

ABCB1 2677G>T/A Genotype and Paclitaxel Pharmacogenetics in Ovarian Cancer

To the Editor: Gréen et al. (1) identified ABCB1 2677G>T/A genotype as a marker of response to paclitaxel therapy in ovarian cancer. Their study was done in 53 tumor samples from ovarian cancer patients treated with 175 or 135 mg/m² paclitaxel for at least four cycles. Response was higher in patients with the variant (T or A) alleles ($P < 0.05$), and increasing number of variant alleles increased the likelihood of response ($P = 0.03$; ref. 1). Despite the common use of paclitaxel to treat ovarian, breast, and lung cancers, this provides one of the first examples of a putative pharmacogenetic marker to predict paclitaxel response (2). However, germ-line studies on markers of paclitaxel response provide conflicting evidence. A study of genomic DNA from plasma of 93 breast cancer patients receiving high-dose paclitaxel (575-775 mg/m²) showed no association between ABCB1 2677G>T/A and paclitaxel pharmacokinetics or response ($P > 0.05$ in all cases; ref. 3). It is possible that the different observations between genotype and outcome were affected by the different cancer types and different treatment regimens between the two studies.

We assessed ABCB1 2677G>T/A using pyrosequencing technology in germ-line DNA from whole blood of 914 ovarian cancer patients receiving carboplatin and either paclitaxel (175 mg/m²; $n = 456$) or docetaxel (75 mg/m²; $n = 458$) as part of the SCOTROC1 Phase III trial (4). Written informed consent was obtained for all patients, and the study received ethics approval from participating institutes. Genotype data were obtained for 900 of 914 samples, and the allele frequencies (G, 0.55; T, 0.42; and A, 0.03) were similar to 200 healthy Swedish individuals (G, 0.56; T, 0.42; and A, 0.02) and 53 ovarian tumor samples (G, 0.53; T, 0.45; and A, 0.02; ref. 1).

Using χ^2 analysis, no significant association was found with ABCB1 2677G>T/A genotype and clinical/radiological response ($P = 0.66$). In addition, no significant association was found between any instance of neurotoxicity, hematologic toxicity, or gastrointestinal toxicity for either docetaxel or paclitaxel ($P > 0.05$ in all cases). Using progression-free survival as a continuous variable, no significant association was found with the log-rank test ($P = 0.862$). To replicate the Gréen et al. analysis (1), we split the sample set using progression-free survival status at 12 months to categorize good or bad response. χ^2 analysis showed no significant association with response ($P = 0.329$).

The conflicting results between the SCOTROC1 and Gréen et al. (1) studies could be the result of several factors, including different sample sizes and populations. Gréen et al. also used DNA from tumor (1), whereas the SCOTROC1 study assessed

germ-line DNA. No difference in allele frequencies was observed, implying germ-line DNA would be an accurate predictor of ovarian tumor genotype; however, the correlation between germ-line and tumor genotype has not been confirmed in either study.

The ultimate role of pharmacogenetics in ovarian cancer treatment would be to identify genetic markers predictive of outcome and/or toxicity to allow individualized therapy selection using a noninvasive screening procedure (e.g., blood and mouthwash; ref. 2). The lack of evidence for a role for germ-line ABCB1 genotype as a predictor of paclitaxel outcome suggests caution and highlights the need for validation in large, well-characterized studies before including this marker for individualized therapy prediction.

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References

1. Gréen H, Söderkvist P, Rosenberg P, Horvath G, Peterson C. MDR-1 single nucleotide polymorphisms in ovarian cancer tissue: G2677T/A correlates with response to paclitaxel chemotherapy. *Clin Cancer Res* 2006;12:854–9.
2. Marsh S. Taxane pharmacogenetics. *Personalized Med* 2006;3:33–43.
3. Marsh S, Somlo G, McLeod HL, et al. Pharmacogenetic analysis of paclitaxel in breast cancer. *Proc Am Soc Clin Oncol* 2005;23:206.
4. Vasey PA, Jayson GC, Gordon A, et al. Phase III randomized trial of docetaxel-carboplatin versus paclitaxel-carboplatin as first-line chemotherapy for ovarian carcinoma. *J Natl Cancer Inst* 2004;96:1682–91.

In Response: We appreciate the attention given by Marsh et al. to our recent publication “*mdr-1* Single Nucleotide Polymorphisms in Ovarian Cancer Tissue: G2677T/A Correlates with Response to Paclitaxel Chemotherapy” (1). In this article, we described the potential value of the ABCB1 2677G>T/A genotype as a marker for paclitaxel response in ovarian cancer. We investigated the allele frequencies of the 2677G>T/A single nucleotide polymorphism (SNP) in 53 patients with ovarian cancer and showed that the response to chemotherapy with paclitaxel and carboplatin was significantly better in patients homozygously mutated (T/T or T/A) at position 2677 ($P = 0.04$). The frequency of the T or A allele was also higher in the group of patients with a good response ($P = 0.03$), and the response improved with increasing number of variant alleles ($P = 0.03$; ref. 1). However, Marsh et al. were not able to reproduce our results in a larger material.

Marsh et al. determined the *ABCB1* 2677G>T/A genotype in patients from the SCOTROC1 trial, a large and well-defined phase III clinical trial designed to compare the effects of paclitaxel and docetaxel in combination with carboplatin in ovarian cancer (2). They were unable to find any association between genotype and toxicity (nor could we), clinical/radiological response, or progression-free survival. To replicate our analysis, they also split the data set into good and poor responders according to our definitions. Although the statistics improved, no significance was achieved. Our study was designed to investigate differences in good and poor responders. To present a different view of our data, we here show a Kaplan-Meier analysis (Fig. 1). The curves show a trend in time to progression due to *ABCB1* genotype, although not statistically significant ($P = 0.19$, log-rank test; $P = 0.09$, Breslow). The mean time to progression for the patients with the G/G genotype was 1.2 years, for heterozygotes with G/T genotype 1.4 years, and for homozygotes (T/T or T/A) the mean time to progression was 2.0 years. Also noteworthy, in our study none of the homozygously mutated patients had progressive disease during treatment.

Marsh et al. used germ-line DNA from whole blood in the SCOTROC1 study, whereas we used tumor DNA. No difference in allele frequencies was observed between a Swedish reference population, the SCOTROC1 study, and the 53 ovarian tumor samples, indicating accurate genotype determination with both DNA sources. However, none of the studies has done a haplotype determination, so the different results might be due to the association of the SNP with different alleles in different populations.

The SCOTROC1 is an international multicenter study and ours is a national case-referent study in the southern part of Sweden. The samples included in our study were from a biobank and that probably has given us an overrepresentation of large tumors. We also have a higher proportion of patients with nonradical surgery than the SCOTROC1 study. The number of patients with International Federation of

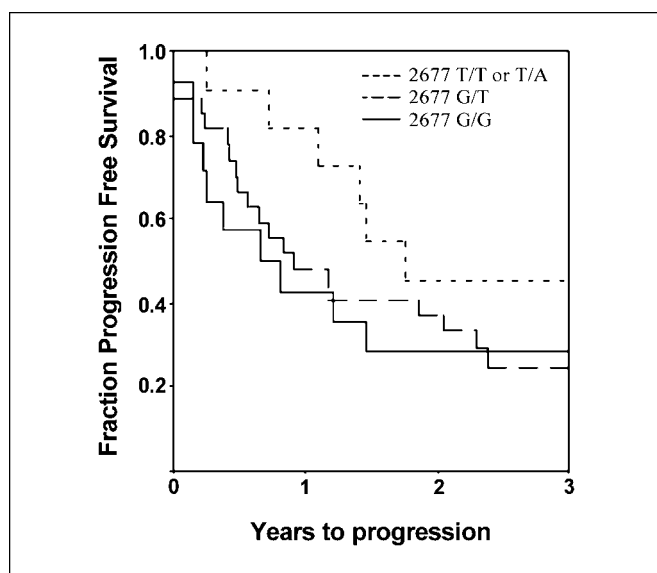


Fig. 1. The effect of the *ABCB1* SNP 2677G>T/A on the fraction of ovarian cancers patients with progression-free survival.

Gynecology and Obstetrics stage IIIc is also high in our material (32 of 53). It has been shown that a gain of the 7q21 region, where the *ABCB1* gene is located, is more common in tumors from patients with International Federation of Gynecology and Obstetrics stage IIIc (3), which might explain a higher effect of *ABCB1* SNPs in these patients. We assume that Marsh et al., although not stated, subdivided the SCOTROC1 patients into paclitaxel-and docetaxel-treated patients because paclitaxel and docetaxel might not be affected by the SNP in the same way. The paclitaxel regimes used in the two studies are probably comparable. In our study, paclitaxel was used at 175 or 135 mg/m² ($n = 5$) in combination with carboplatin compared with 175 mg/m² in the SCOTROC1 study, although the median number of cycles, approximately seven cycles, in our study was slightly higher than in the SCOTROC1 study, six cycles. In another study presented at American Society of Clinical Oncology on breast cancer patients receiving high-dose paclitaxel (575-775 mg/m²), doxorubicin, and cyclophosphamide, Marsh et al. did not find any association between the 2677G>T/A genotype and paclitaxel pharmacokinetics or response (4). However, differences in transport activity of P-glycoprotein due to the different amino acids at position 893 (nucleotide position 2677) might be dependent on the drug concentration, making it difficult to compare different paclitaxel regimes and tumor types. Another potential explanation to the correlation between genotype and response found in our study may be due to effects at the tumor site and not due to a change in pharmacokinetics.

The polymorphisms of the *ABCB1* gene have been investigated in several studies with conflicting results. The first study showing an effect of the SNPs indicated a correlation between the 3435C>T SNP and the level of expression of P-glycoprotein in the intestine and the digoxin area under the plasma concentration time curve (5). This study has later been confirmed and contradicted by others [see review by Marzolini et al. (6)]. Conflicting results have also been noted for other P-glycoprotein substrates, including fexofenadine, cyclosporine, and tacrolimus, as well as expression and function of P-glycoprotein (6). Thus far, the clinical relevance of the *ABCB1* SNPs for response to chemotherapy is not clear and further studies are needed. We believe that the differences in results between our small study and the pharmacogenetic follow-up study of the SCOTROC1 trial might be explained by differences in the composition and/or subdivision of tumor material and/or patients.

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References

1. Green H, Soderkvist P, Rosenberg P, Horvath G, Peterson C. mdr-1 single nucleotide polymorphisms in ovarian cancer tissue: G2677T/A correlates with response to paclitaxel chemotherapy. *Clin Cancer Res* 2006;12:854–9.
2. Vasey PA, Jayson GC, Gordon A, et al. Phase III randomized trial of docetaxel-carboplatin versus paclitaxel-carboplatin as first-line chemotherapy for ovarian carcinoma. *J Natl Cancer Inst* 2004;96:1682–91.
3. Parthen K, Levan K, Osterberg L, Helou K, Horvath G. Analysis of cytogenetic alterations in stage III serous ovarian adenocarcinoma reveals a heterogeneous group regarding survival, surgical outcome, and substage. *Genes Chromosomes Cancer* 2004;40:342–8.
4. Marsh S, Somlo G, McLeod HL, et al. Pharmacogenetic analysis of paclitaxel in breast cancer. *Proc Am Soc Clin Oncol* 2005;23:206.
5. Hoffmeyer S, Burk O, von Richter O, et al. Functional polymorphisms of the human multidrug-resistance gene: multiple sequence variations and correlation of one allele with P-glycoprotein expression and activity *in vivo*. *Proc Natl Acad Sci U S A* 2000;97:3473–8.
6. Marzolini C, Paus E, Buclin T, Kim RB. Polymorphisms in human MDR1 (P-glycoprotein): recent advances and clinical relevance. *Clin Pharmacol Ther* 2004;75:13–33.