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Genetic polymorphisms of SLC28A3, SLC29A1 and RRM1 predict clinical outcome in patients with metastatic breast cancer receiving gemcitabine plus paclitaxel chemotherapy

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Abstract ***Background:*** Paclitaxel and gemcitabine (PG) combination chemotherapy is effective as a maintenance chemotherapeutic regimen in metastatic breast cancer (MBC) patients because it increases progression-free survival (PFS), which increases overall survival (OS). The primary purpose of our study was to investigate the association between genetic polymorphisms in the genes involved in PG pathways and clinical outcomes in MBC patients treated with PG chemotherapy.

Methods: A total of 324 MBC patients were enrolled in this prospective multicenter trial of PG as the first-line chemotherapy. Eighty-five of the 324 patients from two institutes were available for analysis of single nucleotide polymorphisms (SNPs). Germline DNA was extracted from peripheral blood mononuclear cells. Thirty-eight SNPs in 15 candidate genes selected from pathways that may influence the metabolism and transport of, or sensitivity, to PG were analysed.

Results: The median PFS and OS of all 324 patients were 8.7 months (95% confidence interval [CI]: 7.5–9.6 months) and 26.9 months (95% CI: 23.6–30.1 months), respectively. An SNP in

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SLC28A3 (rs7867504, C/T) was associated with OS (CC or CT versus TT: 37 versus 21 months, $p = 0.027$, hazard ratio [HR] 2.6, 95% CI: 1.1–6.3). SLC29A1 GA haplotype had a significantly shorter OS ($p = 0.030$, HR 3.391, 95% CI: 1.13–10.19). RRM1 (ribonucleotide reductase large subunit M1) SNP (rs9937), and haplotypes ATAA and ATGA were significantly associated with neurotoxicity.

Conclusion: Genetic polymorphisms in SLC28A3, SLC29A1 and RRM1 can influence the clinical outcome of MBC patients treated with PG chemotherapy. Further studies on the functional mechanisms relating to these germline polymorphisms in these genes are warranted.

1. Introduction

A phase III multicenter randomised clinical trial comparing combined paclitaxel and gemcitabine (PG) maintenance chemotherapy with observation after achieving disease control to six cycles of the initial PG chemotherapy has been reported recently [1]. In this trial, the overall response rate and disease control rate of the initial six cycles of PG chemotherapy in 324 patients were 50.0% and 78.6%, respectively. The median progression-free survival (PFS) from randomisation was prolonged by 3.7 months, from 3.8 months in the observation group to 7.5 months in the maintenance chemotherapy group ($p = 0.026$, hazard ratio [HR] 0.73, 95% confidence interval [CI]: 0.55–0.97). The median overall survival (OS) from randomisation was longer in the maintenance chemotherapy group than in the observation group (32.3 versus 23.5 months) ($p = 0.047$, HR 0.65, 95% CI: 0.42–0.99). The median number of chemotherapy cycles for these patients after randomisation was 12 (range 9–26 cycles). The rate of grade 3 neutropenia after randomisation was much higher in the maintenance group than in the observation group (61% versus 0.9%, $p < 0.0001$). Quality of life did not differ between the two groups. These trial results imply that PG chemotherapy is effective and feasible as maintenance therapy for metastatic breast cancer (MBC) patients.

Interindividual and interpopulation differences in drug responses are well-known and serious problems in chemotherapy. Gemcitabine (2′2′-difluorodeoxycytidine), a pyrimidine-based antimetabolite, was synthesised in the 1980s by the Lilly Research Laboratories (Eli Lilly and Co., Indianapolis, IN, United States of America (USA)). Gemcitabine is metabolised intracellularly to two active metabolites, gemcitabine diphosphate (dFdCDP) and gemcitabine triphosphate (dFdCTP) (Fig. 1). Gemcitabine is characterised by a narrow therapeutic index, and its liver elimination depends upon a key enzyme step, driven by cytidine deaminase (CDA). In recent years, several studies have also investigated the association of genetic polymorphisms of genes involved in gemcitabine pharmacobiology (*CDA*, *DCK*, *CMPK1*, *RRM1*, *SLC29A1*, etc.) with drug response or toxicity in cancer patients receiving gemcitabine therapy [2–5].

Paclitaxel is one of the most widely used and effective anticancer drugs. Cytochrome P450 (CYP) enzyme subfamilies play major roles in paclitaxel metabolism, most notably the 2C8 and 3A subfamilies. Recent evidence points to the possible association of genetic polymorphisms in these enzymes with paclitaxel response rates, toxicity, pharmacokinetics and pharmacodynamics [6,7]. Single nucleotide polymorphisms (SNPs) of genes involved in drug transport such as ABCB1 are associated with taxane clearance and clinical outcomes in patients treated with taxane [8–11]. However, the use of genotyping to predict the response to chemotherapeutic agents and survival in the treatment of many solid tumours, including breast cancer, has not always produced consistent results.

Based on this background, we aimed to investigate comprehensively the genetic polymorphisms associated with gemcitabine and paclitaxel metabolism in a prospective cohort enrolled in a phase III clinical trial of PG chemotherapy. Knowing whether genetic polymorphisms affect the efficacy and toxicity of PG chemotherapy would influence decisions about the main therapeutic option for individual patients.

2. Patients and methods

2.1. Patients

This prospective pharmacogenetic study included 85 MBC patients enrolled in a randomised phase III study comparing PG maintenance chemotherapy with observation after achieving disease control through the initial six cycles of PG chemotherapy in the Samsung Medical Center and Seoul National University Hospital. Women with histologically confirmed metastatic or recurrent breast cancer were eligible for the study. Both premenopausal and postmenopausal women with measurable and/or non-measurable lesion(s) with no prior history of chemotherapy in the metastatic setting who were candidates for chemotherapy were eligible. The exclusion criteria were prior chemotherapy for MBC, clinically detectable brain parenchymal and/or leptomeningeal metastases, prior treatment with gemcitabine, other severe medical conditions and human epidermal growth factor receptor 2 (HER2)-positive breast cancer with trastuzumab treatment.

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