



Developed by
**EPIQ: Effective Practice,
 Informatics and
 Quality Improvement**
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THE UNIVERSITY OF AUCKLAND
 FACULTY OF MEDICAL AND
 HEALTH SCIENCES
 School of Population Health

CAT Maker

Name & date	Dr S Wells	email address	s.wells@auckland.ac.nz
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Clinical Scenario

The FinHer Study Joensuu H. et al. 2006

In this study - the hypothesis is that trastuzumab administered before other cardiotoxic therapies and concomitantly with potentially synergistic chemotherapy for only nine weeks would limit cardiotoxicity seen in HERA2005/2007 and Romond et al 2006 (Joint analysis of NSABP B-31 and NCCTG N9831) and maintain efficacy.

In this study, HER2 positive women were randomised to 4 regimes:

- 1) 3 cycles of **docetaxel** 100mg/sqm BSA as 1hr infusion day 1 of 21-day cycle. Then 3 cycles **FEC**: IV fluorouracil 600mg/sqm, epirubicin 60mg/sqm and cyclophosphamide 600mg/sqm all on day 1 of 21 day cycle. Nine **trastuzumab** infusions were also administered at one-week intervals from day 1 of first docetaxel cycle.
- 2) 3 cycles of **docetaxel** 100mg/sqm BSA as 1hr infusion day 1 of 21-day cycle. Then 3 cycles **FEC**: IV fluorouracil 600mg/sqm, epirubicin 60mg/sqm and cyclophosphamide 600mg/sqm all on day 1 of 21 day cycle. No trastuzumab infusions
- 3) 3 cycles of **vinorelbine** 25mg/sqm iv infusion days 1, 8 and 15 of 21-day cycles. Then 3 cycles **FEC**: IV fluorouracil 600mg/sqm, epirubicin 60mg/sqm and cyclophosphamide 600mg/sqm all on day 1 of 21 day cycle. No trastuzumab infusions administered at one-week intervals from day 1 of first vinorelbine cycle.
- 4) 3 cycles of **vinorelbine** 25mg/sqm iv infusion days 1, 8 and 15 of 21-day cycles. Then 3 cycles **FEC**: IV fluorouracil 600mg/sqm, epirubicin 60mg/sqm and cyclophosphamide 600mg/sqm all on day 1 of 21 day cycle. The vinorelbine infusion on day 15 omitted from the third cycle to allow initiation of FEC at full dose with delay. No trastuzumab.

Step 1: Ask a clinical question using PECOT framework

P opulation or patient	For women with metastatic breast cancer who have an overexpression of HER2
E xposure (intervention)	Does trastuzumab given for only 9 weeks concomitantly with potentially synergistic chemotherapy (two arms -one with 3 cycles of docetaxel the other 3 cycles of vinorelbine) followed by 3 cycles of FEC
C omparison (control)	Compared to 3 cycles of docetaxel or vinorelbine with no trastuzumab followed by 3 cycles of FEC
O utcomes	influence disease-free survival and overall survival and limit cardiotoxicity?
T ime	1 year, 2 years, 5 years

Step 2: Access (search) for the best evidence using PECO(T) framework

Key search terms

PECO(T) component	Primary search term		Synonym 1		Synonym 2	
P opulation or patient	N/A	OR		OR		AND
E xposure (experimental)	N/A	OR		OR		AND
C omparison (control)	N/A	OR		OR		AND
O utcomes	N/A	OR		OR		AND
(T) ime	N/A	OR		OR		AND
F ilters & limits	N/A	AND		AND		

Databases searched

Database:	Cochrane	Other secondary sources	PubMed / OvidMedline	Other:
Number of hits:				

Evidence selected

Joensuu H. et al Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. N Engl J Med 2006;354:809-20.

Justification for selection (if evidence already independently appraised by reliable source, go to Page 4)

Randomised controlled trials identified by Pharmac via Belgian Health Care Knowledge Centre.

Intervention Studies

Step 3: Appraise the study using the **PECOT** framework

a. "hang" the study on the **GATE** (Graphic Appraisal Tool for Epidemiology) Frame



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Populations				Source Population	Women with breast cancer enrolled from 10 participating institutions in Finland from Oct 2000-September 2003.															
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			...adverse																	
Time	Unit of time (e.g. year) if rate wanted:			Time	3 years (median follow-up)															
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Results (unadjusted) with 95 % confidence intervals					
Calculated in GATE frame	Occurrence per 1 persons		Intervention effects per 1 persons		Number needed to treat (NNT) in 1 person-
	in exposure group (EGO)	in comparison group (CGO)	Relative effect (EGO/CGO)	Absolute effect (EGO-CGO)	
Categorical outcome: Intention to treat analyses 95% CIs	0.10 0.06 to 0.17	0.23 0.17 to 0.32	0.44 0.24 to 0.83	-0.13 -0.22 to -0.03	-7 -4 to -30
Categorical outcome: On-treatment analyses 95% CIs	0.10 0.06 to 0.17	0.23 0.17 to 0.32	0.45 0.24 to 0.84	-0.13 -0.22 to -0.03	-7 -4 to -31
Continuous outcome: Analysis of means 95% CIs	0.00	0.00	0.00	0.00	
Key outcome & analysis method, as published:	Disease free survival -Kaplan-Meir curves presented with Cox proportional hazards regression analysis to estimate hazard ratios and 95% confidence intervals. The hazard ratio was similar when adjustment was made according to type of chemotherapy given, institution or number of positive nodes				
Key results Reported CIs			0.42 0.21 to 0.82		

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	Categorical outcome: On-treatment analyses 95% CIs	0.05 0.02 to 0.11	0.12 0.07 to 0.19	0.43 0.17 to 1.09	-0.07 -0.14 to 0.00	-14 -7 to ∞ to 273														
Continuous outcome: Analysis of means 95% CIs	0.00	0.00	0.00	0.00																
Reported	Key outcome & analysis method, as published:																			
	Overall survival -Kaplan-Meir curves presented with Cox proportional hazards regression analysis to estimate hazard ratios and 95% confidence intervals.																			
	Key results		Reported CIs																	
			0.41																	
			0.16 to 1.08																	

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Intervention Studies			
Step 3: Appraise the study using the PECOT framework			
b. assess study quality (RAAMb) + = good, ~ = mixed, x = poor, nr = not reported, na = not applicable			
Evaluation criteria (RAAMb)		Quality + - x nr na	
Populations	Representative?		
	Source population well described?	+	The source population were women in Finland who developed breast cancer in the time period October 2000-September 2003
	Eligible population well described?	+	Yes, the inclusion and exclusion criteria were reasonably explicit allowing replication within the 10 Finnish centres/institutions and appear appropriate for the study objectives.
	Participants representative of eligibles?	~	Probably. The authors note that those who took part represented 40% of the eligible women in Finland who received a diagnosis of breast cancer within this period. Not sure if this means eligible after applying incl/excl criteria ie post-staging workup or simply 40% of those who had a diagnosis of breast cancer.
Were relevant personal (prognostic) characteristics of participants reported?	-	While there is data on age, tumour size, histology, nodal and hormone receptor status there was no data on menopausal status or other potential confounders such as smoking and socioeconomic status.	
Exposure & Comparison	Allocated appropriately (or Adjusted) and Accounted for?		
	Exposure & comparison interventions well described & valid?	+	The exposure and comparison interventions were described in sufficient detail and appears valid, assuming that the chemotherapy (doxycetel, vinorelbine, FEC and trastuzumab) is able to be delivered in the manner/doses described.
	Allocation to exposure and comparison groups randomised?	+	Yes random assignment into groups with stratification according to HER2 positive or negative status.
	Allocation concealed?	+	Yes the authors report that the assignment was done centrally and with computer assisted blinding so likely that the randomisation sequence was retained at assignment.
	Exposure and comparison groups similar at baseline? If not, were these adjusted?	+	Baseline characteristics are reported in Table 1. The exp and comparison groups are well- balanced except that larger tumours were more common in the doxycetel group than in the vinorelbine group (all participants) and axillary nodal metastases tended to be more frequent in the trastuzumab group than no-trastuzumab group (HER2 subgroup). Adjustments were made in the analyses for type of chemotherapy if HER2 subgroup, centre and the number of positive nodes.
	Participants and/or staff blind to exposure and comparison?	x	No - this is an open-label trial- neither participants or staff were blind to their treatment assignment
	Compliance with exposure and comparison adequate?	+	This was reported extremely well and not likely to cause important bias. The doxycetel dosage was reduced from 100mg/sqm to 80mg/sqm because 36.9% of women by Feb 2002 had received a diagnosis of neutropenic fever. Three cycles of doxycetel or vinorelbine were completed by 94% and 95% of patients respectively. The full dose of trastuzumab was administered in 99.1% of cycles and 93.6% and 96.6% of the protocol specified trastuzumab infusions were delivered to women in the doxycetel and vinorelbine groups respectively. Only one woman assigned to vinorelbine/trastuzumab group did not receive study treatments.
	Contamination acceptably low?	+	The authors do not report any contamination. It appears that no women received trastuzumab who were not randomly assigned to this group.
	Other interventions similar in both groups?	~	Probably given the equal numbers in doxycetel and vinorelbine groups who had adjuvant radiotherapy (97.0% and 97.6%) and tamoxifen (71.1% and 73.8%).
	All participants accounted for at study conclusion?	+	Yes the authors report that no patient was lost to follow-up.
Could interventions be applied in real life?	+	Yes, if the drug was available with appropriate oncology services and follow-up for adverse side effects.	
Outcomes	Measured well (blinded or objective)?		
	Outcome measures well described & valid?	+	Yes primary endpoint well described and objective. Recurrence free survival- death or detection of local, distant or contralateral invasive breast cancer confirmed by histology, cytology or radiology. Secondary outcomes less well described- adverse effects (as recorded on protocol specified forms) and the effect of treatment on LVEF (measured by echocardiography or isotope cardiography). Both are subject to inter-rater variation. Time to distant recurrence and overall survival measured from time of randomisation are objective and valid measures.
	Blinded outcome measurement?	-	No, it appears that outcomes were not assessed by people blind to allocation. I don't think that this would lead to major assessment bias given objective outcomes eg total mortality and fairly objective disease survival outcomes eg, histology confirmation of recurrent distal cancer
	Outcome measurement complete?	+	It appears so other than the one patient in vinorelbine/trastuzumab group who did not receive study treatment.
Were all important outcomes assessed?	+	Other patient outcomes not assessed were longer term effects of trastuzumab ?later cardiac toxicity, differences in quality of life and return to usual daily activities.	
Time	Similar follow-up time in exposure & comparison groups?	+	Yes, follow-up time similar in both groups.
	Was follow-up time meaningful?	~	Yes for the primary endpoint. Three year median follow up showed an 56% reduction in disease free survival with trastuzumab (varying from 44% vinorelbine -72%doxycetel in these crude analyses) which was a 13% absolute difference over 3-4 years. Overall survival tended to be better in the tratuzumab group with similar HR as the combined primary endpoint but the study was not powered for this outcome and the effect estimate did not reach statistical significance. It is possible that a longer follow-up time would show a difference between the 2 groups.
Results	Intention to treat analysis?	~	It appears all who patients were analysed to the groups to which they were originally allocated with the exception of the one woman who did not receive study treatments.
	Estimates of Intervention effects given or calculable?	+	Both given and calculable
	Precision of intervention effects given or calculable?	+	Both given and calculable
	Analytical methods appropriate?	+	Yes appropriate analytic methods using Cox proportional hazards regression analysis
Summary	Are the study results internally valid (i.e unbiased)?	-	The key factors to minimise bias are randomisation, allocation concealment, blinding to allocation and blind and objective outcome assessment. The study was randomised, allocation concealment was reported and outcomes were fairly objective. However both exposure outcomes and outcome assessment were unblinded. This study lacked power/numbers to detect differences in overall survival for trastuzumab treatment.
	Are results precise enough to be meaningful? If not, was power sufficient?	+	Yes, for the primary endpoint the results were precise and power calculations were reported. The study was not powered for the secondary endpoints (overall survival).
	Can the applicability of the results (i.e external validity) be determined?	+	Reasonably- these results apply to women with HER2 positive early stage invasive breast cancer who completed surgical therapy and had normal LVEF and no major cardiac disease. The women were Finnish, median age 50years (ranging from 25-65 yrs) unknown smoking and socioeconomic status and treated in secondary care settings with surgical, radiation, cardiac imaging, pathology and other services available.
	Overall study quality	+	A reasonably well designed study - unfortunately a bigger one is needed to determine overall survival benefit.

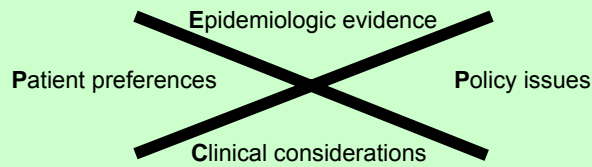
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Intervention Studies



Step 4: Apply the evidence

The X-factor



Summarise epidemiologic evidence

This study	Answered the question but not enough power for overall survival analyses- it appears that concurrent trastuzumab prior to FEC was not associated with any cardiotoxic effects and women with HER2 overexpression and tratsuzumab experienced the same risk as those without thi expression.
Consistency with other studies	
Debate & Discussion	

Identify other issues

Patient preferences	
Policy issues	
Clinical considerations	

The bottom line: weigh everything up

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Step 5: Audit personal EBP skills (for professional development) and audit usual clinical practice (for quality improvement)

Assess personal skills	
Plan to implement decision in your practice setting. How can you (or your team) improve practice with respect to the topic covered in this CAT?	

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