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PROGNOSTIC ROLE OF THE INNATE IMMUNE SYSTEM CIRCULATING CYTOKINES IN ADVANCED LUMINAL BREAST CANCER PATIENTS OF THE GEICAM/2018-03 NIKOLE STUDY

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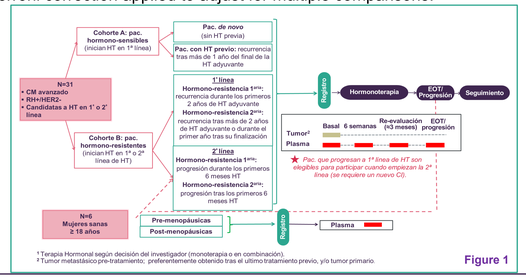
GEICAM 30 years researching breast cancer

INTRODUCTION AND OBJECTIVE

- Luminal BC represents around 70% of breast cancer (BC) cases. Primary or secondary resistance to endocrine therapy (ET) is a treatment limiting factor[1]. Little is known about the potential relationship between ET response and the innate immune system (IIS)[2-4]. The main aim of this study is to characterize the IIS based on levels of circulating cytokines in luminal advanced BC. We previously reported first data about this relation[5]; we do now explore its potential predictive and prognostic value and role in hormone resistance development.

MATERIALS AND METHODS

- NIKOLE is a multicenter, prospective, observational, no post-authorization study in luminal advanced HER2-negative BC patients (pts) assigned to two different hormone-resistance cohorts (CohA, hormone-sensitive or CohB, hormone-resistant) (Figure 1).
- Expression levels of cytokines and/or rNKG2D ligands: IL15, Granzyme, MICA, MICB, Perforin, IFNγ, IL6, IL8, IL10, TNFα, and VEGFA, were measured by the MILLIPLEX® immunoassays HCYTA-60K and HCKP2-11K in serum from serial peripheral blood collected at baseline (pts and healthy controls), after 6 weeks, at radiological re-evaluation (3 months after ET initiation) and progressive disease (PD).
- Log2 expression cytokine values were compared between groups and correlated with outcome including Clinical Benefit (CB) and Progression Free Survival (PFS). Continuous variables were compared using Student´s t-test, and contingency tables were analyzed with Fisher's exact test. Differences in Kaplan-Meier (KM) plots were evaluated using log-rank test, Cox regression models were fitted and Bonferroni correction applied to adjust for multiple comparisons.



¹Terapia Hormonal según decisión del investigador (monoterapia o en combinación).
²Tumor metastásico pre-tratamiento; preferentemente obtenido tras el último tratamiento previo, y/o tumor primario.

Figure 1

- NIKOLE enrolled 6 healthy controls and 31 pts with advanced luminal BC treated with first or second ET. 25 (78%) first treatment pts were considered only; clinical characteristics are summarized in the table (Table 1).
- No differences in baseline cytokines levels were found between pts vs controls nor CohA vs CohB (Figure 2).
- We observed significant increased levels between baseline and 3 months of IL15 (p=0.006) (Figure 3), as well as of Granzyme (Granz, p=0.027), MICA (p=0.009) and MICB (p=0.018) with similar profiles (data not shown), and decreased IFNγ levels (p=0.005) (Figure 3) and VEGFA (p=0.005) with similar profile (data not shown). These changes were independent of pts hormone sensitivity status at the start of treatment.
- We also found better CB in pts with lower levels at 3 months of IFNγ (p=0.04) and VEGFA (p=0.04) (Figure 4).
- Finally, MICA and granzyme baseline levels had prognostic value: pts with lower levels (median value as cutoff) showed longer PFS (26.55 vs 10.91 months) (p=0.035) and 26.55 vs 15.15 months (p=0.03), respectively (Figure 5).

Table 1. Clinical characteristics

Cohorts	CohA (n=16) Hormone sensitive	CohB (n=9) Hormone resistant
Age (years), mean	59	62
Post-Menopausal Status, n (%)	11 (69)	9 (100)
ECOG Performance Status, n (%) (0; 1; 2)	11 (69); 5 (31); 0	7 (78); 0; 2 (22)
Metastasis location, n (%) (Visceral; Bone; LN)	9 (56); 11 (69); 7 (44)	6 (67); 6 (67); 2 (22)
Histology, n (%) (Ductal NOS; Lobular Classical; Lobular Variant)	13 (81); 2 (13); 1 (6)	9 (100); 0; 0
Tumor subtype, n (%) (LumA; LumB (HER2-); Lum NOS (HER2-))	9 (56); 6(38); 1(6)	2 (22); 7(78); 0
Pts status, n (%)		
Treatment on-going	9 (56)	1 (11)
Discontinued for progression	6 (38)	6 (67)
Discontinued for death	1 (6)	1 (11)
Discontinued for Abemaciclib toxicity	0	1 (11)
Treatment* (HT + TT combination), n (%)		
AI + CI	14 (88)	2 (22)
AI + TKI	1 (6)	0
ASI + CI	0	1 (11)
SERMS + CI	1 (6)	3 (33)
SERMS + TKI	0	1 (11)
SERDS + CI	0	2 (22)
Outcome variables, n (%)		
Clinical Benefit Rate (yes, SD 24 weeks)	10 (63)	5 (56)
Progression (yes)	6 (38)	6 (67)

*LN= lymph node
HT=Hormone therapy
TT= Targeted Therapy
AI= Aromatase Inhibitor
CI= Cyclin Inhibitor
TKI= Tyrosine Kinase Inhibitor
ASI= Adrenal Steroids Inhibitor
SERMS= Selective Estrogen Receptor Modulators
SERDS= Selective Estrogen Receptor Degraders
SD= stable disease

Cohort A: Hormone sensitive pts (initiate 1st-line HT)
Cohort B: hormone resistant pts (initiate HT as 1st or 2nd-line HT)

RESULTS

Figure 2. Baseline cytokine levels

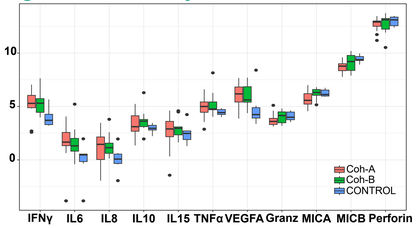


Figure 3. Cytokine dynamics: Baseline - 3 months

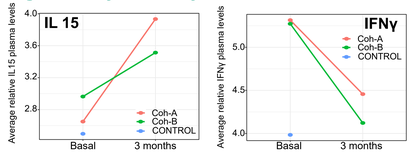
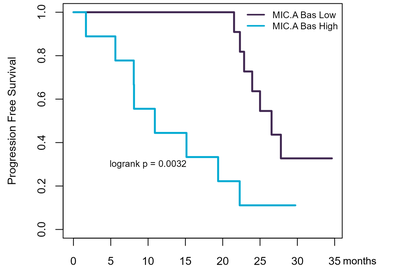


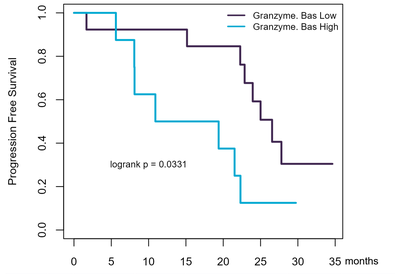
Figure 4. Cytokines at 3 months and Clinical Benefit



Figure 5. Baseline cytokines and PFS



MICA	N	Events	mPFS	HR(CI95%)	p-value	αp-value
Low	14	7(50%)	26.55	1		
High	11	8(72.7%)	10.91	4.45 (1.53-12.88)	0.0071	0.0781



Granz	N	Events	mPFS	HR(CI95%)	p-value	αp-value
Low	14	8(57.1%)	26.55	1		
High	11	7(63.6%)	15.15	3 (1.05-8.59)	0.0471	0.5181

CONCLUSIONS

- ✓ **These results highlight the importance of the innate immune system in advanced luminal breast cancer patients. Circulating cytokines levels are a hormone sensitivity independent factor and could be a key biomarker with potential response predictive and prognostic value.**
- ✓ **These results warrant additional research to investigate the specific role of the cytokines in the hormone-resistant breast cancer and hopefully help in better patients´ selection to new immune therapies.**

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