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CLINICAL TRIAL

Dose intensity in anthracycline-based chemotherapy for metastatic breast cancer: mature results of the randomised clinical trial ANZ 9311

Stephen. P. Ackland[1,4,7] · V. Gebski[2] · N. Zdenkowski[1,4,7] · A. Wilson[4] · M. Green[3] · S. Tees[4] · H. Dhillon[2] · G. Van Hazel[5] · J. Levi[6] · R. J. Simes[2] · J. F. Forbes[1,4,7] · A. S. Coates[2] · for Breast Cancer Trials Ltd (formerly known as the Australia and New Zealand Breast Cancer Trials Group)

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Abstract

Purpose The separate impacts of dose and dose intensity of chemotherapy for metastatic breast cancer remain uncertain. The primary objective of this trial was to compare a short, high-dose, intensive course of epirubicin and cyclophosphamide (EC) with a longer conventional dose regimen delivering the same total dose of chemotherapy.

Methods This open label trial randomised 235 women with metastatic breast cancer to receive either high-dose epirubicin 150 mg/m^2 and cyclophosphamide 1500 mg/m^2 with filgrastim support every 3 weeks for 3 cycles (HDEC) or standard dose epirubicin 75 mg/m^2 and cyclophosphamide 750 mg/m^2 every 3 weeks for 6 cycles (SDEC). Primary outcomes were time to progression, overall survival and quality of life.

Results In 118 patients allocated HDEC 90% of the planned dose was delivered, compared to 96% in the 117 participants allocated SDEC. There were no significant differences in the time to disease progression (5.7 vs. 5.8 months, $P=0.19$) or overall survival (14.5 vs. 16.5 months, $P=0.29$) between HDEC and SDEC, respectively. Patients on HDEC reported worse quality of life during therapy, but scores improved after completion to approximate those reported by patients allocated SDEC. Objective tumour response was recorded in 33 (28%) on HDEC and 42 patients (36%) on SDEC. HDEC produced more haematologic toxicity.

Conclusion For women with metastatic breast cancer, disease progression, survival or quality of life were no better with high-dose intensity compared to standard dose EC chemotherapy.

Australian Clinical Trials Registry registration number ACTRN12605000478617.

Keywords Breast cancer · Chemotherapy · Anthracycline · Dose intensity · Survival · Quality of life

Introduction

Breast cancer is the most common female cancer, and the second most common cause of female cancer death in most developed nations [1]. Although mortality rates are falling [2], once breast cancer has metastasized it is not considered curable. Instead, the primary objective of treatment in

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✉ Stephen. P. Ackland
Stephen.ackland@newcastle.edu.au

✉ N. Zdenkowski
nick.zdenkowski@newcastle.edu.au

1 Calvary Mater Newcastle Hospital, Newcastle, NSW, Australia

2 NHMRC Clinical Trials Centre, University of Sydney, Sydney, NSW, Australia

3 Royal Melbourne Hospital, Parkville, VIC, Australia

4 Breast Cancer Trials Ltd., Newcastle, NSW, Australia

5 Sir Charles Gairdner Hospital, Nedlands, WA, Australia

6 Royal North Shore Hospital, St Leonards, NSW, Australia

7 University of Newcastle, Newcastle, NSW, Australia

metastatic breast cancer is to maintain quality of life and if possible to prolong life without excessive toxicity [3].

The desire to explore new treatments in cancer, such as biological, immunological and targeted therapies, leaves behind incompletely answered questions about the utility of more established treatments. One such question concerns the ideal dose or dose intensity of cytotoxic chemotherapy in breast cancer. While much research has been undertaken in this field, there are still unanswered questions, and as long as cytotoxic agents remain part of the armamentarium of oncologists, answers to these questions remain important.

Increased dose and dose intensity are attractive strategies because of a steep dose–response curve seen with many agents in vitro and in animal models [4]. A linear relationship has been shown between average relative dose intensity, or dose per unit time, and response rate for CMF-based regimens in advanced breast cancer [5]. The three variables that contribute to dose intensification are dose per cycle, cycle interval and total cumulative dose, each of which may impact upon antitumor effects as well as toxicity [6]. Prospective studies have shown that lower dose intensity regimens are less effective than using the conventional dose [7, 8]. In the 1990s, studies began to address the question of dose intensity separately from total dose received [9, 10]. The adjuvant NSABP study B25 showed no improvement in survival or disease-free survival with higher dose cyclophosphamide in an AC regimen compared to standard doses, despite greater toxicity in the intensified regimen [11].

Despite recent developments in biological and targeted agents, anthracycline combinations are efficacious and remain in common usage for advanced breast cancer [3]. Epirubicin lends itself readily to studies of dose and dose intensity since the dose can be escalated above its usual range with little toxicity other than myelosuppression [12]. During the time that ANZ9311 was being conducted, phase II and III studies suggested a dose–response relationship for response rates, but not survival, possibly because of similar cumulative total doses administered [10, 13]. Members of our group found that with filgrastim support, the maximum dose level at which patients could receive repetitive dosing without dose reduction was epirubicin 150 mg/m^2 and cyclophosphamide 1500 mg/m^2. More than 3 cycles resulted in prohibitive myelosuppression and its complications [12].

In 1993, Breast Cancer Trials (BCT) initiated trial ANZ9311 to address the question of the benefit of increased dose intensity as distinct from total dose. The primary objective was to compare a short high-dose intensive course of EC with a longer conventional dose regimen delivering the same total dose of chemotherapy.

Patients and methods

Patients

Eligible patients were women with advanced breast cancer (unresectable locally advanced or metastatic) who had received at most one prior regimen of chemotherapy for advanced disease and no prior anthracycline; measurable or evaluable disease; ECOG performance status of 0–2 and adequate haematopoietic, renal and liver function. Patients were not eligible if they had received adjuvant chemotherapy within the preceding 6 months; prior malignancy; ischemic heart disease or congestive cardiac failure; other significant co-morbidity; radiation therapy to $>25\%$ of haematopoietic marrow or planned surgery or radiation to the sole site of disease.

Chemotherapy

Patients were randomised 1:1 to either standard dose EC (SDEC): epirubicin 75 mg/m^2 and cyclophosphamide 750 mg/m^2 every 3 weeks for 6 cycles; or high-dose EC plus filgrastim (HDEC): epirubicin 150 mg/m^2 and cyclophosphamide 1500 mg/m^2 every 3 weeks for 3 cycles. Daily filgrastim (Neupogen ®, Amgen Australia Pty. Ltd., North Ryde NSW) 5 µg/kg was given with HDEC from day 2 until the post-nadir neutrophil count surpassed 10×10^9/L. Thus HDEC was intended to deliver the same total dose in half the time as SDEC.

During the first 3 cycles patients had full blood counts taken twice each week, thereafter the SDEC patients had a full blood count at day 8–10 and day 21 of each cycle. Dose reductions were not mandated for uncomplicated neutropenia that resolved by day 21. Secondary filgrastim prophylaxis was optional with SDEC. A dose reduction to 75% of the previous cycle was required in the event of febrile neutropenia, grade 4 thrombocytopenia or other grade 3–4 toxicity. Chemotherapy was delayed if the neutrophil count on day 21 was $<2.0\times10^9$/L, or platelet count $<100\times10^9$/L and/or other toxicity had not resolved to grade 0–1.

Assessments

Patients were clinically evaluated every 3 weeks during treatment and then at least every 3 months subsequently. Repeat tumour measurements, using chest X-ray, bone scan and liver CT, plus any other baseline assessments showing sites of disease, were required at week 9 (end of HDEC), week 18 (end of SDEC) and then every 3 months. If progressive disease or patient withdrawal occurred, tumour

measurements were to be repeated using the same imaging technique as originally used.

Quality of life was measured at every clinical evaluation, using: patient-completed linear analogue self assessment (LASA) scales [14], measuring physical well-being, mood pain, nausea, vomiting and appetite; and the GLQ-8 [15], a LASA scale measuring anxiety or depression, feeling sick, numbness or pins and needles, loss of hair, appetite or sense of taste and thought of actually having treatment. The Spitzer QL index measures the physician's assessment of patient quality of life [16].

Statistical analysis

Patients were stratified by ECOG performance status (0–1 vs. 2), receipt of prior chemotherapy for advanced disease, brain or liver metastases (present or absent) and institution. Randomisation was conducted centrally using dynamic balancing. Accrual of 225 patients was planned, in order to detect a change in median survival from 10 to 15 months and a change in one-year survival from 45 to 59% ($\alpha = 0.05$, $\beta = 0.8$). This sample size provided power to detect a meaningful difference in overall quality of life, of 15–20% of full scale (two-tailed t-test, $\alpha = 0.05$, $\beta = 0.8$). Two interim analyses were planned after 50 and 100 patients were enrolled, evaluating quality of life, response rate and serious adverse events only. The trial would have been stopped if a difference of 3 standard deviations was observed in quality of life or serious adverse events; or if the 95% confidence interval of the experimental response rate did not include at least a 20% increase over the control group.

Categorical variables were compared using the Chi square test and the t-test was used to compare treatment effects on continuous outcomes (QoL measures). Time to progression (TTP) was calculated for all assessable patients as the interval from randomisation to the date of first progression of tumour according to the Kaplan–Meier method [17] and compared using the log-rank test [18]. Quality of life (QoL) measures were compared in a number of complementary ways. The mean change from baseline, over the first 9 weeks and the first 18 weeks was assessed and compared between treatments (Chi square test). Secondly, the mean QoL at each time point (± 95% CI) was calculated to produce a graphical evaluation of change in QoL over time for each treatment, allowing assessment of differences between the treatments at each time point.

Ethical considerations

The trial was conceived, designed and conducted by members of BCT. All data were collected, stored and analysed independently of the funding bodies. The trial was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation. Participants provided written, informed consent. It was prospectively approved by site Human Research Ethic Committees, and is registered on the Australia and New Zealand Clinical Trials Registry (ACTRN12605000478617).

Results

Trial population

Between April 1994 and July 1998, 235 patients were recruited from 17 centres in Australia and New Zealand. One hundred and seventeen patients were allocated to HDEC and 118 patients SDEC (Fig. 1). Baseline patient characteristics were well balanced between the 2 treatment groups (Table 1). More patients in the high-dose treatment group had oestrogen and progesterone receptor negative tumours, prior radiation for recurrent cancer and taxanes for advanced disease, suggesting that these patients were a worse prognostic group.

Treatment dose delivery

Complete data on treatment administration are available for 115 (97%) patients allocated to SDEC and 112 (96%) patients allocated to HDEC. Dose delivery, as percentage of planned dose per cycle was similar in both groups. However, 24 SDEC patients discontinued treatment before 6 cycles because of progressive disease, whereas 2 patients progressed before completing 2 cycles of HDEC (Fig. 1, Table 2).

Efficacy

A response at 9 weeks was observed in 39% of patients allocated to HDEC compared to 45% allocated to SDEC ($P = 0.33$) (Table 3). The best overall response rate using standard WHO criteria (requiring two assessments showing response at least 4 weeks apart) for all patients randomised was 28% in the high-dose group and 36% in the standard dose treatment group. At the time of final analysis in August 2013, 99.1% of HDEC and 97.5% of SDEC patients had died. One patient who received SDEC was alive, and 3 were lost to follow-up. The median survival was 14.5 months for HDEC patients and 16.5 months for SDEC patients (Fig. 2) (log-rank $P = 0.29$). Median time to disease progression was not significantly differenct between HDEC and SDEC (5.7 vs. 5.8 months respectively, log-rank $P = 0.19$) (Fig. 3).

Further SDEC (or equivalent) after progression was administered to 13% of patients in the SDEC group and 8% in the HDEC group. After progression, 14% of SDEC patients were treated with a taxane-containing regimen

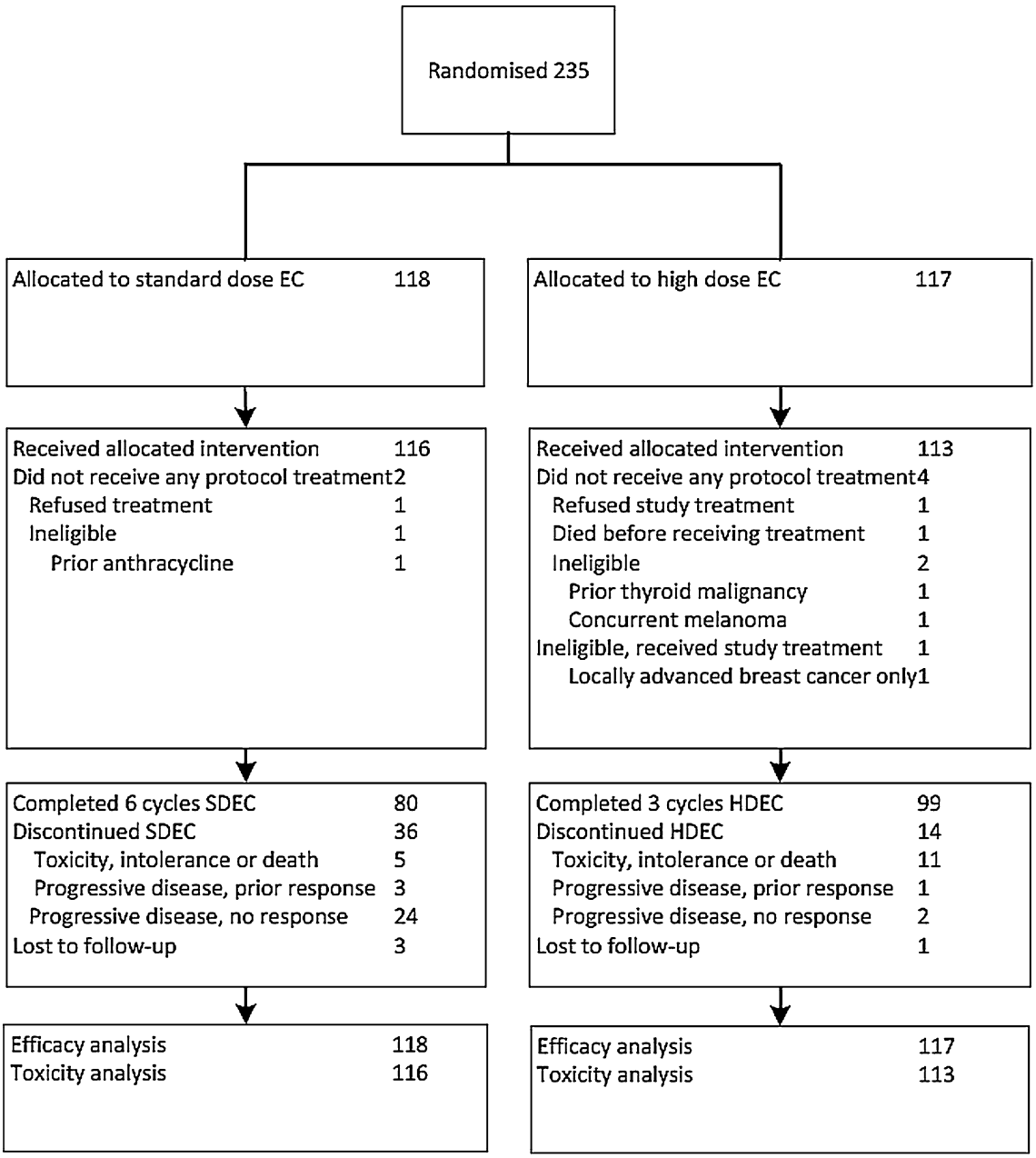

Fig. 1 CONSORT diagram

compared to 13% of HDEC patients. Three percent and 8% respectively were given chemotherapy other than EC or a taxane-containing regimen.

Toxicity

As expected, the majority of patients developed grade 3/4 neutropenia (98% of HDEC patients vs. 87% of SDEC patients: Table 4). Fewer patients on standard dose treatment had episodes of infection requiring antibiotics, febrile neutropenia, grade 3/4 thrombocytopenia, grade 3/4 anaemia. Grade 3/4 haematological and non-haematological toxicities became evident on day 8 for HDEC and day 12–13 for SDEC in the first cycle. Excluding haematological toxicity, 29% of standard dose patients had grade 3/4 toxicity compared to 59% of HDEC patients.

Five patients allocated to SDEC withdrew from treatment because of toxicity, drug intolerance or treatment-related death, compared to 11 patients allocated to HDEC. Two deaths in the SDEC and 4 deaths in the HDEC group were attributed to protocol treatment or a combination of

Table 1 Baseline patient demographics, tumour details and prior treatments according to randomised group

	Randomised group			
	Standard dose $N=118$		High dose $N=117$	
	N	%	*N*	%
Median age (range)	50 (23–78)		50 (28–78)	
Menopausal status				
Pre-menopausal	31	26	27	23
Post-menopausal	79	67	85	73
Unknown	8	7	4	3
No data	0	0	1	1
ER status				
Negative	26	22	37	32
Positive	55	47	48	41
Unknown/equivocal	37	31	32	27
Disease extent				
Locoregional only	7	6	3	3
Distant only	71	60	82	70
Locoregional and distant	40	34	32	27
Initial axillary node status				
Positive	35	30	39	33
Negative	67	57	60	51
Unknown	16	14	18	15
Contralateral breast involvement				
Never	107	91	104	89
Past/present	11	9	13	11
Prior surgery				
None	8	7	8	7
Mastectomy	74	63	76	65
Lumpectomy	30	25	24	21
Biopsy only/other	6	5	9	8
Prior radiation				
Primary	27	23	28	24
Recurrent	24	20	30	26
Both	10	8	10	9
None	57	48	49	42
Adjuvant therapy				
Hormonal[a]	53	45	51	44
Chemotherapy—CMF	42	36	39	33
Chemotherapy—other	3	3	2	2
None	40	34	48	41
Systemic therapy for advanced disease				
Hormonal[b]	56	47	60	51
Chemotherapy—CMF	17	14	15	13
Chemotherapy—taxane	2	2	7	6
Chemotherapy—other	2	2	1	1
None	57	48	49	42
No. of organ sites involved[c]				
1	22	19	25	21
2	39	33	48	41
3	35	30	28	24
4+	21	18	15	13
Disease sites[c]				
Breast	23	19	14	12
Skin	22	19	12	10
Lymph nodes	44	37	34	29
Bone	73	62	69	59
Lung	37	31	32	27
Pleura	4	3	2	2
Liver	55	47	58	50
Brain	1	1	2	2
Other	37	31	45	38
ECOG performance status				
0	41	35	41	35
1	60	51	61	52
2	17	14	14	12
3[d]	0	0	1	1
Disease-free interval (months)				
Median (LQ, UQ)	30 (14,48)		31 (11,52)	

[a]Hormonal therapy for early breast cancer includes at least one of: ovarian ablation, tamoxifen or ovarian ablation and tamoxifen

[b]Hormonal therapy for advanced breast cancer includes at least one of: ovarian ablation, tamoxifen, progestagen or aromatase inhibitor

[c]One patient in the HDEC group did not have data on disease sites involved

[d]One patient was stratified as ECOG = 2, but was randomised as ECOG = 3

Table 2 Treatment dose delivery according to randomised group

	SDEC ($N=115$)[a]	HDEC ($N=112$)[a]
Mean no. of cycles	5.1	2.8
% planned dose/cycle		
Epirubicin	96%	90%
Cyclophosphamide	96%	90%
Filgrastim	–	99%

SDEC Standard dose epirubicin and cyclophosphamide, *HDEC* high-dose epirubicin and cyclophosphamide

[a]Patients with complete data on treatment administration

treatment and tumour-related factors. No instances of cardiac toxicity or leukaemia have been reported.

Table 3 Tumour response to treatment according to randomised group

	SDEC ($N=118$) (%)	HDEC ($N=117$) (%)	
Response at 9 weeks	45	39	$P=0.33$
Best overall response[a]			
Complete	7	8	
Partial	29	21	
No change	40	52	
Progression	20	9	
Unknown	4	11	
Best overall response rate all patients	36	28	$P=0.23$

[a]WHO criteria, confirmed by 2 assessments not less than 4 weeks apart [19]

Quality of life analysis

At baseline there was no difference between the two treatment groups in any patient-reported quality of life parameter, or in the physician-rated Spitzer QL index. General health at trial entry was reported as excellent or good by 43%, and fair to poor by 56%. Most patients had symptoms related to breast cancer as shown by an initial overall quality of life rating of 69% (95% CI 73–65%), which was identical between the 2 treatment groups.

Quality of life information is available for more than 90% of patients during the first 6 months, and more than 75% overall. In the first 9 weeks of treatment, patients assigned SDEC reported better QoL than those assigned HDEC for the parameters of physical well-being, tiredness, appetite/taste, thought of treatment and for the physician-rated QL index (Supplementary material). However, by 18 weeks the differences between treatments had narrowed and were no longer statistically significant, except for appetite or sense of taste.

Discussion

This trial indicates that three cycles of double dose EC with filgrastim support is more toxic and provides no significant advantage over 6 cycles of standard dose therapy in terms of time to tumour progression, survival or quality of life in advanced breast cancer.

These results are consistent with the findings of the French Epirubicin Study Group (FESG) [20] and extend their conclusions into a higher dose range. The FESG evaluated 3 different doses and schedules of FEC (group A: FEC 75 × 11 cycles; group B: FEC 100 × 4 cycles followed by FEC 50 × 8 cycles; group C: FEC 100 × 4 cycles) in 417 patients. Groups A and B had almost identical total dose administered. The more dose-intense regimen was more toxic, but the overall response rate was similar in groups A and B, and poorer in the third shorter regimen. In our trial, the trend to better overall response rate after 9 weeks treatment for HDEC compared to SDEC suggests that high-dose therapy may be able to induce responses more quickly. However, the difference was small and not maintained: by 18 weeks the response rate was if anything better for patients who received standard therapy. The

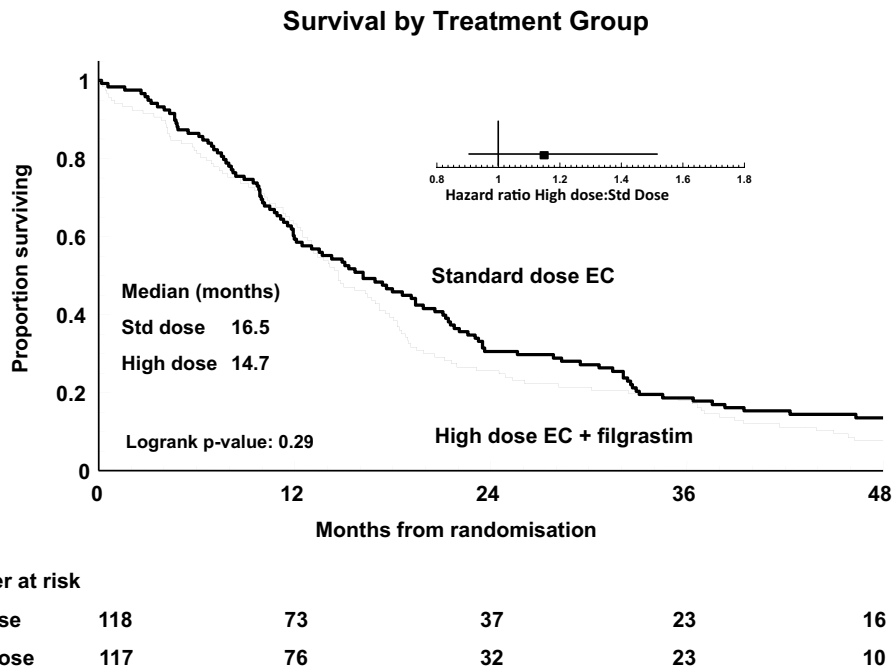

Fig. 2 Kaplan Meier plot of survival. Survival by randomised treatment

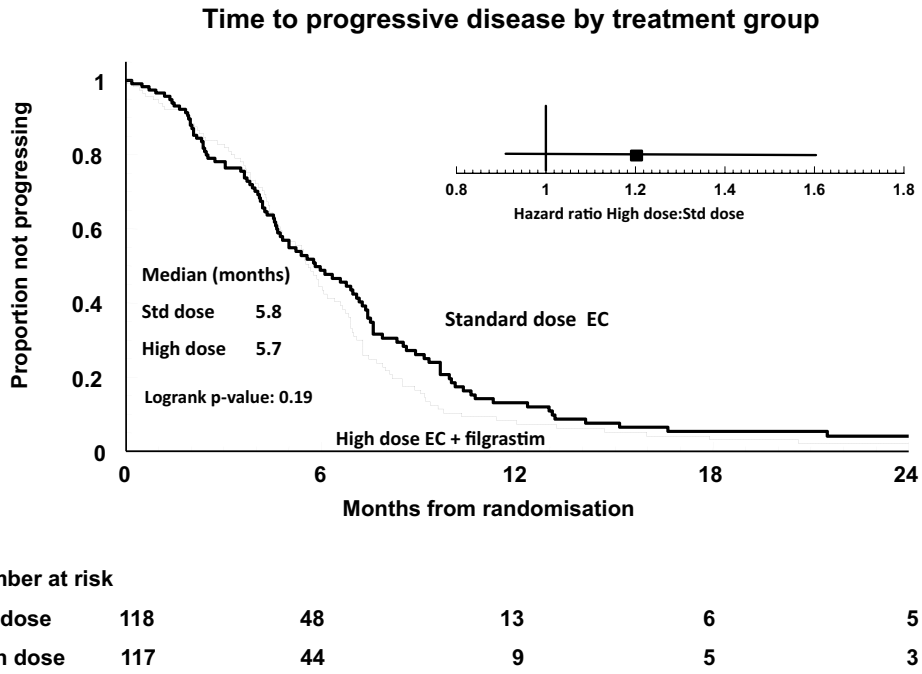

Fig. 3 Kaplan Meier Plot of time to disease progression. Time to disease progression by randomised treatment

Table 4 Adverse events of grade 3 or greater according to treatment received

	At least one episode of grade 3 or 4 toxicity (% of patients)	
	SDEC ($N=116$)	HDEC ($N=113$)
Neutropenia	87	98[a]
Infection (requiring antibiotics)[b]	25	43[a]
Febrile neutropenia	15	50[a]
Thrombocytopenia	6	65[a]
Anaemia	10	37[a]
Nausea and vomiting	10	14
Stomatitis	3	15
Diarrhoea[a]	8	16

[a]P value <0.05 for comparison between SDEC and HDEC

[b]Grade 2–4 toxicity

relatively low rates of best overall response may be partly due to assessment only every 9–12 weeks. Furthermore the best overall response, defined as the best response at any single time point after beginning trial treatment, was greater for standard therapy than for high-dose therapy, suggesting that a longer course of treatment ultimately confers greater probability of response than a short 9 week course. This reflects previous findings by our group that chemotherapy until disease progression resulted in better response rates and quality of life in advanced breast cancer, compared with limiting treatment to three cycles and then resuming the same treatment upon disease progression [14].

We expected that quality of life would be worse for high-dose therapy during the first 9 weeks, offset by improvements after completion of protocol therapy, so that the overall quality of life for HDEC (quality adjusted survival time) may be better than for SDEC. In fact HDEC gave worse scores for physical well-being, tiredness, thought of having treatment as well as worse QL index during the first 9 weeks, consistent with greater treatment toxicity compared to SDEC; while there was a trend to rebound for some QoL parameters after 9 weeks it was not statistically significant. The only parameter in which differences were statistically significant was appetite or sense of taste in the first 9 weeks. Thus, in terms of patient- or physician-rated QoL HDEC was similarly well tolerated as SDEC, and thus could be considered an acceptable regimen to offer patients in some circumstances.

Trials to establish the optimal dose rate of cytotoxic agents are influenced by Gompertzian theory of non-linear growth rate [21], and the Norton-Simon hypothesis, that the rate of tumour regression is proportional to the tumour growth rate [22]. Thus, higher doses might be necessary to kill cells that have a lower growth rate. However, many cancer cells exhibit resistance mechanisms that make them at least as resistant to cytotoxic agents as normal cells [23]. Chemotherapy may also lead to more rapid cellular proliferation due to the removal of growth competition from drug resistant clones [24]. Expression of resistance does not typically require a mutation, rather the increased expression of an existing mechanism. The dose schedule of

HDEC in this trial may not have exerted sufficient control over these resistant clones.

The agents chosen for dose intensification in this trial were in common use at the time. However, survival of metastatic breast cancer patients has improved [2, 25] as a result of new cytotoxics, biological agents and targeted therapies. Paclitaxel, docetaxel, eribulin, vinorelbine and capecitabine are now in common usage in advanced breast cancer [3]. Dose-intense treatments are difficult to apply to these agents due to significant dose-limiting non-haematological toxicity [26, 27]. Escalating the dose of 3-weekly paclitaxel beyond 175 mg/m^2 does not improve response rate, survival or quality of life [28]. Current consensus guidelines recommend hormonal therapy or single-agent chemotherapy for advanced disease unless rapid control of disease is required [3].

Dose-intense EC may be more effective in selected breast cancer subtypes such as triple negative [29], or HER2 positive/TopIIα amplified [30]. However, our trial was conducted before breast cancer subtype-directed therapy was established, and we can only speculate about tumour biology in this population.

An in vivo dose–response relationship has been demonstrated with higher doses of epirubicin than the current standard. Higher response rates were seen with doses of single-agent epirubicin above 60 mg/m^2 compared with lower doses [31]. The highest 3-weekly dose in this trial was 120 mg/m^2, but an upper dose limit was not defined, beyond which the response rate no longer improved. However, response rate and survival were not different in a randomised phase II trial of dose-dense versus dose-intense epirubicin and paclitaxel as first line treatment for metastatic breast cancer [32].

We deliberately avoided using doses of EC that would require autologous stem cell reinfusion for support. Studies of this strategy in both advanced and early breast cancer have yielded inconsistent results. Meta-analyses of randomised trials comparing HDCT followed by autologous stem cell transplant (ASCT) with conventional chemotherapy for metastatic breast cancer showed a progression-free survival benefit, which did not translate into an OS benefit [33, 34]. No subsets were found to derive benefit, although HER2 status was known in only a quarter of patients. Similarly, a meta-analysis of 15 adjuvant HDCT studies found a disease-free survival benefit, which did not translate to an overall survival benefit [29]. On the other hand, increased dose density in neoadjuvant regimens for locally advanced breast cancer is associated with increased response rate, but no overall or disease-free survival benefit [35]. In each of these settings, there was evidence of additional toxicity. Hence, regimens using a dose intensity that is higher than current standard dosage is not recommended for patients with metastatic breast cancer where the goal of therapy is palliation and/or long term control.

In summary, HDEC, as shown using 3 cycles of double dose epirubicin and cyclophosphamide with filgrastim support, has no obvious advantages in terms of tumour control or quality of life compared to 6 cycles of SDEC. Whether the strategy of increased dose intensity may prove worthwhile using other anticancer agents in advanced breast cancer setting is uncertain.

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Compliance with ethical standards

Conflict of interest All authors declare that they do not have a conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent was obtained from all individual participants included in the study.

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