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Triple negative breast cancer - general characteristics and treatment principles

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Abstract

Triple- negative breast cancer (TNBC) is a subtype of breast cancer that does not express the estrogen and progesterone receptors and HER2 protein. This type of cancer represents an important clinical challenge because it does not respond to endocrine therapy or anti- HER2 drugs. In this case, the mainstay treatment is the chemotherapy. The basic principles of diagnosis and management of TNBC are similar to those of breast cancer in general, but the key in managing TNBC remains to find new specific targets that can potentially improve the outcome of the disease.
Keywords: *breast cancer, triple negative, basal like, chemotherapy*

Introduction

Breast cancer is one of the most frequent cancer form in women and among this category of patients one of the leading causes of death. Triple negative breast cancers (TNBC) represent approximate 10- 20% of all breast cancers diagnosed worldwide[1-4].

It is well known the importance of the hormone receptors to the biology of the breast cancer and that the human breast cancers are dependent of estrogen (ER) and progesterone (PR) for growth. This effect is mediated via hormone receptors (ER and PR receptors) which are usually overexpressed in breast cancers. Therefore, an analysis was performed in order to identify new therapies that could interact with the hormone biology for finding a better treatment. The result was clear that an important part for managing breast cancer would be endocrine therapy. Nowadays, all guidelines recommend that testing for ER and PR should be performed in all invasive breast cancers and the result should select patients that can benefit from endocrine therapy.

Initially called human epidermal growth factor receptor 3 (HER2/neu) or receptor tyrosine-protein kinase (erbB2), HER 2 gene encodes a transmembrane receptor HER2, which is part of the epidermal growth factor receptors family (EGFR). These receptors are important in growth, differentiation and possible angiogenesis[5]. Knowing the HER2 status of a breast tumor is important because thus we know if HER2 plays a role in cancer and, if so, these patients can benefit from therapies that target HER2.

In this review triple-negative will be referred to cancers that have ≤1% expression of ER and PR as determined by IHC (immunohistochemistry), and that are either 0-1+ by IHC for HER2, or 2+ and fluorescence in situ hybridization (FISH) negative, according to ASCO/CAP guidelines 2013[6].

General Characteristics of Triple- Negative Breast Cancer

A logic hypothesis would be that TNBC and the basal-like tumors are the same. The basal-like tumors represent 8-37% of all breast cancer[7]. High histological and nuclear grade with high mitotic and proliferative indices are usually associated with the basal-like tumors. The clinical expression for this type of tumors is aggressive and tends to metastasize to the brain and lungs. ER, PR and HER2 are not expressed in the basal-like tumors and therefore they are referred as triple negative. They also express myoepithelial markers (cytokeratin (CK)5, CK14, CK17 and laminin) and P- cadherin and EGFR[7-9]. These cancers are associated with mutations of tumor protein 53 gene and microarray and IHC analyses demonstrate that basal-like cancers constitute approximately ¾ of a breast cancer type 1 (BRCA1) gene-related breast cancers[7].

TNBC express other markers than the basal ones and can be classified as normal breast-like, molecular apocrine or claudin- low subtype by gene expression profiling[10]. Besides, there are other histological types of breast cancers that do not show the basal-like pattern and they express a triple negative phenotype (i.e. pleomorphic lobular carcinomas, apocrine carcinomas a.s.o.)[10]. Luminal markers, such as androgen receptors, with a lower proliferative activity, are expressed in a few number of triple-negative tumor cases[11]. HER1/EGFR, c- Kit expression, p53 mutations, poly adenosine diphosphate (ADP)-ribose polymerase 1 (PARP 1) represent other markers of TNBC that can potentially be targeted[8]. A unique model for the TNBC biology cannot be created at the current moment due to the fact that the above mentioned biological subgroups mix and thus they cannot be combined.

An important note related to the terms triple negative and basal-like must be highlighted, in the idea that they are not completely the same. The triple negative refers to the IHC classification of the breast cancers in which

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the ER, PR and HER2 are not expressed. The basal-like subtype is expressed via gene expression microarray analysis[12] and many genes identified among this type are usually seen in basal or myoepithelial cells of the normal breast[3]. Between the triple-negative and intrinsic basal-like subtype there is an approximate 80% overlap. In the TNBC are also included some special histological types with low risks of distant recurrence, such as medullary and adenoid cystic carcinoma[13].

TNBC is characterized by several clinicopathologic features. Most TN tumors have a ductal origin, but other phenotypes like metaplastic, adenoid cystic, atypical or typical medullary, can be present[8].

They are more prevalent in African- American women and there is a high association related to the metabolic syndrome or obesity[14,15]. Other risk factors implied in the disease are younger age at menarche, high parity, full-term pregnancy at a younger age or shorter duration of breastfeeding[8].

TNBCs are considered interval cancers because they can be discovered or detected between a period of 1 to 12 months after a mammographic screening in which findings are considered normal[3,14]. This evolution is highly suggestive for the rapid progression behavior of the disease and the similarity of the tumor tissue to the normal one[14]. The aggressive pattern of TNBC can be suggested by the onset at a younger age, the greater the tumor volume and grade and the greater chance of BRCA1 expression[16,17]. Other facts that suggest the aggressive pattern of TNBC is that the top of the recurrence is between the first and the third years and most of the deaths appear within the 5 years post treatment. Some may suggest the recurrence peak at 2-3 years after the diagnosis[4]. The risk of recurrence afterwards drops over the next 5 years[4]. The TNBC tend more to distant recurrence with a few cases being preceded by local recurrence[4]. After the appearance of the first metastatic tumor, patients with non-TNBC have a longer survival rate compared to those with TNBC which have a shorter survival rate[8,10,14]. The patients with a complete pathological response after the neoadjuvant therapy are less likely to have local recurrence compared to those without a complete response, whose prognosis is worse[18].

A weak association between the tumor size and the node involvement can be made, meaning that, a high frequency of lymph node involvement is detected even for the small size tumors[14]. The same discrepancy was observed in BRCA1- breast cancers[4,18].

TNBC is more likely to metastasize in central nervous system, lung and liver[14,15,19,20]. The tendency of the basal-like cancers to metastasize in central nervous system is about 10-16%[21].

The prognosis of the disease is inferior compared to non-TNBC[21,22]. The specific cancer survival, the likelihood of distal recurrence and death are all worse in the TNBC[8].

Treatment of the Triple- Negative Breast Cancer

The treatment of TNBC is complex and it implies a multidisciplinary approach for a positive impact on survival outcome and, as other types of breast cancer, it includes surgery, radiotherapy and chemotherapy.

Surgery consists in breast conserving therapy (BCT) or mastectomy. Because of the aggressive pattern of TNBC the question about the best surgical option was raised. There are some studies that doubt the benefit of the BCT and shows that the local recurrence after BCT is higher in TNBC then other breast cancer subtypes[23]. On the contrary, there are some studies that prove the benefit of BCT in TNBC and shows no significant difference in local recurrence between TNBC and non-TNBC[24-27]. It is important to underline the routine use of systemic chemotherapy in TNBC treated with BCT compared to non-TNBC.

Radiation therapy is routinely used in BCT for breast cancers. In TNBC, the question raised about radiotherapy was whether the tumor was radioresistant or not. Some studies suggest the radioresistance of TNBC because of the ERp29 expression, over expression of HER1 or mir-27, biological features of this subtype of cancer[28]. But despite heterogenous entities of TNBC, there are a lot studies that shows the benefit of radiation therapy in overall survival, local recurrence and mortality rate[17,28]. The radiation therapy is prescribed in TNBC based on clinical and pathological characteristics and the biological differences are not taken into consideration. After mastectomy, the indications for radiotherapy are high risk patients, one to three positive axillary lymph nodes, T3-T4 tumors and positive resection margins[29]. More prospective studies are needed to a proper selection of patients with TNBC that can benefit more from radiation therapy.

The mainstay systemic treatment for the TNBC is represented by chemotherapy since there is no response to endocrine or HER2 therapy. A characteristic of these tumors is their chemosensitivity despite their poor outcome. A combination of anthracyclines and taxanes represents the basic treatment[14,30,31]. Their efficacy was proven even in metastatic disease although, in this case, there are some limitations of these regimens: these drugs are usually used in adjuvant therapy, the disease- free interval is short and the maximum anthracyclines doses have cardiotoxicity, thus questioning the chemosensitivity to these drugs[14].

The relation between chemosensitivity and outcome in breast cancers was analyzed in two neoadjuvant studies[32,33]. In both studies patients with a pathologic complete response had a good prognosis regardless of subtype. The women with higher risk of recurrence were those with a residual response after neoadjuvant therapy. What it is important to remember is that there are patients with TNBC who are well treated with common chemotherapy, but this subtype requires more research and more effective therapies capable of dealing with the disease[32,33]. A higher response to chemotherapy is observed for TNBC compared to the luminal A or B, but this subtype on the other side has a shorter disease-free interval and overall survival[34].

In TNBC with BRCA1 mutations, some studies suggest that the chemotherapy should have also in the componence

the platinum salt agents. The action mechanism that they use is that they cause deoxyribonucleic acid (DNA) cross-link stand breaks. This approach can be very effective in cells with BRCA mutantsdue to their dysfunction in repair mechanism[16,30,31,34]. The recommendations for BRCA testing should be offered to all patients with TNBC under 40[30].

Other targeted against TNBC, such as antiangiogenic agents, EGFR inhibitors, are now taken into considerations and scientific efforts are made to discover better and better solutions.

The antiangiogenic agents, such as Bevacizumab (Avastin) are analyzed in approaching TNBC. In the subgroup of TNBC has been observed vascular endothelial growth factor (VEGF) 2 over-expression[15]. Bevacizumab is a monoclonal antibody that targets all forms of VEGF that was approved by the Food and Drugs Administration as first-line treatment for metastatic breast cancer[14]. A clear advantage was showed for the TNBC patients in terms of response rates and time to progression with the addition of the Bevacizumab[14]. Now, there are studies that analyze the use of Bevacizumab in adjuvant and neoadjuvant chemotherapy only in TNBC[14]. For the treatment of TNBC otherpotential antiangiogenic agents are developed and currently under investigation, such as small-molecule kinase inhibitors, including sunitinib and sorafenib[14,15].

For the treatment of TNBC, EGFR inhibitors, such as Cetuximab (Erbitux) are under investigation also[8,14]. They are associated with adverse effects such as fatigue, diarrhea and vomiting, neutropenia and thrombocytopenia[8].

PARP inhibitors represents another target therapy in TNBC, especially in those cancers with BRCA mutations[8,16,34]. PARP1 is a gene that codes an enzyme important in DNA repairing process, especially in cell recovery from DNA damage[8]. When PARP1 is inhibited, the cell requires homologous recombination for the repairing process and this implies the function of both BRCA 1 and 2[8,16]. The use of PARP inhibitors in treatment of BRCA mutations breast cancers, led to the concept of "chemical synthetic lethality"[16]. PARP inhibitors efficacy (alone or in chemotherapy combination) is under investigation in multiple studies for patients with BRCA mutations. In TNBC, PARP inhibitors are under study for adjuvant and neoadjuvant therapy[8,16]. Two such PARP inhibitors are olaparib and talazoparib[8,16].

Assessment the role of the BRCA 1 in breast cancer and identifying the metabolic pathways has led to the progression of new therapeutic options. We need to discover better biological characterization of TNBC in order to develop specific therapies for each subgroup.

Conclusions

In conclusion, TNBC due to its unique characteristics represents at this moment a clinical challenge, from the perspective of molecular, biological and clinical features, prognosis and therapeutic options. The importance of chemotherapy in dealing with the disease has led to new clinical trials that investigate new strategies in understanding and treatment of the challenging TNBC. ■

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