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Prognostic variables in metastatic breast cancer: is there an age differential?

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Background: Whether breast cancer in young is biologically different from elderly is still a debated question.This study was undertaken to delineate prognostic markers to predict risk of recurrence and response to therapy in patients younger than 35 years.
Methods: This is an open labeled, prospective, non randomized study conducted at Kidwai memorial institute of Oncology, Bangalore, a tertiary care hospital with 16,000 new cases/year between January 2004 and December 2006. Patients with diagnosis of limited metastatic breast cancer were enrolled. For each case aged <35 years, 1 control (>35 years) treated during same period was chosen. Pathologic parameters and clinical details noted down with emphasis on previous treatment. Those who are Hormone receptor (HR) positive received Tamoxifen, those with Negative receptor status received Taxanes (3 weekly Paclitaxel 175 mg/m^2) alone or in combination with Herceptin (2 mg/kg/wk) if HER-2 is overexpressed. Toxicity was measured by CTC version 3.0, Response – RECIST criteria and quality of life using indigenously developed QOL questionnaire. Overall survival (OS) and Time to tumor progression (TTP) after treatment were calculated by intention to treat analysis.
Results: 120 patients were studied. Tumor character and response to therapy are detailed in Table 1.
Conclusion: Compared with older patients, young women have more endocrine unresponsive tumor, familial cancer and likely to present with higher grade, size, Her-2 overexpression, more extensively proliferating and vessel invading disease. Younger patients had shorter disease free interval (early relapse) and had high tumor burden and higher number of metastatic sites at time of relapse. The response rates as well as OS&TTP are worse in younger population. Our findings support that younger patients will have more aggressive disease (BMC Cancer 2004, 4:82). It is in contrast to the other major meta-analysis which showed that age is not an important prognostic factor [Eur J Cancer 2005 Jul; 41(10): 1446−52].

Table 1. Prognostic variables and response character

Variable	Age group	
	young (mean±SD)	old (mean±SD)
Age	30.9±3.4	46.2±10.6
Relapse free interval from end of adjuvant chemotherapy (months)	24.4±6.6	39.6±10.8
Family History	45%	15%
Percentage with menopause after adjuvant CT	20%	45%
HR	35%	55%
HEr2	50%	30%
Tumor size (at initial diagnosis)	5.6±2.8	2.9±1.6
nodes	6.4±2.6	2.9±3.2
Grade	1.8±0.8	1.2±0.6
LV invasion	45%	22%
Number of metastatic sites	2.2±0.8	1.8±0.3
Sum of maximum diameters-cm (RECIST)	14.8±5.4	9.6±5.8
Response rates (CR:PR:SD:PD) percentages	15:20:25:40	20:25:30:25
Toxicity including all types (grade III/IV)	33%	50%
QOL improvement from mean	14.8±8.4	11.3±5.4
OS: TTP (weeks)		
HR+/HER2−	45±12/32±10	92±24/68±22
HR−/Her2+	29±8/19±8	46±11/34±12
HR+/Her2+	36±11/21±9	68±18/44±20
HR−/Her2−	39±14/24±7	77±24/50±16

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Economic impact of adding capecitabine (X) to docetaxel (T) and trastuzumab (H) as first-line therapy for HER2-positive advanced or metastatic breast cancer

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Background: A recently published (Wardley et al SABCS 2006) randomised phase II trial (CHAT) compared XTH with TH. The primary endpoint, overall response rate, was similar with XTH (71%) and TH (73%), while XTH showed superior time to progression (TTP) (hazard ratio [HR] 0.70, p = 0.04, median 18.2 vs 13.8 months, respectively) and a trend toward superior progression-free survival (HR 0.72, p = 0.06, median 14.8 vs 12.8 months, respectively). Overall survival data are immature. This analysis evaluates the potential pharmacoeconomic impact of adding X to TH.
Methods: Direct medical costs during the trial were estimated from the Italian health system perspective. Actual doses of both regimens were modelled from trial data. Grade 3/4 adverse events (AEs) and related resources were analysed and an expert panel estimated costs of treating major AEs. Other costs relating to laboratory tests and drug administration were assumed to be the same in both arms.
Results: Based on trial data, the estimated total direct medical costs would be slightly lower for XTH: €31,800 vs €32,000 for TH. XTH and TH safety profiles were different: XTH resulted in more grade 3/4 non-haematological AEs than TH but less grade 3/4 neutropenia, complicated neutropenia and febrile neutropenia. The estimated mean AE costs per patient were similar in both arms. An adjusted mean monthly cost was calculated to correct for the difference in number of cycles of each drug in the two arms: XTH drug costs would be ~€200 lower per month than with TH.
Conclusion: With the convenience of oral therapy, adding X to TH does not increase the number and duration of infusion visits or increase costs. For patients, physicians and payers, XTH is a good alternative for the treatment of advanced/metastatic breast cancer.

Adjusted mean monthly cost per regimen based on trial data (excluded AEs)

	XTH	TH
Trastuzumab	€2200	€2300
Docetaxel	€1000	€1400
Capecitabine	€300	–
Total	**€3500**	**€3700**

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The total fiscal UK costs of managing women with relapsed breast cancer – the strong economic case for adjuvant exemestane

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Background: Switching to aromasin® (E) from tamoxifen (T) at 2 years incurs an absolute reduction in the risk of relapse of 4.7% according to International Exemestane Study (IES). To find out whether this strategy is cost efficient, this randomised retrospective analysis measured the *total hospital and community cost* of managing a patient with relapsed breast cancer, then compared this to the extra cost of adjuvant exemestane.
Methods: Our Breast Unit Data Base identified 168 patients relapsing between March 2000 and 2005. The demographics, ER were recorded. Sealed envelope randomisation selected 77 of these for scrutiny. The costs were derived from hospital notes, computer records, pharmacy records, GP, district nurse and hospice records. Activity included; in and outpatient activity, oncology drugs, radiology, radiotherapy, serum investigations, GP, district nurse, hospice visits and any medical activity which was directly related to the management of their relapsed cancer. Data recording stopped at a predetermined date of 1/1/07 where 52 patients had died. Hospital, GP and district nurse activity costs were derived from the 2005 published DoH index tariffs. Radiotherapy cost were taken from the Reference Costs' National Average Unit Cost. Drug price tariffs referred to the British National Formulary.

Findings: As the extra cost of 2 yrs T + 3 yrs E over 5 yrs T (considering bone density scans) was £3,280, it cost £69,787.2 to prevent one women relapsing (£3,280/4.7%). Our analysis calculated that the average monthly cost of treating a relapse was £752.35. As the mean survival was 32.6 months the mean total cost/patient was £24,526.66. Subtracting this from the initial extra cost of E gives a mean extra cost of £45,260.54 to prevent one patient relapsing. As the median survival of the relapsed women in our analysis was 2.72 yrs and the expected survival if they don't relapse is 18 years, the cost per life year saved was £2,962/yr.
Discussion: Notwithstanding the humanitarian issues, these figures from a single institution suggest it is cost efficient to switch to E at 2 years. As these figures reflect the management of women over the last seven years they are likely to underestimate the future cost. Further modelling of the data in relation to the 25.5% who were HER2+ in terms of the extra cost of herceptin and the longer survival with relapsed disease, together with further detailed subset cost effectiveness analysis will be presented.

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Clinical benefit of trastuzumab plus vinorelbine as second-line treatment for women with HER2-positive metastatic breast cancer beyond disease progression

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Background: The benefits of multiple lines of trastuzumab (Herceptin®; H) therapy have been increasingly reported for women with HER2-positive metastatic breast cancer (MBC). We report the results from the first planned interim analysis of a Phase II, 2 step, multicentre trial evaluating second-line H + vinorelbine (N) in women who received first-line H + taxane therapy for HER2-positive MBC.
Materials and Methods: Women aged ⩾18 years with HER2-positive (IHC3+/2+ and FISH+) MBC who progressed following first-line H + taxane therapy were enrolled. All patients (pts) received H (8 mg/kg iv loading dose followed by 6 mg/kg q3w or 4 mg/kg iv loading dose followed by 2 mg/kg qw) + N (30 mg/m^2 days 1 and 8, q3w) until disease progression (PD). The primary end point was overall response rate (ORR); secondary end points included time to progression, time to treatment failure, overall survival and safety.
Results: To date 17 pts with HER2-positive (16 pts IHC 3+; 1 pt IHC 2+ and CISH+) MBC have been evaluated. Mean age was 54 years (range 42−70). Nine pts had hormone receptor-positive MBC (7 pts ER+/PgR−; 2 pts ER−/PgR+). Prior to enrolling, 12 pts had received previous chemotherapy in the neoadjuvant/adjuvant setting and 6 had undergone adjuvant hormonal therapy. All pts had previously received H in combination with paclitaxel (9 pts) or docetaxel (8 pts) as first-line therapy for MBC. In addition to these treatments for MBC, 3 pts had received hormonal therapy. A median of 6 H + N treatment cycles (range 2−14) were administered, with 2 pts receiving H q3w and 15 pts receiving H qw. The clinical benefit rate was 53% and ORR was 30%, with 2 pts (12%) showing a complete response, 3 pts (18%) experiencing a partial response and 4 pts (23%) achieving stable disease lasting 6 months. Fourteen pts withdrew from the study due to PD. The main serious adverse event was grade 3/4 neutropenia, leading to a delay and dose reduction of N in 4 pts. Only 2 asymptomatic grade 1 cardiac events were reported for the 9 pts for whom cardiac function data were available. No deaths were reported.
Conclusions: First planned interim results indicate that treatment with H + N in pts with MBC who progressed following first-line H + taxane therapy is active and well tolerated. These data provide further evidence for the clinical potential of multiple lines of H in pts with HER2-positive MBC.

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Cost-effectiveness (CE) of lapatinib plus capecitabine (L+C) in women with ErbB2+ (HER2+) metastatic breast cancer (MBC) who have received prior therapy with trastuzumab (TZ) from the United Kingdom (UK) National Health Service (NHS) perspective

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Background: Lapatinib (Tyverb®, Tykerb®) is an oral small molecule dual tyrosine kinase inhibitor that binds intracellularly to the ATP binding site of the EGFR and HER2 receptors. In EGF100151, L+C improved time to progression (TTP) and progression free survival (PFS) vs capecitabine monotherapy (C-only) in women with ErbB2+ (HER2+) MBC who have received prior therapy with TZ. CE of L+C has not been evaluated to date.
Methods: We evaluated CE (ΔCosts/ΔQuality Adjusted Life Years [QALYs]) of L+C vs C-only in women with ErbB2 (HER2+) MBC who have received prior therapy with TZ from the UK NHS perspective using an assumed acquisition cost. Because many patients such in typical clinical practice receive monotherapy with vinorelbine (V-only) or TZ-only or combination therapy with TZ and C (TZ+C) or TZ and V (TZ+V), we also assessed CE of L+C vs these strategies. PFS and overall survival (OS) with L+C and C-only were based on Weibull survival functions estimated using data from EGF100151. Post-progression survival (PPS) for L+C and C-only were calculated as OS − PFS. Lacking data from comparative trials in this population, PFS with TZ+C, TZ+V and TZ-only were estimated from published cohort studies of continued TZ±chemotherapy (TZ±CT) following progression; PPS was assumed to equal that with L+C. PFS and OS with V-only were assumed equal to that with C-only. Drug costs were from the British National Formulary; other costs from NHS reference costs and published studies. Utility values for PFS were from EQ-5D data collected in EGF100151; for PPS, from a UK community-based study of preferences for disease states in MBC. Costs and QALYs were discounted at 3.5% annually.
Results: Results are presented in the table. L+C is dominant (provides more QALYs at a lower cost) vs TZ+V, TZ+C, and TZ-only. In probabilistic sensitivity analyses, the probability (p) that L+C is CE given willingness to pay (WTP) for QALY of £30,000 ranged from. 05 vs C-only to. 95 vs TZ+V.

	L+C	C-only	V-only	TZ+V	TZ+C	TZ-only
Total costs (£)	25,678	11,805	14,094	30,131	27,864	26,753
Total QALYs	0.857	0.686	0.686	0.714	0.714	0.714
CE L+C (£/QALY)		81,129	67,743	Dominant	Dominant	Dominant
p L+C is CE (WTP = £30,000/QALY)		0.05	0.07	0.95	0.89	0.85

Conclusions: The efficacy of L+C has been demonstrated in women with Erb2+ (HER2+) MBC who have received prior therapy with TZ. This study, using indirect comparisons in the absence of head-to-head data, suggests that L+C is a cost effective therapeutic option vs TZ±CT from the UK NHS perspective.

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Expression profile of TRAIL and its receptors in breast cancer patients with invasive ductal carcinoma

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Background: TNF-Related Apoptosis Inducing Ligand (TRAIL) selectively induces apoptosis in cancer cells but not in normal cells, and several clinical trials have been started to assess the safety and anticancer properties of TRAIL in patients with cancer. Four different receptors have been identified to bind to TRAIL: two are known as killer receptors [TRAIL-R1 (DR4) and TRAIL-R2 (DR5)], the other two [TRAIL-R3 (DcR1) and TRAIL-R4 (DcR2)] are decoy receptors which counteract TRAIL-induced cell death. Because high levels of DcR2 expression has recently been correlated with carcinogenesis in synoviocytes, prostate and lung, the significance of