Tumour ecosystem and molecular dynamics in clinical triple-negative breast cancer depend on the chemotherapy regimen

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Background - Triple-negative breast cancer (TNBC) treatment traditionally relies on chemotherapy, increasingly paired with immune checkpoint inhibitors (ICIs) as the standard of care. Distinct chemotherapeutic agents may differently impact both the tumour and its microenvironment (TME), especially regarding immunomodulation. Despite extensive studies in cancer models, data on clinical tumours are scarce. We aimed to compare the early modulation of cancer pathways, immune-related features, and selected genes in TNBC patients undergoing various neoadjuvant chemotherapy regimens.

Methods – Four TNBC patient cohorts with RNA-seq data from paired core biopsies before and after the first neoadjuvant chemotherapy cycle were analysed. Patients received doxorubicin/cyclophosphamide (AC, n=19), nab-paclitaxel/carboplatin (PNabT, n=97), nab-paclitaxel (NabT, n=17), or paclitaxel (T, n=15). We quantified 82 cancer hallmark, immune, and TME genesets in each sample using the singscore R package, assessing their differential modulation through Student's t-test and ANOVA. Additionally, selected single genes were similarly evaluated.

Results – Comparing on-treatment to pre-treatment expression profiles revealed a general upregulation of immune cell- and immune function-related signatures, coupled with a downregulation of proliferation-related signatures. However, significant quantitative treatment-dependent differences emerged. T, NK, and dendritic cells signatures showed the largest upregulation in tumours receiving AC or NabT, while a decrease was observed in over 20% of tumours treated with PNabT or T, particularly in those with high pre-treatment expression. B, plasma, and mast cells signatures exhibited the highest upregulation in patients on NabT. PNabT and NabT groups demonstrated the most significant downregulation of proliferation signatures. PD-L1 was upregulated in 90% of AC-treated tumours, contrasting with a decrease observed in 40-60% of tumours in the other cohorts.

Conclusions – Our study underscores the early immunomodulatory and chemoattractant effects of neoadjuvant chemotherapy in TNBC. Anthracyclines and nab-paclitaxel alone are associated with a quantitatively stronger immunomodulatory response, revealing potential clinical implications for selecting optimal chemotherapy partners for ICIs in TNBC treatment.