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CALGB 9344/CALGB C9741: what have we learned?

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The Cancer and Leukemia Group B (CALGB) 9344 study was the first randomised study to report a benefit for the addition of a taxoid to standard anthracycline-based chemotherapy. This trial was initiated with paclitaxel as data for this taxoid had become available in advance of those for docetaxel. The CALGB 9344 study was initially designed to investigate the value of dose escalation of doxorubicin, but randomisation for the addition of sequential paclitaxel was then incorporated, resulting in a three-by-two factorial trial. Thus, 3121 patients with node-positive, operable breast cancer were randomised to receive either four cycles of AC therapy, consisting of cyclophosphamide (600 mg/m^2) in combination with one of three doses of doxorubicin (60, 75 or 90 mg/m^2) every 3 weeks. All patients were randomly assigned to receive either four cycles of 3-weekly paclitaxel at 175 mg/m^2 or no further therapy [1]. While dose escalation of doxorubicin – which required the concomitant administration of granulocyte colony-stimulating factor (G-CSF) at the highest dose – did not improve outcomes, the addition of paclitaxel resulted in significant increases in both disease-free survival (DFS) and overall survival (OS). Compared with AC alone, the addition of paclitaxel produced a 17% relative reduction in the risk of recurrence ($P = 0.0023$) and an 18% relative reduction in the risk of death ($P = 0.0064$). This study did not stipulate administration of hormone therapy, but recommended that tamoxifen be administered to patients with hormone receptor-positive disease following completion of chemotherapy. Approximately two-thirds of patients had hormone receptor-positive disease and tamoxifen was administered to 94% of these patients. In an unplanned retrospective, hypothesis-generating subset analysis, the benefit of adding paclitaxel was greater in the patient population with oestrogen-receptor (ER) negative disease and among those who did not receive tamoxifen [1].

A second early trial that investigated the potential benefit of the addition of paclitaxel to standard therapy was the National Surgical Adjuvant Breast and Bowel Project (NSABP) B28 study. In this trial, 3060 patients were randomised to receive either four cycles of 3-weekly AC (cyclophosphamide; 600 mg/m^2/doxorubicin; 60 mg/m^2) or four cycles of 3-weekly AC followed by four cycles of 3-weekly paclitaxel at the increased dose of 225 mg/m^2 [2]. As a result of using this increased dose of paclitaxel, there was a reduction in delivery of the planned dose. All patients over the age of 50 years, and those younger than 50 years with ER-positive tumours also received concurrent tamoxifen continuing for 5 years, representing a broader use of tamoxifen compared with the CALGB 9344 study. In addition, the patient population in the NSABP B28 study was older with fewer positive nodes compared with the population entered into the CALGB study. The NSABP B28 trialists conducted a formal evaluation of the interaction of chemotherapy benefit and tamoxifen use, with interim analyses after 50, 130, 250 and 370 deaths, and a definitive analysis after 490 deaths. The results of these analyses revealed that although the addition of paclitaxel was associated with a significant DFS benefit that was similar to that achieved in the CALGB 9344 study (a 17% relative reduction in the risk of relapse; $P = 0.006$), unlike the CALGB 9344 study, this did not translate into a significant increase in OS ($P = 0.46$). It is worthwhile to note here that the definition of DFS in the NSABP B28 study differed somewhat from that in the CALGB 9344 study, thus confounding an inherently unreliable cross-study comparison.

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The most recent CALGB study, the results of which were updated at the 2005 San Antonio Breast Cancer Symposium (SABCS), is the CALGB/Intergroup 9741 study. This was a two-by-two study in 2005 patients with node-positive, early-stage disease that was designed to investigate the safety and efficacy of sequential versus concurrent AC therapy delivered with sequential, single-agent paclitaxel in either case, and also the outcomes of using both regimens either as the standard 3-weekly regimen or as a dose-dense regimen, the latter of which comprised therapy administered every 2 weeks with concurrent G-CSF. It is of importance to note that this trial was not designed as a four-arm comparison, but was designed as a two-by-two comparison that assumed no interaction between schedules and regimens [3,4]. The study was designed so that all patients would receive the same dose of chemotherapy, thereby limiting variability that could confound interpretation. In the updated analysis with 6.5 years' follow-up, there were no changes compared to the initial report [4]. Again there was no statistically significant difference between sequential and concurrent therapy (hazard ratio [HR] = 1.04 [95% CI 0.88–1.24]; $P = 0.65$) and DFS was significantly improved with the dose-dense schedule compared with the 3-weekly schedule (HR = 1.25 [95% CI 1.05–1.49]; $P = 0.012$). Although this study was not designed as a four-way comparison, exploratory analyses do not suggest a significant difference between sequential and combination therapy when delivered in either dose-dense or 3-weekly schedules. The OS outcome was similar; there was no significant difference between sequential and concurrent therapy and an advantage for dose-dense therapy compared with standard 3-weekly therapy, that just reached significance ($P = 0.049$). The longer follow-up did not reveal any changes in the acute toxicities associated with treatment; however, additional data regarding late cardiac and other events is now available [4]. The incidences of acute myeloid leukaemia (AML) and myelodysplastic syndrome (MDS) – which are of concern in patients who receive four or more cycles of AC therapy – were not increased with any of the schedules or regimens used in this study. Interestingly, although it was assumed that cardiac toxicity would be worse with dose-dense compared with 3-weekly chemotherapy, there were numerically fewer such events in patients who received dose-dense therapy compared with 3-weekly schedules [4].

In each CALGB trial, unplanned retrospective subset analyses suggested that larger benefits with the 'better' chemotherapy were observed in patients with hormone receptor-negative tumours compared with those with hormone receptor-positive tumours. To better understand this, the results of three sequential CALGB trials have been analysed in a study conducted by Berry and colleagues [5]. Tamoxifen use was not stipulated across all of these trials and ER testing was not centralised, and hence the results of this cross-trial comparison are only hypothesis-generating. The oldest of these studies – the CALGB 8541 study – investigated increasing doses of the CAF regimen (cyclophosphamide [C]/doxorubicin [A]/5-fluorouracil [F]). Thus, patients were randomised to receive either four cycles of $C_{300}A_{30}F_{300}$, six cycles of $C_{400}A_{40}F_{400}$, or four cycles of $C_{600}A_{60}F_{600}$ [6]. The second and third trials – CALGB 9344 [1] and CALGB C9741 [4], as previously described – investigated the outcomes of the addition of paclitaxel to four cycles of AC, and dose-dense scheduling, respectively.

As reported by Berry and colleagues, DFS was improved among patients with ER-negative disease in all three studies; the CALGB 8541 study, the CALGB 9344 study, and likewise, the CALGB C9741 study [5]. However, in patients with ER-positive disease, no statistically significant differences were observed between the outcomes of either the high- and low-dose anthracycline arms in the CALGB 8541 study, with the addition of paclitaxel in the CALGB 9344 study, or with dose-dense scheduling in the CALGB C9741 study [5]. It is important here, to emphasise that this analysis does not exclude a chemotherapy benefit for patients with hormone-responsive disease; as such a benefit could emerge with longer follow-up of the more recent studies. Berry and colleagues suggested that the explanation for these observations was related to the yearly risk of recurrence in these different patient populations. They suggested that in the first few years of follow-up, high event rates in patients with ER-negative disease may drive the observed differences between therapies of different efficacy and furthermore, that as patients with ER-positive tumours tend to relapse later and at a more constant rate than those

Table 1
Average hazard reductions [95% CI] in ER-negative and -positive patients across three CALGB trials[a]

	ER status	CALGB 8541 low→high	CALGB 9344: no P→P	CALGB C9741: q3w→q2w	Overall low→q2w
DFS	Negative	21 [9–31]	25 [12–36]	24 [1–42]	55 [37–68]
	Positive	9 [-6–22]	12 [-3–25]	8 [-20–29]	26 [-4–48]
OS	Negative	17 [4–29]	24 [10–37]	28 [1–47]	55 [38–69]
	Positive	6 [-11–20]	11 [-8–26]	8 [-28–35]	23 [-17–49]

[a] Adjusted for positive nodes, tumour size, menopausal status; CI: confidence level.
Adapted from Berry DA, *et al* 2006 [5]

with ER-negative tumours, the difference between outcomes of different therapies in these patient subpopulations may not be observed until longer follow-up has occurred.

To summarise, if we consider the average hazard reductions in both ER-negative and -positive patients across these three trials, as demonstrated in Table 1, it can be seen that whereas the average risk reduction for DFS events for patients with ER-negative disease is 55%, the corresponding value for patients with ER-positive disease is 23%. Although the confidence interval (CI) does not exclude zero, it does not preclude a benefit of therapy for patients with ER-positive disease [5]. Hence, we can confirm a benefit in ER-negative disease, but we can not exclude a benefit when hormone-receptors are present.

In summary, the results of the CALGB adjuvant taxoid studies show that the addition of a taxoid improves upon the outcomes obtained with AC therapy. The results of the CALGB C9741 demonstrate that a dose-dense schedule is a better way to deliver doxorubicin, paclitaxel and cyclophosphamide compared with the conventional 3-weekly schedule. Lastly, analysis of the results from multiple trials suggests that ER status influences event rates and the impact of 'better' chemotherapy regimens.

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