Poor survival outcomes in HER2 positive breast cancer patients with low grade, node negative tumours.

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Abstract

We present a retrospective analysis on a cohort of low grade, node negative patients demonstrating that HER2 status significantly impacts on survival in this otherwise very good prognostic group. Our results provide support for the use of adjuvant trastuzumab in patients who are typically classified as very good prognosis, not routinely offered standard chemotherapy, and as such do not fit current prescribing guidelines for trastuzumab.

Keywords

HER2, breast cancer, trastuzumab

Background

HER2 amplification has become the prototype biomarker for translation of a laboratory discovery through to development of a highly successful individualised chemotherapy agent. Slamon et al (Slamon et al., 1987) established HER2 as a poor prognostic marker for survival in breast cancer and developed a monoclonal antibody, trastuzumab, targeted to HER2 as a novel therapy for breast cancer patients. More recently, randomised trials have shown a clinical benefit of trastuzumab with significant overall survival benefit in early breast cancer over observation alone after chemotherapy (Joensuu et al., 2006; Romond et al., 2005; Smith et al., 2007). As a resuslt, trastuzumab has been introduced into routine clinical practice in the UK for HER2 positive patients who have finished their standard adjuvant treatment. Current Scottish and NICE guidelines parallel the HERA trial entry criteria where trastuzumab is offered only to those patients who have already received standard chemotherapy regimes as part of their treatment regime.

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However, there remains a small subset HER2 positive patients who are low grade and node negative who are currently ineligible for trastuzumab treatment as clinically they have deemed to have no requirement for standard adjuvant chemotherapy. In our region approximately 25% of HER2 patients are not offered Herceptin as they are deemed to be ‘low risk’(personal communication). A recent review (Dinh et al., 2008) outlines the controversy and current lack of trial evidence for use of trastuzumab in small, node-negative cancers with none of the randomised clinical trials having addressed this small but important group of patients.

Our study analyses a retrospective cohort of tumours traditionally classed by way of grade and nodal status as 'low risk', to assess if HER2 positivity impacts on survival in this otherwise very good prognostic group.

Methods

Patients

We have a large cohort (n=1351) of breast cancers diagnosed between 1980-2002 with full follow-up (median 6.5yrs) and clinicopathological details. Tissue specimens from these cancers had been used to create TMAs (tissue microarray technology) for research purposes. From this database we wished to identify a group of patients who would classically be identified as 'low risk'. We selected all node negative, grade 1 or 2 cancers (n=362) for further analysis.

HER2 status assessment

HER2 status was identified using currently applicable clinical methodology (Bartlett et al., 2003). Dako Herceptest was used to quantify immunohistochemical staining. All 3+ (high intensity) staining specimens were considered positive. All 2+ (moderate staining) specimens underwent FISH analysis and those who demonstrated HER2 amplification were also classed as positive.

Analysis

SPSS (v15) was used to plot Kaplan-Meier survival curves using breast cancer specific death as an outcome endpoint. Cox Regression analysis was performed to assess hazard ratios for the impact of HER2 status on breast cancer specific death in the subcategories split on ER status, age of patient and size of tumour.

Results

Patient characteristics (table 1)

We selected all node negative, grade 1 or 2 cancers (n=362) from our original cohort. This group were 90% ER positive, with 71% smaller than 20mm. 80% were aged over 50 and 10% received chemotherapy and 91% received endocrine therapy (tamoxifen).

HER2 status and survival

6.1 % of cases were HER2 positive. The overall hazard ratio (HR) for HER2 positivity was 5.65 (95% CI 2.4-13.1, $p < 0.001$) giving 5yr breast cancer specific survival rates of 68% compared to 96% for the HER2 negative group (figure 1). This reduction in survival in HER2 positive cases persisted when patients were split into subgroups by ER status, tumour size and age (table 2).

Discussion

Our results suggest that no HER2 positive patient should be classed as 'low risk'. There have been conflicting reports on the impact of HER2 status in good prognostic groups in the literature. Some have shown similar results in node negative patients (Andrulis et al., 1998; Schmidt et al., 2005; Paik et al., 1990; Harbeck et al., 1999; Kallioniemi et al., 1991; Press et al., 1997; Quenel et al., 1995) even with small 1-10mm tumours (Joensuu et al., 2003) or with lower grade (Paik et al., 1990). Other papers have not confirmed this, (Ko et al., 2007; Richner et al., 1990; Rosen et al., 1995) although care must be undertaken when interpretating older studies that may not use currently accepted methods of HER2 testing or have underpowered studies.

Our results are in keeping with those from HERA trial that suggested that patients with the best prognosis tumours (node negative and size 1-2cm) had benefit similar to

the overall cohort (Untch et al., 2008). We suggest this reinforces the importance of having HER2 results available in MDT on these patients to enable clinicians to make informed decisions on their outlook and treatment options.

The persistence of a reduction in survival in our HER2 positive /ER positive subgroup despite endocrine therapy is in keeping with the recent trans-ATAC and BIG1-98 analysis based on HER2 status (Ranganathan et al., 2007) (Rasmussen et al., 2008) and demonstrated that we cannot not rely solely on adjuvant endocrine therapy (tamoxifen or aromatase inhibitor) in these largely ER positive patients.

Sub analysis was not performed on tumours less than 10mm in size due to the small number of tumours falling into the subgroup. However it may be argued that tumour size is a marker of the timeline over which the cancer is diagnosed, rather than a true reflection of the abnormal biology driving the cancer and hence in the case of HER2 positive disease should not be a criteria for deciding to withhold adjuvant treatment.

In conclusion, these results provide support for the rationale of using of adjuvant trastuzumab in this subgroup of patients who are typically classified as very good prognosis, may not be routinely offered standard chemotherapy, and as such do not fit current prescribing guidelines for trastuzumab. A clinical trial to assess the benefit of adjuvant trastuzumab within this group of HER2 patients would resolve this. Whether trastuzumab would be effective alone in these patient (without the potential side effects of standard chemotherapy regimes) deserves investigation. The combination of hormonal therapy and trastuzumab may be particularly attractive in ER positive patients where trastuzumab may overcome the crosstalk between the HER and ER receptors which is likely responsible for the reduced efficacy of hormonal therapy in this group.

		number	valid %
Grade	**1**	114	31.5
	2	248	68.5
ER status	**Positive**	283	89.6
	Negative	33	10.4
	unknown	49	
HER2 status	**Positive**	340	93.9
	Negative	22	6.1
Histological Type	**ductal**	286	79.2
	lobular	40	11.1
	other	35	9.7
	unknown	1	
Size	**T1 (<20mm)**	230	71.2
	T2 (20-50mm)	93	28.8
	unknown	41	
Age	**<50 years**	71	19.6
	>50 years	161	44.5
	unknown	130	35.9
Chemotherapy	**yes**	33	10.2
	no	290	89.8
	unknown	44	
Endocrine (mainly tamoxifen)	**yes**	296	91.9
	no	26	8.1
	unknown	45	

Table 1: Clinicopathological details

	number in group	Events		Sig.	Hazard Ratio	95.0% CI	
		HER2 pos	HER2neg			Lower	Upper
Whole cohort	362	7/22	26/340	**0.000**	**5.65**	2.43	13.12
ER positive	283	3/13	17/270	**0.010**	**5.07**	1.47	17.51
ER negative	33	3/6	6/27	**0.049**	**4.41**	1.01	19.27
Age<50	71	2/8	3/63	**0.036**	**8.10**	1.14	57.56
Age 50-65	161	3/9	10/152	**0.004**	**6.73**	1.84	24.65
Age>65	130	2/5	13/125	**0.033**	**5.09**	1.14	22.66
Size<20mm	230	5/16	9/214	**0.000**	**8.99**	3.00	26.96
size>20mm	93	2/5	12/88	**0.016**	**6.93**	1.44	33.49

Table 2: Subgroup Hazard Ratio analysis (Cox regression)

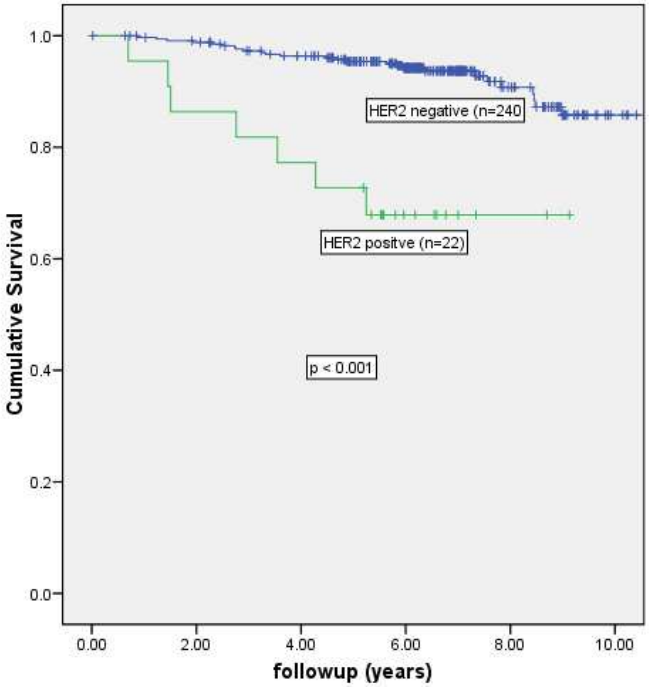
1.0
0.8
0.6
0.4
0.2
0.0
Cumulative Survival
HER2 negative (n=240)
HER2 positve (n=22)
p < 0.001
0.00
2.00
4.00
6.00
8.00
10.00
followup (years)

Figure 1

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