Fluorouracil and dose-dense chemotherapy in adjuvant treatment of patients with early-stage breast cancer: an open-label, 2 × 2 factorial, randomised phase 3 trial

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Summary

Background

Whether addition of fluorouracil to epirubicin, cyclophosphamide, and paclitaxel (EC-P) is favourable in adjuvant treatment of patients with node-positive breast cancer is controversial, as is the benefit of increased density of dosing. We aimed to address these questions in terms of improvements in disease-free survival.

Methods

In this 2 × 2 factorial, open-label, phase 3 trial, we enrolled patients aged 18–70 years with operable, node positive, early-stage breast cancer from 81 Italian centres. Eligible patients were randomly allocated in a 1:1:1:1 ratio with a centralised, interactive online system to receive either dose-dense chemotherapy (administered intravenously every 2 weeks with pegfilgrastim support) with fluorouracil plus EC-P (FEC-P) or EC-P or to receive standard-interval chemotherapy (administered intravenously every 3 weeks) with FEC-P or EC-P. The primary study endpoint was disease-free survival, assessed with the Kaplan-Meier method in the intention-to-treat population. Our primary comparisons were between dose schedule (every 2 weeks *vs* every 3 weeks) and dose type (FEC-P *vs*EC-P). This study is registered with ClinicalTrials.gov, number NCT00433420.

Findings

Between April 24, 2003, and July 3, 2006, we recruited 2091 patients. 88 patients were enrolled in centres that only provided standard-intensity dosing. After a median follow-up of 7·0 years (interquartile range [IQR] 4·5–6·3), 140 (26%) of 545 patients given EC-P every 3 weeks, 157 (29%) of 544 patients given FEC-P every 3 weeks, 111 (22%) of 502 patients given EC-P every 2 weeks, and 113 (23%) of 500 patients given FEC-P every 2 weeks had a disease-free survival event. For the dose-density comparison, disease-free survival at 5 years was 81% (95% CI 79–84) in patients treated every 2 weeks and 76% (74–79) in patients treated every 3 weeks (HR 0·77, 95% CI 0·65–0·92; p=0·004); overall survival rates at 5 years were 94% (93–96) and 89% (87–91; HR 0·65, 0·51–0·84; p=0·001) and for the chemotherapy-type comparison, disease-free survival at 5 years was 78% (75–81) in the FEC-P groups and 79% (76–82) in the EC-P groups (HR 1·06, 0·89–1·25; p=0·561); overall

survival rates at 5 years were 91% (89–93) and 92% (90–94; 1·16, 0·91–1·46; p=0·234). Compared with 3 week dosing, chemotherapy every 2 weeks was associated with increased rate of grade 3–4 of anaemia (14 [1·4%] of 988 patients *vs* two [0·2%] of 984 patients; p=0·002); transaminitis (19 [1·9%] *vs* four [0·4%]; p=0·001), and myalgias (31 [3·1%] *vs* 16 [1·6%]; p=0·019), and decreased rates of grade 3–4 neutropenia (147 [14·9%] *vs* 433 [44·0%]; p<0·0001). Addition of fluorouracil led to increased rates of grade 3–4 neutropenia (354 [34·5%] of 1025 patients on FEC-P *vs* 250 [24·2%] of 1032 patients on EC-P; p<0·0001), fever (nine [0·9%] *vs* two [0·2%]), nausea (47 [4·6%] *vs* 28 [2·7%]), and vomiting (32 [3·1%] *vs* 15 [1·4%]).

Interpretation

In patients with node-positive early breast cancer, dose-dense adjuvant chemotherapy improved disease-free survival compared with standard interval chemotherapy. Addition of fluorouracil to a sequential EC-P regimen was not associated with an improved disease-free survival outcome.

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