Original Article

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Comparison of the docetaxel concentration in human plasma measured with liquid chromatography-tandem mass spectrometry (LC-MS/MS) and a nanoparticle immunoassay and clinical applications of that assay

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Summary **To determine the feasibility of using a nanoparticle immunoassay for clinical therapeutic drug monitoring (TDM) of docetaxel concentrations, a sensitive and simple method of liquid chromatography-tandem mass spectrometry (LC-MS/MS) was established to measure the docetaxel concentration in human plasma and the results of LC-MS/MS and the immunoassay were compared. Docetaxel and paclitaxel (the internal standard, or IS) in human plasma were extracted through protein precipitation, separated on a Diamonsil C18 column (150 mm × 4.6 mm, 5 μm), ionized with positive ions, and detected with LC-MS/MS in multi-reaction monitoring (MRM) mode. Plasma samples from 248 cancer patients were assayed with LC-MS/MS and a nanoparticle immunoassay. Data from the samples were analyzed with the statistical software SPSS and the software MedCalc. Results indicated that the calibration curve of the validated method of LC-MS/MS was linear over the range of 10-2,000 ng/mL, with an lowest limit of quantitation (LLOQ) of 10 ng/mL, and the intra- and inter-day precision and accuracy were both < ± 15%. Comparison of the two methods indicated that results of the LC-MS/MS were closely related to those of the nanoparticle immunoassay, with a correlation coefficient (R) of 0.965 and acceptable 95% confidence intervals (CI) of – 231.7-331.1 ng/mL. Overall, the established method of LC-MC/MS and the nanoparticle immunoassay were both suitable for measurement of the docetaxel concentration in human plasma, and the immunoassay was far more cost-effective and better at clinical TDM of docetaxel in clinical practice.**

Keywords: LC-MS/MS, nanoparticle immunoassay, docetaxel, therapeutic drug monitoring

1. Introduction

Docetaxel (Taxotere) is a widely used antitumor agent of the taxoid family with broad activity against a variety of solid tumors, such as breast cancer, non-small cell lung cancer (NSCLC), hormone refractory prostate cancer, gastric adenocarcinoma, and squamous cell carcinoma of the head and neck (*1-3*). However, the use of docetaxel may be limited by its narrow therapeutic range and unpredictable interindividual variability, which would induce hematologic toxicity and undesirable effects. The interindividual variability of the drug's pharmacokinetics (PK) and thus drug exposure mainly contributes to its unpredictable toxicity (*4*).

The optimal dosage of or regimen for docetaxel was 60-100 mg/m^2 administered intravenously every 3 weeks based on body surface area (BSA). However, BSA-based dosing can cause docetaxel exposure to vary among patients as much as 10-fold (*5*). Population PK analysis indicated that docetaxel exposure was related to α1-acid glycoprotein (AAG) levels, hepatic function,

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age, and BSA (*6-8*), and the variability of PK may induce severe toxicities, including neutropenia, anemia, diarrhea, asthenia, alopecia, and nausea, even at the therapeutic dosage (*9*). Moreover, studies have found that the area under the plasma concentration versus time curve (AUC), a parameter for docetaxel exposure, is associated with hematological toxicity and can predict grade 4 neutropenia (*10*). Therefore, PK-guided dosing of docetaxel may be beneficial because it ensures its antitumor efficacy and it minimizes the incidence of severe toxicities during therapy.

Chromatography (*e.g*. liquid chromatography coupled with mass spectroscopy (*11-13*) or UV detection (*14,15*)) has generally been used to measure the concentration of docetaxel or its metabolites in human plasma or serum. These techniques are more specific and sensitive, but the expensive equipment and the complicated protocol make them ill-suited to routine measurement of docetaxel, and these drawbacks may hinder clinical TDM of docetaxel. A nanoparticle immunoassay based on turbidimetry and monoclonal antibodies that compete with docetaxel has been developed and preliminarily verified to be suitable for clinical TDM of docetaxel (*16*). Therefore, an alternate immunoassay that is simple, rapid, and cost-effective would allow routine monitoring of docetaxel.

Since 2014, a nanoparticle immunoassay performed with an automated biochemistry analyzer has been in clinical use at this Hospital. To provide further evidence that the nanoparticle immunoassay and its corresponding commercial version are suitable for measuring the docetaxel concentration in human plasma, a method of liquid chromatography-tandem mass spectrometry (LC-MS/MS) was established as a "gold standard" and both methods were compared.

2. Materials and Methods

2.1. *Reagents and equipment*

Docetaxel (Lot: 100666-201002, purity: 98.0%), was obtained from the National Institute for the Control of Pharmaceutical and Biological Products (Beijing, China). Paclitaxel (Lot: 100382-201102, purity: 99.6%) was obtained from the National Institute for Food and Drug Control (Beijing, China) and served as the internal standard (IS). Pure water (Lot: 20151102) was obtained from the Hangzhou Wahaha Group Co., Ltd. (Hangzhou, China). Methanol (Lot: 0000118131) and acetonitrile (Lot: 0000059829) were from J.T. Baker (USA), and both were chromatography grade. A Diamonsil C_{18} column was from Dikma Technologies (Beijing, China). The MyDocetaxel™ (Lot: 1504030D) reagent kit and quantity control kit (Lot: 1509040C) were both from Jiangsu Changxing Medical Technology Co., Ltd. (Jiangsu, China).

An Agilent 1200 series HPLC system, equipped with a G1312B duplex pump, G1316B thermostatted column compartment, G1367C auto-sampler, G1379B vacuum degasser, and an Agilent 6410 Triple Quadruple mass spectrometer with electrospray ionization (ESI), were obtained from Agilent Technology. A DiRui CS600-B biochemical analyzer was provided by Changchun Medical Technologies Co., Ltd.

2.2. *Plasma samples*

Two hundred and forty-eight plasma samples were collected from patients receiving docetaxel-based regimens at Qilu Hospital of Shandong University between October 2014 and May 2016. Two blood samples were collected from each patient in EDTA-anticoagulant tubes, one at the end of infusion, and the other 1 hour after the infusion. After centrifugation, the plasma was separated and stored at -80°C for further analysis. This study was conducted in accordance with the Declaration of Helsinki and patient consent was obtained.

2.3. *LC-MS/MS assay*

2.3.1. *Conditions for chromatography and mass spectrometry*

Separation of docetaxel and the IS from plasma was achieved on a Diamonsil C_{18} column (150 mm × 4.6 mm, 5 μm) at 30°C with a thermostatted column oven. The mobile phase was 0.1% formic acid:acetonitrile (40:60, v/v) with a flow rate of 0.6 mL/min. Mass spectrometry was performed in the positive ion MRM mode, with an ion transition of m/z 830.5→550.4 for docetaxel and 876.4→308.2 for the IS, respectively. Other parameters for mass spectrometry were: a spray gas flow of 9 L/min, a spray gas (nitrogen) temperature of 350°C, a capillary voltage of 4,000 V, and a nebulizer pressure of 40 psi. The fragment voltage was 100 V for docetaxel and 120 V for the IS, the collision energy was 23 eV for docetaxel and 32 eV for the IS, and the EMV was 200 V.

2.3.2. *Preparation of stock solutions, working solutions, calibration samples, and quality control samples*

Primary stock solutions of 1 mg/mL of docetaxel and the IS were separately prepared in methanol. Primary stock solutions were diluted with the mobile phase to yield standard working solutions of docetaxel (0.1, 0.5, 1.0, 2.5, 5.0, 10.0, and 20.0 μg/mL). The IS was dissolved in the mobile phase to yield 4 μg/mL of a working solution. All solutions were stored at 4°C and equilibrated to room temperature before use.

Calibration samples and quality control (QC) samples were prepared by spiking blank plasma with a given volume of different working solutions. The calibration samples consisted of seven nonzero concentrations of

docetaxel: 10, 50, 100, 250, 500, 100, and 2,000 ng/mL. QC samples of docetaxel for the lowest limit of quantitation (LLOQ), a low level of QC (L), a middle level of QC (M), and a high level of QC (H) were 10, 25, 200, and 1,600 ng/mL, respectively.

2.3.3. *Sample preparation*

Two hundred μL of a plasma sample was mixed with 10 μL of IS (4 μg/mL) and vortexed for 0.5 min. Six hundred μL of methanol was added and the mixture was vortexed again for 3 min, followed by centrifugation at 10,800 rpm for 5 min. The supernatant was transferred and 10 μL was injected for analysis.

2.3.4. *Validation of the two methods*

The established method of LC-MS/MS for measurement of the docetaxel concentration in human plasma was validated in accordance with FDA guidelines, including specificity, matrix effects, linearity, recovery, precision, accuracy, and stability.

Specificity. The specificity of the method was evaluated by comparing chromatograms for six different lots of blank human plasma to identify the potential interference of endogenous substances in peak regions for docetaxel and the IS according to HPLC.

Matrix effect and Recovery. Six different human blank plasma samples were extracted and spiked with the analyte at high and low QC levels and with the IS. The areas of corresponding peaks were compared to areas of peaks produced by standard solutions, and the peak area ratio was defined as the matrix effect. The mean overall recovery of the analyte and the IS was determined based on the ratio of the peak area (extracted plasma standards/plasma samples after extraction). The analyte was measured at high and low QC levels in six different blank plasma samples and extracted as described above. Recovery of the IS was determined at 200 ng/mL with the method described above.

Calibration curve and LLOQ. Calibration curves were plotted with seven concentrations and each was plotted three times. Calibration curves were typically described by the equation $y = ax + b$, where y corresponds to the peak-area ratio of the analyte to the IS, and x represents the plasma concentration of the analyte. The linearity of the calibration curve was assessed by linear regression with a weighting factor of the reciprocal of the concentration squared ($1/x^2$). LLOQ was also evaluated based on accuracy and precision.

Accuracy and Precision. The intra-day accuracy and precision were estimated by analyzing the docetaxel concentration at four levels, *i.e*. LLOQ (10 ng/mL), L (25 ng/mL), M (200 ng/mL), and H (1,600 ng/mL), in blank plasma within one day, and the inter-day precision was determined by analyzing samples of the four QC levels on three consecutive days.

Stability. Stability was studied using the L and H levels of QC in five samples stored or processed under different conditions, *i.e*. storage at -20°C for 1, 7, or 28 days, freezing (-20°C) and thawing (24 ± 2°C) for one or two cycles, leaving extracted samples to stand on the bench top for 4 h, and leaving samples in the LC-MS/MS auto-sampler for 6 h at room temperature.

2.4. *Nanoparticle immunoassay*

The principle of and protocol for a nanoparticle immunoassay of docetaxel were previously described in detail (*16*). Briefly, this assay was based on a competitive assay format using a selective docetaxel monoclonal antibody. Six different concentration calibrators (0, 75, 150, 300, 600, and 1,000 ng/mL) were used to generate the calibration curve, and three QC standards (115, 225, and 800 ng/mL) accompanied the sample test. A plasma sample was first added to reagent 1, and a reaction was started by adding reagent 2. Photometric detection was performed at 600 nm. The difference in absorbance was determined and the concentration was calculated from the calibration curve. An automated biochemical analyzer was used to measure the concentration of the analyte. The MyDocetaxel kit consists of reaction reagents (reagent 1 and reagent 2), six calibrator concentrations, and three control concentrations. Samples were processed according to the manufacturer's instructions.

2.5. *Statistics*

Data are expressed as the mean ± standard deviation (SD). Statistical analysis was performed using regression analysis. The statistical software SPSS was used to evaluate the correlation between concentrations measured with the two methods and the software MedCalc was used to draw a Bland-Altman plot, which helped to reveal differences and the extent of differences in measurements, any systematic bias, and possible outliers.

3. Results

3.1. *Validation of LC-MS/MS*

Specificity. The specificity of LC-MS/MS was evaluated by comparing chromatograms as shown in Figures 1 and 2. The full-scan and product ion mass spectrum of docetaxel and the IS are shown in Figure 1. Typical MRM chromatograms are shown in Figure 2, where A is the blank plasma, B is the docetaxel standard and the IS, C is blank plasma spiked with docetaxel and the IS, and D is a patient plasma sample (Patient No. 10) spiked with the IS. There was no endogenous interference with measurement of the docetaxel concentration in the blank or human plasma sample.

Matrix effects and Recovery. The recovery of

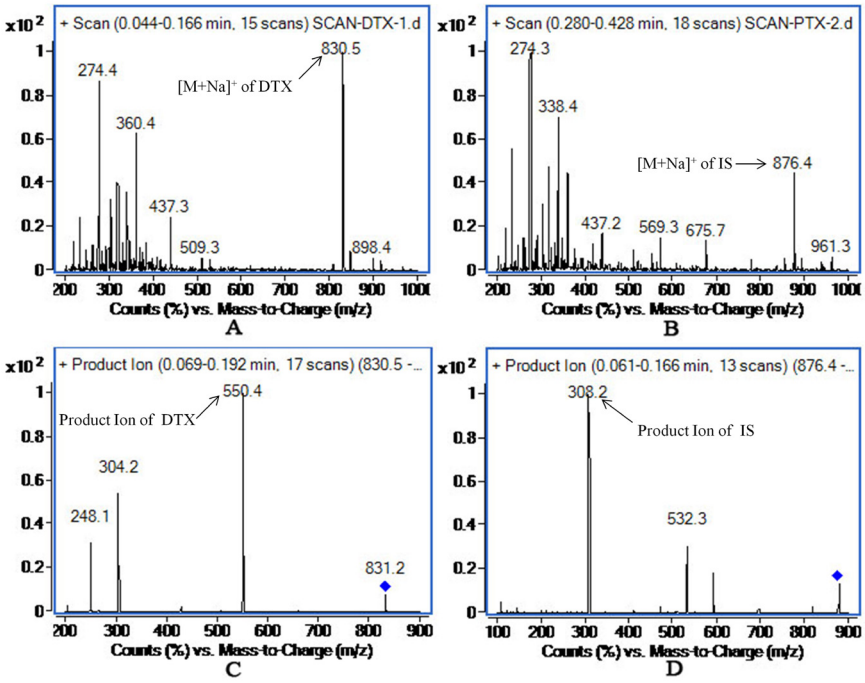

Figure 1. Full-scan and product ion mass spectrum of docetaxel (A, C) and the IS (B, D).

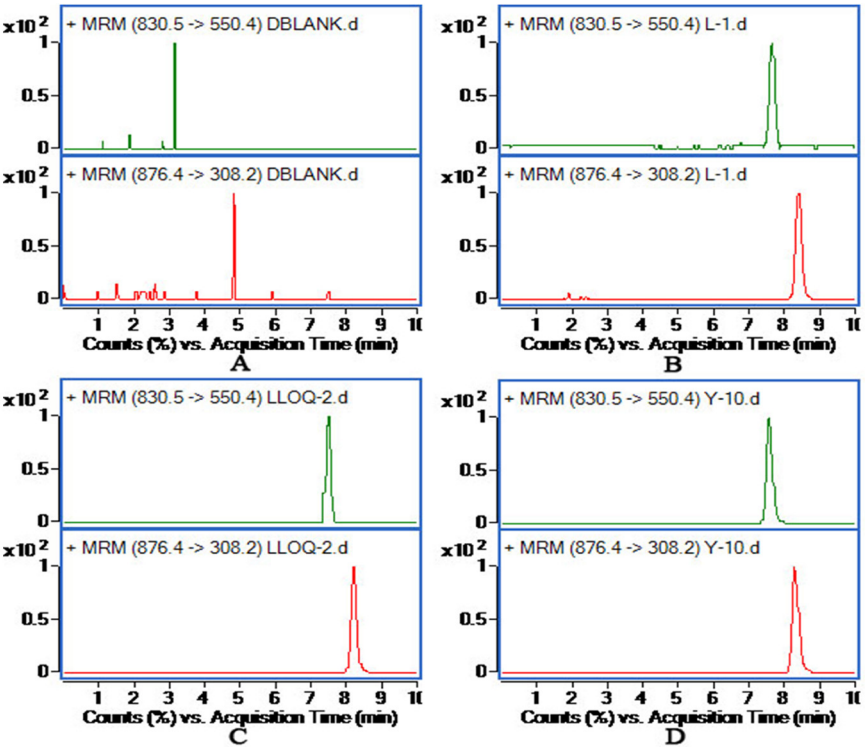

Figure 2. Typical MRM chromatograms of docetaxel and the IS. A: Blank plasma; **B**: Docetaxel and the IS (both were 10 ng/mL); **C**: LLOQ; blank plasma spiked with docetaxel (10 ng/mL) and the IS (100 ng/mL); **D**: Plasma from Patient No. 10 after treatment with docetaxel was mixed with a standard solution of the IS.

docetaxel and the IS was acceptable and reproducible. No matrix effects were observed. The mean recovery and matrix effects were 95.76% and 112.57% for docetaxel and 99.41% and 107.18% for IS, and the RSD was less than 15%, indicating that blank plasma samples were free from interference by endogenous substances, so docetaxel could be quantified.

Calibration curve and LLOQ. The calibration curve for docetaxel was linear over the concentration range with the regression equation (weight = $1/X^2$), as indicated by y = 0.0039x + 0.0025 and a correlation coefficient (r^2) of 0.9986. LLOQ was defined as the lowest concentration on the standard calibration curve with acceptable repeatability and recovery and at least

Table 1. The intra- and inter-day accuracy and precision of docetaxel levels in human plasma (n = 5)

Concentration (ng/mL)	Intra-day			Inter-day		
	Mean ± SD	Accuracy%	RSD%	Mean ± SD	Accuracy%	RSD%
10	9.84 ± 0.48	98.4	4.92	9.51 ± 0.77	95.1	8.12
25	24.10 ± 1.42	96.4	5.88	24.69 ± 1.75	98.7	7.08
200	196.49 ± 8.67	98.2	4.41	198.74 ± 21.07	99.4	10.60
1600	1,530.68 ± 44.03	95.7	2.88	1,603.7 ± 191.29	100.2	11.90

Table 2. Stability of docetaxel in human plasma (n = 5)

Stability study	L (25 ng/mL)			H (1,600 ng/mL)		
	Mean ± SD	Accuracy%	RSD%	Mean ± SD	Accuracy%	RSD%
post-extraction (4 h)	23.98 ± 1.70	95.9	7.09	1,475.89 ± 109.36	92.2	7.41
in auto sampler (6 h)	23.33 ± 1.96	93.3	8.40	1,706.96 ± 118.50	106.7	6.94
freeze-thaw (one cycle)	21.91 ± 3.22	87.7	14.70	1,390.07 ± 44.06	86.9	3.17
freeze-thaw (two cycles)	27.54 ± 1.51	110.2	5.47	1,548.27 ± 60.99	96.8	3.94
frozen (1 day)	24.68 ± 1.42	98.7	5.76	1,594.85 ± 65.09	99.7	4.08
frozen (7 days)	24.22 ± 0.92	96.9	3.78	1,668.02 ± 89.58	104.3	5.37
frozen (28 days)	25.43 ± 2.33	101.7	9.19	1,558.87 ± 160.08	97.4	10.30

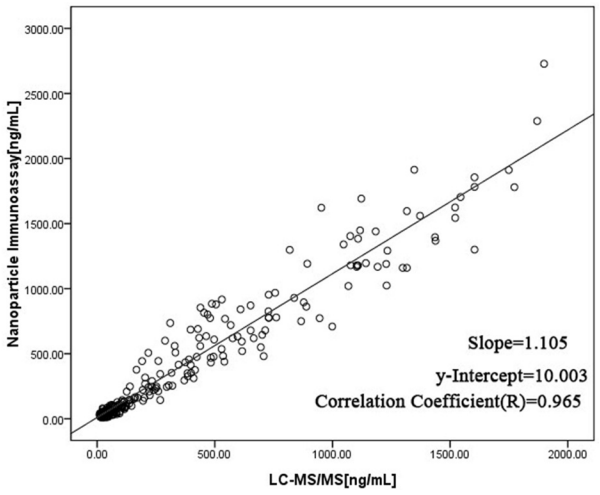

Figure 3. Correlation between the docetaxel concentration measured in plasma samples from cancer patients (n = 248) with a nanoparticle immunoassay and LC-MS/MS.

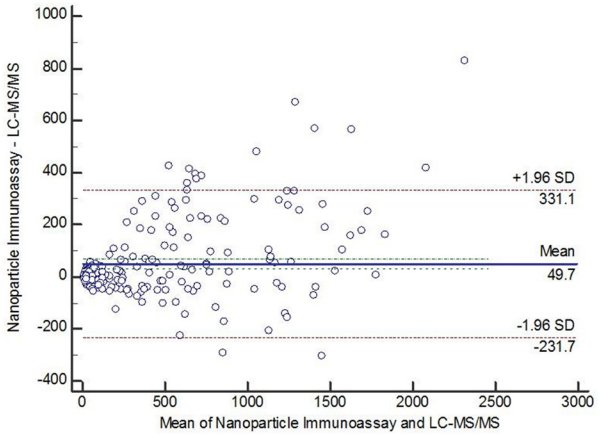

Figure 4. Bland-Altman plot of the mean docetaxel concentration measured with a nanoparticle immunoassay and LC-MS/MS.

10 times the response of the blank at the baseline.

Accuracy and Precision. Accuracy and precision results are as shown in Table 1. The results were within the accepted limits and therefore the assay was accurate and precise.

Stability. Results of a study of the stability of docetaxel in human plasma are shown in Table 2. Data indicated that docetaxel was stable in plasma under the indicated conditions.

3.2. *Methods comparison*

LC-MS/MS and the nanoparticle immunoassay were compared using 248 human plasma samples obtained from patients receiving docetaxel-based therapy commonly used in China. Both methods can be used to measure the docetaxel concentration in plasma samples. The docetaxel concentration ranged from 10.23-1,899.17 ng/mL according to the validated method of LC-MS/MS, with a mean of 378.1 ng/mL. The docetaxel concentration ranged from 9-2,728 ng/mL according to the nanoparticle immunoassay, with a mean of 427.7 ng/mL. Results of Deming regression analysis revealed a slope of 1.105 (95% CI of 1.067 to 1.142) with a y intercept of 10.003 ng/mL (95% CI of – 12.095 to 32.101 ng/mL), a standard error estimate of 135.7, and a correlation coefficient of 0.965 (Figure 3).

In addition, a plot of the differences between the two assays with respect to their mean concentration indicated that their results were similar, although slight differences were noted. The Bland-Altman plot for docetaxel is shown in Figure 4. As is evident from the plot, the 95% CI was – 231.7-331.1 ng/mL, and most results were in the 95% CI, though results from 14 samples fell outside the 95% CI. The mean bias was positive (49.7 ng/mL).

4. Discussion

While the chromatography conditions for the current study were being determined, various combinations of the mobile phase were tested to achieve good separation from the IS, a better peak, a high response, and a short retention time. Moreover, the mobile phase was evaluated to enhance MS sensitivity and minimize matrix effects. All of the mobile phases were combined with ammonium acetate (5 mM), formic acid at 0.1% (v/v), or both. A mobile phase of 0.1% formic acid:acetonitrile (40:60, v/v) was optimal. The column temperature and flow rate parameters were studied to provide fast and reliable separation, and the best results were obtained when the column temperature was 30°C (versus 25, 35, or 40°C) and the flow rate was 0.6 mL/min (versus 0.5 or 0.8 mL/min). Under these conditions, retention times of docetaxel and the IS were consistent and reproducible. A major advantage of the immunoassay is that it involves extraction through protein precipitation, which is easier and more consistent than liquid-liquid extraction (*11,13*) and solid phase extraction (*17-19*). This simple sample pretreatment allowed measurement of the docetaxel concentration and it had acceptable matrix effects.

Personalized medicine is facilitated through TDM of the concentration of a drug or its active metabolites in biological samples, allowing adjustment of the drug dosage to improve its efficacy and minimize its toxicity. Studies have indicated that monitoring the exposure to some anticancer drugs helps to reduce drug-related toxicity and improve therapeutic efficacy (*20-22*). However, clinical TDM of docetaxel has been limited, possibly due to the lack of cost-effective tools to monitor drug concentrations in plasma. A recent study has indicated that the AUC, a parameter for docetaxel exposure, is associated with the drug's therapeutic efficacy and toxicity (*23*). Measuring the docetaxel concentration to calculate the AUC can help with clinical TDM of docetaxel-based chemotherapies.

Plasma samples were collected from cancer patients at this Hospital and the two methods of measuring the docetaxel concentration were compared. Results indicated that the results of the two methods were closely correlated. Thus, the MyDocetaxel nanoparticle immunoassay can be used to measure the docetaxel concentration in plasma samples. The mean concentration measured with the immunoassay was slightly higher than that measured with LC-MS/MS and differed from the concentration reported in a study by Cline *et al*. (*16*). This difference may be due to the fact that docetaxel concentrations in the samples used in the previous study were much higher than those in the current study. Therefore, more clinical samples from patients need to be compared to obtain more definitive results.

The LLOQ of the validated method of LC-MS/MS was 10 ng/mL, which was lower than that of the MyDocetaxel nanoparticle immunoassay (52 ng/mL). The specificity and sensitivity of LC-MS/MS may allow more accurate measurement of the docetaxel concentration in cancer patients treated with a lower dose. The MyDocetaxel nanoparticle immunoassay yielded a docetaxel concentration below the LLOQ (52 ng/mL), but this result may be not accurate and it may partially account for any lack of correlation.

Docetaxel is predominantly metabolized in the liver by the hepatic cytochrome P450 (CYP) 3A isoforms CYP3A4 and CYP3A5 (*8,9*). Docetaxel metabolites include M1, M2, M3, and M4 and degradation products 7-epi-docetaxel and 10-deacetylbaccatin. Antibodies in the immunoassay cross-reacted more or less with metabolites as docetaxel degraded (*16*), which may account for the difference in the mean concentration measured with the nanoparticle immunoassay and LC-MS/MS, resulting in a positive bias of 49.7 ng/mL.

In conclusion, both the established method of LC-MS/MS and the commercial MyDocetaxel nanoparticle immunoassay were accurate, precise, and suitable for measurement of the docetaxel concentration in human plasma. Results of the two methods were closely correlated in the range of 10 to 2,000 ng/mL. Since the nanoparticle immunoassay was more convenient, had a higher throughput, and was more cost-effective, it is a better tool for TDM of the docetaxel concentration and can provide an experimental basis for individualized therapy in routine clinical practice.

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References

1. Baker SD, Sparreboom A, Verweij J. Clinical pharmacokinetics of docetaxel: Recent developments. Clin Pharmacokinet. 2006; 45:235-252.
2. Saloustros E, Mavroudis D, Georgoulias V. Paclitaxel and docetaxel in the treatment of breast cancer. Expert Opin Pharmacother. 2008; 9:2603-2616.
3. Saloustros E, Georgoulias V. Docetaxel in the treatment of advanced nonsmall-cell lung cancer. Expert Rev Anticancer Ther. 2008; 8:1207-1222.
4. Engels FK, Loos WJ, van der Bol JM, de Bruijn P, Mathijssen RH, Verweij J, Mathot RA. Therapeutic drug monitoring for the individualization of docetaxel dosing: A randomized pharmacokinetic study. Clin Cancer Res. 2011; 17:353-362.
5. Rudek MA, Sparreboom A, Garrett-Mayer ES, Armstrong DK, Wolff AC, Verweij J, Baker SD. Factors affecting pharmacokinetic variability following doxorubicin and docetaxel-based therapy. Eur J Cancer. 2004; 40:1170-1178.
6. Bruno R, Olivares R, Berille J, Chaikin P, Vivier N, Hammershaimb L, Rhodes GR, Rigas JR. Alpha-1-acid

glycoprotein as an independent predictor for treatment effects and a prognostic factor of survival in patients with nonsmall cell lung cancer treated with docetaxel. Clin Cancer Res. 2003; 9:1077-1082.
7. Marre F, Sanderink GJ, de Sousa G, Gaillard C, Martinet M, Rahmani R. Hepatic biotransformation of docetaxel (Taxotere) *in vitro*: Involvement of the CYP3A subfamily in humans. Cancer Res. 1996; 56:1296-1302.
8. Shou M, Martinet M, Korzekwa KR, Krausz KW, Gonzalez FJ, Gelboin HV. Role of human cytochrome P450 3A4 and 3A5 in the metabolism of taxotere and its derivatives: Enzyme specificity, interindividual distribution and metabolic contribution in human liver. Pharmacogenetics. 1998; 8:391-401.
9. Alexandre J, Rey E, Girre V, Grabar S, Tran A, Montheil V, Rabillon F, Dieras V, Jullien V, Herait P, Pons G, Treluyer JM, Goldwasser F. Relationship between cytochrome 3A activity, inflammatory status and the risk of docetaxel-induced febrile neutropenia: A prospective study. Ann Oncol. 2007; 18:168-172.
10. Bruno R, Hille D, Riva A, *et al*. Population pharmacokinetics/pharmacodynamics of docetaxel in phase II studies in patients with cancer. J Clin Oncol. 1998; 16:187-196.
11. Rigo-Bonnin R, Cobo-Sacristán S, Gonzalo-Diego N, Colom H, Munoz-Sánchez C, Urruticoechea A, Falo C, Alía P. Measurement of total and free docetaxel concentration in human plasma by ultra-performance liquid chromatography-tandem mass spectrometry. J Pharm Biomed Anal. 2016; 117:140-149.
12. Yamaguchi H, Fujikawa A, Ito H, Tanaka N, Furugen A, Miyamori K, Takahashi N, Ogura J, Kobayashi M, Yamada T, Mano N, Iseki K. A rapid and sensitive LC/ESI-MS/MS method for quantitative analysis of docetaxel in human plasma and its application to a pharmacokinetic study. J Chromatogr B Analyt Technol Biomed Life Sci. 2012; 893-894:157-161.
13. Du P, Han X, Li N, Wang H, Yang S, Song Y, Shi Y. Development and validation of an ultrafiltration-UPLC-MS/MS method for rapid quantification of unbound docetaxel in human plasma. J Chromatogr B Analyt Technol Biomed Life Sci. 2014; 967:28-35.
14. Andersen A, Warren DJ, Brunsvig PF, Aamdal S, Kristensen GB, Olsen H. High sensitivity assays for docetaxel and paclitaxel in plasma using solid-phase extraction and high performance liquid chromatography with UV detection. BMC Clin Pharmacol. 2006; 6:2.
15. Zufia Lopez L, Aldaz Pastor A, Aramendia Beitia JM, Arrobas Velilla J, Giraldez Deiro J. Determination of docetaxel and paclitaxel in human plasma by high-performance liquid chromatography: Validation and application to clinical pharmacokinetic studies. Ther Drug Monit. 2006; 28:199-205.
16. Cline DJ, Zhang H, Lundell GD, Harney RL, Riaz HK, Jarrah J, Li Y, Miyazaki M, Courtney JB, Baburina I, Salamone SJ. An automated nanoparticle-based homogeneous immunoassay for determining docetaxel concentrations in plasma. Ther Drug Monit. 2013; 35:803-808.
17. Navarrete A, Martínez-Alcázar MP, Durán I, Calvo E, Valenzuela B, Barbas C, Garcia A. Simultaneous online SPE-HPLC-MS/MS analysis of docetaxel, temsirolimus and sirolimus in whole blood and human plasma. J Chromatogr B Analyt Technol Biomed Life Sci. 2013; 921-922:35-42.
18. Grozav AG, Hutson TE, Zhou X, Bukowski RM, Ganapathi R, Xu Y. Rapid analysis of docetaxel in human plasma by tandem mass spectrometry with on-line sample extraction. J Pharm Anal. 2004; 36:125-131.
19. Parise RA, Ramanathan RK, Zamboni WC, Egorin MJ. Sensitive liquid chromatography-mass spectrometry assay for quantitation of docetaxel and paclitaxel in human plasma. J Chromatogr B Analyt Technol Biomed Life Sci. 2003; 789:231-236.
20. Kaldate RR, Haregewoin A, Grier CE, Hamilton SA, McLeod HL. Modeling the 5-fluorouracil area under the curve versus dose relationship to develop a pharmacokinetic dosing algorithm for colorectal cancer patients receiving FOLFOX6. Oncologist. 2012; 17:296-302.
21. Bouchet S, Titier K, Moore N, Lassalle R, Ambrosino B, Poulette S, Schuld P, Belanger C, Mahon FX, Molimard M. Therapeutic drug monitoring of imatinib in chronic myeloid leukemia: Experience from 1216 patients at a centralized laboratory. Fudam Clin Pharmacol. 2013; 27:690-697.
22. Alnaim L. Therapeutic drug monitoring of cancer chemotherapy. J Oncol Pharm Pract. 2007; 13:207-221.
23. Rudek MA, Sparreboom A, Garrett-Mayer ES, Armstrong DK, Wolff AC, Verweij J, Baker SD. Factors affecting pharmacokinetic variability following doxorubicin and docetaxel-based therapy. Eur J Cancer. 2004; 40:1170-1178.

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