently, 96 (13%) of 753 patients assigned to the capecitabine group and 83 (11%) of 747 allocated control were given trastuzumab. Respectively, 56 (7%) and 50 (7%) women received single-agent trastuzumab after discontinuation of chemotherapy for up to 12 months, 24 (3%) and 21 (3%) received trastuzumab concomitantly with docetaxel only, and 16 (2%) and 12 (2%) received trastuzumab concomitantly with docetaxel plus single-agent trastuzumab for up to 12 months after chemotherapy. Adjuvant endocrine therapy was given to 592 (79%) and 575 (77%) patients after completion of chemotherapy in the capecitabine and the control groups, respectively. Tamoxifen, anastrozole, and other hormonal treatments were administered, respectively, to 325 (43%), 316 (42%), and 29 (4%) patients assigned to the capecitabine group, and to 287 (38%), 328 (44%), and 27 (4%) women allocated to the control group.

At the time of data lock (Aug 31, 2008), median follow-up was 35 months (IQR 25·5–43·6). 134 events (deaths, distant or local relapses) had happened, 54 (7%) in the capecitabine group and 80 (11%) in the control group, which triggered the interim analysis. The hazard ratio for recurrence-free survival favoured the capecitabine-

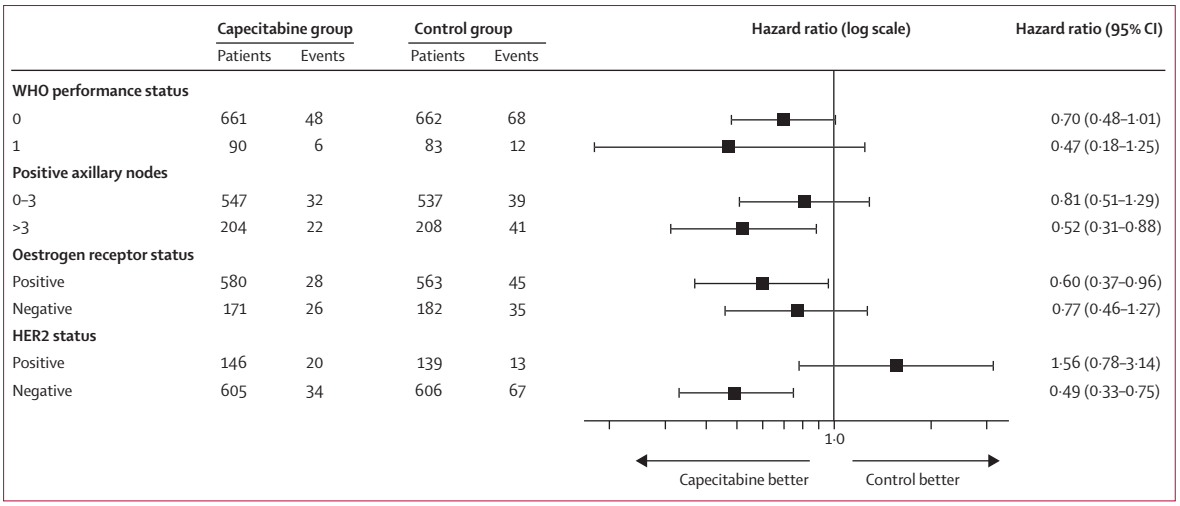

Figure 3: **Forest plot of exploratory subgroup analyses for recurrence-free survival**

containing regimen (0·66, 95% CI 0·47–0·94; p=0·020; table 2; figure 2). In the capecitabine group, three women developed invasive contralateral breast cancer and six had other cancers, compared with two and eight patients, respectively, in the control group. The proportions of women developing these cancers were similar (1·2% *vs* 1·3%, respectively). Disease-free survival (which includes invasive contralateral breast cancers and second cancers) was longer in the capecitabine group than in the control group (0·68, 0·49–0·94; p=0·020). When patients treated with trastuzumab were excluded from the main analysis, the hazard ratio for recurrence-free survival still favoured the capecitabine-containing regimen (0·64, 0·44–0·91; p=0·014).

In exploratory subgroup analyses, recurrence-free survival was better in the capecitabine group than in the control group, with the exception of patients with HER2-positive disease (figure 3). In this analysis, the interaction between treatment and HER2 status was significant (p=0·0049), whereas interactions between treatment and the other subgroups shown in figure 3 were not (p>0·10).

The safety profiles of the two regimens differed. Patients who received capecitabine had more occurrences of grade 3 or 4 hand-foot syndrome, diarrhoea, nail changes, and stomatitis than did those in the control group, whereas neutropenia, febrile neutropenia, infection with neutropenia, amenorrhoea, and myalgia were more frequent in the control group (table 3). Four patients in the capecitabine group died during chemotherapy from possibly treatment-related causes (septic colitis; suicide; myocardial infarction; unknown cause [suspected cardiac arrhythmia]) and two died in the control group (pulmonary arterial embolism; septicaemia).

All six planned cycles of chemotherapy were administered to 566 (75%) individuals assigned the capecitabine-containing regimen compared with 718 (96%) allocated control. Discontinuation of scheduled treatment was most frequent in the capecitabine group (178 [24%] *vs* 23 [3%] assigned control; p<0·0001). Of those allocated to the capecitabine group, 98 (13%) discontinued during docetaxel and capecitabine cycles and a further 80 (11%) during cyclophosphamide,

	N (capecitabine/ control	Capecitabine group (N=744)		Control group (N=741)		p*
		Grade 1 or 2	Grade 3 or 4	Grade 1 or 2	Grade 3 or 4	
Any event†	744/741	38 (5%)	705 (95%)	27 (4%)	714 (96%)	0·20
Alopecia	740/740	720 (97%)	NA	738 (100%)	NA	NA
Neutropenia‡	378/375	33 (9%)	325 (86%)	7 (2%)	368 (98%)	<0·0001
Amenorrhoea§	732/729	102 (14%)	597 (82%)	82 (11%)	635 (87%)	0·0039
Fatigue	740/741	601 (81%)	100 (14%)	619 (84%)	105 (14%)	0·76
Infection with neutropenia	742/741	39 (5%)	43 (6%)	52 (7%)	92 (12%)	<0·0001
Hand-foot syndrome	741/741	510 (69%)	83 (11%)	266 (36%)	2 (<1%)	<0·0001
Febrile neutropenia	742/741	NA	33 (4%)	NA	65 (9%)	<0·0008
Myalgia	740/741	455 (61%)	14 (2%)	549 (74%)	58 (8%)	<0·0001
Pain	741/741	556 (75%)	54 (7%)	587 (79%)	41 (6%)	0·20
Diarrhoea	740/741	402 (54%)	46 (6%)	413 (56%)	25 (3%)	0·011
Nail changes	741/741	547 (74%)	36 (5%)	611 (82%)	4 (1%)	<0·0001
Infection, no neutropenia	742/741	225 (30%)	33 (4%)	218 (29%)	38 (5%)	0·55
Stomatitis	741/741	599 (81%)	31 (4%)	588 (79%)	12 (2%)	0·0048
Dyspnoea	741/741	354 (48%)	22 (3%)	371 (50%)	31 (4%)	0·26
Vomiting	740/741	214 (29%)	11 (1%)	284 (38%)	16 (2%)	0·44
Nausea	740/741	625 (84%)	16 (2%)	678 (91%)	8 (1%)	0·10
Thrombocytopenia‡	379/376	117 (31%)	6 (2%)	110 (29%)	1 (<1%)	0·12
Elevation of serum alanine transferase	740/739	334 (45%)	8 (1%)	245 (33%)	5 (1%)	0·58

Data are number of patients (%). NA=not applicable. *p values calculated with Fisher's exact test for differences between treatment groups with grade 3 or 4 adverse events. †Grade 3 or 4 adverse events are listed if they were reported in 1% or more of all patients. ‡From nadir counts; counts did not need to be measured in all study centres. §Includes premenopausal and postmenopausal patients.

Table 3: **Adverse events in safety population**

epirubicin, and capecitabine cycles. In the control group, 16 (2%) individuals discontinued during docetaxel monotherapy and seven (1%) stopped during cyclophosphamide, epirubicin, and fluorouracil. Adverse events were the most usual reason for treatment discontinuation in both groups.

58 (8%) and 139 (19%) patients assigned to the capecitabine and control groups, respectively, had the docetaxel dose reduced because of toxic effects. 319 (43%) women took less than the scheduled starting dose of capecitabine on one or more occasions owing to toxic effects or for other reasons. Including replaced cycles, most patients (1461 [98%]) received a total of six cycles.

Discussion

Our findings showed enhanced recurrence-free survival for patients who received a regimen containing capecitabine in addition to docetaxel, epirubicin, and cyclophosphamide compared with women who received docetaxel, epirubicin, cyclophosphamide, and fluorouracil. Overall survival data from FinXX are not yet mature, but we noted the hazard ratio for overall survival was similar to that for recurrence-free survival. Single-agent capecitabine has been compared with combination chemotherapy in the adjuvant treatment of elderly patients with breast cancer,[18] but to our knowledge, FinXX is the first adjuvant trial to report efficacy of capecitabine in combination with other agents for treatment of early breast cancer.

Our results suggest that integration of capecitabine upfront with potentially synergistic chemotherapeutic agents and into several cycles might be an effective treatment strategy. This hypothesis is supported by data of randomised studies undertaken in the neoadjuvant setting.[19,20] Inclusion of capecitabine in the taxane and anthracycline-containing parts of the regimen distinguishes FinXX from other trials investigating incorporation of capecitabine into adjuvant regimens. Findings of a randomised trial in the neoadjuvant setting indicated a 20% pathological complete response rate with cyclophosphamide, epirubicin, and capecitabine compared with 13% in patients receiving fluorouracil, epirubicin, and cyclophosphamide.[21]

The enhanced efficacy we recorded in the capecitabine arm was gained at the cost of increased diarrhoea and hand-foot syndrome, although febrile neutropenia was less frequent than with the control regimen, which is probably attributable to the reduced docetaxel dose. Two women in the capecitabine group died from cardiac causes possibly related to study treatment. Cardiotoxicity is a known effect of the fluoropyrimidine class of chemotherapeutic agents, and individuals receiving fluoropyrimidines need to be monitored for symptoms and signs of these cardiac effects, although cardiotoxicity might be less typical with capecitabine than with infused fluorouracil.[22] In our study, most patients who interrupted capecitabine administration could continue treatment with other study agents and complete six cycles of chemotherapy.

The control arm in our study represents a regimen frequently used in Finland and Sweden, which is not dissimilar to the types of regimen administered in many other countries.[8,23,24] Docetaxel 80 mg/m² is a lower dose than the 100 mg/m² regarded as standard in some regions. We selected the dose of 80 mg/m² for two reasons: (1) on the basis of toxic effects recorded with docetaxel 100 mg/m² in the FinHer trial, leading to protocol modification;[25] and (2) because no difference in time-to-progression or survival was recorded between starting doses of 75 mg/m² and 100 mg/m² in the intention-to-treat population of a randomised trial of docetaxel as second-line therapy for advanced breast cancer.[26] Adjuvant docetaxel administered at either 80 mg/m² or 100 mg/m² at 3-week intervals before three cycles of fluorouracil, epirubicin, and cyclophosphamide for early breast cancer might show similar survival.[27] The docetaxel dose of 60 mg/m² administered in the capecitabine group is fairly low, but this amount was effective in combination with other agents and rarely needed to be reduced.

Our results suggest that efficacy is maintained when capecitabine is given at a dose of 900 mg/m² instead of 1250 mg/m² twice a day in combination with docetaxel,[12] and these data are consistent with analyses of capecitabine dose-reduction in metastatic disease.[28] The hypothesis that an even lower capecitabine dose could be appropriate is being tested in an ongoing US Oncology Group trial, in which capecitabine is given at a dose of 825 mg/m² concomitantly with docetaxel.

Retrospective analysis of one study suggests that docetaxel plus capecitabine might be more effective than docetaxel alone for treatment of oestrogen receptor-positive advanced breast cancer in particular, but this idea needs confirmation.[29] Chemotherapy-induced amenorrhoea is unlikely to account for the high efficiency of capecitabine combinations, because persistent amenorrhoea was less frequent in women allocated to the capecitabine group compared with those assigned control.

In conclusion, risk of breast-cancer recurrence was reduced by incorporation of capecitabine into a regimen containing a taxane and anthracycline. The effect was substantial and could be comparable to or greater than that achieved with the introduction of taxanes to adjuvant treatment of early breast cancer.[6,30] However, this possibility needs to be confirmed in ongoing trials of adjuvant capecitabine. Integration of capecitabine was associated with frequent discontinuation of planned chemotherapy, but most patients could tolerate all six scheduled cycles. Studies that focus on further refinement of the current chemotherapy regimen are warranted.

Contributors

HJ, P-LK-L, AJ-V, MT, PA, PB, and HL had the idea for and designed the study. HJ and P-LK-L did the literature search. HJ, P-LK-L, AJ-V, MT, RA, RK, JA, PA, AH, OP, LH, LN, KV, GN, S-LL, KL, MP, PP, PN, VK, PB, and HL provided study materials and obtained data. HJ, P-LK-L, JA, AH, PB, and ML analysed and interpreted data. HJ, P-LK-L, OP, PB, and HL wrote the report. HJ, RH, and HL provided administrative support.

Conflicts of interest

P-LK-L, MP, PP, and PB have received honoraria or consulting fees from Roche. HJ, P-LK-L, and PB have received honoraria or consulting fees from Sanofi-Aventis. MP has received a travel grant from Sanofi-Aventis. All other authors declared no conflicts of interest.

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