Effect of ABCB1 C3435T polymorphism on docetaxel pharmacokinetics according to menopausal status in breast cancer patients

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BACKGROUND: It can be hypothesised that inherited polymorphisms in the drug-transporter ABCB1 gene may interfere with interindividual variations in drug response in breast cancer patients. Docetaxel is a substrate for ABCB1 whose function has been shown to be modulated by oestrogen and progesterone.

METHODS: Whether ABCB1 polymorphisms including T-129C, A61G, C1236T, G2677T/A and C3435T polymorphisms could account for variations in the disposition of docetaxel and whether menopausal status at the time of diagnosis might interact with this effect were analysed in women receiving neoadjuvant chemotherapy for breast cancer (n = 86).

RESULTS: A highly significant association was observed, but restricted to premenopausal women (n = 53), between the pharmacokinetics of docetaxel and C3435T polymorphism, as patients with CC genotype had lower mean values of the area under the plasma concentration-time curve (AUC) of docetaxel than patients with CT and TT genotypes (P < 0.0001). Comparison between pre- and postmenopausal women with the same C3435T genotype yielded a significant difference in docetaxel AUC only for CC genotype (P < 0.0001).

CONCLUSION: These results suggest that C3435T polymorphism genotyping and menopausal status at the time of diagnosis might be useful when considering chemotherapy regimens including docetaxel in breast cancer patients.

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Taxanes, drugs frequently used to treat breast cancer, are substrates for the ATP-binding cassette (ABC) transporter ABCB1 (Scala et al., 1997). This protein was initially discovered as an efflux transporter involved in multidrug resistance of tumour cells (Gottesman et al., 2002). However, ABCB1 is also physiologically expressed at the apical surface of epithelial cells in various organs responsible for drug disposition such as the intestine, liver and kidney and at the apical surface of endothelial cells controlling the availability of drugs at the blood–tissue interface (Schinkel, 1997). ABCB1 is therefore also involved in drug metabolism by having a role in the so-called phase 0 (efflux of unmodified drug) of the metabolism of xenobiotics.

Breast cancer patients treated with taxanes such as docetaxel show major interindividual variations in drug response, which might be at least partly because of inherited polymorphisms in genes encoding proteins involved in drug efflux including ABCB1 transporter (Relling and Dervieux, 2001; Rodrigues et al., 2008). Since the first systematic screening for polymorphisms in ABCB1 coding region and the report of a functional polymorphism (Hoffmeyer et al., 2000), > 45 polymorphisms have been described in coding regions, the promoter and non-coding regions (Kroetz et al., 2003). The polymorphisms for which the frequency of the variant allele is >5% include the T-129C in the promoter region, the synonymous C1236T (exon 12) and C3435T (exon 26) polymorphisms and the non-synonymous A61G (exon 2) and G2677T/A (exon 21) polymorphisms.

There is evidence that the sex steroids oestrogen and progesterone interfere with ABCB1 function as either substrates and/or regulators of ABCB1 expression. Oestrogens such as oestrone and oestradiol have been shown to be a substrate of ABCB1 and to increase ABCB1 protein levels (Kim and Benet, 2004; Ewseenko et al., 2007). Moreover, although not a substrate of ABCB1, progesterone has been reported to inhibit ABCB1-mediated efflux (Yang et al., 1989; Barnes et al., 1996; Hamilton et al., 2001) and increase ABCB1 mRNA (Piekaz et al., 1993) and ATPase activity (Barnes et al., 1996; Kim and Benet, 2004).

To evaluate whether variations in disposition of docetaxel because of ABCB1 polymorphisms could be involved in the response variability of breast cancer patients, the pharmacokinetics of this drug and inherited polymorphisms of ABCB1 gene including...
Previously reported studies (Baille et al., 1997). Five heparinised blood samples (5 ml each) were required: immediately before infusion, 5 min before the end of infusion and 20 min, 2 h and 5 h after the end of infusion. After immediate centrifugation of the blood samples, plasma was stored at −20°C until further analysis. Plasma concentrations of docetaxel were determined using validated high-performance liquid chromatography methods with UV detection (Vergniol et al., 1992). The analytical range for docetaxel determination was 25–5000 ng·ml⁻¹. Individual drug clearances were estimated from docetaxel population pharmacokinetic parameters (Bruno et al., 1998) using the POST HOC option of NONMEM (Beal and Sheiner, 1998). The area under the plasma concentration-time curve (AUC) was calculated as AUC = dose/clearance.

Genotype

Genomic DNA was extracted from whole blood (10 ml) using QIAamp DNA blood Maxi Kit (Qiagen, Hilden, Germany). T-129C (rs13213619), A61G (rs9282564), C1236T and C3435T (rs1045642) polymorphisms were each analysed using two matching primers and two TaqMan MGB probes labeled with 6-FAM or VIC dye for allelic discrimination (assay IDs: C_27487486_10 and C__7586657_20 for T-129C and C3435T, respectively and custom-designed assays for A61G and C1236T with probes FAM (5'-AACTGAAGATAAAG-3') and VIC (5'-TTAACTGACAA-3') and FAM (5'-TCAGGTCCAGGCTT-3') and VIC (5'-TCAGGTTCAGACCCCT-3').

Statistical analysis

Mean values of AUC and mean values of clearance of docetaxel were compared between groups using the nonparametric Mann–Whitney test for two groups or the nonparametric Kruskal–Wallis test for three or more groups (StatView software, version 5.0; SAS Institute, Cary, NC, USA). Owing to multiple comparisons, statistical significance was defined as P < 0.005.

RESULTS

Plasma concentrations of docetaxel were determined in the 86 patients. Genotyping results for the T-129C, A61G, C1236T, G2677T/A and C3435T polymorphisms, the two most frequent

Pharmacokinetics of docetaxel

Pharmacokinetic analysis was performed for the first course of docetaxel. A limited sampling strategy was used according to
haplotypes for A61G, C1236T, G2677T/A and C3435T polymorphisms and the haplotype containing the homozygous variant genotypes, which have a frequency ≥10%, are shown in Table 2.

Table 2 Number of patients for each genotype of ABCB1 polymorphisms

| Polymorphism | Genotype | Number (%) |
|--------------|----------|------------|
| T-129C       | TT       | 74 (86)    |
|              | TC       | 11 (13)    |
|              | CC       | 1 (1)      |
| A61G         | AA       | 78 (91)    |
|              | AG       | 8 (9)      |
|              | GG       | 0 (0)      |
| C1236T       | CC       | 35 (41)    |
|              | CT       | 38 (44)    |
|              | TT       | 13 (15)    |
| G2677T/A     | GG       | 43 (50)    |
|              | GT       | 32 (37)    |
|              | TT       | 10 (12)    |
|              | TA       | 1 (1)      |
| C3435T       | CC       | 34 (40)    |
|              | CT       | 39 (45)    |
|              | TT       | 13 (15)    |
| 61 – 1236 – 2677 – 3435 | AA-CC-GG-CC | 24 (28) |
| 61 – 1236 – 2677 – 3435 | AA-CT-GT-CT | 19 (22) |
| 1236 – 2677 – 3435       | TT-TT-TT | 7 (8)      |

For each polymorphism, the mean AUC of docetaxel was initially compared between each genotype using the nonparametric Mann–Whitney test for two groups or the nonparametric Kruskal–Wallis test for three or more groups. When a significant relationship was found for a polymorphism, pairwise comparisons were then performed between one genotype and the other genotypes for this polymorphism considered as a single group. The same analysis was performed for comparisons of mean clearances between genotypes for each polymorphism. Similar results were obtained whether AUC or clearances were considered as pharmacokinetic parameters for docetaxel. However, there was not always a strict correlation between AUC and clearance for a given genotype. This is probably because of the fact that AUC depends on docetaxel dose, which depends on body surface. The results below will be focused on AUC (for details on clearance, see the corresponding Tables).

A striking association was observed between the pharmacokinetics of docetaxel and menopausal status at diagnosis. Mean values (± standard errors, s.e.) for AUC of docetaxel were lower in premenopausal women (4124 ± 612 μg·h·L⁻¹, n = 53) than in postmenopausal women (4598 ± 298 μg·h·L⁻¹, n = 33, Mann–Whitney test P = 0.0008) (Figure 1).

The influence of menopausal status on the relationship between ABCB1 polymorphisms and the pharmacokinetics of docetaxel was analysed. Results regarding the pharmacokinetics of docetaxel according to ABCB1 polymorphisms in pre- and postmenopausal patients are summarised in Tables 3 and 4, respectively.

A significant association between C3435T polymorphism and the pharmacokinetics of docetaxel was observed in premenopausal women (Kruskal–Wallis test P = 0.0002 for AUC, Table 3).
The AUC of docetaxel was lower for 3435CC patients than for 3435CT and 3435TT patients considered as a single group (Mann–Whitney test $P<0.0001$, Figure 1A). In postmenopausal women, no significant relationship was found between the pharmacokinetics of docetaxel and C3435T polymorphism (Figure 1B, Table 4).

Analysis of the most frequent ethnic group in the study population, that is, Caucasians, showed that the relationship between 3435CC genotype and lower AUC remained significant in premenopausal women (AUC ± s.e. values (μg h⁻¹): 2816 ± 149 and 5094 ± 1050 for 3435CC ($n = 10$) vs 3435CT and 3435TT ($n = 30$), respectively, Mann–Whitney test $P = 0.004$).

Comparison between pre- and postmenopausal women with the same C3435T genotype yielded a significant difference in docetaxel AUC for CC genotype (Mann–Whitney test $P = 0.0001$) with lower AUC in premenopausal women (see Tables 3 and 4: mean AUC (s.e.) values (μg h⁻¹) for CC, CT, and TT were 2727 (104), 5075 (481), and 4251 (425), respectively).
**DISCUSSION**

This study shows an effect of menopausal status on diagnosis on the relationship between C3435T polymorphism of ABCB1 gene and the pharmacokinetics of docetaxel in breast cancer patients.

When evaluating the overall population, no association was observed between C3435T polymorphism and the pharmacokinetics of docetaxel, which is in accordance with the few published studies on this topic (Goh et al., 2002; Bosch et al., 2006; Tran et al., 2006; Lewis et al., 2007). In contrast, when analysing the population according to menopausal status at time of diagnosis of breast cancer, a highly significant association with docetaxel pharmacokinetics was observed in premenopausal women for this polymorphism (P < 0.0001), but not in postmenopausal women. Comparison of pre- and postmenopausal women with the same C3435T genotype yielded a significant difference in docetaxel AUC only for the CC genotype (P < 0.0001) and not for the CT or TT genotypes. Premenopausal CC women had significantly lower AUC than premenopausal CC and CC postmenopausal women. Premenopausal (CT and TT) women had similar AUC to those of premenopausal CC and postmenopausal (CT and TT) women (see Figure 1). To the best of our knowledge, this is the first report of a specific effect of menopausal status at the time of diagnosis on the role of ABCB1 polymorphisms in docetaxel disposition. By contrast, such an effect was not observed for doxorubicin in these patients (data not shown), which suggests that the effect is drug specific. A significant relationship (P = 0.001) between docetaxel pharmacokinetics and C3435T genotype was also found for patients younger than 49 years, which was the mean age at diagnosis (data not shown). As this age is also the mean value of age at menopause, we believe that menopausal status at diagnosis rather than age has an effect on docetaxel pharmacokinetics.

The finding of a highly significant association in premenopausal women between lower AUC of docetaxel and 2677GG-3435CC diplotype and 61AA-1236CC-2677GG-3435CC haplotype is probably because of the strong linkage between these genotypes (Kroetz et al., 2003), although this remains to be evaluated in a large series of women receiving docetaxel neoadjuvant chemotherapy.

The 3435CC genotype has usually been associated with higher levels of ABCB1 mRNA and protein and increased drug efflux in normal tissues and tumours (Hoffmeyer et al., 2000; Hitzl et al., 2001; Tanabe et al., 2001; Fellay et al., 2002; Vaclavikova et al., 2008), although some discrepancies have been reported, especially in Japanese populations (Nakamura et al., 2002). It therefore makes sense to observe lower AUC of docetaxel in CC patients, as their higher levels of ABCB1 in organs involved in drug metabolism would result in higher efflux of docetaxel, higher elimination of the drug and subsequently lower AUC. The mechanisms by which this synonymous polymorphism affects ABCB1 function might be a lower mRNA stability of the 3435T variant (Wang et al., 2005) and/or a change in substrate binding site conformation of the variant ABCB1 protein (Kimchi-Sarfaty et al., 2007). This different protein folding could be due to a different rate of translation when

| Overall population (n = 86) |
|-----------------------------|
| Genotype (n) | AUC (µg h⁻¹) | Clearance (h⁻¹) |
| --- | --- | --- |
| | Mean (s.e.) | P* | Mean (s.e.) | P* |
| T-129C |
| TT (74) | 4386 (452) | 47.5 (2.1) | 0.9 | 48.3 (4.2) | 0.6 |
| TC (11) | 3850 (447) | 58.6 | 0.4 | 44.0 (5.3) | 0.5 |
| CC (1) | 3410 | 48.1 (2.0) | 0.4 | 44.0 (5.3) | 0.5 |
| A61G |
| AA (78) | 4305 (431) | 50.5 (3.2) | 0.4 | 45.8 (2.9) | 0.5 |
| AG (8) | 4314 (558) | 45.9 (3.7) | 0.4 | 44.0 (5.3) | 0.5 |
| GG (0) | 4314 (558) | 45.9 (3.7) | 0.4 | 44.0 (5.3) | 0.5 |
| C1236T |
| CC (35) | 3782 (278) | 50.5 (3.2) | 0.4 | 45.8 (2.9) | 0.5 |
| CT (38) | 4953 (842) | 45.8 (2.9) | 0.4 | 44.0 (5.3) | 0.5 |
| TT (13) | 3825 (297) | 45.9 (3.7) | 0.4 | 44.0 (5.3) | 0.5 |
| G2677T/A |
| GG (43) | 3693 (232) | 51.0 (2.7) | 0.06 | 51.0 (2.7) | 0.08 |
| GT (32) | 5061 (988) | 43.3 (3.7) | 0.2 | 43.3 (3.7) | 0.2 |
| TT (10) | 4060 (324) | 42.3 (2.8) | 0.2 | 42.3 (2.8) | 0.2 |
| TA (1) | 8943 | 20.1 | 0.06 | 20.1 | 0.06 |
| GG (43) | 3693 (232) | 51.0 (2.7) | 0.06 | 51.0 (2.7) | 0.08 |
| GT and TT and TA (43) | 4919 (745) | 45.6 (2.6) | 0.06 | 45.6 (2.6) | 0.08 |
| C3435T |
| CC (34) | 3625 (275) | 52.2 (3.0) | 0.02 | 52.2 (3.0) | 0.04 |
| CT (39) | 5018 (817) | 44.4 (2.8) | 0.2 | 44.4 (2.8) | 0.2 |
| TT (13) | 3935 (347) | 46.2 (4.7) | 0.2 | 46.2 (4.7) | 0.2 |
| CC (34) | 3625 (275) | 52.2 (3.0) | 0.02 | 52.2 (3.0) | 0.04 |
| CT and TT (52) | 4752 (620) | 44.8 (2.4) | 0.02 | 44.8 (2.4) | 0.02 |
| 2677–3435 |
| GG-CC (33) | 3605 (283) | 52.6 (3.1) | 0.02 | 52.6 (3.1) | 0.04 |
| Others (53) | 4743 (608) | 44.7 (2.3) | 0.02 | 44.7 (2.3) | 0.04 |
| 61–1236–2677–3435 |
| AA-CC-GG-CC (24) | 3714 (380) | 52.6 (4.0) | 0.02 | 52.6 (4.0) | 0.04 |
| Others (62) | 4535 (524) | 45.9 (2.1) | 0.02 | 45.9 (2.1) | 0.04 |
| 61–1236–2677–3435 |
| AA-CT-GT-CT (19) | 5949 (1628) | 42.7 (4.2) | 0.02 | 42.7 (4.2) | 0.04 |
| Others (67) | 3840 (189) | 49.2 (2.1) | 0.02 | 49.2 (2.1) | 0.04 |
| 1236–2677–3435 |
| CT-GT-CT (23) | 5644 (1355) | 43.3 (3.7) | 0.02 | 43.3 (3.7) | 0.04 |
| Others (63) | 3818 (193) | 49.4 (2.2) | 0.02 | 49.4 (2.2) | 0.04 |
| 1236–2677–3435 |
| TT-TT-TT (7) | 4293 (437) | 40.0 (3.6) | 0.02 | 40.0 (3.6) | 0.04 |
| Others (79) | 4307 (427) | 48.4 (2.0) | 0.02 | 48.4 (2.0) | 0.04 |

Abbreviations: AUC = plasma concentration-time curve; s.e. = standard error.
*Comparisons between groups used the Mann–Whitney test for two groups and the Kruskal–Wallis test for three or more groups. Statistical significance was defined as P < 0.005.
A significant association between C1236T polymorphism and docetaxel clearance was reported by Bosch et al (2006), as patients homozygous for the variant T allele showed lower clearance. In the present series, in accordance with this report, patients homozygous for the T allele presented a lower docetaxel clearance although not reaching statistical significance (see Table 5).

In conclusion, these results show that menopausal status at diagnosis has an impact on the effect of C3435T polymorphism of ABCB1 gene on the pharmacokinetics of docetaxel in breast cancer patients. This finding raises the question of whether higher doses of docetaxel should be given to 3435CC premenopausal women. To provide further insight into this issue, we are currently analysing whether C3435T polymorphism is involved in the pathologic response of breast cancer patients receiving docetaxel in their neoadjuvant chemotherapy regimen according to their menopausal status.

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