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DOCTORAL SCHOOL OF MEDICINE AND PHARMACY

Summary of Phd Thesis

Title: Neoadjuvant systemic treatment in breast cancer. Predictive factors for response to neoadjuvant therapy in breast cancer

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INTRODUCTION

Breast cancer is the leading cause of diagnosed cancer worldwide seen in women with an estimation of 2.3 million according to recent GLOBOCAN 2020 data. It is reported that one out of four women will be diagnosed with breast cancer, and one out of eight will die cause of breast cancer. Recent clinical trials proved that whether upfront or after surgery, timing of neoadjuvant systemic therapy doesn't influence survival rate. Neoadjuvant systemic therapy(NST) provides prognostic information and guides clinician for adjuvant therapy recommendations. It helps understanding better the tumor biology, and gives the possibility to explore the action of chemotherapy in vivo on the human model. Multiple studies focused their research on the role of neoadjuvant systemic therapy and proved that NST can increase the rate of breast conserving surgery and provide de-escalation in surgical treatment of the axilla, making NST an important treatment option in cases with operable disease. Although neoadjuvant chemotherapy(NAC) is the standard of care in stage II and III Triple negative(TN) and HER2+ breast cancer, the treatment approach and response in hormone positive cases can be challenging, and the sensitivity to chemotherapy its not so high as in other subtypes. The pathological complete response(pcr) rates are lower in hormone positive cancers than in TN or HER2 positive, they reach up to 10-20% and the residual disease after neoadjuvant therapy does not have the same amount of significance as a prognostic factor given the role of endocrine adjuvant therapy. Moreover the choice of giving neoadjuvant chemotherapy for this subgroup of breast cancer cases requires a multidisciplinary assessment in order to decide whether surgery or neoadjuvant treatment should be done first. The role of prognostic factors are to identify which patients would benefit the most from adjuvant therapy while, the predictive factors, are valuable because they can predict which is the most effective therapy and they can be used to measure treatment response in early stages of treatment. But predictive biomarkers in the neoadjuvant setting are limited.

The aim of this thesis was to evaluate which are the predictive factors that can be associated with pathological complete response in breast cancer patients after neoadjuvant systemic therapy and to assess the feasibility of sentinel lymph node biopsy in a large group of inflammatory breast cancer patients who achieved a good response after systemic therapy.

GENERAL METHODOLOGY

In the first study, we assessed the accuracy of digital mammography and breast ultrasonography in the prediction of response to neoadjuvant systemic treatment in breast cancer patients with different tumor subtypes. Its a necessity to asses BC(breast cancer) patients during and after their NAC, hence imaging tools are crucial for predicting pathological complete response and also to monitor response. This study was designed as retrospective diagnostic accuracy trial, gathering data from a single oncology institution from Târgu Mures, Romania. 81 breast cancer cases who underwent surgical resection between 2017 and 2020 were included. The primary outcome was the diagnostic accuracy of combined modalities of mammography and breast

ultrasonography for predicting the pathological complete response. The diagnostic accuracy of combined imaging modalities was analysed for positive and negative predictive values, sensitivity, and specificity rates. We compared the accuracy postNST imaging assessment with the post NST pathological response.

In the second study, as part of the co-tutorship with Prof. Dr.Bahadır M Gulluoglu from Marmara University School of Medicine Istanbul Turkey we aimed to provide rapid and low-cost alternatives for expensive gene profiling tools in order to choose patients who might get benefit from neoadjuvant chemotherapy and otherwise may go to radical surgeries at the breast and axilla. We designed a retrospective multicentric study that included 230 breast cancers. The data were gathered from a prospectively clinical database. Patients from 4 tertiary university hospitals in Turkey and Romania were included. The aim of this study was to assess the role of Magee Equation 3 (MagEq3), IHC4 score and HER2-low status in predicting “satisfactory response (SR)” to neoadjuvant chemotherapy (NAC) in HR+/HER2- breast cancer patients. Secondary outcomes were to assess Magee Equation3 score, IHC4, having low-HER2 status, in predicting satisfactory response at axilla (ypN0-ITC), after NAC in clinically node-positive patients with HER2-negative luminal cancer at admission. Another outcome was to define the independent factors for predicting the clinically satisfactory good response (RCB 0-1) to NAC at breast and axilla overall in patients with HR+/HER2-negative BC. MagEq3 and IHC 4 score were used for response prediction.

In the third study, we assessed SLNB(sentinel lymph node biopsy) feasibility in a larger cohort of IBC(inflammatory breast cancer) cases who achieved a good response in the axilla after systemic treatment. We designed a retrospective study collecting data from a single breast health care institution from Istanbul Turkey. We included all patients who were diagnosed with IBC and had SLNB followed by axillary lymph node dissection after systemic therapy. We evaluated the identification rate(IR), false negative rate(FNR) in all patients. As a secondary outcome we calculated the overall accuracy(OA). Furthermore, we reported the IR, FNR, and OA rate according to each molecular cancer subtype, each level of systemic treatment response, and the number of retrieved SLNs(sentinel lymph nodes).

GENERAL CONCLUSIONS

In the first study, we discovered that combined imaging tools based on digital mammography and breast ultrasound accurately predicted pathological complete response after neoadjuvant systemic treatment in HR+/HER2- BC cases with a very high specificity rate, therefore in this group of patients who achieve pathological complete response in breast and axilla, additional MRI imaging may be omitted. The high value of using these conventional imaging tools may help surgeons to select patients who might benefit from loco-regional treatment de-escalation with higher accuracy.

In the second analysis, we found that immunohistochemistry-based inexpensive tools such as Magee Equation 3, IHC4 score and HER2-low status are helpful in predicting satisfactory response to neoadjuvant chemotherapy in HR+/HER2- breast cancer patients who are not candidates for breast-conserving surgery and/or sentinel lymph node biopsy at admission. Patients with high scores of MagEq3 (≥ 31) and highest quartile (Q4) of IHC4 scores were significantly associated with better RCB-based SR. Also we found out that high levels of Ki67 predicted significantly, satisfactory axillary downstaging in HR+/HER2- patients. We believe that the findings of this study will help surgeons choose those patients who might get benefit from neoadjuvant treatment with easy, rapid and low-cost conventional tools which we think is a need in most parts of the world. On the other hand, by stratifying patients into Her2-0 and HER2- low seems an important factor to consider in the prediction of RCB. Her2-low tumors seem to have different response to treatment than those with HR/HER2-0. Therefore not only chemotherapy but also additional antiher 2 therapies may be administered in HER2-low positive cases but this issue deserves further studies.

In the third study, we found that the sentinel lymph node could be identified in IBC patients who achieved axillary pcr after NST regardless of their subtype. In our study we had a high identification rate and a low FNR. Our findings have shown that the IR is high in nonluminal HER2-positive cancer patients. We also found no false-negative cases in the subgroup with the highest pCR rate among all patients. Therefore, IBC patients with a high probability of achieving pCR would be the best candidates to get the highest benefit from SLNB after NST. From the biological standpoint, this group is more likely to be composed of HER2-positive and TN. This study suggests that in selected IBC patients, especially those who achieve pCR in the breast, SLNB may be considered as an option for axillary assessment. Accurate assessment of the axilla on ultrasonography after systemic treatment may be able to identify patients who will benefit from SLNB and thereby spare some from undergoing more extensive surgery. Patients with Triple-negative and HER2-positive IBC cancer may benefit from SLNB after systemic treatment if they achieve a very good clinical response.