Healthcare Improvement Scotland | Evidence
Advice, guidance and intelligence

Rapid Response

For patients with high-risk early breast cancer are chemotherapy regimens with fluorouracil superior to regimens without fluorouracil in the adjuvant setting?

HIS evidence conclusions

- One randomised controlled trial (n=2,091) of sequential regimens of epirubicin and cyclophosphamide, with or without fluorouracil, followed by paclitaxel for adjuvant chemotherapy in patients with high-risk early breast cancer was identified.
- Including fluorouracil led to greater toxicity without improvement in disease-free survival or overall survival.
- The generalisability of this finding to other anthracycline plus taxane regimens is unknown.

What were we asked to look at?

As part of a process of developing recommendations, we were asked by the Scottish Cancer Network to examine the evidence comparing equivalent adjuvant chemotherapy regimens with and without fluorouracil for patients with high-risk early breast cancer. The parameters of the research question as developed by the topic referrers is set out in Appendix 1.

Overview of the evidence

From a literature search conducted on 30 March 2023 (*see Appendix 2*) twenty-one references were examined in detail as potentially relevant (*see Appendix 3*). Two references which reported a single trial at different time points were selected.[1, 2]

GIM2 Trial

The GIM2 (Gruppo Italiano Mammella 2) Italian multicenter (N=81 centres) randomised controlled trial enrolled patients with node-positive breast cancer in Italy between 2003 and 2006 and compared four adjuvant chemotherapy regimens:

- four cycles of standard interval intravenous epirubicin 90 mg/m² and cyclophosphamide 600 mg/m² (EC) on day 1 every 3 weeks, followed by four cycles of intravenous paclitaxel (175 mg/m²) on day 1 every 3 weeks (q3EC-P), n=545
- four cycles of intravenous fluorouracil 600 mg/m², epirubicin 90 mg/m², and cyclophosphamide 600 mg/m² (FEC) on day 1 every 3 weeks, followed by four cycles of intravenous paclitaxel (175 mg/m²) on day 1 every 3 weeks (q3FEC-P), n=544
- dose-dense EC-P regimen, with the same doses and drugs as the q3EC-P group but administered every 2 weeks (q2EC-P), n=502
- dose-dense FEC-P regimen, with the same doses and drugs as the q3FEC-P group but given every 2 weeks (q2FEC-P), n=500.

Patients receiving dose-dense chemotherapy also received pegfilgrastim. Of 480 patients with human epidermal growth factor receptor 2 (HER2)-positive tumours 130 (27%) received one year of trastuzumab. After completion of chemotherapy, patients with hormone-receptor-positive tumours received endocrine therapy.

Effectiveness outcomes

The primary outcome of the trial was disease-free survival. Secondary outcomes were overall survival and safety. Table 1 outlines trial outcomes at median follow-up period of 15.1 years (interquartile range 8.4 to 16.3 years).

No differences were identified between the rates of disease-free survival events when outcomes from the two FEC-P groups were combined and compared with the two EC-P groups combined. The estimated rate of disease-free survival was 55.4% (95% CI 51.8 to 58.8) in the FEC-P group and 59.4% (95% CI 56.0 to 62.8) in the EC-P group. There was no statistically significant difference between the time to event distribution curves; hazard ratio (HR)=1.12 (95% CI 0.98 to 1.29, p=0.11).

Similarly, there was no statistically significant difference in overall survival between groups having fluorouracil-containing regimens and those receiving regimens without fluorouracil, HR=1.13 (95% CI 0.94 to 1.36, p=0.18).

Findings for both survival outcomes remained when adjusted for prognostic factors (age, menopausal status, type of surgery, histological type, tumour size, nodal status, grade, HER2 status and hormonal receptors).

Rates of death without relapse were similar across treatment groups as were chemotherapy completion rates.

In a post-hoc subgroup analysis examining hormone receptor-positive and HER2-negative (HR=1.09 (95% CI 0.90 to 1.33, p=0.37) HER2-positive (HR=1.01 (95% CI 0.75 to 1.35, p=0.96), and triple-negative breast cancer HR=0.62 (95% CI 0.37 to 1.04, p=0.07), none of the subtypes showed a disease-free survival benefit from FEC-P as compared with EC-P.

Table 1: key outcomes of GIM2 trial

Regimen	Number of patients assigned	Disease-free survival events	Overall survival events	Death without relapse	Patients completing all planned chemotherapy
q3EC-P	545	205 (38%)	126 (23%)	22 (4%)	476 (87%)
q3FEC-P	544	238 (44%)	150 (28%)	25 (5%)	483 (89%)
q2EC-P	502	169 (34%)	97 (19%)	22 (4%)	451 (90%)
q2FEC-P	500	174 (35%)	100 (20%)	19 (4%)	441 (88%)

Adverse events

Rates of grade 3 or 4 adverse events for the FEC-P and EC-P groups are shown in Table 2. Rates of neutropenia, fever, nausea and vomiting were statistically significantly higher in patients receiving fluorouracil. No information was provided on whether hospitalisation was required for these events. Treatment-related serious adverse events were similar across study groups. There were no treatment-related deaths (*see Table 3*).

Table 2: Grade 3 or 4 adverse events, according to EC-P and FEC-P arms

	EC-P group (n=1,032)	FEC-P group (n=1,025)	p value
	Number with event (%)	Number with event (%)	
Anaemia	6 (1%)	10 (1%)	0.22
Neutropenia	250 (24%)	354 (34%)	**<0.0001**
Thrombocytopenia	3 (<1%)	7 (1%)	0.168
Alopecia	466 (45%)	484 (47%)	Not reported
Asthenia	18 (2%)	27 (3%)	0.109
Diarrhoea	3 (<1%)	5 (<1%)	0.359
Bone pain	21 (2%)	31 (3%)	0.098
Fever	2 (<1%)	9 (1%)	**0.031**
Myalgia	24 (2%)	24 (2%)	1
Stomatitis	4 (<1%)	8 (1%)	0.189
Nausea	28 (3%)	47 (5%)	**0.015**
Vomiting	15 (1%)	32 (3%)	**0.006**
Neuropathy	35 (3%)	28 (3%)	0.229
Transaminase elevation (reported differently in the two study publications)	14 (1%) 17 (2%)	10 (1%) 16 (2%)	0.275 Not reported

Table 3: treatment-related serious adverse events

Regimen	Number (%) of patients experiencing serious treatment-related adverse events
q3EC-P	9 (2%) 5 infections (hospitalised) 1 tachycardia 3 severe allergic reactions No treatment-related deaths
q3FEC-P	7 (1%) 3 infections (hospitalised) 2 severe allergic reactions 1 gastrointestinal toxicity (hospitalised) 1 viral infection (hospitalised) No treatment-related deaths
q2EC-P	9 (2%) 5 infections (hospitalised) 2 severe allergic reactions 1 thrombotic event 1 hyperglycaemia No treatment-related deaths
q2FEC-P	9 (2%) 4 infections (hospitalised) 3 severe allergic reactions 1 tachycardia 1 extravasation of epirubicin No treatment-related deaths

References

1. Del Mastro L, De Placido S, Bruzzi P, De Laurentiis M, Boni C, Cavazzini G*, et al.* 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. Lancet (london, england). 2015;385(9980):1863-72.
2. Del Mastro L, Poggio F, Blondeaux E, De Placido S, Giuliano M, Forestieri V*, et al.* Fluorouracil and dose-dense adjuvant chemotherapy in patients with early-stage breast cancer (GIM2): end-of-study results from a randomised, phase 3 trial. The lancet Oncology. 2022;23(12):1571-82.

Appendix 1: research question

Patient group	Patients with high-risk early breast cancer requiring adjuvant chemotherapy. Risk denoted by where chemotherapy provides >5% additional 10 year survival benefit according to PREDICT or using similar criteria. High risk may be defined in trials as: • Nottingham prognostic index (NPI) – combines tumour size, grade and nodal status • Node positive • Node negative AND grade 3 tumour or T3/4 size.
Comparison	Any adjuvant chemotherapy regimen including fluorouracil (eg, FEC-taxane). (These may be dose-dense or standard regimens).
Intervention	Any equivalent adjuvant chemotherapy regimen which does not include fluorouracil, for example a. Dose-dense chemotherapy regimens (8 cycles) excluding fluorouracil b. Standard chemotherapy regimens (6 cycles) excluding fluorouracil
Outcomes	Overall survival Recurrence free survival Invasive breast cancer–free survival Time to recurrence Non breast cancer mortality Total dose received (incorporating dose reductions/stopping early) Adverse events Early acute adverse events (G3/4 toxicities) Hospital admission and length of stay Quality of life
Minimum follow-up period	5 years
Study types	From 1995 to 2023 Systematic reviews RCTs

Appendix 2: literature search strategies

Database: Ovid MEDLINE(R) ALL <1946 to March 30, 2023>

Search Strategy:

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1 exp breast neoplasms/ (338472)

2 (breast$ adj5 (neoplas$ or carcinom$ or cancer$ or tumor$ or tumour$)).tw. (395465)

3 1 or 2 (465151)

4 epirubicin.tw. (6060)

5 ellence.tw. (19)

6 Anthracyclines/ (4732)

7 doxorubicin.tw. (52414)

8 adriamycin.tw. (16425)

9 docetaxel.tw. (17660)

10 taxotere.tw. (1216)

11 paclitaxel.tw. (35066)

12 taxol.tw. (7936)

13 Taxoids/ (13745)

14 cyclophosphamide.tw. (53252)

15 cytoxan.tw. (749)

16 fluorouracil.tw. (40995)

17 adrucil.tw. (8)

18 or/4-17 (200453)

19 (dose adj3 (intens$ or dens$ or frequenc$ or concurrent or sequential)).tw. (15431)

20 (cycle adj2 (frequenc$ or number$ or interval$)).tw. (2642)

21 or/19-20 (18058)

22 3 and 18 and 21 (1016)

23 limit 22 to (english language and yr="1995 -Current") (854)

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Embase

Database: Embase <1974 to 2023 March 30>

Search Strategy:

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1 breast tumor/ (93777)

2 (breast$ adj5 (neoplas$ or carcinom$ or cancer$ or tumor$ or tumour$)).tw. (574862)

3 or/1-2 (603519)

4 epirubicin/ (32350)

5 epirubicin.tw. (9102)

6 ellence.tw. (158)

7 doxorubicin/ (217587)

8 doxorubicin.tw. (73243)

9 adriamycin.tw. (28185)

10 anthracycline/ (26827)

11 taxoid/ (2712)

12 docetaxel/ (71562)

13 docetaxel.tw. (32715)

14 taxotere.tw. (4626)

15 paclitaxel/ (130590)

16 taxol.tw. (15124)

17 paclitaxel.tw. (58775)

18 cyclophosphamide/ (244444)

19 cyclophosphamide.tw. (87079)

20 cytoxan.tw. (4845)

21 fluorouracil/ (156234)

22 fluorouracil.tw. (53211)

23 adrucil.tw. (158)

24 or/4-23 (645802)

25 (dose adj3 (intens$ or dens$ or frequenc$ or concurrent or sequential)).tw. (27008)

26 (cycle adj2 (frequenc$ or number$ or interval$)).tw. (3671)

27 or/25-26 (30634)

28 3 and 24 and 27 (2103)

29 limit 28 to (english language and yr="1995 -Current") (1856)

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Cochrane

ID	Search Hits
#1	MeSH descriptor: [Breast Neoplasms] explode all trees 17634
#2	breast? near/5 (neoplas? or carcinom? or cancer? or tumor? or tumour?) 43526
#3	#1 or #2 44463

#4 epirubicin 3464

#5 ellence 10

#6 doxorubicin 8632

#7 adriamycin 1943

#8 docetaxel 8208

#9 paclitaxel 12173

#10 taxotere 533

#11 taxol 570

#12 cyclophosphamide 13457

#13 cytoxan 206

#14 fluorouracil 11600

#15 adrucil 5

#16 #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 42524

#17 dose near/3 (intens? or dens? or frequenc? or concurrent or sequential) 4379

#18 cycle near/2 (frequenc? or number? or interval?) 490

#19 #17 or #18 4844

#20 #3 and #16 and #19 412

Appendix 3: trial selection

Ellis GK, Livingston RB, Gralow JR, Green SJ, Thompson T. Dose-dense anthracycline-based chemotherapy for node-positive breast cancer. Journal of Clinical Oncology. 2002;20(17):3637-43.	Exclude – not randomised
Therasse P, Mauriac L, Welnicka-Jaskiewicz M, Bruning P, Cufer T, Bonnefoi H*, et al.* Final results of a randomized phase III trial comparing cyclophosphamide, epirubicin, and fluorouracil with a dose-intensified epirubicin and cyclophosphamide + filgrastim as neoadjuvant treatment in locally advanced breast cancer: an EORTC-NCIC-SAKK multicenter study. Journal of Clinical Oncology. 2003;21(5):843-50.	Exclude– neoadjuvant
Bottomley A, Therasse P, Piccart M, Efficace F, Coens C, Gotay C*, et al.* Health-related quality of life in survivors of locally advanced breast cancer: an international randomised controlled phase III trial. Lancet Oncology. 2005;6(5):287-94.	Exclude – neoadjuvant
Burnell M, Levine MN, Chapman JA, Bramwell V, Gelmon K, Walley B*, et al.* Cyclophosphamide, epirubicin, and Fluorouracil versus dose-dense epirubicin and cyclophosphamide followed by Paclitaxel versus Doxorubicin and cyclophosphamide followed by Paclitaxel in node-positive or high-risk node-negative breast cancer. Journal of clinical oncology. 2010;28(1):77-82.	Exclude – fluorouracil not the only different factor Additional factors
Burnell MJ, Shepherd L, Gelmon K, Bramwell V, Walley B, Vandenberg E*, et al.* A randomized trial of CEF versus dose-dense EC followed by paclitaxel versus AC followed by paclitaxel in women with node positive or high risk node negative breast cancer, NCIC CTG MA.21: results of the final relapse free survival analysis. Cancer research. 2012;72(24).	Exclude – fluorouracil not the only different factor Additional factors
Cognetti F, Bruzzi P, De Placido S, De Laurentiis M, Boni C, Aitini E, et al. Epirubicin and cyclophosphamide (EC) followed by paclitaxel (T) versus fluorouracil, epirubicin and cyclophosphamide (FEC) followed by T, all given every 3 weeks or 2 weeks, in node-positive early breast cancer (BC) patients (pts). Final results of the gruppo Italiano mammella (GIM)-2 randomized phase III study. Cancer research. 2013;73(24).	Exclude – conf abstract
Del Mastro L, De Placido S, Bruzzi P, De Laurentiis M, Boni C, Cavazzini G, et al. 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. Lancet (london, england). 2015;385(9980):	**Include NCT00433420**
Brandberg Y, Johansson H, Hellström M, Foukakis T, Gnant M, Von Minckwitz G*, et al.* The adjuvant panther study: A randomized comparison between dosedense and tailored epirubicin (E), cyclophosphamide (C) and docetaxel (D) vs. standard dose 5-fluorouracil (F), epirubicin (E), cyclophosphamide (C) and docetaxel-Health-related quality of life during ongoing therapy. Journal of Clinical Oncology Conference. 2016;34(Supplement 15).	Exclude – conf abstract
Foukakis T, von Minckwitz G, Bengtsson NO, Brandberg Y, Wallberg B, Fornander T, et al. Effect of Tailored Dose-Dense Chemotherapy vs Standard 3-Weekly Adjuvant Chemotherapy on Recurrence-Free Survival Among Women With High-Risk Early Breast Cancer: A Randomized Clinical Trial. JAMA. 2016;316(18):1888-96.	Exclude – fluorouracil not the only different factor Additional factors
Janni W, Harbeck N, Rack B, Augustin D, Jueckstock J, Wischnik A*, et al.* Randomised phase III trial of FEC120 vs EC-docetaxel in patients with high-risk node-positive primary breast cancer: final survival analysis of the ADEBAR study. British journal of cancer. 2016;114(8):863-71. 10.1038/bjc.2016.82	Exclude – fluorouracil not the only different factor Additional factors
Mavroudis D, Matikas A, Malamos N, Papakotoulas P, Kakolyris S, Boukovinas I*, et al.* Dose-dense FEC followed by docetaxel versus docetaxel plus cyclophosphamide as adjuvant chemotherapy in women with HER2-negative, axillary lymph node-positive early breast cancer: a multicenter randomized study by the Hellenic Oncology Research Group (HORG). Annals of oncology : official journal of the european society for medical oncology. 2016;27(10):1873-8.	Exclude – fluorouracil not the only different factor Additional factors

Schwentner L, Harbeck N, Singer S, Eichler M, Rack B, Forstbauer H*, et al.* Short term quality of life with epirubicin-fluorouracil-cyclophosphamid (FEC) and sequential epirubicin/cyclophosphamid-docetaxel (EC-DOC) chemotherapy in patients with primary breast cancer-results from the prospective multi-center randomized ADEBAR trial. Cancer Research Conference: 38th Annual CTRC AACR San Antonio Breast Cancer Symposium San Antonio, TX United States Conference Publication:. 2016;76(4 SUPPL. 1).	Exclude – fluorouracil not the only different factor Additional factors
Foukakis T, Papakonstantinou A, Matikas A, Bengtsson NO, Malmstrbm P, Hedayati E*, et al.* Tailored dose-dense chemotherapy in combination with trastuzumab as adjuvant therapy for HER2-positive breast cancer: a secondary analysis of the phase III PANTHER trial. Journal of clinical oncology. 2019;37.	Exclude – fluorouracil not the only different factor Additional factors
Brandberg Y, Johansson H, Hellstrom M, Gnant M, Mobus V, Greil R*, et al.* Long-term (up to 16 months) health-related quality of life after adjuvant tailored dose-dense chemotherapy vs. standard three-weekly chemotherapy in women with high-risk early breast cancer. Breast Cancer Research & Treatment. 2020;181(1):87-96.	Exclude – fluorouracil not the only different factor Additional factors
Papakonstantinou A, Hedayati E, Hellström M, Johansson H, Gnant M, Steger G*, et al.* Neutropenic complications in the PANTHER phase III study of adjuvant tailored dose-dense chemotherapy in early breast cancer. Acta oncologica (Stockholm, Sweden). 2020;59(1):75-81.	Exclude – fluorouracil not the only different factor Additional factors
Papakonstantinou A, Matikas A, Bengtsson NO, Malmström P, Hedayati E, Steger G*, et al.* Efficacy and safety of tailored and dose-dense adjuvant chemotherapy and trastuzumab for resected HER2-positive breast cancer: results from the phase 3 PANTHER trial. Cancer. 2020;126(6):1175-82.	Exclude – fluorouracil not the only different factor Additional factors
Del Mastro L, Poggio F, Blondeaux E, de Placido S, Giuliano M, De Laurentiis M*, et al.* Dose-dense adjuvant chemotherapy in early-stage breast cancer patients: end-of-study results from a randomised, phase III trial of the Gruppo Italiano Mammella (GIM). Annals of oncology. 2022;33:S599-S600.	Exclude – conf abstract
Del Mastro L, Poggio F, Blondeaux E, De Placido S, Giuliano M, Forestieri V*, et al.* Fluorouracil and dose-dense adjuvant chemotherapy in patients with early-stage breast cancer (GIM2): end-of-study results from a randomised, phase 3 trial. The lancet Oncology. 2022;23(12):1571-82.	**Include NCT00433420**
Duplicate of The lancet Oncology. 2022;23(12):1571-82.	Duplicate
Morganti S, Tolaney SM. Fluorouracil and dose-dense adjuvant chemotherapy in breast cancer: lessons learned from the 20-year-old GIM2 trial. Lancet Oncology. 2022;23(12):1482-4.	Exclude–editorial
Identified by GDG Yu KD, Liu XY, Chen L, Mo M, Wu J, Liu GY, Di GH, Verschraegen C, Stover DG, Zhuang ZG, Bertucci F. Anthracycline-free or short-term regimen as adjuvant chemotherapy for operable breast cancer: a phase III randomized non-inferiority trial. The Lancet Regional Health-Western Pacific. 2021 Jun 1;11:100158	Exclude – fluorouracil not the only different factor Additional factors