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Tumor-infiltrating lymphocytes - a promising predictive and prognostic biomarker for optimizing neoadjuvant treatment response : *a single-institution retrospective analysis*

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BACKGROUND

Tumor-infiltrating lymphocytes (TILs) play a crucial role in the immune response against breast cancer and hold varying prognostic and predictive value depending on the molecular subtype. Elevated levels of TILs have been associated with improved response to chemotherapy and enhanced survival outcomes, particularly in triple-negative (TNBC) and HER2-positive (HER2+) breast cancers. Emerging evidence suggests a strong correlation between TIL levels and the likelihood of achieving an objective response to neoadjuvant therapy (NAT), influenced by breast cancer subtype.

This study aimed to assess the impact of pretreatment TILs on the overall outcomes of NAT across the whole spectrum of breast cancer subtypes, with a specific focus on TNBC and HER2+ subtypes. We evaluated the association between TIL levels and the likelihood of achieving lower Residual Cancer Burden (RCB) scores (RCB 0 and I).

METHODS

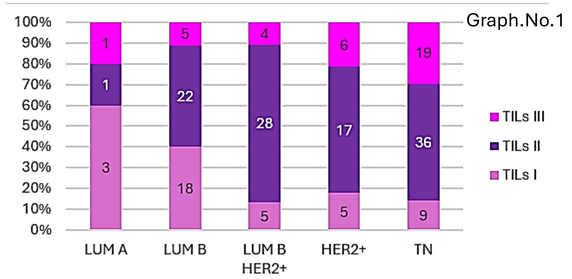
We retrospectively analyzed 181early-stage patients with breast carcinomas treated with NAT. RCB (179 patients) was used to assess pathological response, categorized as RCB 0–III. TILs were scored on diagnostic biopsies and grouped into three categories: I. <10%, II. 11-40%, III. >41%. For HER2+ patients, we compared outcomes based on receipt of anti-HER2 therapy. For TNBC, we assessed response differences between the patients with NAT alone versus those treated with NAT and immune checkpoint inhibitors (ICI). ***Associations between TILs, treatment, and RCB response were explored.***

RESULTS

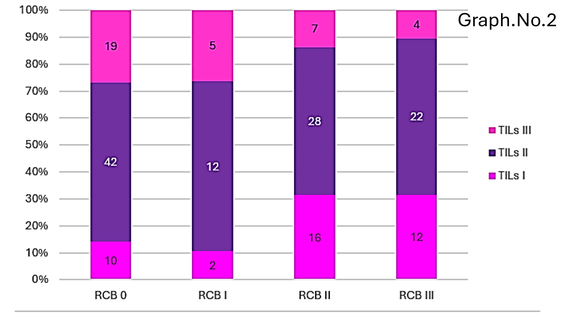
Total cohort (n=179): When stratified by molecular subtype, RCB 0-I was achieved as follows: none of Lum A, 22.2% of Lum B, 48.6% of Lum B HER2+, 85.7% of HER2+ and TN in 59.4%. Immunogenic character is strongly associated with HER2+ and TN tumors where TILs II+III levels were described in Lum B HER2+ (86.5%), HER2+ (82.1%) and TN (86.2%). *We have observed significantly different proportions of TILs categories across molecular subtypes (Fisher-Freeman-Halton exact test; P = 0.0035). The strength of nominal association, measured by Cramer's V, was 0.256, indicating a moderate association between molecular subtypes and TILs levels (graph No. 1).* Low TILs levels were associated with a 3.58-fold higher likelihood of residual disease (non-RCB 0) compared to tumors with high TILs levels. *We have found a moderate ordinal association between TILs and RCB categories (Goodman-Kruskal gamma = -0.317 and Kendall's Correlation Coefficient Tau-b = -0.203 (two-sided P-value = 0.001, graph No. 2).*

HER2-positive cohort (n = 65): Among HER2-positive patients, 60 received anti-HER2 targeted therapy, and five did not. The overall rate of excellent response (RCB 0–I) was higher in patients who received targeted treatment (40/60;66.7%) compared to those who did not (2/5; 40%). Within the treated group, higher TIL levels were associated with better outcomes (Goodman-Kruskal's gamma = -0.361; P = 0.0625). RCB 0–I was achieved in 63.4% of patients with TILs II and 90% of those with TILs III, compared to only 55.6% in TILs I. **Triple-negative cohort (n = 64):** In the TNBC group, 33 patients received standard NAT alone, and 31 received NAT with ICI. The RCB 0–I rate was 57.6% in the non-immunotherapy group versus 61.3% in the immunotherapy group. The incorporation of ICI to patients with TILs I resulted in RCB 0 in 80%, while none of the patients with TILs I without ICI reached RCB 0.

Graph.No.1



Graph.No.2



CONCLUSIONS

Our findings support the use of TILs as a biomarker in identifying patients most likely to benefit from biologic or immunologic therapies. *Notably, HER2-positive and TNBC subtypes demonstrated the most favourable pathological responses (RCB 0-I).*

In the HER2-positive group with targeted treatment, the higher immune infiltration (TILs II–III) resulted in significantly improved pathological response.

In TNBC, particularly in patients with low TILs, the incorporation of ICI resulted in a better outcome in comparison to the patients with the same TIL level without ICI. In patients who received NAT without ICI, the response was strongly influenced by TIL levels only.

These findings support the use of TILs as a biomarker to guide treatment intensification strategies in early-stage breast cancer, particularly in identifying patients most likely to benefit from biologic or immunologic therapies.

References:

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