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Prediction Role of Tumor-Infiltrating Lymphocytes in Triple Negative Breast Cancer Patients Received the Neoadjuvant Chemotherapy: A Meta-Analysis

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Abstract

Introduction: The research of tumor-infiltrating lymphocytes (TILs) has attracted much attention in clinical practice in recent years. We performed this meta-analysis to find the value of tumor-infiltrating lymphocytes after neoadjuvant chemotherapy in triple negative breast cancer.

Methods: A full-scale search strategy was used to retrieve the database of PubMed and Web of science. The association between TIL and TNBC in the prediction for pCR using Review Manager 5.1 software.

Results: Six studies eligible for the meta-analysis reported ORs for pCR. The TIL level was divided into low and high. Outcome showed that the high TIL subgroup was associated with an increase of pCR incidence rate (OR: 1.26, 95%CI=:1.04-1.52 p<0.01). There was statistically significant heterogeneity (Cochran Q=0.00001, I^2=80%).

Keywords: Breast cancer; Neoadjuvant chemotherapy; Triple negative breast cancer; Pathological complete response; Tumor-infiltrating lymphocytes

Introduction

Breast cancer is the most common cancer in various kinds of tumors. It is estimated that about 15% female would be attacked by breast cancer in the lifetime [1]. At the same time, triple-negative breast cancer (TNBC) make up about 15% of all breast cancer subtype which is categorized by the hormone receptor (HR) and the human epidermal growth factor receptor-2 (Her-2). Triple-negative breast cancer (TNBC) is a sensitive subtype to chemotherapy among all the subtypes of breast cancer. Neoadjuvant chemotherapy (NAC) is an important treatment for locally advanced breast cancer. The aim of NAC treatment lies in the superiority of reduction in tumor size and makes it available for surgery treatment. Furthermore, we can evaluate the efficiency of chemotherapy and decide the suitable regimen for patients [2]. Individual index which can predict the efficiency of NAC to tripe negative breast cancer is still absent.

As it is known to us that immune system plays an important part in immune response and so as in the tumor elimination. The tumor-infiltrating lymphocytes (TILs) are part of immune response. There is a growing interest for tumor-infiltrating lymphocytes researches in recent years. The lymphocytes and macrophages usually surround the tumor cells. Although high levels of TIL have been showed a prediction value in breast cancer for patients who can achieve pathological complete response (pCR). Some studies with limited data showed higher TIL levels was linked to better prognosis for breast cancer [3,4]. However, the different subtype of breast cancer may own differ impact by TIL and is still complex. We searched studies research the value of TIL for pCR in TNBC who underwent NAC treatment [5-10]. Analysis was conducted to find out whether the TIL can be a predictive index for triple negative breast cancer.

Materials and Method

Search strategy

In this meta-analysis, a systematic strategy was used to search databases that following guidelines of systematic and meta-analysis statement (PRISMA). PubMed, Web of science were searched including the following words: neoadjuvant chemotherapy; breast; tumor-infiltrating lymphocytes; TIL and etc. The search dates are from January 2012 to October 2017. We mainly focus on essays which are related with neoadjuvant chemotherapy treatment for breast cancer. Two reviewers read the titles and abstractions of the studies which were searched (tan and liu) individually. Agreement will be reached through discussion when facing discordant cases. Relevant studies were retrieved so as to omit articles. Studies are eliminated which are not published in English. The full texts of the articles are reviewed carefully.

Eligibility criteria

Both the prospective and retrospective studies were included in the meta-analysis. Studies will be selected if they met the following criteria:

(a) full articles which are available from January 2010 to October 2017. (b) Articles published or unpublished in English. (c) The amount of patients which are involved in the study is greater than 30. (d) The content of studies is mainly about TIL and prognosis of breast cancer patients treated with neoadjuvant chemotherapy. (e) The endpoint of the studies is pCR or DFS and OS. (f) The OR for each study can be record or calculated using the data from the article.

Quality assessment

In order to assess the validity of the included studies, principles were made to solve this according to criteria made by MOOSE group. The following checklist were made: studies are clearly stated; date can be extract; amount of patient was clearly; sample size is larger than 30; measured TIL expression in tumor or from the blood. To assure the quality of the meta-analysis, all the studies should meet the criteria above.

Data extraction

The data were extracted by two investigators independently using specific method, the data sheet was designed according to the PRISMA guideline. The following fields were recorded: the first author, the publication year, number of patients, outcome, the subtype, PCR rate in TNBC according to different state of TIL, OR and 95%CIs and P value. When facing the same resources or datasets, single data would be extracted (Table 1).

Author	Publication year	Outcome	Sample size	TNBC
Nanyan Rao	2017	pCR DFS OS	52	yes
Makiko Ono	2012	pCR	102	yes
Chang Lim Hyun	2016	pCR	143	yes
In Hye Song	2016	pCR DFS	108	yes
Xiaoxian (Bill) Li	2016	pCR	78	yes
Akira I. Hida	2016	pCR	154	yes

Table 1: The characteristics of included studies.

Statistical analysis

The review manager 5.1 software was used for this analysis. The pCR was defined as no evidence of residual invasive tumor could be found in both the primary site and regional lymph nodes after neoadjuvant chemotherapy. The association between pCR and TIL level in triple negative breast cancer was explored. Amount of patients which achieved pCR in the TNBC group was extracted from the studies which are included. The pCR incidence rate was summarized and extracted for each study. The meta-analysis were calculated from random-effects analysis models.

Odds ratios (ORs) with 95% confidence intervals (95% CIs) were determined according to fixed and random models. We assesses statistical heterogeneity among studies using the Q test and I^2 test. We considered p<0.05 and I^2 value of >50% as random model for statistical analysis. Publication bias was assessed using funnel plots. We consider statistically significant when p value <0.05. All p value were two-tailed.

Results

A flow diagram is presented in Figure 1 which showed the process of studies been included. Totally, 148 studies have been identified from Pubmed and Web of science database. There was no additional resource added to the search. After articles removed which are not related to the topic through reading the title, there were 55 publications left and 93 full articles, which can be obtained. Then we download the publications and read the text briefly. There were 21 articles excluded which have no association to the topic by the outcome. Another 4 studies were removed for which belong to systematical review and meta-analysis. There were also 23 studies not fit for this analysis and ultimately 34 studies included for systematic evaluation. In total, 6 studies were eligible for meta-analysis.

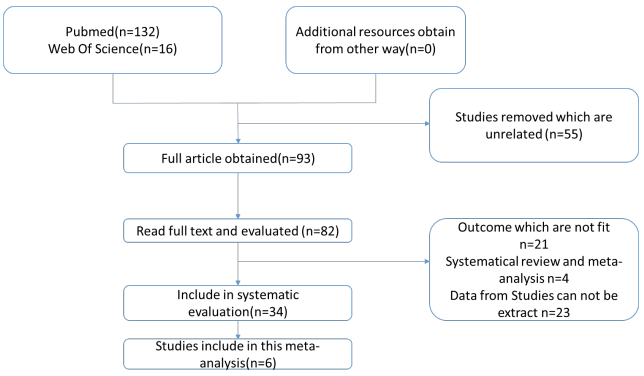

Figure 1: Selected trials.

Totally, there were 637 triple negative breast cancer patients involved in the analysis from 6 studies (chart 2).All the studies included were in recent 2 years and do have enough sample size. These 6 studies reported the pCR incidence rate between high and low level of TIL and TNBC. All the Odds ratios (ORs) with 95% confidence intervals (95% CIs) were extracted or calculated by one reviewer manually from the articles.

Secondary outcome

Association between TIL and pCR incidence rate in the studies: Six studies eligible for the meta-analysis reported ORs for pCR. The TIL level was divided into low and high. After studies involved in the analysis, we found that p<0.05 and I^2 value of 80%.We need to use the random model in the end. Outcome showed that the high TIL subgroup was associated with an increase of pCR incidence rate (OR: 1.26, 95%CI=:1.04-1.52 p<0.01). There was statistically significant heterogeneity (Cochran Q = 0.00001, I^2=80%) (Figure 2).

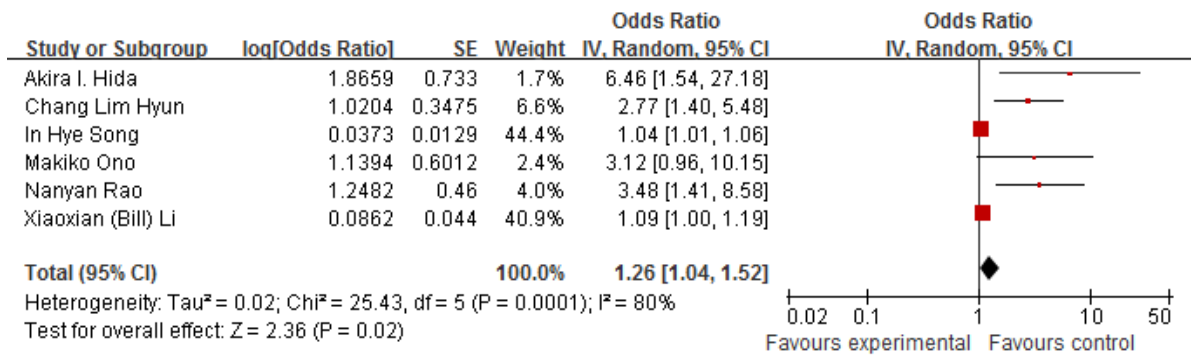

Figure 2: Forest plots TIL and pCR incidence rate in triple negative breast cancer receiving NAC treatment.

Publication bias

A funnel plot was performed to evaluate the potential bias. There was no significant bias among studies included in the meta-analysis.

Discussion

Breast cancer is a kind of tumor with high heterogeneity. The relationship between TIL and the response of TNBC have attracted much attention. The type, density, and location of TILs exhibit different values to estimate the prognosis and progression of breast cancer. As we know, CD8+T consists the majority of effector cell type, which was linked to better prognosis [11]. And Foxp3+ T cells or PD-1+ T cells mediates the tumor immune escape [12]. Mechanism of TIL lies in the follows: first of all, the immunosurveillance of tumor may be affected. Secondly, the ATP-dependent pathway facilitates the local differentiation of inflammatory DCs and may activate the T cells [13]. Moreover, the chemokine expression may be promoted by drugs. The CCL2/CCR2 pathway can afresh the T cell system [14]. Thus, it is unknown whether the stimulatory effects of these cells may have.

The purpose of this meta-analysis was to explore the predictive role of TIL in triple negative breast cancer who were treated with neoadjuvant chemotherapy. There was strong association between TIL and pCR incidence rate (OR: 1.26, 95%CI=:1.04-1.52 p<0.01). The result indicated that patients with high level TIL revealed a better response of neoadjuvant chemotherapy. When treated with neoadjuvant chemotherapy, the TNBC subtype may have better effect and benefit more from it. So the TILs should be detected and may do help in the way of rational stratification and adjusting the treatment strategy.

This meta-analysis still has some short come. Further research need to be done to explore the connection between TIL and breast cancer.

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