



Predictors of HER2 FISH positivity in primary breast cancer diagnosis scored 2+ with IHC: results of a single Institution analysis

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Background

- In breast cancer, the expression of hormone receptors and of HER2 receptor are the main determinant of treatment selection
- Trastuzumab, a humanized monoclonal antibody directed against HER2, is an essential component of HER2 positive breast cancer treatment
- HER-2 positivity is defined as a 3+ score in immunohistochemistry assay (defined as uniform intense membrane staining of > 30% of invasive tumor cells) or FISH amplification (ratio of HER-2 to CEP17 of > 2.2 or average HER-2 gene copy number > six signals/nucleus for those systems without an internal control probe)
- In case of 2+ staining at IHC, the test is considered equivocal and FISH is mandatory
- Up to 15% of breast cancers are IHC 2+

Objective

Aim of this study was to identify potential predictors of HER2 FISH positivity in newly diagnosed breast cancer with HER2 score 2+ by IHC

Patients and Methods

- All breast cancer patients diagnosed in our Institution as having HER2 score 2+ by IHC were processed for FISH analysis
- The following information were collected: age, expression of Hormone receptor, histologic grade and proliferation (Ki 67)
- ER and PgR were defined as positive in case of IHC staining in $\geq 10\%$ of tumoral cells
- Histologic grade was defined according to the Elston and Ellis classification grading system.
- The association between hormone receptor expression, nuclear grade, proliferation and FISH positivity was evaluated by using Pearson chi square test for dichotomic variables, and by logistic regression for continuous variables

Results

Patients	248
Median age at diagnosis (range)	64 (27-97)
Estrogen Receptor expression	
Negative (IHC staining < 10%)	14%
Positive (IHC staining $\geq 10\%$)	83.5%
Not evaluable	2.5%
Progesteron Receptor expression	
Negative (IHC staining < 10%)	27%
Positive (IHC staining $\geq 10\%$)	71%
Not evaluable	2%
Hormone Receptor expression	
Negative (ER and PgR negative)	10.5%
Positive (ER and/or PgR positive)	87.5%
Not evaluable	2%
Proliferation (Ki-67)	
Low proliferation (Ki-67 < 20%)	47%
High proliferation (Ki-67 $\geq 20\%$)	48%
Not evaluable	5%
Median Ki-67 expression (range)	20% (0-98%)
Histologic Grade	
Grade 1/2	33%
Grade 3	53%
Not evaluable	14%
HER2 FISH expression	
Not amplified	77%
Amplified	22%

	FISH not amplified	FISH amplified	p value
HR negative	19 (10.2%)	6 (10.7%)	p=ns
HR positive	167 (89.8%)	50 (89.3%)	
Low Ki-67 (< 20%)	95 (52.8%)	22 (40.7%)	p=ns
High Ki-67 ($\geq 20\%$)	85 (47.2%)	32 (59.3%)	
Grade 1/2	69 (42.9%)	13 (25.5%)	p=0.026
Grade 3	92 (57.1%)	38 (74.5%)	

	Odds Ratio for FISH positivity	95% CI	p value
ER negative	-		
ER positive	1.66	0.54;5.07	p=ns
PgR negative	-		
PgR positive	0.70	0.33;1.49	p=ns
Low Ki-67 (< 20%)	-		
High Ki-67 ($\geq 20\%$)	1.82	0.21;15.52	p=ns
Grade 1/2	-		
Grade 3	2.19	1.08;4.42	p=0.029

Conclusions

- In this study, the expression of hormone receptor or proliferation failed to show a significant association with FISH positivity
- Histologic grade 3 was the only parameter significantly associated with FISH positivity
- This population, selected for having HER2 score 2+, appears unexpectedly enriched in HR positive cases (87% of patients with ER and /or pgR > 10%)
- Evaluation of the prevalence of hormone receptor positivity in patients HER2 IHC 0/1+ or 3+ diagnosed during the same years is ongoing