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Editorial

Are *ABCB1* (P-glycoprotein) polymorphisms clinically relevant in ovarian cancer? – Finally an Answer!

Existing medical treatments for ovarian cancer, including chemotherapeutic, hormonal and biologic agents are merely effective in a subset of patients, often only produce partial responses of short duration, and are frequently associated with significant side effects. The hope is that through pharmacogenetics we will be able to personalize the use of these treatments to maximize their efficacy and tolerability [1]. A growing number of pharmacogenetic studies have focused on inheritable variations in candidate genes believed to influence the absorption, distribution, or clearance of anticancer drugs. This issue of the Journal contains an important article as to whether genetic variations of the *ABCB1* gene in ovarian cancer patients give rise to differing responses to chemotherapy [2].

The product of the *ABCB1* gene, P-glycoprotein, is a transmembrane efflux pump which moves substrates across the cell membrane and out of the cell. It is a member of a superfamily of ATP binding cassette (ABC) membrane transporters and has been described to be a putative mechanism of multidrug resistance in a range of diseases, including ovarian cancer. Chemotherapeutic agents that are affected by P-glycoprotein include vinca alkaloids, anthracyclines and paclitaxel and resistance may result because increased drug efflux lowers intracellular drug concentrations of these agents. Although it seems likely that cancer cells use several different types of ABC transporters to gain drug resistance most clinical studies have focused on P-glycoprotein. Increased expression of P-glycoprotein in tumor tissues has been associated with adverse clinical outcome in ovarian cancer [3–7]. However, many of these studies were small and most used varying methods to assess P-glycoprotein levels, thus uniform conclusions on the clinical relevance of P-glycoprotein expression for drug response in ovarian cancer cannot yet be made. Most importantly, however, membrane transporters, such as P-glycoprotein are critically involved in drug clearance and alter systemic drug levels by actively transporting substrate drugs between organs and normal tissues. As such, heritable germ line polymorphisms in genes encoding these membrane transporters may have significant effects on the absorption, distribution and excretion of chemotherapeutic agents and may alter the pharmacodynamics of many agents.

More than 50 of these polymorphisms have been described in the *ABCB1* gene [8]. Several of these genetic variants result in alterations in mRNA expression levels (e.g., promoter variants), translational efficiency (e.g., alterations in mRNA folding), and protein function (e.g., coding polymorphisms) [9]. However, there are three single-nucleotide polymorphisms (SNPs) that are common in most ethnic groups: A synonymous transition at nucleotide C1236T (Gly411Gly) (rs1128503) in exon 12, a nonsynonymous transition G2677T/A (Ala893Ser/Thr) (rs2032582) in exon 21, and a synonymous

transition C3435T (Ile1145Ile) (rs1045642) in exon 26. It is postulated that these polymorphisms contribute to variability in P-glycoprotein function, and that therefore multidrug resistance is, at least in part, genetically determined. Previous clinical studies, however, have produced inconsistent results. To date six studies of adjuvant platinum and taxane-based therapy have assessed the association between the abovementioned three common polymorphisms in *ABCB1* and treatment outcome in ovarian cancer [10–15]. In four of these studies no associations were found between clinical outcome and the polymorphisms tagging either T1236C [11,12] or G2677T/A and C3435T [12,14,15]. In contrast, two studies demonstrated that the SNP tagging G2677T/A was associated with improved outcome [10,13]. However, the latter two studies only reported on progression free survival and only one included a multivariate analysis [13]. Many of these studies were relatively small and thus likely underpowered for pharmacogenetics studies.

In contrast, the article by Johnatty et al. in this issue represents an impressive example of pharmacogenomic research at its best [2]. It is the most comprehensive study conducted to date on *ABCB1* polymorphisms in ovarian cancer. The authors investigated *ABCB1* SNPs tagging C1236T (rs1128503), G2677T/A (rs2032582), and C3435T (rs1045642) in 4616 European ovarian cancer patients from thirteen Ovarian Cancer Association Consortium (OCAC) studies and the Cancer Genome Atlas (TCGA) research Network. This well designed observational study has many strengths, such as its long median follow-up of 5.9 years, genotype data that conforms to quality assurance criteria, detailed and complete information on the type of adjuvant chemotherapy and the number of cycles given. Additional strengths are its rigorous statistical approach, its restriction of the analysis to an ethnically homogenous population and lastly its very large sample size. Among the 4616 ovarian cancer patients that received any form of adjuvant chemotherapy Johnatty et al. demonstrate that none of the three common coding SNPs tagging either C1236T (rs1128503), G2677T/A (rs2032582), or C3435T (rs1045642) was associated with progression-free or overall survival. Similarly, no association was seen in a subset of 1882 patients known to have received at least 4 cycles of paclitaxel carboplatin chemotherapy. One of the three coding SNPs, C1236T (rs1128503), which has recently been described to be functionally relevant though silent [16], however, was found to be marginally associated with improved overall survival, but only in those patients that were found to have no residual disease following debulking surgery regardless of chemotherapy. Analysis of an additional 1562 SNPs flanking *ABCB1* in ~3000 patients yielded no new signals.

This large scale pharmacogenomic study has evidently been designed and conducted very carefully. Nevertheless, I think that

there are two issues that need to be pointed out which may help to advance future pharmacogenomic studies in ovarian cancer. First, the study conducted by Johnatty et al., like most previous studies, is an observational study. Thus far only few pharmacogenomic studies in ovarian cancer have been performed in phase 3 clinical trial cohorts [12,17]. Phase 3 studies have an advantage over observational studies as they not only provide standardized information on treatment, outcome and toxicity, but also offer a control group that received an alternative treatment. As such, they are better suited for genotype–drug response association-based studies, because they allow a better distinction between the predictive versus the prognostic role a gene variant may have. Secondly, the process of chemotherapy resistance in ovarian cancer is multi-factorial, and measurement of one efflux pump can only provide an incomplete assessment of the mechanisms of drug resistance that are at play in ovarian cancer. There are a total of 49 known ABC genes including ABCB1 (P-glycoprotein), ABCC1 (MRP1), and ABCG2 (BCRP, MXR, ABCP), all of which utilize ATP to move substrates across membranes [18]. Moreover, drug resistance can also be mediated by DNA repair, defective apoptotic pathways, changes in cell cycle check points, nonfunctional p53 and more. The complexity is daunting, but rapid progress in genotyping techniques now allows investigators to assess a much larger number of polymorphisms (up to 2.5 million per sample) at a reasonable cost and allows researchers to move from candidate gene association studies to genome wide association studies. Of note, the current study samples were part of a large scale OCAC ovarian cancer susceptibility study which used a custom Illumina Infinium iSelect array comprising ~24,000 SNPs for genotyping. As such additional information on the relevance of other membrane transporter proteins or resistance mechanisms may be obtainable [19].

Pharmacogenetic studies do hold the promise of providing physicians with objective information that might make it possible to tailor drug selection and/or dose. Examples such as genetic polymorphisms in *CYP2D6* for tamoxifen efficacy or *CYP2C9* and/or *VKORC1* for warfarin dosing demonstrate that it is possible to predict clinically relevant genetic variation that can be used to individualize drug therapy, however, there is still a long way to go before this promise becomes reality in ovarian cancer. Clearly the research environment in this field of gynecologic oncology is in need of improvement. Ideally, pharmacogenomic studies should be performed in large controlled phase 3 clinical trials. Routine standard collection of blood DNA samples in ongoing and planned phase 2 or 3 trials would provide us with an unprecedented opportunity to investigate the causes of lack of efficacy or the occurrence of toxicity in different individuals immediately. Most importantly, better collaboration between national and international clinical trial groups would enable large scale pharmacogenomic studies that are sufficiently powered to generate meaningful data.

As to why such international collaborative research should be performed, the study by Johnatty et al. offers a ready answer. Their data was compiled from 14 international research groups and is finally sufficiently robust to conclude that polymorphisms in the *ABCB1* gene by themselves do not predict clinically meaningful outcomes that would justify further clinical development of a clinical test intended to provide information that improves the risk/benefit ratio of clinical treatment. Johnatty et al. are giving us an excellent example in this issue of what can be achieved when pharmacogenetics is conducted in the realm of such an international multidisciplinary collaboration.

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