SIGNIFICANTLY DIFFERENT IMMUNE MICROENVIRONMENT BETWEEN TRIPLE-NEGATIVE BREAST CANCER WITH AND WITHOUT NEOADJUVANT CHEMOTHERAPY THROUGH MULTIPLEX IMMUNOHISTOCHEMISTRY

Miseon Lee*, Hyun Lee, Gyungyub Gong, Hee Jin Lee. Seoul St. Mary’s Hospital College of medicine, Seoul, Korea, Republic of; NeogenTC corp., Gyeonggi-do, haram-si, Korea, Republic of; University of Ulsan College of Medicine, Seoul, Korea, Republic of

Background Understanding the tumor immune microenvironment in triple-negative breast cancer (TNBC) is essential for the development of successful immunotherapy. Although neoadjuvant chemotherapy (NAC) for TNBC is increasing, studies about the difference in tumor immune microenvironment with or without NAC and the association with clinical data are lacking.

Methods We made tumor microarray for 181 TNBC surgical specimens [84 cases (46.4%) without NAC and 97 cases (53.6%) with NAC] and performed multiplex immunohistochemistry (pan-cytokeratin, CD4, CD8, CD45RO, FOXP3, PD-1, PD-L1, and CD103) (figure 1). In cases without NAC, 23 patients (27.4%) were in stage I and 61 (72.6%) in II or III. In the cases with NAC, the residual cancer burden (RCB) class was 20 (20.6%) in 0, 5 (5.2%) in I, 51 (52.6%) in II, and 21 (21.6%) in III.

Results Tumors without NAC had significantly higher amounts of CD4+, CD8+, CD103+, CD45RO+, FOXP3+, or PD-1+ with CK- cells per area compared to tumors with NAC (p-value range: <0.001 – 0.001). In the Kaplan-Meier survival analysis of patients without NAC, disease-free survival (DFS) was significantly better in the group with higher amount of CK-CD4+PD-1+CD45RO+CD103+ (p=0.023), CK-CD4+PD-1-CD45RO+CD103+ (p=0.018), CK-CD8+PD-1+CD45RO+CD103+ (p=0.023), CK-CD8+PD-1-CD45RO+CD103+ (p=0.023), CK-CD8+PD-1-CD45RO-CD103- (p=0.024) per area than the median value. In tumors with NAC, the DFS was significantly better in the group with a higher amount of CK-CD8+PD-1+CD45RO+CD103+CD103+ (p=0.020) and CK-CD8+PD-1+CD45RO-CD103- (p=0.042) per area than the median. In the multivariable analysis of tumors without NAC, the high histologic grade was a significant prognostic factor of unfavorable DFS [Hazard ratio (HR), 0.029; 95% confidence interval (CI), 0.004 to 0.217; p=0.001] and a higher amount of CK-CD8+ per area than median value was a significant prognostic factor of favorable DFS (HR, 0.094; 95% CI, 0.014 to 0.613; p=0.013). In tumors with NAC, a higher amount of CK-CD8+PD-1+CD45RO-CD103+ per area than median value (HR, 0.398; 95% CI, 0.192 to 0.825; p=0.015) and low RCB class (class 0 vs. class III; HR, 0.097; 95% CI, 0.023 to 0.418; p=0.002, class II vs. III; HR, 0.192; 95% CI, 0.085 to 0.433; p< 0.001) were significantly favorable prognostic factors of DFS.

Conclusions In TNBC, the tumor immune microenvironment between tumors without NAC and tumors with NAC was significantly different, and the immune phenotype with a clinically significant effect was distinct. A deeper understanding of the difference in the tumor immune microenvironment between TNBC with and without NAC will help develop successful immunotherapy.

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