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Review article

Tumor-Infiltrating Lymphocytes and Breast Cancer: Are Immune Checkpoint Inhibitors Ready for Prime Time in Breast Cancer?

Ana Cvetanović[1], Slađana Filipović[1,2], Nikola Živković[2,3], Miloš Kostić[4], Svetislav Vrbić[1,2], Ivica Pejčić[1,2]

[1]*Clinic of Oncology, Clinical Center Niš, Serbia*
[2]*University of Niš, Faculty of Medicine, Niš, Serbia*
[3]*Center for Pathology and Pathological Anatomy, Clinical Center Niš, Serbia*
[4]*Department of Immunology, Medical Faculty, University of Niš, Serbia*

SUMMARY

In recent years, results obtained from different studies with large cohorts have revealed a bond between the presence of extensive lymphocytic infiltration and favourable prognostic associations in the early-stage of breast cancer (BC) and high response rates to neoadjuvant chemotherapy. Examiners used tumors from large cohorts of patients who took part in randomized neoadjuvant and adjuvant clinical trials. The importance of tumor infiltrating lymphocytes (TILs) appears to be subtype-specific and varies depending on the histological characteristics of the tumor. TILs have proven to be a good prognostic marker, but only in highly proliferative breast tumors such as triple negative breast tumors (TNBC) or HER 2 positive BC.

In the era when standard, well-known, prognostic and predictive biomarkers are ever changing and the use of molecular profiling analyses are increasing, we are looking for techniques to improve our understanding of tumor biology and improve patient outcome. The relevance of TILs cannot be ignored but needs to be properly evaluated in larger prospective studies which must encompass the parameters set out in previous studies. The use of TILs as prognostic biomarkers in early breast cancer may represent a new dawn, and use of immunotherapy, especially immune checkpoint inhibitors, probably is the future for the breast cancer but it is not yet ready for prime time.

Key words: **breast cancer, tumor infiltrating lymphocytes, immune checkpoint inhibitors**

Corresponding author:
Ana Cvetanović
Email: ana.stankovic@yahoo.com

INTRODUCTION

Tumor-infiltrating lymphocytes (TILs) are commonly noticed in tumors, suggesting that tumors activate a response of the immune system in the environment. This titled tumor immunogenicity is mediated by tumor antigens which differentiate the tumor from healthy cells, thus supplying an immunological response (1). During the period of the past ten years, new results from different groups of examiners have suggested that TILs have a prognostic and predictive role in breast cancer. However, such results are not new, because since 1940s it has been known that medullary carcinoma has an enormous proportion of lymphocytic infiltrate in tumor stroma, and it has been correlated with excellent prognosis after aggressive therapy in spite of poorly dif-ferentiated tumors and positive axillary lymph nodes (2, 3). Nevertheless, since 1940s, a lot of studies have examined the link between TILs and prognosis in different subtypes of breast cancer and obtained contradictory results (4-7).

Numerous studies report a benefit in survival outcome associated with the presence of TILs, suggesting that TILs have an effect on delaying and preventing tumor progression. On the other hand, it is crucial to differentiate a few types of T lymphocytes, due to their different functions in tumor micro-environment (8-11).

First of all, there are CD8+ cytotoxic or killer T lymphocytes (CTLs) that are destroying cancer cells or other infected cells. CD4+ T helper cells (TH) have two types of cells whose function is secretion of different cytokines. T helper class 1 lymphocytes (TH1) have a key role in activations of killer T lymphocytes. Furthermore, T helper class 2 (TH2) lymphocytes stimulate B cells whose function is secretion of antibody, practically, the maintenance of the humoral immune system. TH2 activation is less important in antitumor immunity (12). Apart from the two types of helper T lymphocytes, a CD4+ regulatory T lymphocyte (TREG) subset suppresses effector T lymphocytes. Killer CD8+ and CD4+ TH1 produce a lot of cytokines like gamma-interferon (IFN gamma) and interleukin 2 and because of that these cells are the most important in anti-tumor activity. In contrast, it is believed that tumor macrophages (TM) produce interleukin-6 (IL-6), tumor-necrosis factor beta (TNF beta), and IL-23 assist in tumor promotion and progression. Because of that, tumor cells and macrophages produce chemokines, and TREG dominantly traffic to tumors (13).

The hypothesis suggesting that ratios between different subsets are most predictive of prognosis has recently gained a lot of attention, when the frequently used ratios are between killer and regulatory cells, and also killer and helper cells (CD8+/CD4+). These ratios may provide a broader view of actions taking place at the site of disease (13-15). An approach which is often used today in clinical trials is to quantify the numbers of TILs, and then correlate them to tumor characteristics and prognostic outcome.

Today we know that "immunogenic" tumors are melanoma or lung cancer and that breast cancer (BC) has not usually been considered an "immunogenic", however, recently published data re-vealed that TILs have been associated with a good prognosis (5, 16–19). It is known that both CD4+ and CD8+ TILs are essential for effective tumor elimination but data from various studies point out the fact that CD4+ TILs can eliminate cancer cells by itself without CD8+ (20-22).

The aim of this article is to find out whether the results of the below studies could lead to the routine practice of reporting the levels of lymphocytic infiltrates in the pathology reports of patients diagnosed with breast carcinoma, especially in cases of triple negative and HER 2 positive disease, and also will the new therapies, like immune checkpoint inhibitors, have reached the clinical setting.

ROLE OF TILs IN ADJUVANT CLINICAL TRIALS

In recent years, results obtained from different studies with large cohorts have revealed a bond between the presence of extensive lymphocytic infiltration and favorable prognostic associations in the early-stage of breast cancer (BC), good prognosis, and high response rates to neoadjuvant chemotherapy which is also a biomarker for longer survival. Examiners used tumors from large cohorts of patients who took part in randomized adjuvant clinical trials (17, 23-27). TILs have proven to be a good prognostic marker, but only in BC with high proliferation rate such as triple negative breast tumors (TNBC) or HER 2 positive BC (5).

BIG (Breast International Group) 02-98 study is a large phase III adjuvant clinical trial which randomized patients in two groups. The first one received only anthracycline chemotherapy, and the second anthracycline and taxane combinations of chemo-

therapy. The goal of this study is to determine whether the presence of TILs have predictive or prognostic role in node positive BC (28). The study presents the analysis of two different types of lymphocytes, stromal TILs (sTILs – described as lymphocytes present within the stroma of the tumor) and intratumoral TILs (iTILs – described as lymphocytes that were in direct contact with the carcinoma cells). Furthermore, the study found that there is a significant association between increasing sTILs and iTILs and a good outcome irrespective of chemotherapy type, but only in the TNBC subgroup. Lymphocyte-predominant BC (LPBC) was defined as ≥ 50% infiltration of either stromal or intratumor lymphocytic infiltration. Also, results showed that for every percentual increase in lymphocytes infiltration, there is a decrease in the risk of relapse or death, therefore, for every 10% increment in sTILs there was a 15% and 17% reduction of the risk of relapse or death, respectively, and better results for iTILs where for every 10% increment in iTILs there is 17% and 27% reduction of the risk of relapse and death, respectively. For TNBC with the LPBC phenotype, the five-year disease free survival (DFS) rate and overall survival (OS) rate were higher than in non-LPBC. (DFS 92% vs 62%: p = .018; OS 92% vs 71%: p = .036). The five-year outcomes for the subset of patients with TNBC disease with the LPBC phenotype were similar to those observed in patients with ER-positive/HER2-negative tumors. The second aim in this study was to determine if the effect of the anthracycline taxanes treatment was different from that of the anthracycline-only containing treatment according to LPBC status in the baseline samples. Only in the HER2-positive BC subgroup there was an evidence of a heterogeneous treatment response according to the percentage infiltration of TILs. Patients with HER2-positive BC with the LPBC phenotype who received anthracycline-based chemotherapy had a five-year DFS of 78.6% versus 57.9% in patients who received anthracycline-taxane chemotherapy (HR, 0.45; 95% CI, 0.12 - 1.71) and those without LPBC phenotype had a five-year DFS of 47% versus 72.7%, respectively (HR, 2.05; 95%CI, 1.41-2.97). (29) Loi et al. reached a conclusion that increasing lymphocytic infiltration was a strong prognostic factor for this subtype of BC. Moreover, they found a close connection between higher levels of lymphocytes infiltration with estrogen and progesterone hormone receptor negativity (both p < 0.001) and no connection between TILs and outcomes of patients with HER-2 positive breast cancer. It is unclear why an interaction between increasing stromal infiltration and chemotherapy type was seen only in the HER2-positive subtype and this finding will require further validation (29, 30).

FinHER, an adjuvant, prospective phase III trial included 1,010 early BC patients. In this cohort 778 were HER2-negative. Among 232 patients with HER2-positive disease, one half was randomized to 9 weeks of trastuzumab plus chemotherapy and one half with chemotherapy without trastuzumab only. Pathologists quantified the presence or absence of stromal TILs in 935 (92.6%) obtained tumor slides. Similar to results from previous studies in TNBC, each 10% increase in TILs was associated with decreased relapse or metastases in TNBC (p = 0.02). For first time, a relationship between levels of TILs and response to trastuzumab therapy was reported, where higher levels resulted in better responses (p = 0.025) (31, 32). Similar results obtained in the N9831 study showed that tumors enriched with immune cells exhibited better survival with anti HER 2 therapy (33). It is widely known that trastuzumab is the standard of care nowadays, and TILs can be used as a prognostic factor in HER2+ disease treated with trastuzumab (31-33).

ROLE OF TILs IN NEOADJUVANT CLINICAL TRIALS

Neoadjuvant chemotherapy of breast cancer induces high clinical response rates of 70% to 90% (34, 35), but pathological complete response (pCR) which is strong indicator of benefits is detected in only 10% to 25% of patients. The pCR can be considered as a surrogate biomarker to point out a lower incidence of relapse and metastases and longer survival. The analysis of predictive biomarkers on pre-treatment core biopsies provides an excellent opportunity to personalize chemotherapy (34-37).

Denkert at al. examined iTILs and sTILs in a total of 1,058 breast cancer core biopsies obtained from two neoadjuvant studies where patients received anthracycline or taxane-based neoadjuvant therapy (GeparDuo, n = 218 and GeparTrio, n = 840). In a multivariate regression analysis, the percentage of iTILs was an important independent parameter for pCR in both cohorts (GeparDuo: p = 0.012; GeparTrio: p = 0.001). In patients with LPBC, with pCR was found in 42% (GeparDuo) and 40% (GeparTrio). In contrast, tumors without sTILs or iTILs had pCR, which was found in only of 3% (GeparDuo) and 7%

(GeparTrio). It was determined that the presence of TILs was an independent predictor factor to neoadjuvant chemotherapy (17, 38). The GeparQuatro study analyzed biopsy specimen from 156 patients with HER 2 positive BC treated with neoadjuvant chemotherapy with trastuzumab. Loi and colleagues also concluded that every 10% increase levels of TILs resulted in 16% increase in achieving pCR. In this study, 47% of patients with high level of TILs had pCR which means that TIL levels may be in a close relationship with the response to trastuzumab-containing chemotherapy (32). Comparable results with anti HER 2 therapy were found in Neo-Sphere study which examined neoadjuvant trastuzumab, pertuzumab, or both, with or without chemotherapy. A high expression of immune checkpoint, like PD1 or PDL1, which role is to suppress the activation of T cells, was associated with lower pCR rate after chemotherapy in combination with biological anti HER 2 therapy like trastuzumab and pertuzumab (39).

Another study which showed a connection between LPBC, especially high percent of sTILs, and increased pCR rate is PREDICT, the substudy of neo-adjuvant GeparQuinto study. The quantification of TILs was prospectively assessed in tumor slides from a total of 313 core biopsies from HER2-negative patients (40).

Moreover, a link between neoadjuvant chemo-therapy with carboplatin and high level of TILs has been found by some other examiners. Denkert and colleagues studied tumor samples from 580 core biopsies from patients who received neoadjuvant chemotherapy containing or not carboplatin. In this Gepar Sixto trial, among patients with high levels of TILs, pCR was found in 74% in patients who received carboplatin, in comparison to 46.6% in patients who did not received carboplatin (41).

Furthermore, results from a several small studies have revealed that TILs, CD3, CD4, CD8, FOXP3 had high positive correlation with pCR (42-47).

CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS

The important goal in cancer research is the classification of prognostic and predictive biomarkers. This is necessary, especially in the adjuvant setting, as the possibility to calculate the relapse rate allows personalization of therapy. Today, it is known that "one therapy does not fit all". As has been shown in the recent studies, special attention has been focused on the effect of the immune system on tumor response and prognosis as new therapies, like immune check-point inhibitors, changing the immune system, have reached the clinical setting and showed some promising results (29, 31, 48-53).

The problem with these studies is that they do not have the standard for measuring or do not report a cutoff point for TILs. In 2014, International TILs Working Group published recommendations for the quantification of TILs in breast cancer. The point of this article is that pathologists should measure the percentage of sTILs in hematoxylin and eosin-stained slides obtained from primary tumor before any therapy given. This will make easier the use of TILs as a biomarker in clinical studies (54).

As has been shown that the recent prospective studies provide level I evidence that sTILs are significant prognostic marker in TNBC in patients having received anthracycline therapy and HER 2 positive disease in patients who received trastu-zumab, we do not know yet what the clinical utility of TILs is in these groups of patients. Moreover, we are waiting for the results from prospective studies which will provide answers if TILs is predictive of response to immunotherapies, especially T-cell check-point inhibition, which in conclusion should be its clinical utility.

In the era when standard, well-known, prognostic and predictive biomarkers are ever changing and the use of molecular profiling of tumors is increasing, we are looking for some new molecules to further our better understanding of very complex and variable tumor biology and increase patient survival. The applicability of TILs cannot be disregarded but we have to wait for the results from clinical trials to confirm it. Recently, a new consensus guideline for standard quantification of TILs has been introduced, which was necessary to help investigators develop a new biomarker for use in clinical practice, and now a confirmation from prospective studies is needed (54). As such, the use of TILs as prognostic biomarkers in BC may represent a new sunrise, and immune checkpoint inhibitors probably is the future for the breast cancer but it is not yet ready for prime time.

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Tumor-infiltrišući limfociti i karcinom dojke: Da li je pravo vreme za primenu imunskih "checkpoint" inhibitora u terapiji raka dojke?

Ana Cvetanović[1], Slađana Filipović[1,2], Nikola Živković[2,3], Miloš Kostić[4], Svetislav Vrbić[1,2], Ivica Pejčić[1,2]

[1]Klinika za onkologiju, Klinički centar Niš, Srbija
[2]Univerzitet u Nišu, Medicinski fakultet, Niš, Srbija
[3]Centar za patologiju i patološku anatomiju, Klinički centar Niš, Niš, Srbija
[4]Univerzitet u Nišu, Medicinski fakultet, Departman za imunologiju, Niš, Srbija

SAŽETAK

Rezultati poslednjih godina, dobijeni iz različitih kliničkih studija sa velikim brojem bolesnika pokazali su povezanost između opsežne limfocitne infiltracije tumora i dobre prognoze ranog karcinoma dojke kao i odličnog odgovora na neadjuvantnu terapiju. Istraživači su koristili tkiva tumora velikog broja bolesnika koji su učestvovali u randomizovanim neoadjuvantnim i adjuvantnim studijama. Značaj tumor infiltrišućih limfocita (TILs) zavisi od podtipa i histoloških karakteristika tumora. Dokazano je da su TILs dobar prognostički marker, ali samo u visoko proliferativnim karcinomima dojke kao što su trostruko negativni i HER 2 pozitivni karcinom dojke.

U vreme kada se standardni, dobro poznati, prognostički i prediktivni markeri stalno menjaju i upotreba molekularnog profilisanja tumora stalno raste, tragamo za tehnikama koje bi nam omogućile bolje razumevanje biologije tumora i poboljšale ishod lečenja bolesnika. Važnost TILs se ne sme ignorisati, ali je potrebno potvrditi ga u većim randomizovanim studijama koje bi obuhvatile i sve parametre navedene u već sprovedenim studijama. Upotreba TILs kao prognostičkog biomarkera u ranom karcinomu dojke može predstavljati novo svanuće kao što i upotreba imunoterapije, posebno imunoloških ''çheckpoint'' inhibitora, verovatno predstavlja budućnost u lečenju karcinoma dojke, ali mora sačekati pravo vreme.

Ključne reči: **karcinom dojke, tumor infiltrišući limfociti, imunološki ''checkpoint '' inhibitori**