Adjuvant Dose-Dense Chemotherapy for Breast Cancer: Available Evidence and Recent Updates

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Keywords

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Summary

Adjuvant chemotherapy has greatly improved the prognosis of early breast cancer. Dose-dense chemotherapy seeks to increase efficacy by changing the interval between cycles of treatment without the need of increasing doses and toxicity. According to the Gompertzian model, the smaller tumors are and the more rapid they grow, the more benefit could be expected from dose-dense therapy. Some clinical trials showed reduced mortality when adjuvant chemotherapy is administered in shorter intervals, while others had discordant results. Interpreting results is difficult due to a great variability in doses and schemes used in different trials. Dose-dense chemotherapy does not seem to increase adverse events and appears to be the most efficacious in higher-risk individuals and in hormone receptor-negative tumors. This review intends to summarize the available evidence and recent research about this subject.

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Introduction

Adjuvant chemotherapy has greatly improved the prognosis of early breast cancer [1]. While its benefit seems to be too small or even non-existent in very early-stage or very low-risk tumors, patients with more aggressive or advanced disease are much

more likely to have a reduction in the risk of recurrence and mortality, thus making the indication for chemotherapy stronger in these cases [2]. Since hormone receptor-negative disease has a higher recurrence risk, a more aggressive clinical course after progression, and less available treatment options when compared to hormone receptor-positive disease, adjuvant therapy may have a higher impact in patients with hormone receptor-negative tumors.

Latest advances in adjuvant chemotherapy for breast cancer involved the sequential addition of taxanes to anthracycline-based chemotherapy which has led to an additional 5% absolute reduction in clinical outcomes [1]. There is a clear lack of new and more effective treatments for high-risk patients, making the concept of trying different doses and different administration schemes an attractive possibility.

Dose-Dense Chemotherapy: Rationale

Dose intensity in chemotherapy is calculated as the total dose received by a given patient per unit of time. It is possible to augment intensity by escalating the dose per cycle or by decreasing the interval between cycles, known as dose density [3]. A dose-response relationship in chemotherapy is known from both experimental murine models and clinical experience [4]. Clinical trials of adjuvant chemotherapy in breast cancer have shown that not only the total dose received but also the dose intensity can be a factor affecting curability [3, 5].

According to the Gompertzian principle, smaller tumors grow proportionally faster than bigger ones – up to a certain point at which a plateau is reached [6]. This occurs because, as tumors grow, feedback mechanisms take place to decelerate growth and limit tumor size [7]. Therefore, when tumors shrink as a result of

chemotherapy, their cells start to proliferate even faster, making cure unattainable [8]. At the same time, it has been hypothesized that chemotherapy would result in a proportionally higher cell kill rate in smaller, faster growing tumors (Norton-Simon hypothesis) [9]. The idea behind dose-dense chemotherapy is that it would make more sense to decrease the interval between chemotherapy cycles giving tumors less time to grow back than to simply escalate the dose which has been shown to be of limited efficacy in some situations [10].

This theory could also explain why efficacy is sometimes increased when drugs are administered at shorter intervals and in a sequential manner as compared to using them concomitantly (which requires smaller doses for each drug) [8] and to alternating between different drugs at the same dose level (requiring larger intervals of administration) [11].

Dose density could also affect cancer resistance because the emergence of resistant cells depends on the time after chemotherapy and tumor burden. Giving doses at shorter intervals could kill malignant cells before they develop a drug-resistant phenotype [3].

Dose-Dense Chemotherapy Trials Comparing Different Doses or Drugs

In the German AGO trial, 1,284 women with extensive lymph node involvement (4 or more affected lymph nodes) were randomized to a dose-dense regimen or a conventional every-3-week (q3w) schedule [12]. The first scheme consisted of the sequential administration of 3 cycles of epirubicin (150 mg/m²), paclitaxel (225 mg/m²), and cyclophosphamide (2,500 mg/m²) at 2-week intervals (q2w) with epoetin alfa and filgrastim support. The second group received 4 cycles of epirubicin/cyclophosphamide (90/600 mg/m²) followed by 4 cycles of paclitaxel (175 mg/m²) q3w. The dose-intense treatment resulted in a 28% reduction in the relative risk of relapse in 5 years (event-free survival of 62% in the conventional arm and 70% in the dose-dense arm; $p < 0.001$), irrespective of the subgroup analyzed. The dose-intense group had a 5-year overall survival (OS) rate of 82% compared to 77% in the conventional arm, representing a 24% reduction in the relative risk of death with dose-intense treatment ($p = 0.0285$).

In a second trial (Canadian NCIC MA.21), 2,104 patients with node-positive or high-risk node-negative disease were randomized to 3 different schemes: i) cyclophosphamide 75 mg/m² orally days 1–14, epirubicin 60 mg/m² intravenously (IV) days 1 and 8, and fluorouracil 500 mg/m² IV days 1 and 8 (CEF regimen) for 6 cycles every 28 days; ii) epirubicin/cyclophosphamide (120/830 mg/m²) q2w for 4 cycles with filgrastim and epoetin alfa support followed by paclitaxel (175 mg/m²) q3w for 4 cycles (EC-T regimen); and iii) doxorubicin/cyclophosphamide (60/600 mg/m²) followed by paclitaxel (175 mg/m²) q3w for 4 cycles each (AC-T regimen). The 3-year adjusted recurrence-free survival (RFS) rates for each group were 90.1, 89.5, and 85%, respectively [13]. The authors found a non-statistically significant trend towards a possible superiority of the EC-T regimen over the CEF arm in the subgroup of estrogen

receptor (ER)-negative patients. Additionally, AC-T was inferior to both CEF and EC-T [13, 14].

The ECOG 1199 trial looked more closely at the question of intervals between taxane doses after anthracycline-based therapy [15]. After receiving 4 cycles of adjuvant AC every 21 days, 4,950 patients with node-positive or high-risk node-negative breast cancer were randomized to docetaxel or paclitaxel weekly for 12 cycles, or q3w for 4 cycles. Cumulative doses were higher both in the weekly paclitaxel and weekly docetaxel arms (960 and 420 mg/m², respectively) than in the q3w arms (700 and 400 mg/m²), but the difference was much higher in the paclitaxel arm. The weekly paclitaxel arm, when compared to the q3w paclitaxel arm, had superior 5-year disease-free survival (DFS) (81.5 vs. 76.9%; $p = 0.006$) and 5-year OS (89.7 vs. 86.5%; $p = 0.01$) irrespective of hormone receptor status. Docetaxel q3w had better DFS than standard-dose paclitaxel, but no improved OS. Weekly docetaxel was not superior in any of the outcomes. When both weekly regimens were compared with the other 2 q3w regimens, no significant differences were found. A long-term data analysis of the ECOG 1199 trial has been published showing that weekly paclitaxel retained its OS benefit only for triple-negative patients (hazard ratio (HR) 0.69; $p = 0.019$) [16].

Some clinical trials comparing conventional-dose with dose-dense anthracycline regimens have presented negative results [17–19]. More recently, Foukakis et al. [20] randomized 2,017 patients to nadir-based tailored dose-dense EC-T (each drug for 4 cycles) or to standard interval FEC-T (fluorouracil + EC-T) for 3 cycles each. The dose-dense arm had a better event-free survival at 5-years (86.7 vs. 82.1%; HR 0.79; $p = 0.04$) and a trend towards superior RFS at 5-years (88.7 vs. 85%; HR 0.79; $p = 0.06$). There was no difference in OS (92.1 vs. 90.2%; HR 0.77; $p = 0.09$). Non-hematologic grade 3 or 4 adverse events were more common in the dose-dense treatment group.

In the above trials (table 1), different cumulative doses and different drug schemes were used which may have influenced the results.

Dose-Dense Chemotherapy Trials Comparing Similar Treatment Groups

In the Intergroup C9741/CALGB 9741 trial, 2,005 patients were randomized based on a 2×2 distribution to 1 of 4 groups: i) sequential anthracycline followed by cyclophosphamide and paclitaxel (AC-T) q2w (dose-dense) or q3w; or ii) concomitant AC followed by paclitaxel q2w or q3w [21]. The dose-dense regimens were supported by the use of filgrastim for 7 days starting 72 h after chemotherapy. The q2w schedules improved DFS (risk ratio (RR) 0.74; $p = 0.010$) and OS (RR 0.69; $p = 0.013$) when compared to the q3w regimens. 4-year DFS was 82 versus 75%. Neither DFS nor OS were related to treatment sequence; concomitant AC seemed to be as effective as sequential A-C but with the advantage of a shorter overall treatment time and less grade 3 emesis and post-chemotherapy neuropathy. The benefit in the dose-dense arms occurred

Table 1. Dose-dense trials comparing different treatment doses or regimens

	n	Dose-dense group	Standard treatment group	Disease-free survival	Overall survival
Kümmel et al., 2006 [18]	216	ET (×4) q14 → CMF (×3) q14	EC (×4) q21 → CMF (×3) q21	4y: 64 vs. 58% (HR 1.32; p = 0.12)	4y: 85 vs. 75% (HR 1.76; p = 0.092)
Linden et al., 2007 [19]	3,176	A (×4) q21 → C (93) q14	AC (×6) q21	5y: 81 vs. 79% (HR 0.92; p = 0.2)	5y: 89 vs. 88% (HR 0.9; p = 0.25)
Sparano et al., 2008 [15, 16]	4,950	AC (×4) q21 → wT (×12)	AC (×4) q21 → T (×4) q21 ^a	5y: 81.5 vs. 76.9% (HR 1.27; p = 0.006)	5y: 89.7 vs. 86.5% (HR 1.32; p = 0.01)
Burnell et al., 2010 [13]	2,104	EC (×6) q14 → T (×4) q21	AC (×4) q21 → T (×4) q21	3y (RFS): 89.5 vs. 85% (HR 0.59; p = 0.0006)	NA
Moebus et al., 2010 [12]	1,284	E → T → C q14 (each ×3)	EC (×4) q21 → T (×4) q21	5y (EFS): 70 vs. 62% (HR 0.69; p < 0.001)	5y: 82 vs. 77% (HR 0.76; p = 0.029)
Gogas et al., 2012 [26]	1,121	E (×3) → T (×3) → CMF (×3) q14	ET (×4) q21 → CMF (×3) q14	5y: 74 vs. 85% (p = 0.78)	5y: 86 vs. 85% (p = 0.45)
Swain et al., 2013 [27]	4,894	AC (×4) → T (×4) q14	TAC (×6) q21	5y: 82.2 vs. 80.1% (HR 0.87; p = 0.07)	5y: 89.1 vs. 89.6% (HR 1.01; p = 0.96)
Foukakis et al., 2016 [20]	2,017	EC (×4) q14 → D (×4) q14	FEC (×3) q21 → D (×3) q21	5y (EFS): 82.7 vs. 86.1% (HR 0.79; p = 0.04)	5y: 92.1 vs. 90.2% (HR 0.77; p = 0.09)

^aDocetaxel data not shown.

A = Adriamycin; C = cyclophosphamide; D = docetaxel; E = epirubicin; T = paclitaxel; wT = weekly paclitaxel; AC = adriamycin + cyclophosphamide; CMF = cyclophosphamide + methotrexate + 5-fluorouracil; EC = epirubicin + cyclophosphamide; EFS = event-free survival; ET = epirubicin + paclitaxel; FEC = fluorouracil + epirubicin + cyclophosphamide; HR = hazard ratio; NA = not available; y = year; q14/21 = every 14/21 days; RFS = recurrence-free survival.

irrespective of tumor size, number of affected lymph nodes, or menopausal status. Further analysis showed that the benefit was increased in the ER-negative subgroup and was non-significant for the ER-positive subgroup.

The Italian GONO-MIG-1 trial randomized women to FEC (fluorouracil 600 mg/m², epirubicin 60 mg/m², and cyclophosphamide 600 mg/m²) every 14 days (FEC14) or every 21 days for a total of 6 cycles [22]. The FEC14 arm received filgrastim support per protocol. Accrual fell below the planned figures; only 1,214 women were randomized to 1 of the 2 groups. No statistically significant differences in the HR for death (HR 0.87, 95% confidence interval (CI) 0.67–1.13) and recurrence (HR 0.88, 95% CI 0.71–1.08) were found between the 2 groups, and no benefit was detected in any of the previously specified subgroups (tumor size, nodal stage, hormone receptor positivity, grade, menopausal status, and proliferative rate). The lack of statistical benefit in this study was attributed to the low rate of events in both arms which greatly reduced its statistical power [14].

A 2010 systematic review with meta-analysis [23] included the 2 above trials plus a third trial that utilized CEF q2w or q3w in the neoadjuvant setting [24]. In aggregate, these 3 trials showed a reduced risk of death in the dose-dense arms (HR 0.84, 95% CI 0.72–0.98; p = 0.03) with no heterogeneity for this result. In the 2 trials that analyzed DFS [21, 22], a significant improvement was found with dose-dense regimens (HR for relapse or death: 0.83, 95% CI 0.73–0.94; p = 0.005) with heterogeneity (I² = 0%). In a sensitivity analysis based on ER and progesterone receptor (PR) status, dose-dense chemotherapy had a statistically significant benefit with respect to DFS only for receptor-negative patients (HR for relapse or death: 0.71, 95% CI 0.56–0.89; no heterogeneity) [23]. 7 other trials

were identified in which the dose-dense and the conventional dosing arms did not receive the same regimens or doses. When these trials were included in the meta-analysis, there was still a significant improvement in OS (HR 0.85, 95% CI 0.77–0.93) and DFS (HR for relapse or death: 0.81, 95% CI 0.75–0.88) in the dose-dense arms with no significant heterogeneity.

A more recent work, published by Cameron et al. [25] in 2017, compared in a 2×2 design epirubicin 100 mg/m² q3w or q2w (accelerated). Patients in the last group received pegfilgrastim on day 2 after epirubicin (TACT2 trial). Patients were also randomized to receive either CMF (cyclophosphamide/methotrexate/fluorouracil with oral or IV cyclophosphamide) or capecitabine 2,500 mg/m²/day for 14 days. The ‘standard’ combination, epirubicin q3w followed by CMF, is commonly used in the UK where the study was set. All drugs were used for 4 cycles each. With 4,391 patients enrolled and a median follow-up of 85.6 months, no difference was found in the primary endpoint of time-to-tumor recurrence. OS at 5 years was 85.1% for patients in the standard epirubicin group and 87.1% in the accelerated epirubicin group, which could be attributed to the risk profile of the trial participants of which only 54% had involved axillary nodes.

Overall, dose-dense treatment has not shown to increase grade 3 or 4 toxicities [23]. It usually increases the rate of anemia requiring transfusion [12, 13], thrombocytopenia, and grade 3 or 4 non-hematologic (bone pain, asthenia) but not hematologic toxicities [23]. This is probably a consequence of the required use of granulocyte colony-stimulating factor (G-CSF) in these groups, which decreases the incidence of leukopenia and febrile neutropenia [21, 22, 25]. Its use can also prevent dose reductions and delays [21] but is associated with increased treatment costs (table 2).

Table 2. Trials with similar dose-dense regimens

	n	Dose-dense group	Standard treatment group	Disease-free survival	Overall survival
Citron et al., 2003 [21]	2,005	TAC (×4) → T (×4) q14 A (×4) → C (×4) → P (×4) q14	AC (×4) → T (×4) q21 A (×4) → C (×4) → T (×4) q21	4y: 82 vs. 75% (HR 0.74; p = 0.010) ^a	4y: (HR 0.69; p = 0.013) ^a
Venturini et al., 2005 [22]	1,214	FEC (×6) q14	FEC (×6) q21	10y: 80 vs. 78% (HR 0.87; p = 0.29)	10y (EFS): 63 vs. 57% (HR 0.88; p = 0.22)
Del Mastro et al., 2015 [28]	2,091	FEC (×4) → T (×4) q14 EC (×4) → T (×4) q14	FEC (×4) → T (×4) q21 EC (×4) → T (×4) q21	5y: 81 vs. 76% (HR 0.65; p = 0.001) ^a	5y: 94 vs. 89% (HR 0.65; p = 0.001) ^a
Cameron et al., 2017 [25]	4,391	E (×4) q14 → CMF (×4) q28 E (×4) q14 → X (×4) 14q21	E (×4) q21 → CMF (×4) q28 E (×4) q21 → X (×4) 14q21	5y (TTR): 87.1 vs. 85.9% (HR 0.94; p = 0.42) ^a	5y: 89.7 vs. 90.7%

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

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

Trials Comparing More Than One Dose-Dense Regimen

The Hellenic Cooperative Oncology Group (HeCOG) conducted a randomized trial in Greece with node-positive breast cancer patients (n = 1,121) [26]. Patients were randomized to receive i) epirubicin every 14 days for 3 cycles followed by paclitaxel every 14 days for 3 cycles and then 3 more cycles of intensified CMF every 14 days or ii) paclitaxel and epirubicin every 21 days for 4 cycles followed by intensified CMF every 14 days. All groups were treated with filgrastim support during the dose-dense treatment; cumulative doses were the same for every drug. The 5-year DFS for both arms was 74%, and OS was not different between the 2 groups. Thus, sequential chemotherapy administration failed to reach its expected superiority upon combined administration.

The NSABP B-38 answered 2 questions at the same time: the addition of a 4th agent to adjuvant chemotherapy, and the comparison of dose-dense chemotherapy with the combined use of all 3 main adjuvant drugs (A, C, T) [27]. The 4,894 women with node-positive breast cancer included were randomized to 3 groups: i) 6 cycles of docetaxel, doxorubicin, and cyclophosphamide (TAC) q3w; ii) dose-dense AC followed by 4 cycles of paclitaxel 175 mg/m² q2w (AC-T); and iii) the same as the second regimen with the addition of gemcitabine 2,000 mg/m² during the paclitaxel phase. No significant differences in terms of DFS or OS were found among the 3 groups. Patients in the TAC group had more diarrhea, febrile neutropenia, and hospitalizations, but less neurotoxicity than the other 2 groups.

The Italian GIM group randomized 2,091 patients in a 1:1:1:1 ratio to EC-T with or without fluorouracil (FEC-T) in q2w or q3w intervals [28]. DFS at 5 years was 81% in the q2w arms and 76% in the q3w arms (HR 0.77; p = 0.004); OS was 91 and 86%, respectively (HR 0.65; p = 0.001). There were no differences in outcomes between the FEC-T and the EC-T arms, but the FEC-T arm showed increased toxicity. As in the NSABP B-38 trial [27], adding a 4th drug to the dose-dense regimen did not appear to be beneficial (tables 1, 2).

The question of the dose interval for the taxane component of adjuvant treatment was addressed again in the SWOG 0221 trial.

Patients (n = 2,716) were randomized based on a 2×2 factorial design to i) standard dose-dense AC for 6 cycles or doxorubicin 24 mg/m² IV once per week plus cyclophosphamide 60 mg/m²/day orally for 15 weeks (with pegfilgrastim and filgrastim support, respectively), and later to ii) paclitaxel 175 mg/m² q2w with pegfilgrastim support for 6 cycles or weekly paclitaxel 80 mg/m² for 12 weeks [29]. Randomization to the AC arms was suspended as the continuous AC group crossed the futility boundary and showed a trend towards an increase in DFS. There was no difference among the 4 arms regarding DFS (p = 0.11), but a marginally significant difference was found in OS favoring the q2w regimen (p = 0.04). OS was numerically higher when both q2w treatments were used and was mostly confined to triple-negative patients. The weekly paclitaxel arm had more hematologic toxicities and less musculoskeletal pain and neuropathy than the q2w paclitaxel arm.

Special Populations and Final Remarks

A systematic review of adjuvant dose-dense trials included 3 additional clinical trials published after 2010 in a total of 8 studies [30]. All trials reported DFS with significantly lower rates of death or relapse in the dose-dense arms when compared to the conventional schedule arms (HR 0.84, 95% CI 0.77–0.91; p < 0.0001). In the 7 trials that reported OS, the risk of death was also lower for patients in the shorter interval arms (HR 0.85, 95% CI 0.79–0.93; p = 0.0001). After subgroup analysis, this OS benefit was present only in HR-negative patients (HR 0.8, 95% CI 0.69–0.92; p = 0.002).

A more recent individual patient data meta-analysis was conducted and presented in abstract form showing that in 7 trials that compared the same drugs and doses with different intervals (q2w vs. q3w), the dose-dense, more frequent applications reduced disease recurrence by 17% (HR 0.83; p = 0.00004) and breast cancer mortality by 14% (HR 0.86; p = 0.004) [31]. Contrary to the previous analysis, the benefit was similar in hormone receptor-negative and -positive tumors and was not influenced by age, HER2 status, tumor grade, or stage. The idea that only hormone receptor-nega-

tive patients truly benefit from dose-dense treatment was supported by clinical trial results [13, 21, 22, 27] and by the concept that those tumors exhibit faster growth and can be more efficiently treated by more frequent doses. The new evidence is convincing in the sense that the benefit is consistent across all breast cancer subtypes and that hormone receptor status alone should not influence the decision whether or not to use dose-dense treatment [31].

The same is true regarding the indication for adjuvant treatment in patients with HER2-overexpressed tumors. Combining dose-dense AC and paclitaxel with HER2-targeted therapy appears to be safe from a cardiac point of view, and toxicity does not seem to be increased in relation to previous non-dose-dense HER2 clinical trials [32–34]. This makes sense if we consider that no trial has shown increased cardiac risk with reduced anthracycline intervals [21, 22, 25, 28]. Despite the scarcity of data in this particular setting, dose-dense chemotherapy should be strongly considered in this population as well.

In the neoadjuvant setting, studies have used pathologic complete response (pCR) as a surrogate endpoint, and the long-term results have been inconsistent [35]. Randomized clinical trials failed to demonstrate that the dose-dense approach could increase pCR [24, 36]. Nonetheless, its efficacy in the adjuvant setting and

its relative safety make dose-dense treatment an attractive choice also for neoadjuvant treatment. This discussion is beyond the scope of this article.

In terms of safety, dose-dense regimens do not increase neutropenia and febrile neutropenia, which can be explained by the required use of G-CSF, and do not increase the rate of treatment-related deaths. Further, the previous concern about a significant increase in the incidence of acute myeloid leukemia after dose-dense treatment and G-CSF use has not been supported by evidence [30]. If toxicities are increased, they are probably grade 1 or 2, and non-breast cancer-related deaths are not increased during or after treatment [31].

The idea of increasing efficacy with reduced toxicity using the same drugs and doses is compelling and makes dose-dense chemotherapy a first-line option in the adjuvant treatment of high-risk breast cancer patients [37]. This option should be discussed with patients regardless of age, tumor stage, or subtype.

Disclosure Statement

The authors have no potential conflicts of interest to disclose.

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