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Androgen Receptor Blockade as Treatment of Triple Negative Metastatic Breast Cancer

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ABSTRACT

In 2006 a 35-year old female patient was having a tumour mass (4,5cm) on the right breast. It was biopsied and histologically verified invasive ductal carcinoma – ER 0%; PR 0%; HER2 (0) – TNBC, $cT_3N_xM_0$. She underwent 4 cycles neoadjuvant therapy with anthracyclines (FEC). Afterwards it was perfomed a right sided mastectomy with axillary lymph node dissection (12 lymph nodes without metastases) and she was staged as $pT_3N_0M_0$, G2 invasive ductal carcinoma, ER 0%; PR 0%; HER2 (0); Ki67 = 15%. She has no family history for cancer; BRCA1/2 negative. The patient had 4 cycles with Docetaxel (75mg/m^2) in adjuvant aspect and 50 Gy radiotherapy on the thoracic wall and the axill.

She was on a dynamic control for 7 years (between 2007 – 2015). Computer tomography (CT), bone scintigraphy and abdominal ultrasound were regularly made.

In 2015 it was observed a slight progression of the tumor marker up to 35 U/ml. A bone scintigraphy was performed, that showed bone metastases, and treatment was started with Denosumab 120mg s.c.

In November 2016 a PET/CT (positron emission tomography) was made and it was detected a new progression of the disease with three new mediastinal lymph nodes. She started systemic treatment with Docetaxel (75mg/m^2) for six cycles together with Denosumab 120mg. A control CT showed stable disease. She continued with Capecitabine 1250 mg/m^2 + Denosumab. This treatment lasted four months due to poor tolerance and toxicity. Palliative radiotherapy for mediastinum was made.

On 12.02.2018 another PET/CT showed progression of the mediastinal lymph nodes. The patient received treatment with Eribulin 1.23mg/m^2 (day 1,8) for five months.

In September another progression was detected with more than 20% enlargement of the observed mediastinal lymph nodes. A biopsy was performed, which proved the same histology of the tumor – invasive ductal carcinoma ER 0%; PR 0%; HER2 (0); Androgen Receptor positive (2+3=5/8). The patient agreed on treatment with Bicalutamide 50mg p.o. daily + Denosumab 120mg s.c. monthly. The treatment with antiandrogen started in December 2018 and continued until 08.2019 when another progression of the mediastinal lymph nodes was detected.

The treatment with Bicalutamide was well tolerated without any adverse events or any toxicity during the whole period of nine months.

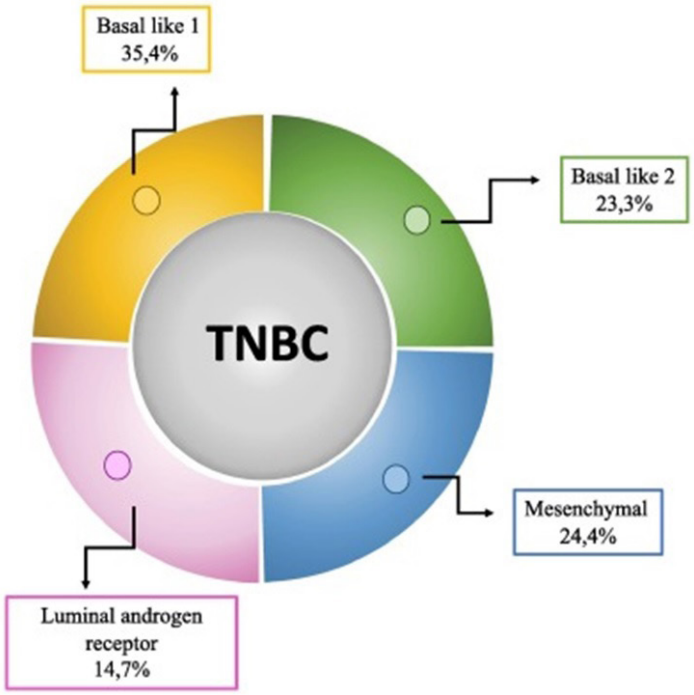
Keywords

Triple negative breast cancer, Antiandrogen therapy, Hormonal therapy, Ductal cancer.

Introduction

Breast cancer is the cancer type with the highest incidence and mortality rate among women, who develop malignancies [1].

Despite the fact that the most common histological type is the ductal carcinoma, the treatment of breast cancer is not unique and depends on many other factors like hormonal status (estrogen [ER] or progesterone [PR] positive or negative), activity of human epidermal growth factor receptor 2 (HER2), the level of Ki67 (index of proliferation), mutation in BRCA1 or BRCA2 genes. On the other side, a tumor without hormonal expression and HER2 (0) is considered triple-negative (TNBC). The triple negative breast cancer represents 15% – 20% of all breast cancer types [2]. It is well known with its extremely aggressive behavior. Many clinical studies came up with data, proving that the triple negative breast cancer is not only a subtype of a breast cancer, but it gathers together different profiles such as basal like 1 and 2, mesenchymal and the luminal androgen receptor (LAR) [2] (Figure 1).



Sub-types	Characteristics	Treatment
BL1	Cell cycle control, DNA damage response and high cell proliferation	Antimitotic agents such as platinum salts and PARP inhibitors
BL2	Expression of EGFR, TP63, MET and activation of glycolysis and gluconeogenesis pathways	Antimitotic agents such as platinum salts and PARP inhibitors
M	Pathways involved in cell motility, extracellular matrix interaction, EMT , growth factor. Mutation of PIK3CA or PTEN deficiency.	TKI, mTOR inhibitor, eribulin mesylate
LAR	Hormonale-mediated signaling-androgen receptor	Anti-androgen therapies

Figure 1: Lehmann classification 2016. (A) Triple negative breast cancer (TNBC) was classified into main six subgroups: two basal like classes (BL1 and BL2), an immunomodulatory (IM), a mesenchymal (M), a mesenchymal stem cell (MSL) and the luminal androgen receptor (LAR) class. (B) Triple negative breast cancer (TNBC) was classified into main six subgroups: two basal like classes (BL1 and BL2), an immunomodulatory (IM), a mesenchymal (M), a mesenchymal stem cell (MSL) and the luminal androgen receptor (LAR) class [3].

Androgens (testosterone and dihydrotestosterone (DHT)) are the male sex hormones required for development of the male reproductive system and secondary sexual characteristics [4,5]. The androgen receptor (AR) is a nuclear receptor that functions as a transcription factor. It also regulates the development and growth of the prostate by males. Namely AR is the primary target for endocrine therapy of prostate cancer [6].

However, the androgen receptors might be target also for treatment of triple negative breast cancer, as there are some subtypes (LAR) that are expressing them. AR is expressed in 60% – 70% of breast tumors independent of estrogen status, and in 20 – 32% of TNBC patients [9].

Case Report

In 2006 a 35-year old female patient was having a suspicious tumour mass (4,5cm) on the right breast. It was biopsied and histologically verified invasive ductal carcinoma – ER 0%; PR 0%; HER2 (0) – TNBC, $cT_3N_xM_0$. She underwent 4 cycles neoadjuvant therapy with anthracyclines (FEC). Afterwards it was perfomed a right sided mastectomy with axillary lymph node dissection (12 lymph nodes without metastases) and she was staged as $pT_2N_0M_0$. The tumor size had shrunk up to 2cm, G2 invasive ductal carcinoma, ER 0%; PR 0%; HER2 (0); Ki67 = 15%. She has no family history for any type of cancer.

She had 4 cycles with Docetaxel (75mg/m^2) in adjuvant aspect and 50 Gy radiotherapy on the thoracic wall and the axill. She was on a dynamic control for 7 years (between 2007 – 2015). Computer tomography, bone scintigraphy and abdominal ultrasound were regularly made.

In 2015 it was observed a slightly progression of the tumor marker up to 35 U/ml. A bone scintigraphy was performed, that showed bone metastases, and treatment with Denosumab 120mg s.c. was started.

In November 2016 a PET/CT was made and it was detected a new progression of the disease with three new mediastinal lymph nodes – 11mm SUV max 4,7; 15mm SUV max 5.9; 14mm SUV max 7.7 thus a new bone metastase on the sternum was detected SUV max 7.2. She started systemic treatment with Docetaxel (75mg/m^2) for six cycles together with Denosumab. A control CT showed stable disease. She continued with Capecitabine 1250 mg/m^2 + Denosumab. This treatment lasted four months due to poor tolerance and toxicity. Palliative radiotherapy for mediastinum was made.

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Eribulin 1.23mg/m^2 (day 1,8) for five months.

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The treatment with Bicalutamide was well tolerated without any adverse events or any toxicity during the whole period of nine months.

Discussion

The LAR – subtype is characterized with better prognosis, but also lower responsiveness to chemotherapy. It was also found that the androgen receptors interact with the BRCA 1 gene. Both BRCA1 and PARP 1 play important role in DNA repairing processes thus they act as coactivators of AR and promote AR-targeted gene transcription. Finally, a breast cancer positive for BRCA1 shows a lower expression of AR [2,7,8]. This is a prove, that the LAR type gives a better prognosis and longer overall survival (OS).

The first clinical Phase II study on antiandrogens as therapy for triple negative breast cancer was made with Bicalutamide (NCT00468715)62. It had been used immunohistochemistry (IHC) to evaluate the androgen receptors on the nuclear surface and it appeared that 12% or 51 patients (n=424) demonstrated AR positivity. The patients were with either primary or metastatic disease and they started treatment with Bicalutamide 150mg orally daily. The clinical benefit rate was 19%. The antiandrogen therapy was well tolerated, without grade 4-5 adverse events. Aim of the study was to prove the efficacy of androgen blockade in selected group patients with ER (-) PR (-) AR (+) breast cancer [2].

Another study was performed in 2009 – seventy-seven female patients with triple negative breast cancer and AR (+) received adjuvant Bicalutamide 50mg (Casodex TM 50mg) once daily, Ki67>14%. The median follow-up period was 24 months. Improved survival with AR-positive expression group for 2-year and 3-year DFS was 85% and 78% respectively with (P = <0.001, Cl 95% 39.17–51.39) and for OS at 2-year and 3-year was 100% (P = 0.0005) [9].

AR expression is significantly related to older age at diagnosis, smaller tumor size, well differentiated tumors, lower proliferative index, lack of lymph node metastasis and of ductal type [10,11]. Fatima Zakaria et al. state that AR inhibition can stabilize disease in TNBC patients. Bicalumide is well tolerated in AR positive patients and could offer an alternative to cytotoxic chemotherapy in those patients. TNBC needs for a paradigm shift in personalized treatment than one size fits all [9].

Another Phase II clinical study with Enzalutamide in women with advanced AR (+) TNBC (AR IHC>0%) (NCT001889238) the clinical benefit rate was correlating with the AR status namely 16 and 24 weeks compared to those who were lacking this gene variety [12].

Conclusion

The triple negative breast cancer is a heterogenous malignancy with many subtypes that define the aggressive character of the disease. The luminal androgen receptor (LAR) subtype shows a better prognosis, due to the fact that can be treated with an androgen inhibitor and also that correlates with stability in BRCA1 gene. The only systemic treatment for metastatic triple negative breast cancer used to be chemotherapy. In 2019 an outbreak was made after FDA and EMA approved Atezolizumab combined with nab-Paclitaxel for first line metastatic triple negative breast cancer. However, immunotherapy is not accessible everywhere also we still try to understand, avoid and deal with the adverse events caused by the monoclonal antibodies. In comparison, the antiandrogen receptor blockade does not show any adverse events and it was well tolerated during the treatment, as it was described in the case report and the clinical studies with Bicalutamide and Enzalutamide.

This is a prove that we may have to try to understand better the molecular biology of the different subtypes of TNBC and create a specific strategy for their treatment.

LAR type of TNBC shows good response of antiandrogen blockers and their role might be crucial before starting with other systemic treatment of metastatic disease.

References

1. WHO Breast Cancer statistics. 2018.
2. Gerratana L, Basile D, Buono G, et al. Androgen receptor in triple negative breast cancer A potential target for the targetless subtype. Cancer Treat Rev. 2018; 68: 102-110.
3. Gerratana L, Fanotto V, Bonotto M, et al. Pattern of metastasis and outcome in patients with breast cancer. Clin Exp Metastasis. 2015; 32: 125-133.
4. Rachel A Davey, Mathis Grossmann. Androgen Receptor Structure, Function and Biology: From Bench to Bedside. Clin Biochem Rev. 2016; 37: 3-15.
5. MacLean HE, Chu S, Warne GL, et al. Related individuals with different androgen receptor gene deletions. J Clin Invest. 1993; 91: 1123-1128.
6. Parth K. Modi, Isaac Yi Kim MD. Androgen Receptor - in Prostate Cancer Second Edition. 2016.
7. McNamara KM, Moore NL, Hickey TE, et al. Complexities of androgen receptor signalling in breast cancer. Endocr Relat Cancer. 2014; 21: T161-T18.
8. Luo J, Jin J, Yang F, et al. The correlation between PARP1 and BRCA1 in AR positive triple-negative breast cancer. Int J Biol Sci. 2016; 12: 1500-1510.
9. Fatma Zakaria, Nehal El-Mashad, Dareen Mohamed. Androgen receptor expression as a prognostic and predictive

marker in triple-negative breast cancer patients. 131-140.
10. Emad A Rakha, Maysa E El-Sayed, Andrew R Green, et al. Prognostic makers in triple-negative breast cancer. Cancer. 2007; 109: 25-32.
11. Park S, Koo JS, Kim MS, et al. Androgen receptors expression is significantly associated with better outcomes in ER-positive breast cancer. Ann Oncol. 2011; 22: 1755-1762.
12. Parker JS, Peterson AC, Tudor IC, et al. A novel biomarker may predict clinical activity from enzalutamide in triple-negative breast cancer Poster presented at 2015 ASCO Annual Meeting. 2015.