The Egyptian Journal of Hospital Medicine (April 2018) Vol. 71 (2), Page 2590-2592

Predictive Role of Molecular Subtypes in Response to Neoadjuvant Chemotherapy in Breast Cancer Patients

Soheir Helmy Mahmoud; Amr Shafik Tawfik; Doaa Atef Mohamed; Kamal Ahmed Shata
Clinical Oncology and Nuclear Medicine Department
Faculty of Medicine - Ain Shams University
Corresponding author : Kamal Ahmed Shata , email: kamalshata84@gmail.com

ABSTRACT

Background: Breast cancer is increasingly regarded as a heterogeneous disease which can be classified into distinct molecular subtypes with prognostic significance.

Objectives: Retrospective evaluation of the response to neoadjuvant chemotherapy for patients with the major molecular subtypes of breast cancer as classified using immunohistochemical assay and to investigate the patterns of benefit from the neoadjuvant chemotherapy in different molecular subtypes

Materials and methods: ER, PR, HER2 and ki-67 were used to divide102 breast cancer patients treated with neoadjuvant chemotherapy (NCT) into 4 subtypes: luminal A (ER+,PR+,HER2-, and ki-67 ≤14%), luminal B (ER+, PR+,HER2- and ki-67>14% ; ER+ and/or PR+, HER2+), HER2-overexpression (ER-, PR- and HER2+) and triple-negative (ER-, PR-,and HER2-). **Results:** Of the 102 patients analyzed, 9 patients (8.8% of all patients) achieved pCR with 2.6% (2/76) for luminal subgroup, 0.0% (0/8) for HER2-overpression subgroup and 38.9% (7/18) for triple-negative subgroup with a high statistical significant value (p=0.000). **Conclusions:** Molecular subtypes are good predictors for response to NCT in breast cancer patients. Compared to luminal A tumors, HER2-overexpression and triple-negative subtypes are more sensitive to NCT.

Keywords: Breast cancer - molecular subtype - predictive factor - chemotherapy - pathologic complete remission.

INTRODUCTION

Breast cancer is a heterogeneous disease, therefore, tumor with the same clinicopathological characteristics may be diverse in disease behavior, response to therapy and prognostic. Gene expression profiling studies have identified at least four categories of breast cancer: luminal A, luminal B, HER2-overexpression, and basal-like subtype [(1)].

Traditionally, neoadjuvant chemotherapy (NACT) has been used in locally advanced breast cancers that are deemed inoperable. Also, it has been increasingly used for tumors that are resectable, but the intent is to reduce the tumor size by NACT and subsequently remove a smaller portion of breast tissue than would otherwise be removed at primary surgery**.** The aim of NCT is to downstage the tumor load to increase the rate of breast-conserving surgery and to gain information on drug response by breast assessment [(2)]. Moreover, NCT provides the opportunity to discover predictive markers of chemotherapy. Several researches had demonstrated that patients achieved pathologic complete remission (pCR) had better prognosis than those that did not. The prediction of the possibility of pCR before starting NCT can be used to maximize the treatment and minimize unnecessary toxicity [(3)]. It is well accepted that various subtypes of breast cancer show different sensitivities to NCT. A large number of clinical trials had revealed that pCR was related to good treatment outcomes and could be used as a surrogate marker of better survival [(3)]. Luminal tumors are considered to be less chemotherapy responsive, and someone even believe that luminal A tumors should receive endocrine therapy only and should avoid NCT**.** However, we implemented NCT in breast cancer patients not only to achieve pCR but also to change the choice of surgery. Treatment of luminal tumors with NCT can allow breast-conserving surgery to take place and as such can be an effective treatment option for this group [(2)].

AIM OF THE WORK

The aim of this study is to report and evaluate retrospectively the response to neoadjuvant chemotherapy for patients with the major molecular subtypes of breast cancer as classified using immunohistochemical assay and to investigate the patterns of benefit from the neoadjuvant chemotherapy in different molecular subtypes in Clinical Oncology Department, Ain Shams University hospitals from 2011 to 2014.

PATIENTS AND METHODS

Study Population

Our study is retrospective study included 102 patients from 2011 till 2014. The patients who were initially diagnosed by core needle biopsy and treated with NCT followed by definitive surgical resection were retrieved from the Clinical Oncology Department, Ain Shams University

Received:19 / 2 /2018 DOI**: 10.12816/0045661**
Accepted: 1/ 3 /2018

hospitals. **The study was approved by the Ethics Board of Ain Shams University.**

Response evaluation

The response to treatment at the time of surgery was taken as an end point. Both pathology and clinical findings were used for response evaluation. After two cycles of chemotherapy, we evaluated the treatment outcome by using ultrasound or MRI. Patients with favorably responding tumors continued their initial chemotherapy to four cycles or more, and patients with minimal response or stable disease were switched to the alternative chemotherapy regimen or immediate surgical operation. According to the diameter of primary tumor and the axillary lymph node status, the clinical response was classified as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD).

Molecular subtyping

Luminal A tumors were defined as ER+, PR+, HER2, and ki-67 ≤14%. Luminal B tumors were defined as ER+, PR+, HER2-ki-67>14%; ER+ and/or PR+, HER2+. HER2-overexpression tumors were defined as ER-, PR-, and HER2+. Triple negative tumors were defined as ER-, PR-, and HER2-.

RESULTS

A total of 102 patients were eligible for final analysis. Luminal subtype was detected in 76 (74.5%) patients, HER2 overexpression subtype was detected in 8 patients (7.8%) while triple-negative subtype was detected in18 patients (17.6%).

Of the 102 patients analyzed, 9 patients (8.8% of all patients) achieved pCR with 2.6% (2/76) for luminal subgroup, 0.0% (0/8) for HER2-overpression subgroup and 38.9% (7/18) for triple-negative subgroup with a high statistical significant value (p=0.000) as shown in table (1) .Four patients had stationary disease and all are in the luminal subgroup and no patients developed progressive disease in our study.

Table (1): Response of different molecular subtypes to neoadjuvant chemotherapy

		luminal		**HER2**		**ripple –ve**		**value***	**alue**	**g.**
		o.	**%**		**%**	**o.**	**%**			
	Minimal	9	.6%		0%		6%			
	Good	1	.5%		0%	0	.6%			
ponse to eoadj.	pathological plete response		6%		0%		.9%	.054	001	S
	tionary disease		3%		0%		0%			
	rogressive		0%		0%		0%			

NS: Non significant; S: Significant; HS: Highly significant
*:Chi-square test

DISCUSSION

Breast cancer (BC) is a heterogeneous disease not only in clinical but also in biological features. The heterogeneity of BC results in significant differences between certain histo-molecular subgroups in treatment efficacy and prognosis. Gene expression profiling has led to identification of 4 different molecular subtypes (luminal A, luminal B, basal-like, HER2+) **(4).**

Neoadjuvant chemotherapy (NAC), known as induction or preoperative treatment, has been widely used to treat locally advanced and inflammatory breast cancer. In addition, this approach was introduced in operable BC with the initial aim to downstage the tumor for better loco-regional control and increased conservative surgery rate **(5).** Another important advantage of using NAC was an early identification of unresponsive tumors that gives an opportunity to terminate the ineffective therapy and/or to switch to an alternative regimen **6).**

Regarding pathological response for neoadjuvant therapy, 9 patients achieved pCR (8.8%). The percentage of pCR cases differed significantly among the 3 molecular subtypes with highest percentage in triple-negative subtype 38.9% (7/16). Much lesser percentage for luminal subtype 2.6% (2/76) being luminal B with HER2- and no cases had pCR in HER2-overpression subtype (0/8) (p=0.000).

Our results are similar to results of ***Krijgsman et al.*** **(7)** who tested neoadjuvant chemotherapy response in 133 breast cancer patients, treated with FAC /Taxotere neoadjuvant chemotherapy. BluePrint classification of a patient cohort that was treated with neoadjuvant chemotherapy (n = 133) showed significant difference of pathological complete response (pCR),

among molecular subgroups, 3% of patients in MammaPrint low-risk, luminal-A type subgroup, 11% of a patients in the MammaPrint high-risk, luminal- B type subgroup.

In our study pathologic complete response in HER 2 enriched breast cancer was 0.0% (0/7) and this shows disagreement with all studies as in our study no anti HER 2 therapy used. This indicates the importance of using anti HER2 therapy in all HER2 enriched molecular subtype of breast cancer and its significant difference in pathologic complete response.

In our study, pCR was 38.9% (7/18) for triple-negative subtype (p=0.000). This result shows agreement with ***Wu et al.*** [8] retrospective study where 249 patients treated with neoadjuvant chemotherapy were included in this retrospective study. All the patients were classified as TNBC and non-TNBC Among all 249 cases, 54 (21.7%) were TNBC patients, 195 (78.3%) were non-TNBC patients. Compared with non-TNBC patients, the pathological complete response (pCR) rate of patients with TNBC was 25.9%, which was significantly higher than that of patients with non-TNBC (P = 0.019). Patients with TNBC were more sensitive to neoadjuvant docetaxel plus epirubicin chemotherapy. Compared with non-TNBC patients, TNBC patients had increased pCR rate.

CONCLUSION

Molecular subtypes based on ER, PR, HER2 and ki-67 can predict the pathological response of breast cancer patients treated with neoadjuvant chemotherapy. pCR rate varies significantly among different breast cancer molecular sub-groups. pCR rate is higher in triple negative breast cancer than HER 2 enriched and luminal subtypes.

REFERENCES

1. **Carey LA, Berry DA, Ollila D *et al.* (2013):** Clinical and translational results of CALGB 40601: a neoadjuvant phase III trial of weekly paclitaxel and trastuzumab with or without lapatinib for HER2-positive breast cancer. J Clin Oncol., 31(l): 500.
2. **Mieog JS, van der Hage JA, van de Velde CJ (2007):** Neoadjuvant chemotherapy for operable breast cancer. Br J Surg., 94:1189–200.
3. **Rastogi P, Anderson SJ, Bear HD *et al.* (2008):** Preoperative chemotherapy: updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27. J Clin Oncol., 26: 778–85
4. **Prat A, Ellis MJ, Perou CM (2012):** Practical implications of gene-expression-based assays for breast oncologists. Nat Rev Clin Oncol., 9: 48–57.
5. **Minghao W, Lingmi H, Maoshan C, Yan Z, Yueyang L, Shushu W, Jun J, Yi Z (2017):** Neoadjuvant Chemotherapy Creates Surgery Opportunities For Inoperable Locally Advanced Breast Cancer. Sci Rep., 7: 44673.
6. **Teshome M and Kelly K(2014):** "Neoadjuvant Therapy in the Treatment of Breast Cancer." Surgical oncology clinics of North America, 23(3): 505–523.
7. **Krijgsman O, Roepman P, Zwart W *et al.* (2012):** A diagnostic geneprofile for molecular subtyping of breast cancer associated withtreatment response. Breast Cancer Res Treat., 133: 37–47.
8. **Wu J, Li S, Jia W *et al.* (2011):** Response and prognosis of taxanes and anthracyclines neoadjuvant chemotherapy in patients with triple-negative breast cancer. J Cancer Res Clin Oncol., 137:1505-10.