Tumor Immune Microenvironment as a Predictive Marker of Neoadjuvant Pembrolizumab Combined with Chemotherapy (KEYNOTE-522 Regimen) Efficacy in Early Triple-Negative Breast Cancer

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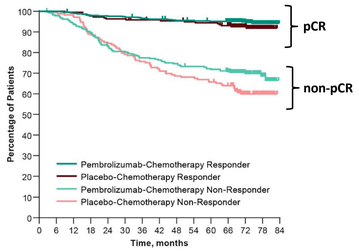
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Abstract

Background: The current standard of care based on the KEYNOTE-522(KN522) trial for high-risk early triple-negative breast cancer (TNBC) is neoadjuvant pembrolizumab combined with chemotherapy. Tumor infiltrating lymphocytes (TILs) and tertiary lymphoid structures (TLS) have been identified in multiple solid tumors and are gaining attention as indicators of predictive biomarkers for immune check point inhibitors (ICIs). We report on the relationship between KN522 regimen treatment efficacy and immune microenvironment.
Methods: We retrospectively analyzed cStage II-III TNBC patients diagnosed from September 2022 to March 2024 who underwent surgery following neoadjuvant treatment with KN522 regimen. We investigated the TILs and TLS in baseline biopsy samples, histological treatment effect (Strict pCR; ypT0N0, pCR; ypT0/isN0), clinical overall response rate (ORR; CR+PR), and axillary lymph node conversion rate (cN+→ypN0). TILs assessment followed the International Immuno-Oncology Biomarker Working Group guidelines, with lymphocyte-predominant breast cancer (LPBC) defined as TILs occupying ≥50% of the area. TLS was defined as lymphoid follicles with germinal centers.
Results: A total of 66 patients were analyzed, with the median age at diagnosis was 51 (25-74) years. cStage II/III comprised 48 cases (73%)/18 cases (27%). TLS was observed in 13 cases (20%), and 19 cases (29%) were LPBC. Univariate analysis showed a mild association between TLS and TILs (p=0.08). Strict pCR/pCR was achieved in 36 cases (55%)/39 cases (59%). While Strict pCR/pCR showed no significant association with TLS (p=0.35/0.53), it was significantly associated with LPBC (p=0.0025/0.0002). The Strict pCR rates for TLS+/LPBC+, TLS-/LPBC+, TLS+/LPBC-, TLS-/LPBC- were 83%(5/6), 85%(11/13), 57%(4/7), and 40%(16/40) respectively. The pCR rates were 83%(5/6), 100%(13/13), 57%(4/7), and 43%(17/40); ORR was 100%(6/6), 100%(13/13), 86%(6/7), and 88%(35/40); and axillary lymph node conversion rates were 100%(3/3), 86%(6/7), 60%(3/5), and 48%(11/23).
Conclusion: Cases identified as LPBC in baseline biopsy samples showed high response rates to KN522 regimen. The immune microenvironment profile could be a potential predictive biomarker for ICI containing treatment.

Introduction

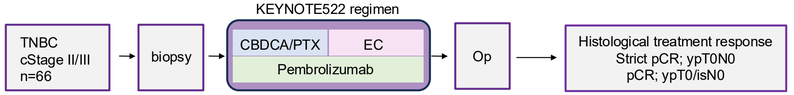
KEYNOTE-522[1)]
Overall survival by pathological response

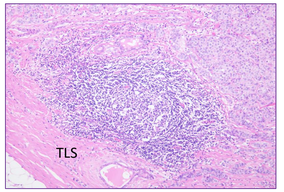


- KN522 regimen, neoadjuvant pembrolizumab combined with chemotherapy, significantly improved TNBC survival.
- Non-responders in KN522 trial still show poor prognosis.
- Adverse events in our institution,
  irAE(grade 3 or higher): 15.2%
  Unexpected hospitalization: 34%
- Biomarker research for accurate identification of patients who are most likely to benefit from ICIs is an urgent issue.

This study aims to elucidate the relationship between immune profile and treatment efficacy.

Patients and Methods





- TILs and TLS are evaluated in initial biopsy specimen.
- **Tumor infiltrating lymphocytes (TILs) [3)]:**

The stromal compartment (%) with mononuclear infiltrate.
% stromal TILs are evaluated in each CNB cores and averaged.

- low : 0≦sTIL<10%, intermediate: 10≦sTIL<30%, high: 30%≦sTIL
- Lymphocyte-predominant breast cancer (LPBC) : Stromal TILs ≧ 50%

- **Tertiary lymphoid structures (TLS)[4,5]:**
- Lymphoid follicles with germinal centers
- Typically localized in the surrounding area of the tumor

Results

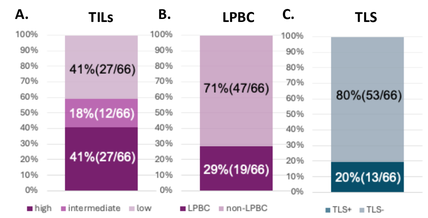
Table. Patient characteristics (n=66)

characteristics		n (%)
Age (median, range)		51 (25-74)
menopause	pre	40 (61)
	post	26 (39)
Tumor stage	T1	3 (5)
	T2	49 (74)
	T3	8 (12)
	T4	6 (9)
LN metastasis	N0	28 (42)
	N1	25 (38)
	N2	0 (0)
	N3	13 (20)
cStage	II	48 (73)
	III	18 (27)
Histological grade (HG)	1	1 (1)
	2	15 (23)
	3	50 (76)
Ki67(median, range)		90 (15-99)

characteristics		n (%)
ER	—	58 (88)
	+*	8 (12)
PR	—	64 (97)
	+*	2 (3)
HER2	0	36 (54)
	1+	19 (29)
	2+	11 (17)
Strict pCR	ypT0N0	36 (55)
pCR	ypT0/isN0	39 (59)
BMI		22 (17-33)
Breast surgery	Bp	19 (29)
	Bt	47 (71)
Axillary surgery	SLNB	25 (38)
	Ax	29 (44)
	TAS** /sampling	12 (18)

*ER, PR <10%
**Targeted axillary surgery

Results



TILs low : 0≦sTIL<10%, intermediate: 10≦sTIL<30%, high: 30%≦sTIL
LPBC: Lymphocyte-predominant breast cancer (sTIL ≧ 50%)
TLS: Tertiary lymphoid structures

Figure 1. Proportion of TILs, LPBC and TLS in biopsy specimen.

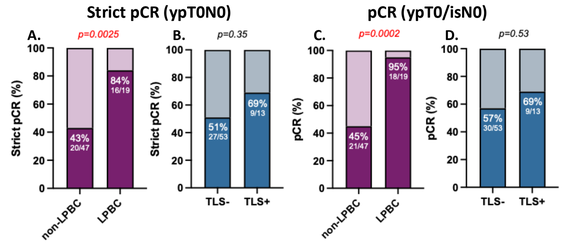


Figure 3. TIL/TLS and KN522 regimen treatment efficacy.

LPBC is significantly accompanied by higher response to KN522 regimen (A,C). The cases with TLS showed higher response compared to those without TLS, however, they were statistically not significant (B,D).

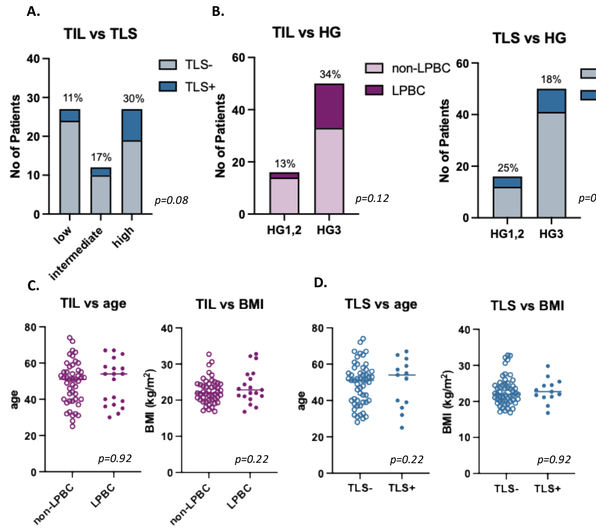


Figure 2. TIL/TLS and patient characteristics.

Mild association was observed between TIL and TLS (A). No significant association was observed between TIL/TLS and HG, age and BMI(B-D).

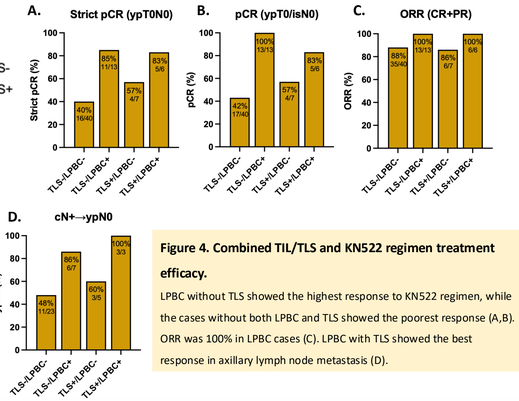


Figure 4. Combined TIL/TLS and KN522 regimen treatment efficacy.

LPBC without TLS showed the highest response to KN522 regimen, while the cases without both LPBC and TLS showed the poorest response (A,B). ORR was 100% in LPBC cases (C). LPBC with TLS showed the best response in axillary lymph node metastasis (D).

Conclusions

Cases identified as LPBC in baseline biopsy samples showed high response rates to KN522 regimen. The immune microenvironment profile could be a potential predictive biomarker for ICI containing treatment.

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