ORT_21 - Evaluation of the immune signature in response to chemotherapy in MMTV-PyMT mouse model

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Introduction: The knowledge of the leukocyte infiltrate allows us to understand and evaluate the efficiency of different antitumor therapies. In this project, we use a transgenic murine model that develops breast cancer, the PyMT mice. Currently, anthracyclines followed by taxane are used for the chemotherapeutic treatment of breast cancer, but there is no biological basis to support this order, and this sequence was established by the order in which these chemotherapeutic agents were developed and clinically used. The Phase II NeoSamba Clinical Trial (INCA) demonstrated that there was better overall and disease-free survival in patients treated with the reverse order of chemotherapy arms: taxane (T) followed by anthracyclines (FAC).

Objective: Based on the rationale of the NeoSamba protocol, the impact of neoadjuvant treatment with combinations of FAC followed by taxane and the reverse order (taxane followed by FAC) on the leukocyte infiltrates will be inferred in the PyMT murine model.

Methodology: Tumors (untreated; treated only with FAC or with taxane; FAC-T and T-FAC) were collected when a volume between 800mm$^3$ and 1400mm$^3$ was reached or after the end of treatment and were referred for flow cytometry, immunohistochemistry and RNA sequencing procedures.

Results: We performed initial studies to characterize the leukocyte tumor infiltrate in untreated and FAC-only treated mice. We could observe some differences in the two groups initially analyzed. In the FAC group, there was an overall decrease in the cancer stem cell population compared to the untreated control. We also observed decreased percentage of TIM-3$^+$ cells amongst CD3$^+$ and also CD4$^+$ cells in the FAC group when compared with untreated animals. Furthermore, we observed that TIM-3 is mostly expressed in CD4$^+$ cells while PD-1 is expressed in CD8$^+$ cells, although we observed no differences between treated and untreated groups.

Conclusion: As next steps, we will continue the treatments of the animals and qualitatively and quantitatively evaluate the leukocyte infiltrates after each of the chemotherapy blocks. RNASeq analysis will be performed in the samples already collected. By doing so, we hope to characterize the impact of different chemotherapeutic regimens on the tumor immune response.

Keywords: Leukocyte Infiltrate; PyMT mice; NeoSamba protocol