



MOLECULAR CLASSIFICATION OF BREAST CANCER TUMOURS FROM PATIENTS TREATED WITH DOXORUBICIN AND DOCETAXEL

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Abstract

It is known that four main molecular breast cancer subtypes have different prognoses and different responses to therapy. Luminal A tumours have a better prognosis and they tend to be sensitive to anti-estrogen drugs. Luminal B tumours have incomplete sensitivity to endocrine therapy. Her2 tumours, which have an aggressive natural history, are sensitive to trastuzumab. Finally, basal-like tumours might be eligible for chemotherapy. The aim of this study was to evaluate the chemosensitivity to docetaxel and doxorubicin of breast cancer subtypes. Patients with locally advanced breast cancer were randomized to receive 4 cycles of full dose doxorubicin (75 mg/m²) or docetaxel (100 mg/m²). After the fourth cycle, patients were submitted to surgery to ascertain pathological response.

Treatment response was assessed according to Symmans classification. Among 130 samples analysed most ER positive tumours were luminal subtype. 41% of Her2 positive tumours assessed by immunohistochemistry and FISH were Her2 according to the gene expression profile. Luminal A and normal-like tumours have low expression of proliferation genes as well as ki67, whereas Her2 and basal-like tumours are highly proliferative. Both treatments have the same efficiency (20% of responses). However, basal tumours have the poorest outcome in the doxorubicin branch (0% of responses) while they are the most sensitive to docetaxel (50% of responses). Luminal and normal-like tumours have the poorest responses to both treatments. Finally, Her2 tumours had similar outcome in both branches (20% of responses).

Genomic classification may assist the physician to choose a specific treatment based on the sub-type of tumour. This study provides the basis for building individualized neoadjuvant therapies for breast cancer.

INTRODUCTION

It has been established that there are four main molecular breast cancer subtypes according to gene expression profiles that are: basal-like tumours, which mostly correspond to triple negative tumours, luminal A tumours, which are ER (oestrogen receptor) positive tumours with low expression of proliferation genes, luminal B tumours which are ER positive tumours with high expression of proliferation genes and Her2 tumours which express high levels of Her2 and other genes that are in the same amplicon (1).

There is a reasonable correlation between these subtypes and the histological grade, proliferation markers and hormone receptor status as well as Her2 receptor status.

Also, it is known that these subtypes have different prognoses and different responses to therapy. Luminal A tumours have a better prognosis and they tend to be sensitive to anti-estrogen drugs. Luminal B tumours have incomplete sensitivity to endocrine therapy. Her2 tumours, which have an aggressive natural history, are sensitive to trastuzumab. Finally, basal-like tumours might be eligible for chemotherapy (2).

AIM OF THE STUDY

To evaluate the chemosensitivity to docetaxel and doxorubicin of breast cancer subtypes.

PATIENTS AND METHODS

Patients with locally advanced breast cancer were randomized to receive 4 cycles of full dose doxorubicin (75 mg/m²) or docetaxel (100 mg/m²). After the fourth cycle, patients were submitted to surgery to ascertain pathological response.

RNA was extracted from the pre-treatment tumour biopsy using Quiagen RNeasy Mini Kit following the instructions of the manufacturer. Whole Human Genome Oligo 4x44 Microarray (Agilent Technologies, Santa Clara, CA, USA) were hybridised following Low RNA Input Fluorescent Amplification 4 x 44k Perou lab protocol (available on <http://peroulab.med.unc.edu/protocols/index.htm>). Samples were classified as previously described (3). Treatment response was assessed according to Symmans classification (4).

RESULTS

130 samples were analysed. Most ER positive tumours were luminal subtype. Similarly, we found that all basal-like tumours were triple negative by immunohistochemistry. Only 41% of Her2 positive tumours assessed by immunohistochemistry and FISH were Her2 according to the gene expression profile. Luminal A and normal-like tumours have low expression of proliferation genes as well as ki67, whereas Her2 and basal-like tumours are highly proliferative. As previously described, we also found that there is a correlation between tumour subtype and histological grade. The average age of diagnosis is lower in the basal-like tumours.

Regarding chemosensitivity, we found that both treatments have the same efficiency (20% of responses). Basal tumours have the poorest outcome in the doxorubicin branch (0% of responses) while they are the most sensitive to docetaxel (50% of responses). Luminal and normal-like tumours have the poorest responses to both treatments. Finally, Her2 tumours had similar outcome in both branches (20% of responses).

DISCUSSION

Several gene signatures have been developed to predict tumour prognosis and treatment response. However, there are few data concerning tumour sensitivity to single agent chemotherapy regimens. Two gene signatures predictive for treatment response to docetaxel have been published (5,6) but none of them give information about tumour subtype. One study developed in a cohort of patients treated with doxorubicin found that luminal B profile was associated with resistance to doxorubicin (7).

The genomic classification by Perou et al has been widely accepted. This classification may assist the physician in the choice of a specific treatment based on the sub-type of tumour. Therefore, it is important to assess the sensitivity of the different subtypes to chemotherapy agents.

FUTURE WORK

This study provides the basis for building individualized neoadjuvant therapies for breast cancer. Testing the value of the addition of other therapies than docetaxel in Her2 (i.e. trastuzumab) or basal-like carcinomas (i.e. antiangiogenics or platinum salts) might be the logical next step.

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