Breast Cancer Res Treat (2013) 139:421–428
DOI 10.1007/s10549-013-2545-7

CLINICAL TRIAL

Influence of *ABCB1* polymorphisms and docetaxel pharmacokinetics on pathological response to neoadjuvant chemotherapy in breast cancer patients

Pierre Lévy · Joseph Gligorov · Martine Antoine · Keyvan Rezai · Eric Lévy · Frédéric Selle · Pierre Saintigny · François Lokiec · Danielle Avenin · Karine Beerblock · Jean-Pierre Lotz · Jean-François Bernaudin · Anne Fajac

Received: 6 February 2013 / Accepted: 19 April 2013 / Published online: 11 May 2013
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Abstract We have previously reported an association between ABCB1 C3435T polymorphism and docetaxel pharmacokinetics in breast cancer patients. We therefore investigated whether these parameters could account for variations in pathological response. Five ABCB1 polymorphisms including C3435T polymorphism were analyzed in breast cancer patients receiving neoadjuvant chemotherapy with doxorubicin and docetaxel ($n = 101$). Pathological response was assessed using the Sataloff classification. Pharmacokinetic analysis was performed for the first course of docetaxel ($n = 84$). No significant association was found between ABCB1 polymorphisms or docetaxel pharmacokinetics and pathological complete response. C3435T genotype was an independent predictive factor of good response in breast (response >50 %, i.e., Sataloff T-A and T-B): OR: 4.6 (95 % CI: 1.3–16.1), $p = 0.015$, for TT patients versus CT and CC patients. Area under the plasma concentration–time curve (AUC) of docetaxel was the only independent predictive factor of the total absence of response in breast (Sataloff T-D): OR: 14.3, (95 % CI: 1.7–118), $p = 0.015$, for AUC of docetaxel <3,500 µg h/L versus ≥3,500 µg h/L. These results suggest that C3435T polymorphism and docetaxel exposure are involved in the response to neoadjuvant chemotherapy in breast cancer patients and may be useful to optimize individualized therapy.

Keywords Breast cancer · Docetaxel pharmacokinetics and pharmacodynamics · ABCB1 · Polymorphisms · Pharmacogenomics · Drug resistance · Neoadjuvant · Chemotherapy

Joseph Gligorov & Pierre Lévy are the first co-authors. Anne Fajac, Pierre Lévy & Joseph Gligorov equally contributed to the study.

Electronic supplementary material The online version of this article (doi:10.1007/s10549-013-2545-7) contains supplementary material, which is available to authorized users.

P. Lévy
Département de Santé Publique, hôpital Tenon, AP-HP, Inserm UMR S 707, Université Pierre et Marie Curie, 4 rue de la Chine, 75020 Paris, France

J. Gligorov (✉) · F. Selle · D. Avenin · K. Beerblock · J.-P. Lotz
Medical Oncology Department, Francilian Breast intergroup, hôpital Tenon, AP-HP, ER2 UPMC Université Pierre et Marie Curie, 4 rue de la Chine, Paris 75020, France
e-mail: joseph.gligorov@tnn.aphp.fr

M. Antoine
Service d'Anatomo-Pathologie, hôpital Tenon, AP-HP, ER2 UPMC Université Pierre et Marie Curie, 4 rue de la Chine, 75020 Paris, France

K. Rezai · F. Lokiec
Service de Pharmacologie, Centre René Huguenin, 35 rue Dailly, 92210 St-Cloud, France

E. Lévy
Service d'Oncologie, Intergroupe Francilien du sein, HEGP, AP-HP, 20 rue Leblanc, 75015 Paris, France

P. Saintigny
Service d'Oncologie, Hôpital Avicenne, AP-HP, 125 rue Stalingrad, 93000 Bobigny, France

J.-F. Bernaudin · A. Fajac
Service d'Histologie-Biologie Tumorale, hôpital Tenon, AP-HP, ER2 UPMC Université Pierre et Marie Curie, 4 rue de la Chine, 75020 Paris, France

Introduction

The primary established clinical benefit of neoadjuvant systemic therapy in breast cancer consists of downstaging of locally advanced, inflammatory or large tumors to improve surgical options [1, 2]. It has also been demonstrated that the prognosis of the disease is correlated with the absence of residual invasive tumor after neoadjuvant therapy. Among the various chemotherapy regimens used in the neoadjuvant setting, anthracycline- and taxane-based regimens are considered to be the standard of care in breast cancer [3].

Various tumor parameters such as tumor size, grade, estrogen receptor (ER), and cerbB2 status, are known to influence the response of breast cancer patients after neoadjuvant chemotherapy [4, 5]. It can be hypothesized that host genetic factors influencing drug disposition could also be involved in interindividual variations in drug response. Among these genetic factors, the ATP-binding cassette (ABC) efflux drug-transporter, ABCB1, is a potential candidate.

Initially discovered as an efflux transporter involved in multidrug resistance of tumor cells [6], ABCB1 is physiologically expressed in various organs responsible for drug disposition including intestine, liver, and kidney and is an efflux transporter for anthracyclines and taxanes [7]. We have previously shown that C3435T polymorphism in *ABCB1* gene was associated with docetaxel pharmacokinetics in breast cancer patients [8]. The area under the plasma concentration–time curve (AUC) of docetaxel was lower for patients with 3435CC genotype and this difference between genotypes was restricted to premenopausal women.

In the present study, we analyzed the pathological response in breast cancer patients receiving neoadjuvant chemotherapy with doxorubicin and docetaxel according to *ABCB1* polymorphisms, including T-129C, A61G, C1236T, G2677T/A, and C3435T polymorphisms, and according to docetaxel pharmacokinetics. Moreover, given that a tumor is characterized by acquired genetic alterations, C3435T polymorphism was also analyzed in breast tumor tissues for a subset of patients to assess whether the tumor genotype was the same as the inherited germline genotype.

Patients and methods

Patients

Women with breast cancer receiving neoadjuvant chemotherapy were included in the present study, namely patients with tumors >20 mm (T2, T3, and T4 tumors) and the absence of metastatic disease. Of the 106 patients included, 101 were evaluable for pathological response and analyzed in the present study. Chemotherapy consisted of four cycles of doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2) followed by four cycles of docetaxel (100 mg/m^2). Fifteen of the 101 patients did not complete the eight cycles because of disease progression, as assessed by clinical and radiological parameters, and the subsequent decision to perform surgery: 1 patient had incomplete doxorubicin treatment (three cycles) and no docetaxel, and 14 patients had four cycles of doxorubicin but no ($n = 6$) or incomplete (1–3 cycles) docetaxel treatment ($n = 8$). Trastuzumab was administered to five patients with c*erbB2* amplification in tumor cells during courses of docetaxel. Patient characteristics are listed in supplemental Table S1. Most patients were Caucasians ($n = 73$).

The protocol was approved by the Independent Ethics Committee of Pitié-Salpêtrière hospital, Université Pierre et Marie Curie, Paris, France and all patients provided written informed consent before inclusion in the study including specific written informed consent for the pharmacogenetic analysis.

Pathological response

To evaluate the pathological response, breast biopsies obtained before chemotherapy, and breast tissue and axillary lymph nodes obtained at surgery after chemotherapy were examined. In the case of lumpectomy ($n = 46$), surgically removed breast tissue was sectioned if a macroscopic lesion was present. When a macroscopic lesion was present, different sections representative of the lesion were performed. Sections of breast tissue in the vicinity of the tumor were performed horizontally and perpendicularly to the lesion to delineate the lateral margins and the superficial and deep planes of the tumor. When no macroscopic lesion was present, the entire lumpectomy specimen was examined. In the case of mastectomy ($n = 55$), a dozen tumor sections and two sections of each breast quadrant, the breast center and the nipple were performed. All lymph nodes obtained during axillary dissection were entirely examined when no macroscopic lesion was present. Pathological response was assessed by the same pathologist (MA) using the Sataloff classification [9]. Estrogen or progesterone receptor status was considered positive according to the French guidelines when at least 10 % of tumor cell nuclei were immunoreactive. CerbB2 status was assessed according to ASCO guidelines [10].

Genotyping

The method used has been previously reported [8]. In brief, genomic DNA was extracted from whole blood collected at the time of diagnosis (10 ml) using QIAamp DNA blood Maxi Kit (Qiagen, Hilden, Germany). T-129C (rs3213619),

A61G (rs9282564), C1236T (rs1128503), and C3435T (rs1045642) polymorphisms were each analyzed using 2 matching primers and 2 TaqMan MGB probes labeled with 6-FAM or VIC dye for allelic discrimination. For G2677T/A (rs2032582) polymorphism, the analysis was based on the PCR–RFLP.

Analysis of C3435T polymorphism in breast tumors

Three to five sections (15–20 μm each) from paraffin-embedded tumor samples obtained at surgery were submitted to deparaffinization in ATL buffer (Qiagen) and subsequent DNA extraction using 100 U proteinase K overnight and QIAamp DNA Mini Kit. DNA (125 ng) was amplified for analysis of C3435T polymorphism as reported above. Two other sections cut before and after the sections devoted to C3435T polymorphism analysis were stained with hematoxylin and eosin to check for the presence of tumor cells.

For the two patients with different C3435T genotypes in blood and in the tumor obtained at surgery, the results were checked in another blood sample, in another paraffin-embedded tumor sample and in a frozen tumor sample obtained at surgery. Two independent paraffin-embedded tumor samples of the initial biopsy were obtained before chemotherapy and checked for the presence of tumor cells were also examined for C3435T polymorphism for these two patients.

Pharmacokinetics

Pharmacokinetic analysis was performed for the first course of docetaxel as previously reported [8]. In brief, a limited sampling strategy was used with five heparinized blood samples (5 mL each): immediately before infusion, 5 min before the end of infusion and 20 min, 2 and 5 h after the end of infusion [11]. Plasma concentrations of docetaxel were determined using validated high-performance liquid chromatography methods with UV detection [12]. The analytic range for docetaxel determination was 25–5,000 ng/ml. Individual drug clearances were estimated from docetaxel population pharmacokinetic parameters [13] using the POSTHOC option of NONMEM [14]. The area under the plasma concentration–time curve (AUC) was calculated as AUC = dose/clearance.

Statistics

Sample size

The sample size was calculated to detect a minimum difference of 30 % for complete pathological response between 3435CC patients and (3435CT and 3435TT) patients with a power of 80 % and a two-sided type I error of 5 %. Given that ~25 % patients have a complete pathological response and that CC genotype proportion is around 20 % in Caucasians, the required number of patients was 100 (Casagrande and Pike method). A difference of 25 % between AUC could also be detected with this number of patients (with a power of 80 % and a two-sided type I error of 5 %).

Definition of response

For analysis of pathological response, complete response (pCR), i.e., complete absence of tumor in both the breast and axillary lymph nodes (Sataloff T-A, N-A and T-A, N-B) was primarily considered. As the main objective of neoadjuvant chemotherapy is to reduce tumor size in an attempt to make conservative surgery feasible, response >50 % in breast (Sataloff T-A and T-B) and the total absence of response in breast (Sataloff T-D) were also examined.

Analysis of genotype data

Seven genotypes were analyzed. For C3435T polymorphism, CC genotype was compared to (CT and TT) genotype considered as a single group and TT genotype was compared to (CT and CC) genotype considered as a single group. For the other polymorphisms, analysis was performed taking into account the frequencies of the homozygous variants. For T-129C: TT versus (TC and CC), for A61G: AA versus AG, for C1236T: CC versus (CT and TT) and TT versus (CC and CT), for G2677T/A: GG versus (GT, TT and TA).

Analysis of pharmacokinetic data

AUC of docetaxel was analyzed as a continuous variable. AUC of docetaxel was also analyzed as a qualitative variable. The median value was chosen as the cut-off value, i.e., 3,500 μg h/L.

Statistical analysis

StatView 5.0 and SAS Enterprise Guide 4.3 software was used. Qualitative variables were analyzed using χ^2 test or, when appropriate, Fisher's exact test. Quantitative variables were analyzed using the nonparametric Mann–Whitney test. Owing to multiple testing, significance was defined as $p < 0.0025$ (seven genotypes and three kinds of response tested). Descending stepwise logistic regression analyses were used to identify the independent predictive factors of response. The significance level was 0.25 for the univariate phase and 0.05 for the multivariate phase.

Results

Results for pathological response using the Sataloff classification are shown in Table 1. Results for genotype analysis of -129C, A61G, C1236T, C3435T, and G2677T/A polymorphisms according to pathological response are listed in Table 2.

Complete response (pCR, Sataloff T-A, N-A and T-A, N-B)

Complete response, i.e., complete absence of tumor in both the breast and axillary lymph nodes, was primarily analyzed (Sataloff T-A, N-A and T-A, N-B). No significant relationship was found between pCR and any of the genotypes studied (Table 2, all p values $\geq$0.25). However, the pCR rate was twofold higher among 3435TT patients compared to 3435CC or 3435CT patients [Table 2, 4/15 (27 %) vs 12/86 (14 %)]. Pharmacokinetics for the first course of docetaxel was able to be evaluated in 84 patients of the present series. No significant relationship was found between pCR and first-course docetaxel AUC ($p = 0.9$).

Response >50 % in breast (Sataloff T-A and T-B)

A relationship was found between response >50 % in breast (Sataloff T-A and T-B) and 3435TT genotype, ($p = 0.04$, not significant due to adjustment for multiple statistical testing, Table 2). This type of response was observed in 10/15 (67 %) patients with 3435TT genotype versus 33/86 (38 %) patients with 3435CC or 3435CT genotypes. No significant relationship was found between response >50 % in breast and any of the other polymorphisms (Table 2, all p values $\geq$0.15). No significant relationship was found between response >50 % in breast and AUC of docetaxel ($p = 0.7$).

Table 1 Pathological response in the primary breast tumor and axillary lymph nodes using the Sataloff classification ($n = 101$)

	T-A	T-B	T-C	T-D	
N-A	5	1	0	2	8
N-B	11	9	17	4	41
N-C	6	10	16	1	33
N-D	0	1	6	12	19
	22	21	39	19	101

T-A total or near total therapeutic effect, *T-B* >50 % therapeutic effect but less than total or near total, *T-C* $\leq$50 % therapeutic effect, *T-D* no therapeutic effect, *N-A* evidence of therapeutic effect, no metastatic disease, *N-B* no nodal metastasis or therapeutic effect, *N-C* evidence of therapeutic effect but nodal metastasis still present, *N-D* metastasis, no therapeutic effect

Multivariate analysis was performed on the factors identified to be predictive of response >50 % in breast on univariate analysis ($p \leq 0.25$, supplemental Table S2), namely age, tumor stage, tumor grade, progesterone receptors, and C3435T polymorphism. Tumor stage, tumor grade, and C3435T polymorphism were found to be independent predictive factors of response >50 % in breast (Table 3). Patients with stage T1 or T2 tumor or grade III tumor or 3435TT genotype obtained a better response than the other patients. Patients with 3435TT genotype had a 4.6 odds ratio (OR) (95 % CI: 1.3–16.1) of achieving response >50 % than patients with CT or CC genotype ($p = 0.015$) which was higher than the ORs for tumor stage and grade.

Absence of response in breast (Sataloff T-D)

No significant relationship was found between the absence of response in breast (Sataloff T-D) and any of the polymorphisms (Table 2, all p values $\geq$0.25). Docetaxel AUC was lower for patients with the absence of response in breast than for other patients considered as a single group: AUC $\pm$ SE values (µg h/L): 2,910 $\pm$ 162 ($n = 11$) versus 4,514 $\pm$ 457 ($n = 73$), (Fig. 1) ($p = 0.007$, not significant due to adjustment for multiple testing). However, docetaxel AUC below the median value of docetaxel AUC (3,500 µg h/L) was significantly associated with the absence of response in breast ($p = 0.002$, supplemental Table S3).

Multivariate analysis was performed for the predictive factors of the absence of response in breast identified on univariate analysis (supplemental Table S3), namely tumor stage, tumor grade, ERs, and AUC of docetaxel. Only docetaxel AUC was found to be an independent predictive factor of the absence of response in breast (OR: 14.3, 95 %

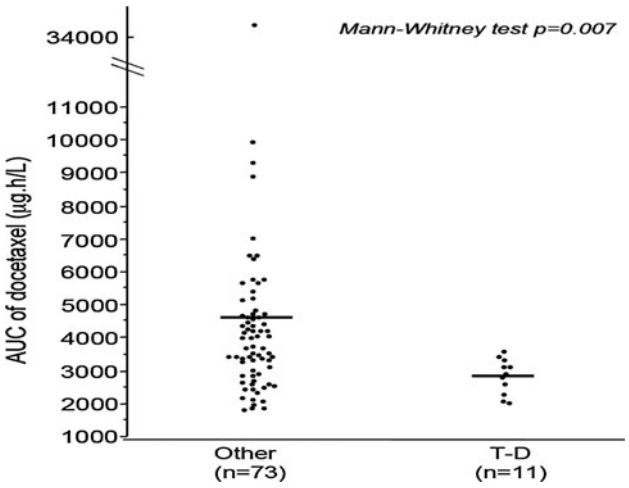

Fig. 1 AUC of docetaxel according to pathological response in breast (Sataloff T-D: absence of response, other: Sataloff T-A, T-B and T-C)

Table 2 Analysis of pathological response according to *ABCB1* polymorphisms ($n = 101$)

Polymorphism	Genotype	Number ($n = 101$)	Complete response (T-A, N-A and T-A, N-B)		>50 % in breast (T-A and T-B)		No response in breast (T-D)	
			n	*p**	*n*	*p**	*n*	*p**
T-129C	TT	88	14	TT vs TC + CC	37	TT vs TC + CC	15	TT vs TC + CC
	TC	12	2	0.90	6	0.80	3	0.25
	CC	1	0		0		1	
A61G	AA	90	14	AA vs AG	37	AA vs AG	16	AA vs AG
	AG	11	2	0.70	6	0.60	3	0.45
	GG	0	0		0		0	
C1236T	CC	40	6	CC vs CT + TT	14	CC vs CT + TT	6	CC vs CT + TT
	CT	46	6	0.85	21	0.20	11	0.45
	TT	15	4	TT vs CT + CC	8	TT vs CT + CC	2	TT vs CT + CC
				0.25		0.35		0.75
G2677T/A	GG	48	9	GG vs	17	GG vs	8	GG vs
	GT	40	4	GT + TT + TA	19	GT + TT + TA	8	GT + TT + TA
	TT	12	3	0.45	7	0.15	3	0.60
	TA	1	0		0		0	
C3435T	CC	38	7	CC vs CT + TT	16	CC vs CT + TT	6	CC vs CT + TT
	CT	48	5	0.60	17	0.95	10	0.55
	TT	15	4	TT vs CT + CC	10	TT vs CT + CC	3	TT vs CT + CC
				0.25		0.04		0.90

* Significance was set at $p < 0.0025$ due to multiple testing

CI: 1.7–118, $p = 0.015$ for AUC of docetaxel <3,500 μg h/L versus ≥3,500 μg h/L, Table 4).

Analysis of C3435T polymorphism in primary breast tumors

To investigate whether the inherited C3435T genotype, obtained from blood cells, and the C3435T genotype in the primary breast tumor were identical, this polymorphism was analyzed on the residual tumor obtained at surgery for 65 patients. The genotype was the same in blood and tumor for most patients ($n = 63$, 97 %), but different for two patients. The genotype was CC in blood and CT in the tumor for one patient and TT in blood and CT in the tumor for the other patient. For each of these two patients, the genotype in the initial biopsy obtained before chemotherapy was the same as in blood.

Discussion

Pathological complete response after neoadjuvant chemotherapy is a clearly established prognostic factor for disease-free and overall survival in breast cancer [3, 15]. In the present study, no significant association was demonstrated between docetaxel pharmacokinetics or any *ABCB1* polymorphism and pCR according to Sataloff classification (T-A, N-A and T-A, N-B).

However, a significant relationship was found between docetaxel pharmacokinetics or C3435T polymorphism and intensity of response. Lower exposure to the first course of docetaxel (AUC <3,500 μg h/L) was an independent predictive factor of the absence of response in the primary breast tumor (Sataloff T-D). 3435TT genotype was an independent predictive factor of pathological response >50 % in breast. In each case, the low explained variance ($r^2 = 0.16$ and $r^2 = 0.10$, respectively) indicates the role of other factors in breast cancer response.

Our results suggest that first-course docetaxel AUC can be considered to be a negative predictive factor of response. The ability to predict the total absence of response is clinically relevant in the neoadjuvant setting, as it could modify the treatment strategy. Various treatment options could include switching to surgery or to another systemic treatment or possibly increasing the doses of docetaxel, as the dose-dependent antitumor efficacy of docetaxel has been suggested in several trials. In a large phase 3 trial including 407 patients with advanced breast cancer, increasing docetaxel dose was shown to increase tumor response. For the 69 patients of this study in whom pharmacokinetic analysis was performed, despite the linear relationship between docetaxel dose and AUC, no significant relationship was observed between response rate and AUC, probably because of the small number of patients, as discussed by the authors [16]. Furthermore, in 151 patients treated for metastatic lung cancer,

Table 3 Multivariate logistic regression analysis of factors predictive of pathological response >50 % in breast (Sataloff T-A and T-B)

	Initial table ($n = 96$) OR (95 % CI)	r^2* = 0.12 Hosmer–Lemeshow, $p = 0.38$ p
Age (years)		
<50	1	
≥50	0.5 (0.2–1.3)	0.2
Tumor stage		
T3–T4	1	
T1–T2	2.9 (1.1–7.6)	0.03
Tumor grade		
I–II	1	
III	2.2 (0.8–6.3)	0.1
PR status		
Negative	1	
Positive	0.6 (0.2–1.6)	0.3
C34 35T		
CC and CT	1	
TT	5.3 (1.4–19.8)	0.01
	Final table ($n = 98$) OR (95 % CI)	r^2* = 0.10 Hosmer–Lemeshow, $p = 0.85$ p
Tumor stage		
T3–T4	1	
T1–T2	2.8 (1.1–7.2)	0.03
Tumor grade		
I–II	1	
III	3.1(1.2–8.0)	0.015
C34 35T		
CC and CT	1	
TT	4.6 (1.3–16.1)	0.015

OR odds ratio, *CI* confidence interval, *PR* progesterone receptor

* r^2 = Explained variance

Table 4 Multivariate logistic regression analysis of factors predictive of the absence of pathological response in breast (Sataloff T-D)

	Initial table ($n = 81$) OR (95 % CI)	r^2* = 0.21 Hosmer–Lemeshow, $p = 0.90$ p
Tumor stage		
T3–T4	1	
T1–T2	0.4 (0.1–1.8)	0.2
Tumor grade		
I–II	1	
III	3.1 (0.5–18.9)	0.2
ER status		
Positive	1	
Negative	0.8 (0.2–3.7)	0.8
Docetaxel AUC		
≥3,500 μg h/L	1	
<3,500 μg h/L	11.7 (1.4–100.5)	0.025
	Final table ($n = 84$) OR (95 % CI)	r^2* = 0.16 Hosmer–Lemeshow, $p = 1$ p
Docetaxel AUC		
3,500 μg h/L	1	
3,500 μg h/L	14.3 (1.7–118)	0.015

OR odds ratio, *CI* confidence interval, *ER* estrogen receptor

* r^2 = Explained variance

first-course docetaxel AUC was a significant predictor of time to progression [13]. According to certain preclinical data suggesting different mechanisms of action of docetaxel at higher doses [17], the feasibility of increasing docetaxel doses up to 185 mg/m^2 with G-CSF support has been demonstrated in adults and children and a linear relationship has been demonstrated between docetaxel dose and AUC [18, 19].

3435TT genotype was found to be significantly associated with response >50 % in breast (Sataloff T-A and T-B). Identification of factors predictive of response >50 % in breast is clinically relevant as such factors may support conservative surgery options. We also found that the pCR rate was twofold higher among 3435TT patients compared to 3435CC and 3435CT patients. The lack of statistical significance may be due to an insufficient sample size, as the number of patients was calculated to show a 30 % difference, while this difference in pCR rate was only 13 % (see Statistics section).

We also analyzed C3435T genotype in breast tumors obtained at surgery for a subset of patients and showed that the genotype was the same as in blood cells in most patients (97 %). Determination of the C3435T genotype in blood, which is technically easier than in the tumor, therefore constitutes a marker at both the host and tumor level. The difference in genotype between the initial tumor and the tumor obtained at surgery observed for two patients might be due to drug-induced selection in a tumor with an initially heterogeneous cellular composition or a direct mutagenic effect of the drug.

The finding of 3435TT genotype associated with good response to a regimen containing doxorubicin and docetaxel, which are both effluxed by ABCB1, is functionally relevant, as 3435TT genotype has usually been associated with lower ABCB1 mRNA and protein levels and decreased drug efflux in normal and tumor tissues [20–24]. 3435TT genotype is therefore mostly associated with higher drug exposure of normal tissues and tumor cells.

Few studies have dealt with the response of breast cancer patients according to inherited *ABCB1*

polymorphisms [25–27]. 3435TT genotype was more frequently associated with better clinical response [26, 27]. Surprisingly, as emphasized by the authors, a single study reported 3435CC genotype to be associated with better clinical response [25–27]. We have previously shown that 3435CC premenopausal patients had lower first-course docetaxel AUC [8]. In the present study, the combination of docetaxel AUC <3,500 μg h/L and 3435CC genotype was associated with poorer response in both the breast and axillary node sites, i.e., Sataloff T-D and N-D response ($p = 0.05$, data not shown). This combination is observed only in premenopausal patients and not in postmenopausal patients. The low level of significance may be due to the small number of patients presenting this combination.

In a study focusing on pathological response, based on a smaller series of 68 breast cancer patients mostly exposed to an anthracycline–taxane regimens, a similar association of 3435TT genotype was reported with better clinical response but not with pCR [27]. However, the intensity of the pathological response was not analyzed.

In conclusion, as the main objective of neoadjuvant chemotherapy in breast cancer is to optimize surgical treatment options [3], identification of factors predictive of pathological response, whether positive or negative, is clinically relevant. Indeed, factors predicting a response >50 % in breast may support conservative surgery options and factors predicting no treatment effect may lead to earlier treatment switch. Our preliminary results suggest that ABCB1 C3435T polymorphism and first course-docetaxel exposure may be predictive factors of pathological response and may be able to guide individualized therapy in breast cancer patients, particularly when using agents targeting ABCB1 [28]. Further studies in larger cohorts are needed to confirm these results.

Acknowledgments The authors would like to thank Assistance Publique-Hôpitaux de Paris and ACTT (Amis du Centre des Tumeurs de Tenon) association for financial support, URC-Est for help in the design of this study, and Jean-Pierre Lotz, Florent Soubrier and Serge Uzan for their constant support. This study was supported by Assistance Publique-Hôpitaux de Paris (Grant Number PHRC AOR03015) and ACTT (Amis du Centre des Tumeurs de Tenon) association.

Conflict of interest The authors declare that they have no conflict of interest.

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