5O TILs in ER+/HER2- breast cancer

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Background: The role of tumor-infiltrating lymphocytes (TILs) in ER+/HER2- breast cancer (BC) is debated. We evaluated the association of TILs and clinico-pathological (CP) features with distant disease-free survival (DDFS) in a large series of patients (pts) with ER+/HER2- BC.

Methods: A case-cohort was built by randomly selecting 17% of an initial cohort of 3986 pts who underwent surgery at IEO in the period 1998-2002, and for whom long-term follow-up data was available (680 pts). 307 more pts with an event were added to this cohort. TILs were assessed for these 987 cases on centralized H&E slides. TILs were considered both as continuous variable, and dichotomized in low (<5%) vs high (≥5%). DDFS was calculated from the date of surgery to the date of any first event or the date of last contact with the patient. Median f-up was 7.5 years (0.1-10). Differences between BC subtypes were assessed using the log-rank test. Univariable and multivariable Cox proportional hazards regression with inverse sub-cohort sampling probability weighting were used to evaluate the risk across groups. Analyses were carried out with the SAS software version 9.4.

Results: Median TILs was 2%. Higher TILs were positively associated with pN ($p = 0.003$), grade ($p < 0.0001$), peritumoral vascular invasion ($p = 0.003$), Ki-67 ($p = 0.0001$), lumB subtype ($p < 0.0001$), and chemotherapy ($p < 0.0001$), while they were inversely associated with ER ($p < 0.0001$) and age ($p = 0.02$). In multivariable regression analysis, only Ki-67 expression retained significant association with TILs. Age and ER showed a trend towards negative association with TILs. In univariate Cox regression, TILs expression (≥5% vs. <5%) was not associated with DDFS (HR 1.08, 95% CI 0.80-1.46, $p = 0.62$). At stratified cox exploratory analyses, we found an association between high TILs and low risk in very young women ($p = 0.03$) and G3 tumors ($p = 0.047$); high TILs were associated with worse outcome in G1 tumors ($p = 0.05$). TILs were not associated with DDFS in the group without chemo. Instead, in the group with chemo, high TILs were associated with better DDFS ($p = 0.006$), particularly for ki67≥20% ($p = 0.01$).

Conclusions: High TILs in ER+/HER2- BC are significantly associated with several CP features of dismal outcome. This subgroup might be more immunogenic, thus deserving the exploration of immunotherapy approaches.

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