Retrospective cohort study on the safety and efficacy of docetaxel in Japanese non-small cell lung cancer patients with nondialysis chronic kidney disease stage 3b or higher

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Abstract

Background: It has been reported that 20% of lung cancer patients have renal impairment caused by chronic kidney disease (CKD). Since docetaxel is predominantly excreted by the hepatobiliary system, it is administered to non-small cell lung cancer (NSCLC) patients with renal impairment. However, few clinical data are available on the toxicity and efficacy of docetaxel for patients with nondialysis renal impairment. Furthermore, some cases of tubular nephrotoxicity caused by docetaxel in NSCLC patients have been reported. Therefore, a retrospective cohort study was conducted to assess the influence of nondialysis CKD on the toxicity and efficacy of docetaxel in NSCLC patients.

Methods: NSCLC patients who received docetaxel were assessed for renal function, occurrence of adverse events and treatment efficacy.

Results: A total of 34 NSCLC patients who received docetaxel were studied. Eight (23.5%) patients had nondialysis CKD stage 3b or higher, with an estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m². Although the differences were not statistically significant, the starting dose of docetaxel (mg/m²) was lower (60 mg/m²; 37.5% vs. 69.2%) in patients with an eGFR <45 than that in patients with an eGFR ≥45. No significant association was observed between pretreatment eGFR and hematological and nonhematological toxicities. No significant difference was observed in the disease control rate (62.5% vs. 65.4%, \( P = 1.000 \)) or in the median overall survival (10.7 vs. 11.7, \( P = 0.735 \)) between patients with an eGFR <45 and those with an eGFR ≥45.

Conclusion: Docetaxel is a reasonable option for NSCLC patients with nondialysis CKD stage 3b or higher. Dose reduction of docetaxel is also a possibility for NSCLC patients with CKD stage 3b or higher.

Key points

Significant findings of the study: No significant association was observed between pretreatment eGFR (patients with an eGFR <45 or those with an eGFR ≥45) and hematological and nonhematological toxicities in NSCLC patients who received docetaxel.

What this study adds: Docetaxel is a reasonable option for NSCLC patients with nondialysis CKD stage 3b or higher.

Introduction

The antitumor action of docetaxel is due to stabilization of microtubules, which impairs mitosis and has significant activity against non-small cell lung cancer (NSCLC). Docetaxel is the standard of care for pretreated NSCLC patients and is a treatment option for patients with a performance status (PS) of two or higher and who are aged ≥70 or 75 years. Docetaxel is primarily metabolized to its inactive derivatives by the liver and is excreted into the
biliary system. Renal excretion is minimal (less than 5%). Therefore, according to review articles, docetaxel is identified as a therapeutic option in stage III or IV NSCLC patients with renal impairment. However, in Japanese clinical trials, patients with inadequate renal function (serum creatinine >1.1–1.5 mg/dL) are excluded. Additionally, clinical evidence on adverse events caused by docetaxel in patients with nondialysis-dependent renal impairment appears in only one report. In this report, 11 urothelial carcinoma patients with nondialysis-impaired renal function (post renal failure) were assessed for toxicity of docetaxel chemotherapy, after which docetaxel was safely administered. In contrast, Superfin et al. noted that, according to a review, few reports containing clinical data of docetaxel for patients with nondialysis renal impairment are available. It has been reported that 20% of lung cancer patients have renal impairment (estimated glomerular filtration rate [eGFR] < 60 mL/min/1.73 m²). A GFR below 60 mL/min/1.73 m² for three months or more indicates chronic kidney disease (CKD). The safety of docetaxel remains unclear for NSCLC patients with renal impairment caused by CKD. CKD stage 3b or higher (eGFR <45 mL/min/1.73 m²) was defined as advanced CKD because an eGFR <45 mL/min/1.73 m² is an independent risk factor for progression to end-stage renal disease (the condition in which dialysis or transplant is needed to stay alive) and all-cause mortality in the elderly (≥65) population. Furthermore, some cases of tubular nephrotoxicity induced by docetaxel in NSCLC patients have been previously reported. These observations suggest the possibility that adverse events caused by docetaxel are increased in patients with nondialysis CKD stage 3b or higher. Here, we performed a retrospective study to examine the influence of docetaxel in patients with NSCLC with nondialysis renal impairment. The purpose of the present study was to assess whether the safety and efficacy of docetaxel in Japanese NSCLC patients is associated with nondialysis CKD stage 3b or higher (eGFR <45 mL/min/1.73 m²).

Methods

Patients and clinical information

We analyzed nondialysis NSCLC patients who had received docetaxel at Harasanshin Hospital between May 2005 and May 2018. The patients were divided into two groups (moderate to severe renal impairment or not: eGFR <45 or ≥45 mL/min/1.73 m²). We retrospectively evaluated the clinical data for patient characteristics (age, sex, histology, epidermal growth factor receptor [EGFR] gene mutation status, previous treatment, evidence of distant metastasis, Eastern Cooperative Oncology Group PS, and smoking history), dosage and schedule of docetaxel chemotherapy, clinical course, and concurrent use of other drugs such as nonsteroidal anti-inflammatory drugs. The eGFR was calculated using the Japanese Society of Nephrology formula. We examined the data on hematologic and nonhematologic toxicities during the entire course of docetaxel chemotherapy. Severe toxicity was defined as hematological toxicity of grade ≥4 or nonhematological toxicity of grade ≥3 according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). Serum creatinine concentration was measured by an enzymatic method in blood samples collected in the morning. A change in serum creatinine concentration was defined as the maximum concentration over the entire course of docetaxel therapy minus the baseline value. Creatinine clearance (Ccr) was calculated using the Cockroft-Gault formula: creatinine clearance (mL/min) = (140 – age [years]) × weight [kg] × 0.85 (if female)/(72 × serum creatinine [mg/dL]). The efficacy was evaluated using a computed tomography (CT) scan in line with clinical practice using the Response Evaluation Criteria in Solid Tumors (version 1.1). This study was performed according to the opt-out method of our hospital website and in accordance with the Declaration of Helsinki; it was also approved by the Institutional Review Board of Harasanshin Hospital.

Statistical analysis

Differences in the changes in the serum creatinine level, eGFR, and Ccr were analyzed using unpaired Student’s t-tests, while differences in the frequency of toxicities and efficacy were determined using Fisher’s exact test. Overall survival (OS) was defined as the period from the start of docetaxel chemotherapy until death from any cause or the date of censoring at the last follow-up examination. Survival was evaluated by the Kaplan-Meier method, and differences in survival were analyzed by log-rank test. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). A P-value <0.05 was considered statistically significant.

Results

Patient characteristics

A total of 34 patients who had received docetaxel for NSCLC were studied. The demographics and clinical characteristics of the study participants are shown in Table 1. Eight (23.5%) patients had renal impairment with CKD stage 3b or higher (eGFR <45 mL/min/1.73 m²). The median age (77.5 vs. 69.5 years, P < 0.050) was higher, and
the Cr before docetaxel (mean of 32.077 vs. 67.883 mL/min, P < 0.00001) was significantly lower in patients with an eGFR <45 mL/min/1.73 m² than those with an eGFR ≥45 mL/min/1.73 m² (Table 1). One (12.5%) patient with an eGFR <45 mL/min/1.73 m² had an activating EGFR mutation, while four (15.4%) patients with an eGFR ≥45 mL/min/1.73 m² had activating EGFR mutations (Table 1). The proportion of patients who had received no prior systemic chemotherapy (62.5% vs. 15.4%, P < 0.050) was higher in patients with an eGFR <45 mL/min/1.73 m² than in those with an eGFR ≥45 (Table 1). The proportion of patients with hypertension (75.0% vs. 30.8%, P < 0.050) was higher in patients with an eGFR <45 mL/min/1.73 m² than in those with an eGFR ≥45 mL/min/1.73 m² (Table 1).

**Treatment exposure**

The starting docetaxel dose was lower (60 mg/m²; 37.5% vs. 69.2%, 50–59 mg/m²; 50.0% vs. 40–49 mg/m²; 12.5% vs. 0%, P = 0.112) for patients with an eGFR <45 mL/min/1.73 m² than for those with an eGFR ≥45 mL/min/1.73 m², although the differences were not statistically significant (Table 2). The mean docetaxel dose for each cycle and the mean number of docetaxel chemotherapy cycles were similar in patients with an eGFR <45 and an eGFR ≥45 mL/min/1.73 m². The proportion of patients who stopped docetaxel chemotherapy because of adverse events (25.0% vs. 34.6%, P = 1.000) was lower in patients with an eGFR <45 mL/min/1.73 m² than in those with an eGFR ≥45 mL/min/1.73 m², although the difference was not statistically significant (Table 2).

**Renal function and docetaxel-related toxicity**

No significant association was observed between pretreatment eGFR and renal toxicity as assessed by adverse events caused by docetaxel (Table 3). The frequency of an increase in the serum creatinine level of grade 1 was 50% in patients with an eGFR <45 and 73.1% in patients with an eGFR ≥45 mL/min/1.73 m². Furthermore, the changes in

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**Table 1** Patient characteristics

| eGFR (mL/min/1.73 m²) | ≥45 (n = 26, 76.5%) | <45 (n = 8, 23.5%) | P-value |
|-----------------------|---------------------|-------------------|---------|
| Gender (male/female)  | 21/5                | 6/2               | 1.000†  |
| Median age (range, year) | 69.5 (57–86)       | 77.5 (67–84)     | <0.050‡ |
| Performance status (ECOG) |                 |                   | 0.429†  |
| 0–1                   | 15 (57.7%)          | 3 (37.5%)         |         |
| ≥2                    | 11 (42.3%)          | 5 (62.5%)         |         |
| Smoking history       |                     |                   |         |
| Never-smoker          | 5 (19.2%)           | 1 (12.5%)         | 1.000†  |
| Smoker                | 21 (80.8%)          | 7 (87.5%)         |         |
| Histology             |                     |                   | 0.664†  |
| Adenocarcinoma        | 22 (84.6%)          | 8 (100%)          |         |
| Squamous cell         | 3 (11.6%)           | 0 (0%)            |         |
| NSCLC                 | 1 (3.8%)            | 0 (0%)            |         |
| Mean Cre (range, mg/dL) | 0.765 (0.500–1.200) | 1.443 (1.230–2.300) | <0.00001‡ |
| Mean Ccr (range, mL/min) | 67.883 (42.277–89.194) | 32.077 (14.486–39.227) | <0.00001‡ |
| EGFR gene mutation status |                 |                   | 0.805†  |
| Wild type             | 18 (69.2%)          | 7 (87.5%)         |         |
| exon 19 deletion      | 0 (0%)              | 1 (12.5%)         |         |
| exon 21 L858R         | 3 (11.6%)           | 0 (0%)            |         |
| exon 21 L861Q         | 1 (3.8%)            | 0 (0%)            |         |
| Unknown               | 4 (15.4%)           | 0 (0%)            |         |
| Prior systemic chemotherapy |             |                   | <0.050† |
| No                    | 4 (15.4%)           | 5 (62.5%)         |         |
| Yes                   | 22 (84.6%)          | 3 (37.5%)         |         |
| Complications         |                     |                   |         |
| Hypertension          | 8 (30.8%)           | 6 (75.0%)         | <0.050† |
| Diabetes              | 7 (26.9%)           | 1 (12.5%)         | 0.645†  |
| Cardiac diseases      | 2 (7.7%)            | 2 (25.0%)         | 0.229†  |
| Liver diseases        | 2 (7.7%)            | 0 (0%)            | 1.000†  |
| Hypoalbuminemia (<3.5 g/dL) | 7 (26.9%) | 4 (50.0%) | 0.388† |
| Regular use of NSAIDs | 13 (50.0%)          | 3 (37.5%)         | 0.693†  |

*P*-values <0.05 are shown in bold. †Fisher’s exact test. ‡Unpaired Student’s t-test.
Table 2 Docetaxel chemotherapy information

| eGFR (mL/min/1.73 m²) | ≥45 (n = 26) | <45 (n = 8) | Value |
|-----------------------|-------------|-------------|-------|
| The starting dose of docetaxel (mg/m²) | 0.112† | | |
| 60 | 18 (69.2%) | 3 (37.5%) | |
| 50–59 | 8 (30.8%) | 4 (50.0%) | |
| 40–49 | 0 (0%) | 1 (12.5%) | |
| The mean dose of docetaxel for each cycle (mg/m²) | 0.666‡ | | |
| 60 | 12 (46.2%) | 3 (37.5%) | |
| 50–59 | 13 (50.0%) | 4 (50.0%) | |
| 40–49 | 1 (3.8%) | 1 (12.5%) | |
| The mean number of docetaxel chemotherapy cycles | 2.615 | 2.875 | 0.696‡ |
| The reason for docetaxel completion | | | 1.000† |
| Progressive disease | 17 (65.4%) | 6 (75.0%) | |
| Adverse events | 9 (34.6%) | 2 (25.0%) | |

†Fisher’s exact test. ‡Unpaired Student’s t-test.

serum creatinine concentration (mean of 0.031 vs. 0.060 mg/dL, P = 0.655), eGFR (mean of −0.475 vs. −4.971 mL/min/1.75 m², P = 0.310) and Ccr (mean of −0.841 vs. −4.715 mL/min, P = 0.253) were not significantly different in patients with an eGFR <45 and an eGFR≥45 mL/min/1.73 m² (Fig 1). Although the frequency of grade 1–3 neutropenia was higher (100.0% vs. 57.7%, P < 0.050) in patients with an eGFR <45 than in those with an eGFR ≥45 mL/min/1.73 m², no significant difference was observed in the rates of grade 3 or higher nonhematological toxicity or in grade 4 hematological toxicity, including neutropenia and febrile neutropenia, between patients with an eGFR <45 and an eGFR ≥45 mL/min/1.73 m² (Table 3). No patients progressed to end-stage renal disease.

Efficacy

The rates of partial response (0% vs. 23.1%, odds ratio [OR] 0.971, 95% confidence interval [CI] 0.142–132.498, progressive disease (37.5% vs. 34.6%, OR 1.129, 95% CI 0.142–132.498, and partial response (65.4% vs. 62.5%, OR 0.666, 95% CI 0.112–6.997) between patients with an eGFR <45 and those with an eGFR ≥45 mL/min/1.73 m² (Table 3). No significant difference was observed in the median OS (11.7 vs. 11.7, P = 0.735) between patients with an eGFR <45 and those with an eGFR ≥45 mL/min/1.73 m² (Fig 2).

Table 3 Number (%) of patients with toxicities during docetaxel therapy according to eGFR status

| Toxicity | Grade | eGFR (mL/min/1.73 m²) | ≥45 (n = 26) | <45 (n = 8) | OR | 95% CI | P-value† |
|----------|-------|----------------------|-------------|-------------|----|-------|---------|
| Febrile neutropenia | ≥3 | 5 (19.2%) | 1 (12.5%) | 0.608 | 0.011–6.997 | 1.000 |
| | 1–3 | 19 (73.1%) | 7 (87.5%) | 2.518 | 0.214–132.498 | 0.645 |
| | 4 | 3 (11.5%) | 1 (12.5%) | 1.092 | 0.018–132.498 | 1.000 |
| Neutropenia | ≥3 | 15 (57.7%) | 8 (100.0%) | Inf | 0.971–Inf | <0.050 |
| | 1–3 | 7 (26.9%) | 0 (0.0%) | 0 | 0–2.152 | 0.160 |
| Anemia | 1–3 | 26 (100.0%) | 8 (100.0%) | — | — | — |
| Thrombocytopenia | 1–3 | 9 (34.6%) | 2 (25.0%) | 0.638 | 0.053–4.624 | 1.000 |
| Increased serum creatinine level | 1 | 19 (73.1%) | 4 (50.0%) | 0.381 | 0.053–2.639 | 0.388 |
| Elevation in T. Bil | 1 | 1 (3.8%) | 0 (0.0%) | 0 | 0–126.501 | 1.000 |
| Elevation in AST | 1–2 | 13 (50.0%) | 3 (37.5%) | 0.609 | 0.078–3.918 | 0.693 |
| | ≥3 | 1 (3.8%) | 0 (0.0%) | 0 | 0–126.501 | 1.000 |
| Elevation in ALT | 1–2 | 9 (34.6%) | 2 (25.0%) | 0.638 | 0.053–4.624 | 1.000 |
| Elevation in ALP | 1–2 | 13 (50.0%) | 2 (25.0%) | 0.344 | 0.029–2.407 | 0.257 |
| | ≥3 | 0 (0%) | 1 (12.5%) | Inf | 0.083–Inf | 0.235 |
| Elevation in γ-GTP | 1–2 | 10 (38.5%) | 1 (12.5%) | 0.237 | 0.005–2.329 | 0.228 |
| | ≥3 | 1 (3.8%) | 2 (25.0%) | 7.653 | 0.347–508.508 | 0.131 |
| Hyponatremia | 1 | 13 (50.0%) | 3 (37.5%) | 0.609 | 0.078–3.918 | 0.693 |
| | ≥3 | 4 (15.4%) | 2 (25.0%) | 1.798 | 0.132–16.641 | 0.609 |
| Hyperkalemia | 1–2 | 6 (23.1%) | 4 (50.0%) | 3.200 | 0.451–23.577 | 0.195 |
| Hypokalemia | 1–2 | 6 (23.1%) | 1 (12.5%) | 0.485 | 0.009–5.268 | 1.000 |
| | ≥3 | 3 (11.5%) | 1 (12.5%) | 1.092 | 0.018–16.382 | 1.000 |

†Fisher’s exact test. P-values <0.05 are shown in bold. No patients developed anemia grade 4, thrombocytopenia grade 4, increased serum creatinine grade ≥2, elevation in T.Bil grade ≥2, elevation in ALT grade ≥3, or hyperkalemia grade ≥3. ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; Inf, infinity; OR, odds ratio; T. Bil, total bilirubin; γ-GTP, γ-glutamyl transpeptidase.
Discussion

This study has shown that the incidence of toxicity associated with docetaxel was not significantly higher in NSCLC patients with nondialysis CKD stage 3b or higher (eGFR <45 mL/min/1.73 m²). Additionally, no significant difference was observed in tumor response and median OS between patients with an eGFR <45 and an eGFR ≥45 mL/min/1.73 m². Existing reviews6,7 of cancer chemotherapy in patients with nondialysis renal impairment referenced an article by Dimopoulos about docetaxel therapy,9 in which 11 urothelial carcinoma patients with impaired renal function caused by post renal failure who did not undergo dialysis were assessed for docetaxel toxicity. In this article, docetaxel was safely administered to them. To our knowledge, no other clinical article has reported the influence of docetaxel on patients with nondialysis-dependent renal impairment, although some articles have reported the influence of docetaxel on patients with dialysis-dependent renal impairment.20,21 This is the first study to assess the safety and efficacy of docetaxel in NSCLC patients with nondialysis CKD stage 3b or higher.

The presumed pathological entities of CKD are generally associated with aging, diabetes, hypertension, obesity, heart and blood vessel disease, as well as diabetic glomerulosclerosis and hypertensive nephrosclerosis.12 Older age, hypertension, treated diabetes, and smoking status are risk factors for CKD stage III or higher.22 In our study, the median age (77.5 vs. 69.5 years, P < 0.050) and the proportion of patients with hypertension (75.0% vs. 30.8%, P < 0.050) were significantly higher in patients with an eGFR <45 mL/min/1.73 m² than in those with an
The dose reduction of 60 to 50 mg/m² docetaxel is an option for NSCLC patients with CKD stage 3b or higher.

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Disclosure

No authors report any conflict of interest.

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