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Original Research

Identification of single nucleotide polymorphisms of the PI3K-AKT-mTOR pathway as a risk factor of central nervous system metastasis in metastatic breast cancer

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Abstract ***Introduction:*** The PI3K-AKT-mTOR pathway may be involved in the development of central nervous system (CNS) metastasis from breast cancer. Accordingly, herein we explored whether single nucleotide polymorphisms (SNPs) of this pathway are associated with altered risk of CNS metastasis formation in metastatic breast cancer patients.
Methods: The GENEOM study (NCT00959556) included blood sample collection from breast cancer patients treated in the neoadjuvant, adjuvant or metastatic setting. We identified

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Prediction;
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patients with CNS metastases for comparison with patients without CNS metastasis, defined as either absence of neurological symptoms or normal brain magnetic resonance imaging (MRI) before death or during 5-year follow-up. Eighty-eight SNPs of phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT)/mammalian (or mechanistic) target of rapamycin (mTOR) pathway genes were selected for analysis: AKT1 (17 SNPs), AKT2 (4), FGFR1 (2), mTOR (7), PDK1 (4), PI3KR1 (11), PI3KCA (20), PTEN (17), RPS6KB1 (6).

Results: Of 342 patients with metastases, 207 fulfilled the inclusion criteria: One-hundred-and-seven patients remained free of CNS metastases at last follow-up or date of death whereas 100 patients developed CNS metastases. Among clinical parameters, hormonal and human epidermal growth factor receptor-2 (HER2) status as well as vascular tumour emboli was associated with risk of CNS metastasis. Only PI3KR1-rs706716 was associated with CNS metastasis in univariate analysis after Bonferroni correction ($p < 0.00085$). Multivariate analysis showed associations between AKT1-rs3803304, AKT2-rs3730050, PDK1-rs11686903 and PI3KR1-rs706716 and CNS metastasis .

Conclusion: PI3KR1-rs706716 may be associated with CNS metastasis in metastatic breast cancer patients and could be included in a predictive composite score to detect early CNS metastasis irrespective of breast cancer subtype.

1. Introduction

Breast cancer represents the most common cancer in women. Central nervous system (CNS) metastases occur in up to 10% of patients [1] and herald poor outcome: survival varies from 2.7 to 26.8 months with solid brain metastases, by breast cancer subtype [2] and is 4 months with leptomeningeal metastases [3–6]. Treatment of CNS metastasis aims not only for prolonging survival, but also at prevention or delay of neurological deterioration [7].

The identification of patients at risk could help to increase the efficacy of treatment of CNS metastasis. While cerebrospinal imaging is not part of standard follow-up in patients without neurological signs, the identification of subgroups of patients at risk could allow the implementation of more intensive follow-up and early intervention strategies.

Brain metastases risk is increased in triple-negative breast cancers (TNBCs) and human epidermal growth factor receptor 2 (HER2)-positive tumours [1,8–14]. Risk factors for leptomeningeal metastases include opening of the cerebral ventricular system during surgery for solid brain metastases and resection of cerebellar metastases [15,16] and breast cancer patients specifically lobular subtype and TNBCs [4–6,17].

Genetic variations could also help to define populations at risk. Single nucleotide polymorphisms (SNPs) represent the most frequent type of variations of the human genome [18]: they represent a single nucleotide variation at a specific position in the genome present at a frequency of 1–50% in the general population that is maintained through heredity. While not causing disease, SNPs can modify protein structure and function and thereby influence susceptibility to disease, including cancer [18].

The phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT)/mammalian (or mechanistic) target of rapamycin (mTOR) [PI3K-AKT-mTOR] pathway controls cell cycle, survival, differentiation, proliferation, motility, metabolism and genomic stability and may be the most frequently activated pathway in human cancer [19–21]. Moreover, it also regulates the behaviour of normal cells and contributes to host cell–tumour cell interactions, e.g. during angiogenesis and inflammation [21–27]. PI3K-AKT-mTOR pathway genetic lesions are frequent in breast cancer and may mediate resistance to HER2-targeted agents and hormonal agents [28]. Activation of the PI3K pathway has specifically been observed in brain metastases from breast cancer, regardless of subtype as defined by hormone receptor or HER2 status [29,30], potentially mediated by the loss of PTEN expression as demonstrated in paired primary tumour and brain metastasis samples [31]. In fact, the loss of phosphatase and tensin homologue deleted on chromosome ten (PTEN), a tumour suppressant, may directly promote brain invasiveness of metastatic breast cancer cells [27]. Herein, we sought to identify SNPs of the PI3K-AKT-mTOR pathway associated with increased risk of CNS metastasis formation in patients with metastatic breast cancer.

2. Materials and methods

2.1. Patients

We conducted a secondary analysis in a subpopulation of patients from the GENEOM study (NCT00959556) that aimed at identifying constitutional genetic variants predictive of response to chemotherapy and hormone therapy in adult patients with histologically confirmed breast cancer and included 914 women between November 2007 and January 2012. Our aim was to identify biomarkers of CNS metastasis risk among

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