

Current status and novel directions in triple negative breast cancer patients. Risk factors. Role of the platinum-based chemotherapy

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ABSTRACT

Rationale. Breast cancer (BC) has been recognized to be the most common type of cancer in women all over the world. One of the most aggressive subtype of BC is the triple negative breast cancer (TNBC) which is defined by the absence of estrogen receptor (ER) and progesterone receptor (PR) as well as the lack of over-expression of the human epidermal growth factor 2 (HER2).

Aim. As the estrogen and progesterone receptors as well as the expression of HER2 are lacking, a targeted therapy with anti-hormone agents and anti-HER2 cannot be utilized, the therapeutic possibilities for TNBC women are limited.

The aim of this review is to present the current scientific data as well as the latest research in TNBC with focus on the risk factors as well as the current role of platinum-based chemotherapeutic agents and their future implications in TNBC treatment.

Method. Information about the risk factors associated to TNBC as well as the chemotherapeutic regimens was searched through Pubmed and Medline using controlled vocabulary (e.g. breast cancer) and key words (e.g. neoadjuvant, triple negative, platinum). Systematic reviews, randomized and controlled clinical trials were analyzed. No restrictions regarding date or language were used.

Conclusions. TNBC is a complex and heterogeneous disease, divided into many subtypes and with an aggressive evolution. Premenopausal women and African American women are far more likely to develop TNBC. More research is required in order to confirm the association between obesity, BMI, parity, use of oral contraceptives, alcohol and cigarette smoking and TNBC. Randomized clinical trials presented at the San Antonio Symposium suggest that platinum chemotherapy play an important role in the treatment of TNBC, especially early stage TNBC. Tumor-based measures of genomic instability will help to clarify the optimal use and activity of platinum in TNBC. However, it is clear than more epidemiological studies as well as the discovery of novel therapeutic possibilities are mandatory in order to unravel the complexity of this BC subtype, hence offering a chance to women diagnosed with TNBC.

Keywords: breast cancer, triple negative, platinum, neoadjuvant

ABBREVIATIONS

BC = breast cancer; TNBC = triple negative breast cancer; ER = estrogen receptor; PR = progesterone receptor; HER2 = human epidermal

growth factor 2; DFS = disease-free survival; PARP = poly (ADP-ribose) polymerase; pCR = pathological clinical response; BMI = body-mass index;

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INTRODUCTION

In recent years, breast cancer (BC) has become an important malignancy worldwide being responsible for almost 1,4 million new cases annually, a statistic that positions BC on the first most common disease almost everywhere throughout the world (1). Its incidence rate is constantly increasing, excepting United States of America where a lower incidence rate in women aged 50-69 years old diagnosed with positive ER BC has been recorded since 2002, one possible explanation being the decision to prescribe hormone replacement therapy (2).

Although still very complex with regard to its etiology and molecular pathways, recent research has achieved to impose a novel, modern classification of BC tumors, mainly taking into consideration immunohistochemical features and molecular aspects (e.g cDNA microarray). Hence, nowadays we can consider 5 sub-types of breast tumors as follows (3):

- Luminal A: ER positive and/or PR positive, HER2 negative, histologically low grade.
- Luminal B: ER positive and/or PR positive, HER2 positive, histologically high grade.
- HER2 overexpressing: ER negative, PR negative, high expression of HER2 gene.
- Basal-like: ER negative, PR negative, HER2 negative, cytokeratin 5/6 positive and/or HER 2 positive;
- Normal breast-like tumours.

TNBC account for 10-20% of all invasive BCs, and, compared to luminal-like tumors (A or B) they carry a poorer prognosis with a high recurrence rate. Because of being defined by the absence of ER and PR as well as the lack of HER2 expression, TNBCs are nowadays considered a representative for the Basal-like BC subtype although approximately 75% of TNBC present the expression of basal-markers (4). The percentage of 10-20% may be explained either by variation in BC classification or differences between results regarding BC in different tumor centers. However, one aspect must be taken into consideration: not all TNBC are basal-like BC subtypes (5).

With regard to epidemiological aspects, it has been estimated that TNBC represents almost 170000 cases of all the BCs (6). TNBC is more frequent in young (most frequent premenopausal). Afro-American women with a poor nutritional status which generally present a positive family history of BC with BRCA1 mutation. At initial diagnosis, women generally present with advanced disease characterized by

high grade tumors with ductal histology, high proliferation and mitotic rates (7). Lara Medina and its coworkers (8) have observed that TNBC women present a high risk of local recurrence, which is higher in the first 3 to 5 years after the initial diagnosis, a lower disease-free survival (DFS) rate as well as cancer-specific survival rate.

Specific risk factors have not been completely elucidated, but there is strongly evidence that Afro-American and American women have a 3-fold risk of developing TNBC. Explanations of this phenomenon are not available although research is being conducted in the direction of genetics and lifestyle which may explain the poorer survival of black women with BC (9).

When we make reference to the therapeutic possibilities, it is generally known that TNBC presents a high response to neoadjuvant and adjuvant chemotherapy, all the clinical trials studying TNBC patients in the neoadjuvant setting demonstrating that a pathologic complete response (pCR) after neoadjuvant chemotherapy followed by surgical treatment is associated with a better prognosis (10-12). However, the latter mentioned study (12) have surprisingly showed that women with TNBC have a more aggressive recurrence and a worse overall survival rate with the highest risk of recurrence only in the first 3 to 5 years after the initial diagnosis and not thereafter. Moreover, the median overall survival time (months) from the moment of recurrence to the point of death is shorter in TNBC women compared with non-TNBC. Therefore, we can assume that TNBC responds better to chemotherapy than other types of BCs even tough, during its clinical course, owing to unknown mechanisms, it relapses and presents a more aggressive clinical course.

In recent years, it has been evidenced that BRCA1 mutations are play a significant role in DNA repair mechanisms and that there is a correlation between the expression of BRCA1 mutations and the appearance of sporadic TNBCs. Basing on these theory, it has been assumed that DNA repair defects may explain the pathogenesis of TNBCs and the fact that this BC subtype is responds to chemotherapy similar to the BCs with confirmed BRCA1 mutation (13). Furthermore, studies have demonstrated that basal-like BC tumors present sensitivity to cisplatin, poly (ADP-ribose) polymerase (PARP) inhibitors and gemcitabine, a hypothesis that has been further investigated in TNBCs (14).

More and more scientific information emphasize the need to implement platinum-based

chemotherapy both in the neoadjuvant treatment of TNBC (both early stage and advanced TNBC). Aside from presenting the current knowledge regarding the risk factors of TNBCs, this review tries to present the benefits of platinum-based agents as well as their future implication in the treatment of TNBC.

RISK FACTORS

Among the most cited risk factors associated with TNBC we mention: age, race, ethnic, body mass index, parity and the use of oral contraceptives. With regard to the scientific research on risk factors of TNBC, we make reference to the study of Stead and its coworkers (15) who analyzed 415 women of different races and ethnics with BC of whom 47% were obese and 72% of them had ER positive and/or PR positive tumors, 20% triple negative tumors and 13% HER2 positive tumors. They observed that the risk of developing TNBC is threefold higher in African-American women compared with white women. When it comes to the age and BMI of the African-American women, the percentage of TNBC in women before 50% was 31%, similar to TNBC in women after 50 years (29%). In the same way, 29% of African-American women who were obese developed TNBC compared to 31% non-obese black women. The conclusion of the study was that, independently of age or BMI, Afro-American women have a higher predisposition to TNBCs.

Other observations come from the study of Kurian (16) who showed that 1,98% of the African-American women developed TNBC compared with 1,25% of the white women, 0,77% of the Asian women, 1,04% of the Hispanics. More than half of the luminal BC were seen in women more than 70 years old.

The strong correlation between TNBC and women with African-American, American and Ghanaian/African origins has been also revealed by Stark and its coworkers (17) showed that from 1664 women of different ethnic – 1008 white Americans, 581 African-Americans and 75 Ghanaians – TNBC was seen in 82%, 26%, and 16% of cases, respectively. 82% of the Ghanaians women developed Grade 3, palpable TNBC, compared to 33% African-Americans and 10% white Americans.

The results of the studies conduct to the conclusion that African-American and African women are more likely to be diagnosed with TNBC. Moreover, breast tumors who express

the BRCA1 mutation are most frequently ER-/PR-/Her2neu-/ (18).

The association between TNBC and obesity is debatable. Some authors (19,20) have stated that premenopausal women with overweight or obese are more have a higher risk of being diagnosed with TNBC than normal weighted or underweighted pre-menopausal women. On the other hand, Stead (15) obtained opposite results the main conclusion being that the higher the BMI, the lower the rate of TNBC.

As regards the classical risk factors associated with invasive BC, it is not yet clear if they are also available in TNBC. For example, Dolle (21) and his coworkers found that the use of oral contraceptives increases the risk of TNBC while Phipps et al. (22) reported no association with TNBC risk and oral contraceptive use. In the same way, Kabat (23) and coworkers concluded that smokers and alcohol drinkers have not a higher risk of developing TNBC than non-smokers and never drinkers although they can develop ER positive BC.

ROLE OF PLATINUM IN TNBC. FUTURE IMPLICATIONS

Preliminary reports have showed that BCs which presents mutations of the genes BRCA1 and BRCA2 are more sensitivity to platinum am gemcitabine compared to BRCA1 and BRCA2-proficient BCs which better respond to taxanes (24,25). Studies have reported that TNBC patients treated only with taxanes agents showed unsatisfactory response and pregression-free survival rates if the breast tumor was BRCA1 deficient (26).

The phase II GeparSixto trial from the German Breast Group presented at the ASCO Annual Meeting in 2013 provided important randomized data regarding a regimen of dose-intense anthracycline and taxane-based chemotherapy with bevacizumab with or without carboplatin in the treatment of early-stage TNBC (27). The 315 patients with early-stage TNBC showed a better pCR when the treatment regimen consisted of neoadjuvant paclitaxel 180 mg/m²/week for 18 weeks, non-pegylated liposomal doxorubicin 20 mg/m² and Bevacizumab 15 mg/kg every 21 day with additional weekly carboplatin AUC 1.5 compared with those that did not (p CR 59% vs.38%). In spite of these results, many patients did not achieve the completion of the whole neoadju-

vant regimen (with or without carboplatin) because of the side effects.

Another study (28) which revealed that the addition of carboplatin to standard anthracycline and taxane-based chemotherapy with or without bevacizumab (paclitaxel 80 mg/m² for 12 weeks followed by doxorubicine 60 mg/m² and cyclophosphamide 600 mg/m² every 2 weeks for 4 cycles) in patients with TNBC stages II-III was presented at the San Antonio Breast Cancer Symposium in 2013 and proved that the addition of carboplatin results in a better pCR -54% vs a pCR of 41% when the regimen did not include carboplatin. Moreover, the use of bevacizumab also increases the pCR (52% with bevacizumab vs. 44% without bevacizumab). Similar to the GeparSixto study (27) the patients could not complete the chemotherapy with additional carboplatin and/or bevacizumab owing to the significant adverse effects.

For patients with metastatic TNBC the data on the efficacy of carboplatin or cisplatin together with the standard chemotherapeutic agents are not yet definitive in order to consider the platinum-based agents may improve the pCR in advanced TNBC. More reports are required in order to implement cisplatin-based agents in the chemotherapeutic regimens in women with advanced TNBC.

One report that provided valuable results is a phase trial randomized clinical trials on metastatic TNBC conducted by O'Shaughnessy J. (29). The overall response rate and PFS were 30% and 4.1 months respectively when gemcitabine and carboplatin were used in combination with iniparib compared to 34% and 5,1 months respectively when iniparib was not added. In the same way, Isakoff et al (30) reported an overall response rate of 30.2% in the phase III TBCRC009 in which 86 women with metastatic TNBC have been treated with a platinum agent (cisplatin or carboplatin) as first or second line therapy. For women with breast tumors that express BRCA1 or BRCA2 mutations.

Although there is evidence that women diagnosed with TNBC can benefit from a combination of platinum agents with anthracycline and taxanes, more trials are necessary especially as regards the effect of adding platinum agents to standard chemotherapeutic regimen on event-free and overall survival. For example results of an ongoing trial – phase III study of car-

boplatin AUC 6 every 3 weeks versus docetaxel 100 mg/m² every weeks as first line treatment in metastatic TNBC could provide valuable information (13). Moreover, it is also important to know the optimal moment of the therapy to implement platinum agents as in almost all the above presented studies the platinum-associated toxicity represented an obstacle for the whole completion of the chemotherapy.

Other interesting discovery that might detect breast tumors that can respond to platinum chemotherapeutic agents is the Myriad HRD assay a tumor-based assay that measures the genomic instability and identifies the levels of genomic scarring caused by the accumulation of DNA damage. Other important biomarkers that are currently under development and may contribute to the selection of patients with TNBC who can benefit from platinum-based therapy are the telomeric allelic imbalance and large-scale state transition (31,32).

CONCLUSIONS

The current clinical studies have shown that risk factors such race, age, premenopausal status, increased parity, oral contraceptives are independently associated with TNBC. With regard to the first-line therapy of this special type of BC, the fact that BRCA1 deficient BC are most frequently TNBCs is an important consideration that can be used as hypothesis in order to understand the need to implement platinum agents that target DNA repair deficiencies. Randomized neoadjuvant trials have demonstrated that a significant better pCR can be obtained if cisplatin is added to the standard combination chemotherapy. However, worth to be taken into consideration are the toxic effects of the platinum agents that most frequently represent a barrier to successful treatment completion.

Innovative developments that are capable to identify women with BRCA-like tumors but who do not present BRCA1 and BRCA2 mutations and in whom platinum agents will significantly improve the pCR of women with TNBC are the tumor-based assays which can measure the genomic instability such as the telomeric allelic imbalance and large-scale state transitions. These biomarkers may play in the future an essential role in determining the clinical potential of platinum-based therapy in TNBC.

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