



Role of dose-dense chemotherapy in high-risk early breast cancer

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Purpose of review

Adjuvant chemotherapy for breast cancer significantly reduces the risk of recurrence and improves overall survival (OS). The purpose of the current article is to review available evidence on dose-dense chemotherapy, also focusing on special population, including premenopausal women and those with HER2-positive disease.

Recent findings

A recent patient-level meta-analysis showed that the use of dose-dense chemotherapy is associated with significant reduction in disease recurrence, breast cancer mortality and improvement in OS. The benefit of dose-dense chemotherapy is irrespective from HER2 status, although women with HER2-positive disease enrolled in trials included in the meta-analysis did not receive the current standard of treatment with anti-HER2 agents. Among premenopausal women, dose-dense chemotherapy improved OS, and thus should be considered standard of care for them.

Summary

In conclusion, high-risk early stage breast cancer patients should be treated with (neo)adjuvant dose-dense anthracycline-based chemotherapy followed by paclitaxel. In the era of trastuzumab, the benefit of dose-dense chemotherapy is still unclear for patients with HER2-positive breast cancer.

Keywords

breast cancer, dose-dense, HER2-positive, premenopausal

INTRODUCTION

According to the Gompertzian principle, smaller tumours grow proportionally faster than bigger ones until a plateau is reached [1]. Therefore, Norton–Simon hypothesized that chemotherapy results in a rate of regression in tumour volume that is proportional to the rate of growth for an unperturbed tumour of that size [2,3]. Thus, reducing intervals between cycles of chemotherapy would kill a proportionally higher cell rate in smaller, faster growing tumours.

ESTABLISHING THE ROLE OF ADJUVANT CHEMOTHERAPY

Because adjuvant chemotherapy significantly reduces the risk of recurrence and improves overall survival (OS) in breast cancer patients [4], many trials attempted to establish the best dose and schedule of chemotherapy.

Early trials of adjuvant chemotherapy demonstrated a statistically significant 11% reduction in the risk of relapse and a 16% increase in OS for patients receiving adjuvant anthracycline-based chemotherapy compared to standard cyclophosphamide, methotrexate and fluorouracil (CMF) regimen [5].

Because anthracycline can lead to long-term adverse events, such as myelodysplasia, heart failure and leukaemia, some trials tried to outline anthracycline-free chemotherapy regimens at least as effective as anthracycline containing ones. Jones *et al.* [6] demonstrated, at a median follow up of 5.5 years, that docetaxel and cyclophosphamide are superior to standard interval doxorubicin and cyclophosphamide in terms of disease-free survival (DFS) with no benefit in OS.

Afterwards, trials of concomitant or subsequent anthracycline and taxane chemotherapy regimens showed superiority to anthracycline only regimens. Particularly, the combination of both anthracycline

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KEY POINTS

- Adjuvant chemotherapy significantly reduces the risk of recurrence and improves the OS in breast cancer patients.
- Dose-dense chemotherapy improves DFS and OS compared to standard-interval chemotherapy in breast cancer patients independently from hormone-receptor status and nodal status.
- No additional benefit from dose-dense chemotherapy is demonstrated in patients with HER2-positive tumours.
- Premenopausal women receiving dose-dense chemotherapy have better outcomes compared to women receiving standard interval chemotherapy, without additional gonadotoxicity.
- High-risk early stage breast cancer patients should be treated with four cycles of dose-dense anthracycline followed by 12 cycles of weekly paclitaxel.

and taxane leads to a further reduction by 13% in relapse risk and a further increase in OS by 11% [5]. Thus, anthracycline and taxane-based regimens became standard of care for early stage breast cancer [7,8]. Sequential regimes of both agents are associated with a better toxicity profile than combination regimens, reducing the total dose of anthracyclines administered.

THE ERA OF DOSE-DENSE ADJUVANT CHEMOTHERAPY

In order to further reduce breast cancer relapse and mortality, many trials tried to increase dose intensity of chemotherapeutic agents by increasing the

single dose per cycle or by reducing intervals between cycles (i.e. dose-dense regimens). Among all trials of dose-dense adjuvant chemotherapy, we consider trial with highly comparable arms (i.e. that compare the same drugs, doses and number of cycles between dose-dense and control arm) and trials with confounded study design (i.e. where additional treatment was given in the dose-dense or control arm).

Among the unconfounded trials (Table 1), MIG1 was one of the first to attempt the efficacy of dose-dense chemotherapy and is the only one with available long-term results [9,10^a]. In the MIG1 study, node positive and high-risk node negative breast cancer patients were randomized to receive six cycles of adjuvant fluorouracil, epirubicin and cyclophosphamide regimen administered every 3 (standard-interval arm) or 2 (dose-dense arm) weeks. At the first analysis of the trial, at a median follow-up of 10.4 years, no statistically significant difference in the hazard of death [hazard ratio 0.87, 95% confidence interval (CI) 0.67–1.13] or recurrence (hazard ratio 0.88, 95% CI 0.71–1.08) was observed between the two treatment arms [9]. At an updated analysis of the study, at a median follow-up of 15.8 years, no statistically significant differences in both OS and event-free survival (EFS) were observed in the overall study population (hazard ratio 1.13, $P=0.25$ and hazard ratio = 1.13, $P=0.19$ for OS and EFS, respectively). Among patients with hormone receptor-negative disease, EFS was improved with the use of dose-dense chemotherapy (hazard ratio = 1.47; 95% CI 1.08–2.01; $P=0.016$) [10^a].

In the CALBG 9741 trial, node-positive early breast cancer patients were randomized to receive concurrent doxorubicin + cyclophosphamide for

Table 1. Trials with similar dose-dense adjuvant regimens

	Trial name	No. of patients	Dose-dense group	Standard treatment group	pN+ (%)	Estimated disease-free survival	Estimated overall survival
Citron <i>et al.</i> , 2003	CALGB 9741	2005	TAC (×4) → T (×4) q14 A (×4) → C (×4) → P (×4) q14	AC (×4) → T (×4) q21 A (×4) → C (×4) → T (×4) q21	100	3y: 82 vs. 75% (HR 0.74; $P=0.010$) ^a	NA (HR 0.69; $P=0.013$) ^a
Venturini <i>et al.</i> , 2005	MIG 1	1214	FEC (×6) q14	FEC (×6) q21	64.5	10 y (EFS): 63 vs. 57% (HR 0.88; $P=0.22$)	10 y: 80 vs. 78% (HR 0.87; $P=0.29$)
Del Mastro <i>et al.</i> , 2015	GIM 2	2091	FEC (×4) → T (×4) q14 or EC (×4) → T (×4) q14	FEC (×4) → T (×4) q21 or EC (×4) → T (×4) q21 ^a	100	5 y: 81 vs. 76% (HR 0.77; $P=0.004$) ^a	5 y: 94 vs. 89% (HR 0.65; $P=0.001$) ^a
Cameron <i>et al.</i> , 2017	TACT 2	4391	E (×4) q14 → CMF (×4) q28 or E (×4) q14 → X (×4) 14q21	E (×4) q21 → CMF (×4) q28 or E (×4) q21 → X (×4) 14q21		5 y (TTR): 87.1 vs. 85.9% (HR 0.94; $P=0.42$) ^a	5 y: 89.7 vs. 90.7% (HR 1.04 $P=0.68$) ^a

^aResults shown only for dose-dense versus nondose-dense comparisons.

A, adriamycin; AC, adriamycin + cyclophosphamide; C, cyclophosphamide; CMF, cyclophosphamide + methotrexate + 5-fluorouracil; E, epirubicin; EC, epirubicin + cyclophosphamide; EFS, event-free survival; FEC, fluorouracil + epirubicin + cyclophosphamide; HR, hazard ratio; NA, not available; q14/21, every 14/21 days; T, paclitaxel; TTR, time to tumor recurrence; X, capecitabine; y, year.

Table 2. Adjuvant dose-dense trials comparing different treatment doses or regimens

	Trial name	No. of patients	Dose-dense arm	Standard treatment arm	pN+ (%)	Estimated disease-free survival	Estimated overall survival
Burnell <i>et al.</i> , 2010	MA 21	2104	EC (×6) q14 → T (×4) q21	AC (×4) q21 → T (×4) q21	81.3	3y: (RFS): 89.5 vs. 85% (HR 0.59; $P=0.0006$)	NA
Foukakis <i>et al.</i> , 2016	PANTHER	2017	EC (×4) q14 → D (×4) q14	FEC (×3) q21 → D (×3) q21	97%	5y: (EFS): 86.1 vs. 82.7% (HR 0.79; $P=0.04$)	5y: 92.1 vs. 90.2% (HR 0.77; $P=0.09$)

AC, adriamycin + cyclophosphamide; D, docetaxel; EC, epirubicin + cyclophosphamide; EFS, event-free survival; FEC, fluorouracil + epirubicin + cyclophosphamide; HR, hazard ratio; NA, not available; q14/21, every 14/21 days; RFS, recurrence-free survival; T, paclitaxel; y, year.

four cycles followed by paclitaxel for other four cycles administered every 2 or 3 weeks [11]. At a median follow up of 36 months, dose-dense chemotherapy was associated with improved DFS and OS [relative risk (RR)=0.74, $P=0.01$; RR=0.69, $P=0.01$, for DFS and OS, respectively]. The benefit was observed in hormone-receptor negative patients and not in hormone-receptor positive patients.

The GIM 2 trial randomized node-positive early breast cancer patients in a 2x2 factorial design to receive epirubicin + cyclophosphamide with or without 5-fluorouracil followed by paclitaxel administered every 2 or 3 weeks. Five-year DFS was 81% in dose-dense arm and 76% in standard interval arm (hazard ratio 0.77, 95% CI 0.65–0.92; $P=0.004$), whereas 5-year OS rate was 94 and 89% for dose-dense and standard interval arm, respectively (hazard ratio 0.65; $P=0.001$) [12]. The benefit of dose-dense chemotherapy was observed irrespective of the hormonal receptor status (hazard ratio 0.80, $P=0.033$ and 0.69, $P=0.046$ for hormone-receptor positive and hormone-receptor negative, respectively). Similarly, a statistically significant improvement for OS was demonstrated with a hazard ratio of 0.69 for hormone-receptor-positive and a hazard ratio of 0.55 for hormone-receptor-negative patients.

A more recent dose-dense trial, TACT2, randomized patients to receive four cycles of epirubicin administered either every 3 weeks (standard-interval) or every 2 weeks (dose-dense arm) followed by four cycles of either CMF or capecitabine. In total, 4391 patients were enrolled and 54% of them had involved axillary nodes. At a median follow-up of 85.6 months, no difference was observed in the primary endpoint of time-to-tumour recurrence (hazard ratio 0.94; $P=0.42$). Comparably, OS at 5 years was 89.7% for patients in the standard-interval arm and 90.7% in the dose-dense arm (hazard ratio 1.04; $P=0.68$) [13].

Recently, a patient-level meta-analysis of all trials of dose-dense chemotherapy showed significant reduction in both disease recurrence (RR 0.83;

$P=0.00004$) and 10-year breast cancer mortality (RR=0.85; $P=0.003$) and an improved OS (RR 0.86; $P=0.003$) for patients receiving dose-dense compared to standard-interval chemotherapy [14^{***}]. Restricting the analysis to the trials with unconfounded study design, still a benefit for patients receiving dose-dense chemotherapy was demonstrated (RR 0.83; $P<0.0001$). Importantly, the proportional reductions in recurrence with the dose-dense schedule were independent from hormone-receptor status and nodal status [14^{***}].

After standard adjuvant doxorubicin and cyclophosphamide, paclitaxel or docetaxel given with a weekly schedule improved DFS and OS compared to the same agent given on a 3-weekly basis [15]. The SWOG S0221 trial showed that dose-dense paclitaxel (e.g. paclitaxel given every 2 weeks) is similar, in terms of both DFS and OS, to weekly paclitaxel [16]. Given the better tolerability, weekly paclitaxel, may be the preferred schedule after dose-dense anthracycline-based chemotherapy.

Among trials with confounded design, we can distinguish between trials with additional chemotherapy in the dose-dense arm and trials with additional chemotherapy in the standard interval arm (Table 2).

Among trials with additional chemotherapy in the dose-dense arm, MA21 randomized node-positive or high-risk node-negative breast cancer patients to receive epirubicin and cyclophosphamide for six cycles administered every 14 days (dose-dense arm) or doxorubicin and cyclophosphamide every 21 days (standard interval) for four cycles (e.g. two cycles less than in dose-dense arm). Both arms received additional four cycles of paclitaxel every 21 days. A statistically significant improvement in the 3-year relapse-free survival was demonstrated for the dose-dense arm, whereas data on OS were immature [17].

Among trials with additional chemotherapy in the control arm, in the PANTHER trial, early stage breast cancer patients were randomized to four cycles of nadir-based tailored dose-dense epirubicin

and cyclophosphamide followed by four cycles of tailored dose-dense docetaxel or to standard interval fluorouracil-epirubicin-cyclophosphamide followed by standard interval docetaxel for three cycles each (e.g. one cycle more of epirubicin and cyclophosphamide and one cycle more of docetaxel than in dose-dense arm). The dose-dense arm had a better 5-year EFS (86.7 vs. 82.1%; hazard ratio 0.79; $P=0.04$), whereas no benefit for OS was demonstrated (92.1 vs. 90.2%, respectively; hazard ratio 0.77; $P=0.09$) [18].

In the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis joining data from trials with confounded design, as expected, the benefit from dose-dense appeared somewhat less extreme in trials with extra drugs in the control arm (RR 0.89, $P=0.13$) than in trials with higher doses or extra drugs in the dose-dense arm (RR 0.79; $P=0.004$) [14[■]].

SPECIAL POPULATION

Neoadjuvant setting

The neoadjuvant approach may be considered the preferred strategy for HER2-positive and triple negative breast cancer, also in the earlier stage [19]. Randomized trials aiming to compare neoadjuvant dose-dense vs. standard-interval chemotherapy failed to report increased pathological complete response rate and better long-term outcomes in the dose-dense arm (Table 3) [20–22]. However, the confounded design of these trials makes the interpretation of the results difficult. Taking into account the efficacy and safety demonstrated in the adjuvant setting, the use of dose-dense regimen might be an option also in the neoadjuvant approach.

HER2-positive

The EBCTCG meta-analysis reported similar benefit among HER2-positive and HER2-negative patients

treated with dose intensification (hazard ratio 0.83, 95% CI 0.67–1.02; hazard ratio 0.86, 95% CI 0.79–0.94, for HER2-positive and HER2-negative patients, respectively) [14[■]]. Nevertheless, the majority of women analysed did not receive the current standard of treatment with an anti-HER2 agent. Thus, it is difficult to determine the real benefit derived from dose intensification in trastuzumab-treated patients [23].

Recently, an exploratory analysis of the GIM2 trial was performed to identify a potential interaction between HER2 status, trastuzumab use and chemotherapy schedule treatment [24[■]]. Lambertini *et al.* [24[■]] investigated the efficacy of dose-dense chemotherapy in the subgroup of HER2-positive breast cancer patients with or without subsequent exposure to adjuvant trastuzumab and in those with HER2-negative/unknown disease. The authors observed no significant interaction between HER2 status, trastuzumab treatment and the effect of dose-dense chemotherapy, with no differences in terms of both DFS and OS between the dose-dense and standard interval arm among HER2-positive patients treated with adjuvant trastuzumab, thus suggesting the dose-dense chemotherapy could be avoided in this subgroup of patients.

Premenopausal women

Breast cancer is the most common tumour diagnosed in young women, and it is characterized by a more aggressive behaviour (i.e. higher proportion of triple-negative, poorly differentiated tumours) compared to breast cancer arising in older women [25]. Thus, the majority of young breast cancer patients are candidates for adjuvant chemotherapy [26].

A pooled analysis including only premenopausal breast cancer patients enrolled in the MIG1 and GIM2 trials showed a significant 29% improvement in OS for premenopausal women treated with a dose-dense schedule as compared with those who

Table 3. Neoadjuvant dose-dense trials

	Trial name	No. of patients	Dose-dense arm	Standard treatment arm	pCR rate	Median follow up (years)	Disease-free survival	Overall survival
Therasse <i>et al.</i> , 2003	EORTC MA 10	448	EC q14 (x6)	CEF q28 (x6)	10 vs. 14% (NA)	5.5	NA ($P=0.68$)	NA ($P=0.94$)
Von Minckwitz <i>et al.</i> , 2005	GEPARUO	913	AD q14 (x4)	AC q21 (x4) → D q21 (x4)	7 vs. 14.3%	NA	NA	NA
Untch <i>et al.</i> , 2011	PREPARE	733	EC q14 (x3) → T q14(x3) → CMF (x3)	EC q21 (x4) → T q21 (x4)	NA	43.5 months	3y (DFS): 78.8 vs. 75.8% (HR 1.14; $P=0.37$)	3y: 91.5 vs. 88.4% (HR 1.26; $P=0.24$)

AC, adriamycin + cyclophosphamide; AD, adriamycin + docetaxel; CEF, cyclophosphamide + epirubicin + fluorouracil; CMF, cyclophosphamide + methotrexate + 5-fluorouracil; D, docetaxel; DFS, disease-free survival; EC, epirubicin + cyclophosphamide; HR, hazard ratio; NA, not available; q14/21, every 14/21 days; T, paclitaxel; y, year.

received the standard interval regimen (hazard ratio 0.71; 95% CI 0.54–0.95, $P=0.021$). The benefit was larger in patients with hormone-receptor negative disease (hazard ratio 0.65, 95% CI 0.40–1.06) as compared to those with hormone-receptor positive disease (hazard ratio 0.78, 95% CI 0.54–1.12) [27].

The most worrisome side-effect of chemotherapy in premenopausal patients is the development of iatrogenic premature ovarian failure, with subsequent infertility and several long-term side-effects [28]. The pooled analysis observed no increased risk of treatment-induced amenorrhoea with dose-dense regimen (OR 1.00; $P=0.989$) [27].

Therefore, young women could be the ideal candidate to receive dose-dense chemotherapy: the shorter duration of the treatment might also be more socially convenient for young women, in terms of return to work and recovery from side-effects (including alopecia) [27].

TOXICITY

In the GIM2 trial, patients treated with dose-dense chemotherapy had more frequently grade 3–4 anaemia, transaminitis and myalgias but had less frequently grade 3–4 neutropenia [12]. Patients enrolled in the dose-dense arm of TACT2 trial had significantly more cases of grade 3–4 hand-foot syndrome and any grade anaemia, arthralgia and back pain [13], whereas grade 3–4 leukopenia, neutropenia and febrile neutropenia were lower in the dose-dense arm than in the standard interval arm [13]. In the EBCTCG meta-analysis, the use of dose-dense chemotherapy is not associated with higher rate of treatment-related deaths, although an increase of grade 3–4 anaemia was showed in some trials [14[■]]. Lower incidence of leukopenia and febrile neutropenia is reported in the dose-dense arms, probably because of the use of granulocyte colony-stimulating factor (G-CSF) to allow bone marrow recovery [14[■]]. The concern about a significant increase in the incidence of acute myeloid leukaemia after dose-dense treatment and G-CSF use has not been supported by evidence [29]. Moreover, no difference in cardiotoxicity or other non-haematological toxicities was demonstrated between dose-dense and control arms [14[■]].

CONCLUSION

Dose-dense schedule is associated with improved outcomes in high-risk early breast cancer patients candidate for adjuvant chemotherapy. The magnitude of the benefit is greater in patients with hormone-receptor negative tumours than in those with hormone-receptor positive disease. Premenopausal

breast cancer patients also benefit from dose-dense chemotherapy, whereas the benefit is controversial in patients with HER2-positive breast cancer receiving adjuvant anti-HER2 agents.

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Conflicts of interest

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- of special interest
- of outstanding interest

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