

PEER REVIEW

on dissertation thesis from Jeliazko Iliev Arabadjiev, MD entitled:
“Predictive and prognostic value of tumorinfiltrating lymphocytes in women with breast cancer”

Peer reviewer: Prof. Tzana Boshnakova-Praznikova, MD, DSc.

The dissertation thesis of Dr. Jeliazko Iliev Arabadjiev is dedicated to an important problem in breast cancer - the predictive and prognostic value of tumor-filtering lymphocytes.

Twenty-five percent of the causes of death in women worldwide are due to breast cancer. Every year, 1,200 women die in Bulgaria, and 3,500 learn for the first time that they have the disease. Cancer is represented by various biological subtypes, the nature of which plays a role in determining the prognosis and therapeutic approach.

The morphological diversity in breast cancer found in histological and immunohistochemical studies is a harbinger of an era of increasingly effective therapies that include biologics, endocrine modulators, and targeted small molecules in addition to systemic drugs and an appropriate surgical approach.

Over the last decade, efforts have focused on supplementing the morphological classification of breast cancer with molecular parameters that can provide a clearer understanding of its diversity and better predict tumor behavior in order to improve therapeutic strategies. The cancer community now describes cancer in four biological molecular subtypes according to the immunological profile - estrogen, progesterone and HER2.

Deciding on therapeutic behavior in each case depends on these molecular constellations. Numerous efforts are now being made to better understand the biology of breast cancer in order to improve the ability to individualize therapy.

Multiple analyzes try to improve the behavior of breast cancer and introduce us to the era of personalized disease management through the molecular profile. Neoplastic transformation of tumor cells damages the well-ordered tissue system and induces an immune response that can eliminate incipient tumors. Recently, due to advances in the development and use of immunomodulatory drugs for the treatment of some cancers, the importance of tumor infiltrating lymphocytes (TIL) - the substrate of the immune response against the tumor has increased significantly. exactly TIL therapies are the focus of research to find reliable prognostic and predictive factors in the treatment of so-called immunogenic types of cancer, among which breast cancer has recently been included. The data published so far in the literature on the effect of lymphocytic infiltration of the stroma of breast cancer in terms of treatment and the patient's prognosis are scarce and contradictory. All this indicates that the dissertation work of Dr. Arabadjiev is quite timely and there is a need to fill a gap in the field of diagnosis and treatment of breast cancer.

The dissertation is written on 118 pages and contains the following parts: introduction - 10 pages, literature review - 54 pages, purpose and tasks - 1 page, material and methods - 5 pages, results and discussion - 26 pages, conclusions and contributions - 2 pages. Appendices - 5 pages. The literature includes 246 authors and is presented on 15 pages.

In the literature review the author indicates the factors that determine the course of the disease / genetic, epigenetic, morphological characteristics of tumors, nodal status and distant metastasis./He provides up-to-date data on the prevalence, classification, diagnostic methods, prognostic factors and therapeutic approaches in breast cancer , as well as the advantages of targeted therapy. In the literature review the means of immunotherapy, etc. check point inhibitors that provide an immune response to tumor cells. An emphasis in the literature review is the assessment of the immune response - whether the degree of peri- and intratumoral infiltration can serve as a prognostic and predictive factor in breast cancer. The prognosis of the patient with breast cancer. Literature data show that increasing the number of tumor infiltrating lymphocytes in the tumor stroma prolongs overall survival (OS), disease-free survival (DFS) and improves clinical response to treatment. In other publications such dependence is not established. This definitely indicates the need to undertake the present study and indicate an exemplary algorithm for assessment of lymphocyte factor with a recommendation for clinical practice. The survival of patients with this diagnosis depends on the stage of diagnosis and therapy.

The search for new independent prognostic factors creates an opportunity for adequate treatment and reduction of mortality rates, as well as for improving the quality of life in these patients. This determines the need for the development of the present work undertaken by Dr. Arabadjiev. .

Based on the extensive literature review, Dr. Arabadjiev formulates the purpose of the dissertation thesis - to study the degree of TILs in patients with breast cancer in order to establish their prognostic and predictive value and the possibility of specific application in practice.

The six tasks are clearly formulated and correspond to the set goal. The material used is quite sufficient in volume - 118 patients with breast cancer were studied for the period from 1997 to 2020 and after an in-depth study for final examination were selected 58 women with lobular or ductal carcinoma in the first to fourth stage. of Acibadem City Clinic Tokuda Hospital with studied immunohistochemical hormonal status and HER2 status. All patients received adjuvant treatment and / or palliative treatment for metastatic disease - drug treatment (chemotherapy and / or hormone therapy) and / or radiation therapy. Regarding the stage of the disease, patients are divided into three groups: adjuvant without progression, adjuvant with progression and metastatic at diagnosis.

The following methods were used: anamnesis, imaging, histological examination of the primary tumor or metastatic lesion in a paraffin block, stained with hematoxylin - eosin and assessment of the degree of infiltration of TILs.

The medical record includes the following information: demographic data, medical history, performance status, information about the oncological disease:, location of the primary tumor, TNM staging, type and date of the surgical intervention,

Morphological examination-histological result - number, date, immunohistochemical characteristics of the tumor, Date of initiation of adjuvant and metastatic therapy,

Initial and control imaging studies: CT, MRI, 5 - WT, RECIST evaluation

Type and duration of (neo) adjuvant therapy, type and duration of first-line therapy, adjuvant radiation therapy. Progression-free survival and overall survival.

Specific research methods:

Pathoanatomical methods - routine histological specimens stained with hematoxylin and eosin at microscopic magnification of 100 and 200 were used.

In operative materials, TILs were evaluated in all histological specimens, and in core biopsies - in the stroma of the entire tumor area.

The percentage of TILs is the fraction of tumor stromal infiltration of lymphocytes and plasma cells relative to the total area of the tumor stroma. TILs were reported only in the tumor stroma. Excluded are those located among tumor cells, among large central fibrosis or necrosis, in areas of carcinoma in situ and in an area with crush artifacts, as well as in the adjacent tumor mammary parenchyma.

Materials from the primary tumor or metastases stained with hematoxylin - eosin were examined semi-quantitatively under a microscope for peritumoral (stromal) lymphocytic infiltration and were stratified into four groups - without infiltration, from 1% to 10%, from 19% to 50% , and over 50%.

The following methods of statistical analysis were used:

descriptive statistics, Chi-square test, or Fisher's Exact Test, Kaplan-Meier analysis to estimate survival curves, and Log Rank Test.

The results of the study present the data of 118 women with breast cancer for the period from January 2019 to January 2020, and retrospectively analyzed the medical records of patients diagnosed with breast cancer since 1997. until 2020 Fifty-eight women have confirmed lobular or ductal carcinoma in stages one to four with included (immunohistochemical) hormonal status and HER2 status. All patients received adjuvant treatment and / or palliative treatment for metastatic disease, chemotherapy and / or hormone therapy, and / or radiation therapy.

The results of the study show that the degree of lymphocyte infiltration in the stroma of tumors, assessed only on the basis of hematoxylin and eosin-stained tumor sites, provide reliable and statistically confirmed prognostic and prognostic value in some subtypes of breast cancer (triple negative) H triple negative and HER2. , therefore at this stage the need for detailed information on the immune subpopulations of the infiltrate is not associated with additional information for the prognosis of the patient with breast cancer.

The conclusions follow from the dissertation thesis work.

Contributions of original value and scientific-theoretical nature may include:

First, for the first time in Bulgaria, a study of the relationship between overall survival and the rate of tumor infiltrating lymphocytes in breast cancer.

Second, the correlation analyzes conducted for the first time in Bulgaria report data on the relationship between the degree of TILs and overall survival depending on the IXX status, statistically confirming the prognostic value of TILs in HER2 + / HER2-patients with breast cancer.

Third, for the first time in Bulgaria, statistically significant results are reported from an analysis that confirms the predictive value of TILs compared to the treatment with sequential administration of HT and ET, or HT and ET as a stand-alone treatment for breast cancer.

Fourth, for the first time, there is a tendency for a correlation between the value of TILs and the conduct of ALL and their impact on overall survival in patients with breast cancer.

Contributions of scientific and practical nature:

Determination of the degree of stromal tumor lymphocyte infiltration in primary tumor material or from hematoxylin-eosin-stained metastasis may be the subject of further studies

to confirm a potential correlation for response to drug and radiation antitumor treatment in breast cancer, such as predictive biomarker in breast cancer.

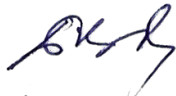
The results of the conducted research should be reported as contributions of the dissertation thesis. The work is representative of the high level of diagnostic activity in the country.

The author has six publications and announcements related to the dissertation thesis, as well as participation with a published summary of the 8th National Conference of USBALO, 2018. The presented abstract fully and accurately reflects the work performed and documents the results achieved.

The dissertation thesis is realized at a high level with a large set of modern techniques, a sufficient number of patients have been studied, valuable conclusions have been made and it should receive a positive assessment.

The work fully meets all the qualities of the Law on Scientific Degrees and Titles for obtaining the general education and scientific degree "Doctor" of its author - Dr. Jeli azko I liev Arabadjiev and I strongly suggest to the Honored Scientific Jury to vote positively for his choice.

Author:



/ Prof. Tzana Boshnakova-Praznikova, MD, DSc./