Ki-67 as a predictor of response and long term survival in hormone receptor positive/HER2 negative breast cancer patients treated with preoperative chemotherapy

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BACKGROUND

- Preoperative chemotherapy (PCT) represents the ideal setting for an in vivo testing of prognostic/predictive role of tumor biomarkers
- The achievement of a pathologic complete response (pCR) after PCT is one of the most powerful surrogate for long-term outcome
- pCR rate is higher in poorly differentiated tumors, with high proliferation and without expression of hormone receptors (HR)
- HR+ tumors are not an homogenous group and behave differently in terms of response to PCT and have a different prognosis
- Ki67 is a marker of tumor proliferation and is associated with a worse long-term outcome
- Newer technologies have identified different molecular classes of HR+ breast cancers (Luminal A and Luminal B)
- Luminal A is characterized by low proliferation and HER2 negativity; Luminal B tumors express a high proliferation and/or HER2 positivity
- Ki-67 may help to classify HR+/HER- tumors in Luminal A and Luminal B

STUDY AIMS

- To evaluate if Ki67 is able to discriminate patients with HR+/HER2- tumor with a higher probability of obtaining a pCR after preoperative chemotherapy
- To evaluate if Ki67 is able to discriminate prognosis among patients with HR+/HER2- receiving preoperative chemotherapy

PATIENTS AND METHODS

- 275 stage II-III primary breast cancer patients treated with PCT were included in this analysis
- ER and PgR were defined as positive in case of IHC staining in ≥ 10% of tumor cells
- Patients were re-classified as follows:
  - Luminal A (HR+, HER2-, Ki67<15%)
  - Ki67-Luminal B (HR+, HER2-, Ki67≥15%)
  - HER2-Luminal B (HR+, HER2+)
  - HER2 (HR-, HER2+)
  - Triple negative (HR-, HER2-)
- The association between baseline HR, Ki-67 expression, tumor subtypes and pathologic complete response was assessed by using Pearson chi square test
- Survival curves were estimated with the Kaplan-Meier method and the log rank test was used to test for differences between groups
- DFS was calculated from the date of surgery to the date of disease relapse (local or distant), death from any cause or last follow up
- OS was calculated from the date of diagnosis to the date of death or last follow up

RESULTS

Table 1 - Patients and tumor characteristics (overall population)

Patients	N 275 (100%)
Median Age (Range)	50 (27-76)
STAGE	
I-II	213 (78.6%)
III	58 (21.4%)
HISTOLOGY	
Ductal	176 (64%)
Lobular	16 (5.8%)
Other/NA	83 (30.2%)
HISTOLOGIC GRADE	
Grade 1-2	80 (29.1%)
Grade 3	172 (62.5%)
NA	23 (8.4%)
HORMONE RECEPTORS (HR)	
Negative (ER - & PgR -)	77 (28%)
Positive (ER+ and/or PgR+)	179 (65.1%)
NA	19 (6.9%)
PROLIFERATION (Ki67)	
Median Value (Range)	25% (1-90)
HER-2 (IHC)	
Positive	68 (24.7%)
Negative	182 (66.2%)
NA	25 (9.1%)
TUMOR SUBTYPES	
Luminal A (HR+, HER2- , Ki67 <15%)	40 (14.5%)
Ki67 Luminal B(HR+, HER2-, Ki6 ≥15%)	89 (32.3%)
HER2+ Luminal B (HR+, HER2+)	44 (16%)
HER2+ (HR-, HER2+)	22 (8%)
Triple negative (HR-, HER2-)	50 (18.2%)
NA	30 (11%)

NA: not available;

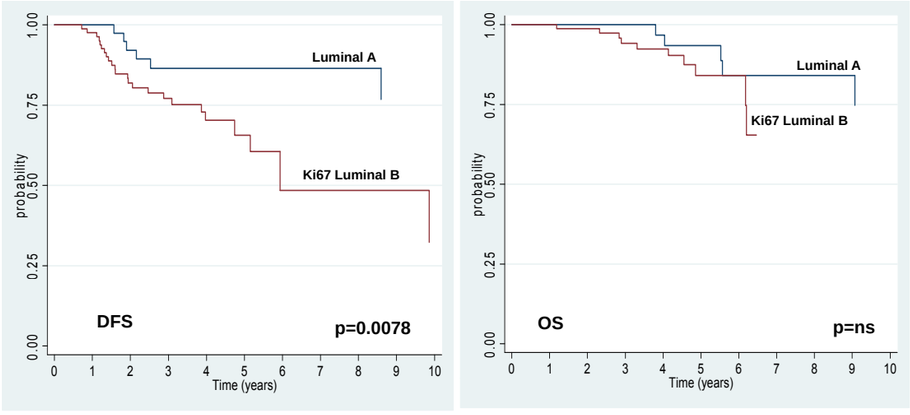
Table 2 - Treatment and efficacy outcomes (overall population)

CHEMOTHERAPY	
Anthra	50 (18.1%)
Anthra/Taxanes	219 (79.7%)
Other	6 (2.2%)
PATHOLOGIC RESPONSE	
no pCR	243 (88.4%)
pCR	29 (10.6%)
Missing	3 (1.1%)
SURGERY	
Mastectomy	144 (52.4%)
Conservative	129 (46.9%)
Missing	2 (0.7%)

Table 3 - pCR by tumor biomarker expression and subtypes (overall population)

	pCR rate	p-value
HR negative	**14/77 (18.2%)**	**p=0.006**
HR positive	**12/176 (6.8%)**	
Low Ki-67 (< 15%)	**2/45 (4.4%)**	**p=ns**
High Ki-67 (≥ 15%)	**24/205 (11.7%)**	
Luminal A (HR+, HER2- and Ki67 < 15%)	**0/40 (0%)**	**p=ns**
Ki67 Luminal B (HR+, HER2- and Ki67 ≥ 15%)	**2/89 (2.2%)**	
HER2 negative	**7/180 (3.9%)**	**p < 0.001**
HER2 positive	**17/67 (25.4%)**	

Fig 1 - Kaplan-Meier for DFS and OS by tumor subtype pre-PCT



SUMMARY & CONCLUSIONS

- In this study we performed a re-classification of HR+/HER2- tumors based on IHC, by using Ki67
- HR+/HER2- patients were reclassified in:
  - Luminal A (14.5%)
  - Ki67 Luminal B (32.3%)
- A pCR was observed in 10.6% of the patients: the probability of obtaining a pCR was significantly higher in case of HR negativity and in case of HER2 positivity
- Among HR positive/HER2 negative patients, Ki67 failed to predict the probability of achieving a pCR
- Patients with HR positive and Ki67≥15% (Ki67-Luminal B) experienced a significantly shorter DFS as compared to Luminal A patients

References

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- Jones RL et al. Breast Cancer Res Treat. 2010 Jan;119(2): 315-23