PERIPHERAL T-LYMPHOCYTES SENESCENCE AND RESPONSE TO NEOADJUVANT THERAPY (NAT) IN OPERABLE BREAST CANCER (BC).

Feba Mariam Varughese1, Veronica Martini2, Alessia Rua1, Erica Gioffi1, Carmen Branni2, Paola Maria Maggiora1, Andrea Tassone1, Arianna Stella1, Simone Gobbato1, Margherita Ciocca1, Ajay Ram Vachanaram1, Rahma Ben Ayed1, Rami Alsati1, Francesca D'Avanzo2, Valentina Rossi2, Chiara Saggia2, Francesca Platini2, Gloria Borra2, Carla Angelillo1, Alessia Barcellini1, Renzo Luciano Boldorini3, Ivan Dodaro4, Daniela Ferrante1, Alessandra Gennari5

1. Dimet - Università Del Piemonte Orientale, Novara, Italy. 2. SCDU Oncologia - AOU Maggiore della Carità, Novara, Italy. 3. SCDU Anatomia Patologica - Università del Piemonte Orientale, Novara, Italy. 4. SSD Unità di Senologia - AOU Maggiore della Carità, NO, Italy. 5. SCDU Oncologia – Università del Piemonte Orientale, Scuola di Medicina, Novara, Italy.

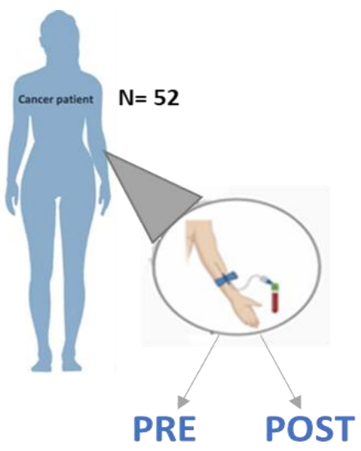
BACKGROUND

Increasing evidence suggests a link between T-cell senescence and tumour prognosis. In particular, high levels of circulating senescent T-lymphocytes have been correlated with a worse response to treatment. In this perspective, a therapeutic approach aimed at T-cell senescence clearance is regarded as an innovative strategy and is currently under investigation in pre-clinical and clinical models.

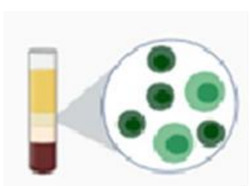
OBJECTIVE

The purpose of the present study is to characterize the impact of circulating T-cell senescence as a predictive factor of response in patients with operable Breast Cancer (BC) treated with Neoadjuvant Therapy (NAT), according to the different biological subtypes.

METHODS



Seventy-four women with histologically proven early stage BC and eligible for preoperative therapy were enrolled so far. Among that, fifty-two patients have been tested for T-cell senescence at baseline (PRE) and after NAT (POST).



Peripheral blood mononuclear cells (PBMCs) were isolated from peripheral blood (PB) by density gradient centrifugation (Lympholyte-H; Cederlane).

CD3+ve T cells were purified from PBMC by immunomagnetic sorting using CD3 microbeads (Miltenyi Biotec) following the manufacturer's procedure.

The relative expression of cyclin-dependent kinase inhibitor (CDKi) p16INK4a was used to characterize T-cell senescence, by RT-PCR. The RPLP0 gene was used as housekeeping gene and healthy controls were used for data normalization (2-ΔΔCt). The Mann-Whitney test was used to highlight a possible association between p16 expression and response to NAT.

RESULTS

p16 relative expression in operable BC patients.

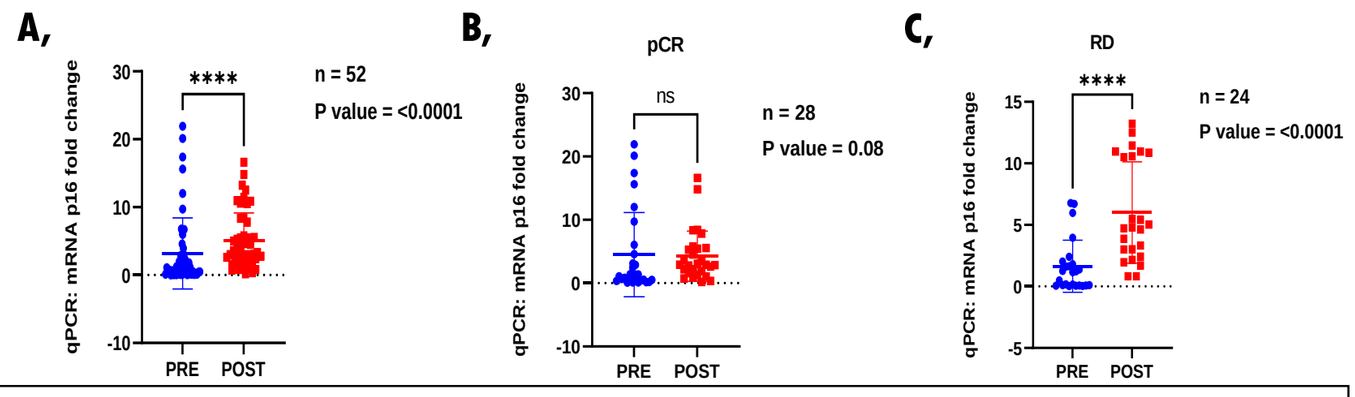


Figure1: There was a significantly higher expression of p16 after NAT, before surgery (POST), respect to baseline (PRE): 3.18±5.24 vs 5.06±4.09; (p= <0.0001) (A). We distinguished the patients who achieved pathological complete response (pCR): 4.50±6.64 vs 4.26±3.96; (p= 0.08) (B) from who having residual disease(RD): 1.63±2.11 vs 6.01±4.12; (p= <0.0001) (C) and observed that after NAT, p16 expression was significantly higher only in RD group. The values were expressed as Mean±SD.

Relative expression of p16 between pCR vs RD group before and after NAT.

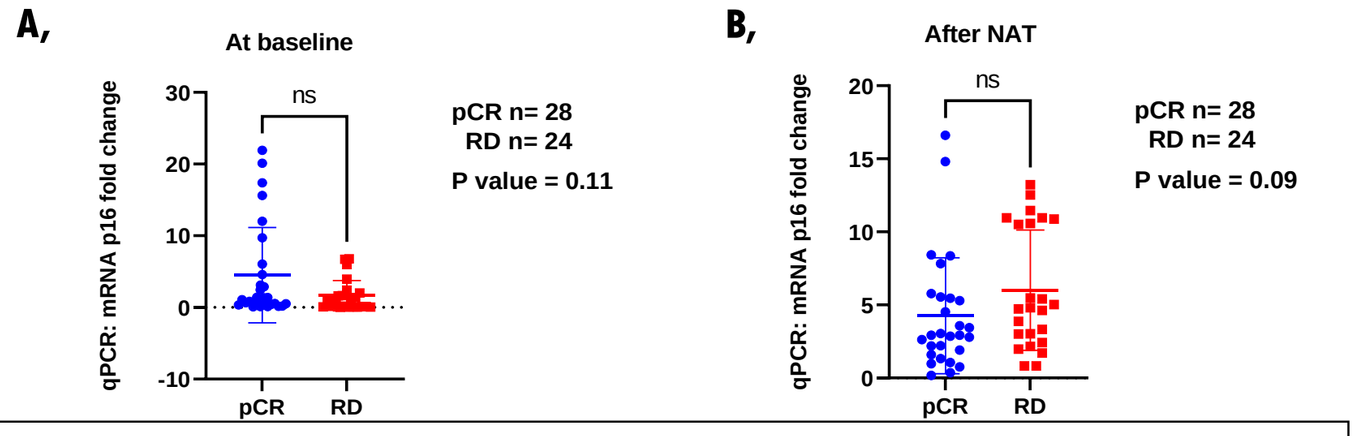


Figure2: p16 expression was not significantly associated with treatment response (A) 4.50±6.64 vs 1.63±2.11; (p= 0.11); (B) 4.26±3.96 vs 6.01±4.12 (p= 0.09). The values expressed as Mean±SD.

p16 expression within molecular breast cancer subtypes.

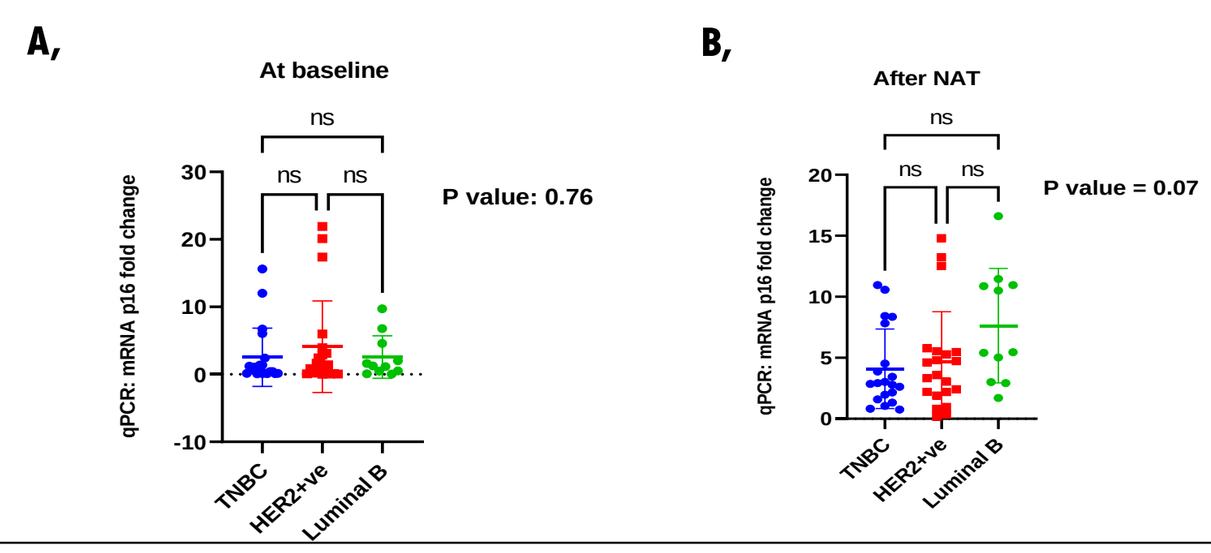


Figure3: There was no significant difference in p16 expression within BC molecular subtypes, neither at baseline (A) 2.54±4.31 vs 4.10±6.78 vs 2.56±3.14 (p= 0.76) nor after NAT (B) 4.09±3.25 vs 4.65±4.11 vs 7.62±4.69 (p= 0.07). The values were expressed as Mean±SD.

Expression of p16 between pCR vs RD group within molecular breast cancer subtypes.

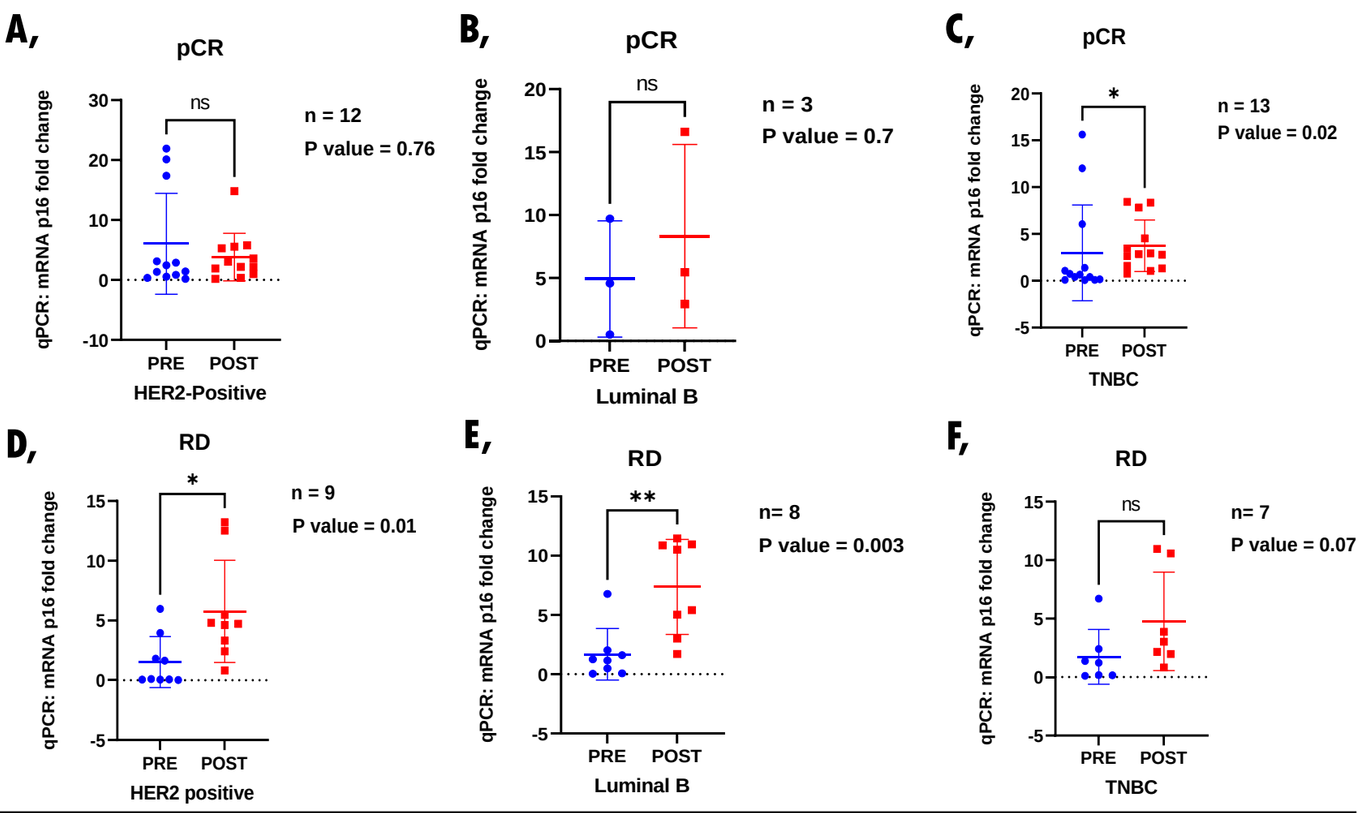


Figure4: Expression of p16 was significantly increased after NAT in patients who having RD in both HER2+ (D) 1.52±2.13 vs 5.77±4.27 (p= 0.01) and Luminal B (E) 1.67±2.17 vs 7.36±4.00 (p= 0.003) as compared to TNBC subtype (F) 1.73±2.34 vs 4.76±4.20 (p= 0.07). The values were expressed as Mean±SD.

Conclusions

These preliminary results suggest that the increase of circulating senescent T-cells after NAT is correlated with a worse response to treatment and $p16^{INK4a}$ might be a predictive biomarker in response for NAT in early BC patients.

References

1. Campisi J. Aging, cellular senescence, and cancer. Annu Rev Physiol. 2013;75:685–705.
2. Demaria, M etal. Cellular senescence promotes adverse effects of chemotherapy and cancer relapse. Cancer Discov. 2017 February; 7(2): 165–176.

UPO AGING PROJECT
UNIVERSITÀ DEL PIEMONTE ORIENTALE