TRIPLE NEGATIVE BREAST CANCER IN ELDERLY PATIENTS CLINICAL APPROACH

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ABSTRACT

***Aims**: 15-18% of Breast cancer is a "Triple Negative Breast Cancer", without estrogen, progesterone and HER2 receptors. This type of tumour has an aggressive behaviour and does not respond to conventional hormonal or anti-HER2 therapies. In this article we examine different cases of Triple Negative Breast Cancer (TNBC) in the ederly in order to show a diagnostic-therapeutic algorithm.*

***Materials and methods**: In this paper there were examined three heterogeneous clinical case of Triple Negative Breast Cancer (TNBC).*

***Results**: TNBC has an aggressive behaviour and the only treatment that guarantees a response is chemotherapy. The first of the three patients was free relapse for 15 months; the second had a relapse in homolateral breast after 12 months with a liver metastases; the third patient, seven years after a TNBC, had a second breast tumour, but this time hormonal positive.*

***Conclusion**: TNBC is still a challenge for surgeons and oncologists but soon new knowledge helps in the diagnosis, in the surgical and in the pharmacological treatment of this disease*

***Key words**: Breast cancers, subtype, BRCA1 Gene, triple-negative, adjuvant chemotherapy.*

***Received** January 18, 2014; **Accepted** January 24, 2014*

Introduction

Breast cancer is one of the most widespread tumors in western world. Breast cancer cases significantly increased from the 's70 years to nowadays, because of the changed lifestyles. It was estimated that 5-10% of breast cancer is caused by germline mutations; the most important are inherited mutations that inactivate BRCA1 (Breast Cancer Susceptibility gene1) and BRCA2 genes[1]. Triple negative breast cancer (TNBC) is a biological entity that lacks estrogen receptors (ER), progesterone receptors (PgR) and Human Epidermal Growth factor receptor 2 (HER2)[2,3].

Statistical studies have estimated that women with BRCA1 mutation have a relative increased risk of around 65% to develop a cancer after 70 years old while, in patients with BRCA2 mutation, the risk increases about of the 45%[4,5]. TNBCs comprise 15% to 20% of breast cancers in western countries and the vast majority are sporadic[6].

Hereditary breast cancer associated with BRCA-1 mutation[7] is frequently invasive, and it's characterized by the following features: high-grade, rich lymphocyte component, ER and PgR negative and p53 positive[8]. The BRCA-1 and BRCA-2 proteins are involved in the homologus repair of the DNA double stranded[9,10].

There are several lines of evidence to suggest a link between basal-like breast cancer and BRCA1 deficiency. Many phenotypical, immuno-histochemical, clinical characteristics and molecular features are shared by basal-like breast cancers and tumors that arise in carriers of BRCA1 germline mutations. The majority of BRCA1-associated tumors are triple-negative and express basal CKs,

p53, P-cadherin, and EGFR and both patient groups have a poor outcome[11].

Approximately the 70-80% of breast carcinomas express estrogen receptor ERα (ER +). These tumors tend to grow slowly; they are differentiated and associated with a good prognosis; about the 50% are both ER + and PgR+, approximately 15-20% are ER + and PgR- and respond less to therapy, whereas only the 5% are ER- and PgR +. This type of cancers shows an intermediate response to endocrine therapy.

Triple negative breast cancer (TNBC) refers to breast cancer that is negative for estrogens receptor, progesterone receptor and human epidermal growth factor receptor (HER2) and often, but not always, have a histological subtype basal-like.

Both triple-negative and basal-like cancers preferentially have an onset at a younger age, a larger mean tumour size, higher grade, higher rate of node positivity, appear more frequently in patients of African origin and cause an elevated number of recurrences and metastasis[12].

An estimated 1 million cases of breast cancer are diagnosed annually worldwide, and the so-called "triple negative tumors" constitute the 15% of the BC, resulting in about 170.000 cases of the triple-negative (ER-/PR-/HER2-) phenotype[13]; in Italy there are about 40.000 new cases of breast cancer each year, of which 6000 are "triple negative" carcinomas.

An analysis of the Polish Breast Cancer Study found that in premeopausal women early age at menarche and the highest body mass index (BMI) were associted with basal-like disease, whereas elevated BMI decreased risk of luminal A tumors[14]. An evaluation among post-menopausal women observed that early age at menarche was associated with HER2+ disease and that breastfeeding was portective for luminal subtypes and triple-negative tumors[15].

TNBC usually responds poorly to endocrine therapy and HER2-targeted therapy and often grows rapidly, resulting in poor outcomes[16,17].

The TNBC is an aggressive subtype marked by higher rates of visceral and central nervous system metastases and poorer disease-specific survival than hormone receptor-positive subtypes[18]. Therefore an aggressive loco-regional approach is not particularly suitable.

In this study there are selected three paradigmatic cases of TNBC.

Case 1

A 76 years old woman, with family history positive for breast cancer malignancy, was seen for a breast-infiltrating lesion in the upper outer quadrant of about 5 cm x 6.5 cm with cutaneous involvement. A mammogram found a 6-cm suspicious mass and an ultrasound confirmed the presence of an irregular lump. A biopsy revealed an invasive breast ductal carcinoma no otherwise specified (NOS).

In the pre-operatory diagnostic phase were not found metastases.

A neo-adjuvant chemotherapy with FEC-T schedule (fluorouracil 500 mg/m2, epirubicin100 mg/m2, and cyclophosphamide 500 mg/m2) was administered intravenously (i.v.) on day 1 every 21 days (3 cycles) followed by docetaxel (TXT) i.v. (75 mg/m2) every 21 days.

After the three cycles of FEC chemotherapy there was a reduction of tumor diameter (4 cm x 4 cm) with mild side effect.

However, after the 1th cycle of the TXT, the patient showed a drug intolerance with nausea grade IV, febrile neutropenia and abdominal pain. For this reason, it was decided to discontinue therapy and send the patient to surgery. Before surgery, it was estimated a reduction of the primary lesion, approximately 2 cm x 2 cm, fixed both with skin and the deep plans.

The patient was subjected to quadrantectomy 11x8x4.5 cm with completion Axillary Lymph Node Dissection (cALND). Histological Diagnosis evidenced an invasive ductal carcinoma of breast NOS type, with peripheral high-grade ductal in situ (DCIS), extensively infiltrating breast tissue and sub-epidermal vessels with venous and lymphatic vascular invasion G3 p T4b, pN2a (7/14 nodes). Neoplastic vascular emboli were also found in non-neoplastic mammary tissue. Research of receptors showed the following results:

Estro-progestinic receptors negative;
Mib-1 negligible (5%);
c-ERB2 negative.

At the time of admission and during the follow up the serum was analysed for estimation of levels of various tumour markers (Table1).

The patient was subjected to post-operatory chemotherapy and radiotherapy. 3 cycles of CMF (cyclophosphamide, methotrexate, and 5-fluorouracil) 1-8 schedule (CTX 600 mg/m^2, MTX 40 mg/m2, 5FU 600 mg/m^2, on days 1 and 8, every 4 weeks) were administered, followed by radiothera-

py with 50 Gy and 10 Gy Boost. Thereafter, three others cycles of CMF were administered.

	CEA ng/Ml	CA 15.3 IU/Ml	CA 125 U/Ml
At admission	1,1	14,6	7,6
2 months after surgery	1,5	16,4	10,7
At relapse	1,6	32,4	11,04

Table 1: Case 1: Tumour Markers.

After 15 months of follow up the patient accused headaches and dizziness. Magnetic resonance imaging evidenced the presence of metastases (32 x 32 x 32 mm) in the posterior fossa of the cranium, in the mid vermis, deforming the lower portion of the vermis. Other formation (6 x 6 mm), with peripheral enhancement after gadolinium administering, was found in right frontal cortex.

It has been planned a visit in radiotherapy for symptom reduction and then in Oncology for a new chemotherapy.

Case 2

A 71 years old woman was admitted to our department for a bilateral breast cancer. In the left breast she presented a nodule of approximately 1,7 cm x 1,2 cm between the inner quadrants, around the areola; while, in the upper inner right quadrant she had a nodule of about 7 cm x 2,5 cm. The patient had a familiar history positive for cancer. Both parents (father smoker, mother no smoker) died for lung cancer. An ultrasound found in both left and right breast the presence of an irregular lobular mass (Table2).

A biopsy was performed and both the samples were positive for invasive lobular carcinoma. Distant metastases were not detected. A Neo-adjuvant chemotherapy (3 cycles of CMF 1-8 schedule CTX 600 mg/m2, MTX 40, 5FU600 mg/m^2, i.v.day 1 and 8, q days 28) was performed; subsequently both nodules reduced their dimensions. The left nodule measured 1.34 x 1 cm while the right one was 2.34 cm x 1.83 cm.

It was performed a double quadrantectomy of both the inner quadrants and a sentinel node in the left breast and a Madden mastectomy with a cALND in the right breast.

The histological exam evidenced:

• Left breast between the inner quadrants: infiltrating lobular Carcinoma; marked tumor stromal fibro-elastosis; fibrous mastopathy in the surrounding parenchyma. Free skin and resection margins. Immunohistochemical assessment of hormone receptors: Estrogen and Progesterone negative, HER2 negative, Ki-67< 5%. Sentinel Lymph nodes free of malignancy. P TNM T1bN0 (sentinel node).

• Right breast and right axilla: pronounced fibro-elastosis and areas of necrosis, remnant traces of infiltrating lobular carcinoma; nests of ductal canceration. Free resection margins and skin. Lymph node metastases in 13/14. Immunohistochemical determination of hormone receptors: Estrogen 5%, Progesterone 5%, Ki-67 <10%: C-erbB -2: negative, pTNM: T3 N3.

	CEA ng/Ml	CA 15.3 IU/Ml	CA 125 U/Ml
At admission	2,8	10.9	6
12 months after surgery	2,6	24	6,5
At the relapse	2,7	42	7,2

Table 2: Case 2: Tumour Markers.

The patient underwent to total left breast radiotherapy and, subsequently, adjuvant chemotherapy with CMF1-8 schedule. At the 12th months of follow up a liver ultrasonography revealed metastases in the VII segment. For these metastases she has performed a FEC chemotherapy (500/80/500) for 6 cycles.

Case 3

A patient 79 years old, affected by a triple negative tumor at age of 70 years in the 2004, presented in post menopause a new breast cancer, but this time with positive receptors.

The patient had a positive story of multiple cancer familiarity: sister died at the age of 62 years for a breast cancer, mother deceased for a multiple myeloma, father deceased for not better specified neoplasia and a brother underwent surgery for a testicular cancer. She was a former smoker (10 cigarettes/day) for 30 years, non-smokers since three months.

In 2004 she was operated of quadrantectomy to remove a TNBC from the upper outside quadrants of the right breast. The histological exam evidenced infiltrating lobular carcinoma (G2 to Ellston-Ellis) pT1 NO Mx. Estrogenic and

Progestinic receptors negative, c-erb-B2: negative, c-kit: positive (<10%).

The malignancy was treated with chemotherapy regimen AC (adriamycin 60 mg/m2 and Cyclofosfamide 600 mg/m2, i.v. day 1 q 21 days) and radiation therapy: 5000cGy-200cGy/day+ boosts 1000cGy-200cGy/day for a total of 6000cGy.

In 2011, in the left breast, between the uppers quadrants around the areola, she has been diagnosticated a nodular image of greater diameter of 11.8 x 11.7 x 11.6 mm to refer to heteroplasia and in right breast was evidenced breast thickening of mastophatic type with small dystrophic micro-calcifications.

A core needle biopsies of the lump relived an infiltrating lobular carcinoma (G2) ER: 80% PgR: 10% c-erbB -2: 2 +, proliferative Index (Ki67): 20%.

A left quadrantectomy in UO quadrant was performed with sentinel node research. Histologic response evidenced:

• Sentinel lymph node: Intraoperative diagnosis Histiocytosis, sinus, but definitive diagnosis (staining for pan-Cytokeratin): micrometastases (600 microns) of lobular carcinoma. For that reason a left completion Axillary Lymph Node Dissection (cALND) was performed: negative 13/13 Lymph Node

• Breast Parenchyma: near the deep edge, a white hard lump, 2.5 cm maximum diameter. Invasive lobular Carcinoma (G2); peripheral niduses of lobular carcinoma in situ (LCIS). Skin and surgical resection margins free of neoplastic infiltration.

Neoplastic cell receptor: ER: 50%, PgR : 30%, Ki-67: 20%, c-erbB -2: 2 + (complete membrane moderate positivity 10%). pT2 N1 (sn) (mi). FISH research of HER2 gene amplification: negative.

The patient was subjected to radiotherapy 5000cGy-200 cGy/day and then to hormonal therapy with letrozole 2,5 mg/day, actually on going. The patient is disease-free now.

Discussion

In the first case, neo-adjuvant and adjuvant chemotherapy were administered but the patient developed SNC metastases; in the second case the patient presented TNBC synchronous to another breast cancer and she showed liver metastases after 12 months of follow up. The third patient, instead, had a positive receptor second breast cancer, with an anamnesis positive for TNBC, seven years before.

In 2000, Perou issued a new classification based on the molecular expression, with five new subtypes of breast cancer: luminal A, luminal B, HER2, normal breast like and basal like. Different subtypes require different therapeutic strategies[19].

The group "luminal" is characterized by a high expression of many genes expressed by the luminal breast cells, including ER and cytokeratins (CK) 8/18.

Tumours defined "normal breast" express distinctive genes of the epithelial basal cells and adipose cells with a low expression of the genes present in the luminal cells.

Basal like breast cancer has quickly become a major subtype because of its features, such as the lack of expression of ER, PgR and HER2 receptors, the worse prognosis and no therapeutic target. The tumours of the group "basal like" are characterized by high expression of CK 5, 6, 14 and 17, smooth muscle actin, EGFR, P-cadherin and Caveolin (CAV) 1 and 2, while lacking express ER and many other genes that are usually included with it. Also the AR positivity is less frequent than in luminal tumors. Other markers are vimentin, p53 mutation, mediators of angiogenesis (VEGF), tyrosine kinase receptor such as MET and KIT.

Triple-negative breast cancer (TNBC) status is characterized by the lack of expression of ER, PgR, and human epidermal growth factor receptor-2 (HER-2), whereas basal-like breast cancers are defined by a unique mRNA expression profile measured by DNA microarrays. The concordance between the gene expression-based or IHC-based basal-like class and the clinical phenotype-based (ER/PR/HER-2) TN status is around 70-80%.

Many studies have shown that TNBC is chemo-sensitive. Currently, it is recommended to use the same chemotherapy regimens as in non triple-negative disease. Anthracycline and taxane chemotherapy is recommended for neoadjuvant theraphy. Others tratment approaches use neoadjuvant platinum, mainly in BRCA-1 related cancers, Bevacizumab, an inhibitor of VEGF (Vascular Endothelial growt factor) or Everolimus, an inihibitor of Mammalian Target of Rapamycin[20]. This subtype of cancer has a worse prognosis than the luminal ones. The TNBC tumours and particularly the basal-like subtype, despite their high response to chemotherapy, have got a higher risk of recur-

rence (but only in the first 3 years), and the median survival from the time of relapse is significantly lower than in no-TNBC[21].

TN tumours share morphological characteristics that include high mitotic counts, tumor necrosis, invasion of the margins, lymphocytic stromal response and high nucleus-cytoplasm ratio. Histologically they are usually invasive ductal carcinomas, but there may be other histological types like metaplastic or medullary.

Patients TN undergoing neo-adjuvant chemotherapy have a higher rate of pathological complete response than patients with luminals ones. PCR is correlates to a better outcome, however comparing patient that did not have a PCR, TN patient had a worse prognosis.

The pattern of metastatic relapse is aggressive with predominance for visceral organs, mainly lung, CNS and lymph nodes[22].

Drug susceptibility should be checked before starting systemic therapy[23,24,25].

Two-phase II studies, that include treatment with cetuximab, have been presented. In the first one using irinotecan and carboplatin with or without cetuximab there was a modest higher response rate (from 30% to 49%) with the combination in triple-negative breast cancers. In the second, in patients randomized to receive either cetuximab in monotherapy or in combination with carboplatin, Cetuximab alone had a low response rate as single agent, but the combination of cetuximab plus carboplatin was more active with a response rate of 18% and a clinical benefit seen in 27% of the patients[26]. Other option in chemotherapy are Ixabepilon associated with capecitabine[27]; the Eribulin, that reduce CA 27-29 levels[28]; the association of paclitaxel/bevacizumab[29].

The addition of iniparib to chemotherapy improved the clinical benefit and survival of patients with metastatic TNBC without significant increased toxic effects[30].

Angiogenesis is a fundamental mechanism in tumor growth and Bevacizumab is a humanized monoclonal antibody against vascular endothelial growth factor (VEGF). The FDA approved bevacizumab in the beginning of 2008 in combination with paclitaxel in the first line treatment of metastatic HER-2 negative breast cancer. The addition of bevacizumab or other antiangiogenics drugs to chemotherapy in patient with TNBC is being explored in many on going trials[31]. Bone-direct therapies are biphoshonate or denosumab.

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