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Tumor Infiltrating Lymphocytes and Axillary Lymph Node Positivity: A Systematic Review

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Abstract

Tumor infiltrating lymphocytes were associated with a good prognosis in some types of cancers, including breast cancer, with an important role in host immune response to the tumor. Axillary lymph node involvement is one of the most important prognostic factors of breast cancer. Authors carried out a systematic review to understand the predictive value of tumor infiltrating lymphocytes and axillary lymph node involvement. This review was based in literature search on PubMed, Cochrane Library and studies presented at European Society of Medical Oncology and at American Society of Clinical Oncology. These studies, published over the last 30 years, provided data from 776 patients. A correlation between tumor infiltrating lymphocytes and axillary lymph node involvement in breast cancer was found, although, their predictive value for axillary lymph node metastization is not clear.

Keywords

Breast neoplasm; Lymphocytes tumor-infiltrating; Axillary lymph node; Neoplasm metastasis; Predictive value

Introduction

Breast cancer is the leading cause of cancer-related deaths in women of the so called Western-World [1]. Advances in screening tests that lead to an early diagnosis and improvements of systemic therapies enabled decrease in the rate of related deaths in the last years [2]. Immune cells infiltration is common in solid tumors. Breast cancer is not an exception, and several authors have described that these tumors are infiltrated by different types of immune cells, like T cells, B cells, natural Killer (NK) cells and macrophages [3,4]. They are mainly tumor infiltrating lymphocytes (TILs), and they represent the hosts immune response against the tumor [5]. They were first identified in the early twentieth century and recently, TILs were associated with a good prognosis in various types of cancer, including breast cancer [6-9], with an important role in tumor progression and metastization [10]. An association of TILs with human epidermal growth factor receptor 2 positivity (HER2+), triple negative breast cancer (TNBC) or high grade have been described [11,12]. Various subtypes of TILs were identified, with different roles in the immune response to breast cancer. From the TILs already mentioned, CD8+ T cells, CD4+ T cells and on the other hand, regulatory T cells (forkhead

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box P3-positive (FoxP3+) Tregs) are the most important for immune surveillance and tolerance, respectively [13]. CD8+ T cells play their role in the antitumor immunity inducing direct tumor cells lysis, and their increased presence has been correlated with increased survival in various types of human solid tumors [6,14-17]. CD4+ T cells are important in anti-tumor immunity by their helper and/or memory cell function, as effector, priming tumor specific cytotoxic macrophages or T cells [15]. Tregs represent about 5% to 10% of CD4+ TILs, they regulate the immune response by suppressing proliferation and cytokine production by effector T cells, enabling tumors to escape the antitumor response. An association between increased Tregs TILs and poor clinical outcome has been made in some cancer [18,19]. Axillary lymph node involvement (pathologic examination) remains one of the most important prognostic factors and predictor of breast cancer survival. Even in small tumors a minimal involvement of axillary lymph node confers a worsened prognosis, when compared with patients without nodal involvement. A correlation between the number of axillary involved nodes and the risk of recurrence has been described [20]. The mean infiltrating NK cells, CD3+T, CD8+T and the CD4+/CD8+ ratio have been correlated with lymphovascular permeation and lymph node metastasis [21]. To understand the predictive value of TILs in axillary nodal involvement in breast cancer, we performed a systematic review of papers published over the last 30 years.

Material and Methods

Search method

This systematic review was based in literature search on PubMed and Cochrane Library. Relevant studies presented at European Society of Medical Oncology (ESMO) and at American Society of Clinical Oncology (ASCO) were also included. The following key-words were used: "Neoplasm Metastasis" "Breast Neoplasms", "Lymphocytes, Tumor-Infiltrating", "Lymph Node", "Axillary", "predictive value". Two investigators independently conducted the search. Reference lists of selected papers were used to search additional articles. Inclusion criteria: The review included all original articles, cohort studies or retrospective studies since 1990, that met the following inclusion criteria: 1) used human subjects, 2) axillary lymph node status was assessed by histological examination, 3) TILs identification method and/or immunohistochemical staining was described, 4) considered a correlation between TILs and lymph node involvement, 5) described the statistical methodology 6) contained the minimum information of measures of uncertainty (confidence interval, P-values, standard errors or variance), 7) written in English or Portuguese. All Studies that didn't meet the inclusion criteria were excluded. Data extraction and quality assessment: Two reviewers independently assessed the selected articles and extracted data in a standardized manner. Disagreements were resolved by consensus. The data obtained from each article were: first author's name, population's country, publication year, number of participants, T category, N category, definition of positive staining or TILs identification method and TILs correlation with axillary node positivity (confidence interval, P-values, standard errors or variance). Authors determined the T category according to the American Joint Committee on Cancer (AJCC) cancer staging manual seventh edition. The reviewers assessed the quality of each study

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resorting to the Newcastle-Ottawa Quality Assessment Scale (NOS) [22]. This scale was developed to assess the quality of nonrandomized studies by a "star system" that comprises 3 main evaluation criteria: selection of the study groups, the comparability of the groups and the ascertainment of the exposure or outcome of interest for case-control or cohort studies, respectively. Scores from 1-3 are defined as low, 4-6 as intermediate and 7-9 as high-quality studies (Table 1). Disagreements were again resolved by consensus.

Statistical analysis: The heterogeneity of these publications on TILs definition, TILs identification methods and types of TILs searched did not allow us to perform a meta-analysis.

Results

Studies eligibility

The initial search (see the Material and Methods section) yielded 44 articles. Thirty six articles were excluded because they didn't meet the inclusion criteria, there was a lack of information or were irrelevant to this review. Two articles were duplicated. These studies provided data from 776 patients, with sample size ranging from 23 to 489 patients. Scores from NOS scale ranged from 5 to 8, meaning that the included studies have an acceptable quality (Table 1).

Studies characteristics

The characteristics of the six included studies are summarized in Table 1. These were published between 1992 and 2009. TILs specific subsets were described in four studies [4,23-25] but not in the other two [3,21]. In all of the studies, TILs were analyzed after surgical management of patients (lumpectomy or mastectomy with or without axillary dissection). None of them included patients submitted to neoadjuvant chemotherapy. TILs identification method was variable between studies. Two studies used flow cytometry (FC) [21,23], three studies used immunohistochemistry (IMHC) [4,24,25] and one used hematoxylin-eosin staining (H&E) [3]. The majority of the included studies considered TILs only in intra-tumoral tissue [21,23-25]. Two studies considered TILs in both intra-tumoral and stromal sites [3,4].

Correlation between total TILs and lymph node involvement

The included studies analyzed the relation between various subsets of TILs (view results below) and axillary lymph node positivity. One of the studies didn't explore or specify these subsets [3]. Aaltomaagraded the density of TILs into three categories: absent/ weak, moderate and dense. Using a multivariate regression analysis TILs were related to axillary lymph node status, in high proliferative tumors. A relation between TILs and lymph node involvement (P=0.011) was established using the Chi-square test [3].

Correlation between NK cells and axillary lymph node involvement

Three studies identified NK cells, but only two made the correlation between these cells and axillary lymph node status [4,23]. Vgenopoulous, used the Chi-square method to perform an association analysis between lymphocytic subsets and lymph node status. A relation between an increased number of intra-tumoral NK cells and patients with more than 3 involved lymph nodes was demonstrated with statistical significance (P=0.047). The absence of endo-tumoral NK cells was more frequent in patients without lymph node involvement (P=0.038) [4]. Macchetti used different cut-offs, based in mean value of lymphocytes infiltration (CD3+Cells 24.72 ±

17.37%; B-lymphocyte 4.22 \pm 6.27%; NK cells 4.41 \pm 5.22%; and for CD4+ and CD8+ T-lymphocyte 12.43 \pm 10.12% and 11.30 \pm 15.09%). To compare TILs between groups (axillary lymph node involvement versus no axillary lymph node involvement) the authors used a 2-Tailed unpaired Student t-test. Statistical significance was defined as *P*<0.05. The authors didn't find a statistically significant difference between the mean of NK cells infiltration when comparing patients with lymph node involvement and those without (*P*>0.05) [23].

Correlation between CD4+ T-lymphocytes and axillary lymph node involvement

Four studies characterized this association [21,23-25]. Using 2-tailed unpaired Student t-test, Macchetti, demonstrated a positive correlation between patients with lymph node involvement versus no node involvement (means: without lymph node involvement: 15.35 \pm 2.36% and 8.41 \pm 6.22% versus 36.90 \pm 18.60% and 17.64 \pm 12.05% in those with lymph node involvement), with P=0.001 and 0.02 respectively [23]. A relation between CD4+ T lymphocytes and axillary lymph node involvement was also demonstrated by Matkowski, using Student t-test, with P<0.05 (CD4 and clinical axillary involvement (cN) P=0.016; CD4 and histopathological axillary involvement (pN) P=0.037) [24]. Sheu BC concluded that the presence of CD4+ T-lymphocytes was lower in the axillary node positive patients than in the negative group P < 0.01, using Student t-test (19.61 ±8.53% versus 34.8 ± 8.27%)[21]. Tae Kim, analyzed the relation between the increased ratio of Foxp3Treg/CD4+ T lymphocytes and axillary involvement, with statistical significance (P=0.011, Spearman Test) [25].

Correlation of CD8+ T-lymphocytes with lymph node involvement

This association was analyzed in five studies [4,21,23-25]. Vgenopoulous [4] described a correlation between increased number of peritumoral CD8 T-lymphocytes and axillary lymph node involvement (P=0.045, Chi-square test)[4]. A statistical significant relation between this subset of T-lymphocytes and axillary involvement was also described by Matkowski (CD8 TcN, P=0.005; CD8 pN, P=0.0008), using Student t-test [24]. Tae Kim [25], corroborate this tendency, showing a statistically significant difference between means of CD8 T-infiltration (Mean 51.066 for positive lymph node versus 31 for negative lymph node) with P=0.027 [25]. Other authors Sheu [21], also showed that the mean percentage of CD8+ T-lymphocytes was higher in patients with axillary lymph node metastasis (64.72 \pm 8.24% versus 46.85 \pm 7.07%) P<0.001, using Student t-test [21]. This relation was not demonstrated by Macchetti [23], with P>0.05, using the 2-tailed Student t-test (mean CD8+ T cells infiltration 17.89 \pm 11.50 in node positive patients versus 13.25 \pm 15.20 in node negative patients) [23].

Correlation between CD3+ T-lymphocytes and axillary lymph node involvement

Sheu [21], showed that the mean percentage of CD3 T cells was higher in patients with lymph node involvement, P=0.011 (85.38 ± 1.56% versus 82 ± 3.94%), using Student t-test [21].

Discussion

Data to explain the role of TILs, their association with histopathological features, prognosis or predicting recurrence in breast cancer is still limited. Denkert [26] suggest a correlation between high levels of TILS and some characteristics of breast cancer Citation: Romeira D, Rodrigues C, Cardoso D, Pinto M, Miranda M, et al. (2016) Tumor Infiltrating Lymphocytes and Axillary Lymph Node Positivity: A Systematic Review. J Clin Exp Oncol 5:2.

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| Author | Study | Country | Pub.vear | N N | TNM | TILs | TILs ID | TILs | n | Quality Score |
|-------------------|----------|------------|----------|-----|----------------|-----------------------------------|---------|----------|----------|---------------|
| | design | | | | | | method | Location | (node +) | |
| Maccheti AH [23] | Prosp. | Brazil | 2006 | 23 | T1-T2 N0-N+ | B, T CD4+, T CD8+, NK cells | FC | IS | 10 | **** |
| Matkowski R [24] | Retrosp. | Poland | 2009 | 88 | T1-T2 N0-N1 | CD4+ T, CD8+ T | IMHC | IS | 43 | **** |
| Aaltomaa S [3] | Retrosp. | Finland | 1992 | 489 | T1-T4 N0-N+ | Notspecified | H&E | BS | 209 | **** |
| Tae Kim S [25] | Retrosp. | SouthKorea | 2013 | 72 | T0-T4 N0-N+ | T CD8+, T CD4+, Foxp3+Tregs | ІМНС | IS | 30 | ***** |
| Sheu BS [21] | Prosp. | Taiwan | 2008 | 24 | T1-T3 N0-N2 | Al types | FC | IS | 12 | ***** |
| Vgenopoulou S [4] | Prosp. | Greece | 2003 | 64 | n.s. | NK cells, B, T CD8+ | IMHC | BS | n.s. | ***** |

(high differentiation, hormone receptor negative, triple negative and Her-2 positive) [26]. The new theories, like the immunoediting theory, brought the notion of a dynamic interaction between tumor cells and the host immune system, resulting in tumor resistant cells [27] that escape the immune-mediated destruction [28]. It is believed that the tumor may activate an immune response in the early stages and that anti-tumorimmune responses are housed in the draining lymph nodes [29]. There is also evidence that immune-inhibitory factors, produced by tumor cells, arrest the immune response [30]. This balance, between immune surveillance and evasion, is critical for tumor progression [31]. On the other hand, it is known that the two most important prognostic factors in breast cancer are tumor size and histologically confirmed positive axillary lymph nodes [32,33], even the involvement of one axillary lymph node worsens the prognosis when comparing patients with or without lymph node involvement [34]. In this systematic review, we try to understand if TILs and their subsets are predictive of lymph node invasion, at the time of diagnosis. The studies show a marked heterogeneity, not only in the definition of TILs and evaluation of subsets, but also in the identification method. For this reason the authors decided not to do a meta-analysis. So far, to the extent of our knowledge, this is the first systematic review about the predictive value of TILs in respect to axillary lymph node involvement. The studies included in this review (with an acceptable quality), demonstrate that the presence of total TILs can predict axillary involvement in early breast cancer [3,24,25]. When taking into account the subtypes, the results were different. NK cells are a component of the innate immunity with activity not depending of prior sensitization. NK cells have a role in the vigilance of MHC class I molecules loss, from tumoral cells surface. When these molecules are diminished on the cells surface, these become more vulnerable to NK cells activity [35]. Two studies included in this review specified the relation between NK cells and axillary lymph node status. Vgenopoulous [4], describe a relation between an increased number of intra-tumoral NK cells and patients with more than 3 involved lymph nodes and that the absence of endo-tumoral NK cells were more frequent in patients without lymph node involvement. Some literature describes that draining lymph nodes of cancer patients, may give origin to specific or non-specific suppression of NK and CD8+ T-lymphocytes, resulting in a poor immunological activity [36]. On the other hand, Macchetti [23], failed to find a correlation between the presence of intra-tumoral NK cells and axillary lymph node involvement [23]. It has been described that the generation of a CD8+ T-lymphocytes cytotoxic specific anti-tumoral response depends from activated CD4+ T-lymphocytes [37], but some authors have shown that CD4+ T-lymphocytes may be only necessary to amplify the cytotoxic response [38]. This review wasn't conclusive in respect

to CD8+ T cells and their relation to nodal status. Vgenopoulous [4] and Sheu [21] found that elevated CD8+ T cells were more frequent in patients with axillary lymph node involvement [4,21]. Matkowski [24] demonstrated in 88 patients, a strong correlation between CD8+ cells and axillary lymph node metastasis. Macchetti [23] didn't find any relation between CD8+ T cells and axillary lymph node, in a small sample study, with only 23 patients [23] and Tae Kim [25] described in their study, with 72 patients, that those with lymph node involvement had a decreased number of CD8+ cells infiltrating tumor [25]. Although there is a trend to a correlation between increased number of CD8+ T cells and axillary involvement in early breast cancer, evidence is lacking to fully understand the value of CD8+ T cells predicting axillary lymph node involvement. The differences in these studies might have been related to the low number of patients included and to different methods of TILs identification. Our search reveals that the correlation between the number of CD4+ T cells and axillary lymph node involvement is not consistent. Some authors concluded that a low number of CD4+ T cells predicts lymph node involvement [21,25], while Macchetti [23] and Matkwoski [24] concluded the opposite [23,24]. As referred above, a low number of CD4+ T cells and high values of CD8+ T cells may correlate with an anti-tumor response and tumor progression [39]. On the other hand, Wong [40] suggests that increased TILS on patients with axillary involvement create a favorable environment for the tumor [40].

Conclusion

Although the authors found a correlation between TILS and axillary lymph node involvement in breast cancer, their role and their predictive value for axillary lymph node metastization is not clear. The studies included in this review show a trend to correlate some subsets of TILs with axillary involvement but larger studies are needed. In the future this could be a way to identify lymph node involvement which confer a higher risk of recurrence, and could have implications on these patients follow-up.

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