Report from the San Antonio Breast Cancer Symposium

Moira Rushton-Marovac, MD FRCPC, PGY5 Medical Oncology, University of Ottawa;
Susan Dent, MD, FRCPC, Medical Oncologist, Professor of Medicine, The Ottawa Hospital Cancer Centre

Early-stage breast cancer

DOSE-DENSE ADJUVANT CHEMOTHERAPY

TRIAL SUMMARY: Dose intensification

Gray RG, Bradley R, Braybrooke J, et al. Increasing the dose density of adjuvant chemotherapy by shortening intervals between courses or by sequential drug administration significantly reduces both disease recurrence and breast cancer mortality: An EBCTCG meta-analysis of 21,000 women in 16 randomised trials. San Antonio Breast Cancer Symposium (SABCS), December 2017. Abstract GS1-01.

Three-weekly scheduling is commonplace in adjuvant chemotherapy. However, cytokinetic modelling suggests that increasing the dose density of cytotoxic therapy by shortening the intervals between courses, or by using sequential rather than concurrent treatment schedules, may enhance efficacy.[1] This meta-analysis by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) brings together evidence from 15 randomized trials that have tested this hypothesis to clarify the risks and benefits of dose-dense chemotherapy. Individual patient data for 98% of the almost 22,000 women randomized in relevant trials was obtained. Among the trials, 7 compared dose-dense 2-weekly against standard 3-weekly dosing of a same chemotherapy; 9 trials compared sequential with concurrent anthracycline and taxane-based chemotherapy. Primary outcomes were time to recurrence and breast cancer mortality.

Results: Highly significant reductions in disease recurrence (rate ratio [RR]=0.83 [95% CI: 0.76–0.91], p=0.00004) were seen with 2-weekly compared with 3-weekly chemotherapy, and 10-year breast cancer mortality was 3.0% lower (16.7% vs 19.7%: RR=0.85 [95% CI: 0.76–0.95], p=0.003). Overall survival (OS) was also improved (RR=0.86 [95% CI: 0.78–0.95], p=0.003). Similarly, for sequential vs concurrent taxane plus anthracycline chemotherapy, the rate ratio for disease recurrence was 0.86 (95% CI: 0.79–0.93, p=0.0001), 10-year breast-cancer mortality was 2.3% lower (19.2% vs 21.5%: RR=0.87 [95% CI: 0.79–0.96], p=0.005), and OS was improved (RR=0.85 [0.78–0.94], p=0.0008).

Reductions in recurrence with dose-dense chemotherapy were similar and highly significant (both p<0.002) in estrogen receptor (ER)-positive and ER-negative disease, and did not differ significantly by any other patient or tumour characteristics, including age, HER2 status, nodal status, tumour size or grade. Non-breast-cancer mortality was similar with 2-weekly and 3-weekly chemotherapy (RR=0.93 [95% CI:0.74–1.17], p=0.6) and was somewhat lower with sequential than with concurrent chemotherapy (RR=0.73 [95% CI: 0.55–0.97], p=0.03). Growth factor support is required for the administration of dose-dense chemotherapy, yet the authors did not find a significant increase in toxicity with the dose-dense approach. The authors conclude that increasing the dose density of adjuvant chemotherapy is safe and results in fewer disease recurrences and fewer deaths from breast cancer.

At the San Antonio Breast Cancer Symposium (SABCS), Dr. Richard Gray also presented an extension of the analysis (Abstract GS1-0) that included 25 trials (over 34,000 patients). In addition to the trials mentioned above, the new analysis included a number of trials where there were some differences in the chemotherapies administered at different dose intensities. In all trials, patients were required to receive concurrent treatment with granulocyte colony-stimulating factor for immune system support.

Trials involving over 10,000 women showed that giving patients the same drugs, but for a shorter interval, reduced the absolute risk for breast cancer recurrence by 4.3% at 10 years compared to the standard every-3-weeks regimen (24% vs 28.3%; p=0.00004). Mortality from breast cancer at 10 years was 2.8% lower with dose-dense regimens, compared with standard chemotherapy (16.8% vs 19.6%; p=0.004). Comparing sequential and concurrent chemotherapy, both given every 3 weeks, 28.1% of women treated sequentially experienced disease recurrence within 10 years, vs 31.2% of those treated concurrently (p=0.0006); 10-year mortality was 1.9% lower in women treated sequentially than in those receiving concurrent treatment (17.7% vs 19.8%; p=0.03). Trials in which a sequential approach was combined with a shorter interval between cycles (over 6500 women in all) showed a major benefit in favour of dual intensification, with 4.5% lower 10-year recurrence (30.4% vs 34.9%; p=0.0001) and 3.9% lower 10-year breast cancer mortality in favour of dose intensification, compared with standard chemotherapy (22.1% vs 26%; p=0.001).

COMMENTARY: Breast cancer (BC) is the most common malignancy in women, with an estimated 26,300 new cases diagnosed in Canada in 2016.[1] Chemotherapy for early stage breast cancer has evolved over the last few decades, bringing improvements in overall survival (OS). Clinical trials have demonstrated superior outcomes with the addition of a taxane to anthracycline-based chemotherapy regimens,[2-10] which is reflected in current treatment guidelines. Acceptable chemotherapy regimens have included AC-P (doxorubicin and cyclophosphamide followed by paclitaxel) given every 3 weeks, AC (doxorubicin, cyclophosphamide) q 3 weeks followed by weekly P x 12, and FEC-D (5-fluorouracil, epirubicin, cyclophosphamide, docetaxel) given every 3 weeks. Dose-dense ACP (given every 2 weeks) has typically been reserved for those with higher-risk early breast cancer, including node-positive and triple-negative disease. Cancer Care Ontario guidelines for taxane use in early BC[11] recommend ACP to be given in a dose-dense (every 2 weeks) schedule for "qualifying patients", meaning node-positive, stage II and III patients. However, this recommendation may be too restrictive. Should all BC patients deemed to benefit from chemotherapy be considered for dose-dense chemotherapy?

The latest meta-analysis by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) addresses the question of dose-dense vs traditionally dosed chemotherapy. The results should be interpreted as practice-changing for those clinicians not already giving taxanes and anthracyclines sequentially and/or in a dose-dense schedule. Their findings, which demonstrate an absolute decrease in breast cancer-specific mortality and improved OS at 10 years, are compelling. This is even more so when we consider that the benefit was seen regardless of tumour size, nodal stage, ER status, HER2 status, age or tumour grade, and that there was no significant difference in safety profile. In 2018, oncologists in Canada treating early breast cancer should consider using a sequential, dose-dense strategy whenever combination anthracycline and taxane chemotherapy is part of the treatment plan.

IN BRIEF

Already known

- Increasing the dose density of adjuvant cytotoxic therapy is thought to enhance efficacy.

What this study showed

- This meta-analysis of 15 RCTs found that increasing dose density in adjuvant chemotherapy is safe, and reduces recurrence and deaths from breast cancer.

Next steps

- Oncologists treating early breast cancer should consider a sequential dose-dense strategy when treatment involves anthracycline and taxane chemotherapy.

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