Nail Toxicity after Treatment with Docetaxel: A Prospective Analysis in Patients with Advanced Non-small Cell Lung Cancer

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Objective: Nail toxicity is one of the most frequent non-hematologic toxicities of docetaxel and often deteriorates patients’ quality of life, leading to treatment discontinuation. To define the incidence of nail change as well as its association with specific risk factors, we prospectively investigated data of 84 consecutive patients with advanced non-small cell lung cancer who received first-line docetaxel/cisplatin combination chemotherapy.

Methods: Chemotherapy-naïve patients were treated with docetaxel, either 3-weekly or weekly, in combination with cisplatin. All patients received adequate premedications including corticosteroids, antiemetics and intravenous hydration. Toxicity was evaluated using National Cancer Institute (NCI) CTCAE version 3.

Results: Twenty-two patients (26%) developed nail changes, including nine (11%) with grade 3. Nine patients who developed grade 3 nail changes (seven of whom received weekly docetaxel) were not able to complete planned chemotherapy despite topical and/or oral antibiotic treatment. Most occurrences of nail changes were diagnosed in patients who were treated with weekly schedule ($P = 0.02$). The number of chemotherapy cycles and cumulative docetaxel doses were strongly associated with the development of nail changes. The cumulative hazard of developing nail changes increased above 10% after 2.8 months up to 40% at 6 months. A multivariate analysis of factors associated with the development of nail changes identified the following to have independent adverse significance: weekly docetaxel administration (odds ratio, 0.084; 95% CI, 0.014–0.510; $P = 0.01$) and the number of chemotherapy cycles given (odds ratio, 0.232; 95% CI, 0.067–0.805; $P = 0.02$).

Conclusion: Nail changes occur with more frequent and prolonged use of docetaxel.

Key words: docetaxel – nail changes – chemotherapy

INTRODUCTION

Docetaxel, a semisynthetic taxane with a broad spectrum of antitumor activity (1), has shown activity against non-small cell lung cancer (NSCLC). The toxicity profile of docetaxel is generally described as manageable, with neutropenia being the main one (2). Neutropenia occurs in a substantial number of patients treated with a standard 3-weekly docetaxel regimen. Management of severe neutropenia, with or without infection, often includes hospitalization, hematopoietic growth factors and intravenous antibiotics. To reduce severe myelosuppression, alternative docetaxel schedules with weekly administration were investigated (3–7). Most randomized studies undertaken to date have been performed in a second-line setting, and in most of these, weekly docetaxel suggested similar activity against advanced NSCLC.

Myelosuppression associated with the use of weekly docetaxel was infrequent. In contrast, cumulative toxicities including fatigue, mucositis, excessive tearing and skin/nail changes were prominent. We recently compared 3-weekly and weekly docetaxel, both in combination with cisplatin, in...
previously untreated patients with advanced NSCLC (8). To define the incidence of nail change as well as its association with specific risk factors, we analyzed prospectively data of all patients enrolled in the trial.

**PATIENTS AND METHODS**

Patients were eligible if they were 75 years of age or younger with cytologically or histologically confirmed NSCLC that was advanced (stage IIIb with malignant pleural effusion and stage IV) or recurrent and had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 and adequate bone marrow, hepatic and renal function. Patients were enrolled only if they had received no prior chemotherapy, or if prior therapy consisted of adjuvant chemotherapy which had been completed more than 6 months before the study entry. Exclusion criteria were as follows: severe comorbidities, known history of anaphylaxis of any origin, or a history of any other primary tumors except adequately treated in situ carcinoma of the uterine cervix and basal or squamous cell skin cancer. Patients were required to give written informed consent before inclusion in the study. The study protocol was approved by Gil Medical Center institutional review board and the study was conducted in accordance with the principles of the Declaration of Helsinki.

Patients were randomly assigned to receive docetaxel 3-weekly (75 mg/m² on day 1 every 3 weeks) or weekly (35 mg/m² on days 1, 8 and 15 every 4 weeks), in combination with cisplatin 75 mg/m² on day 1. In both regimens, premedications included adequate antiemetic therapy and dexamethasone before each docetaxel infusion (15 mg given at −12, 0 and +12 h of every docetaxel administration in the 3-weekly regimen and at 0 h in the weekly regimen). Docetaxel was infused for 1 h. Cisplatin was mixed with normal saline 150 ml and given with pre- and post-treatment intravenous hydration and mannitol diuresis. Chemotherapy was repeated for a maximum of six cycles, assuming no unacceptable toxicities or evidence of disease progression were seen. Supportive care, including administration of blood transfusions, use of hematopoietic growth factors, antiemetics and analgesics, was provided if judged appropriate by investigators.

Toxicities were evaluated during treatment according to the National Cancer Institute criteria (NCI-CTCAE) version 3. Three-weekly regimen patients were seen on day 1 every 3 weeks. In the weekly regimen, clinical adverse events and blood counts were checked on day 1 and day 15. Time to the occurrence of nail changes was calculated from the date of initiation of therapy to the day on which the toxicity was first noticed.

Comparisons were made using Mann–Whitney U test for non-normally distributed data and paired t-tests for normally distributed data. The χ²-square test was used for comparison of categorical variables. To examine the impact of clinical and treatment variables on the incidence of nail toxicity, multiple logistic regression models were used. Covariates included age, gender, ECOG performance status (0–1 versus 2), disease status (stage IIIb versus IV) and chemotherapy schedules (3-weekly versus weekly). Factors affecting the time to the occurrence of nail changes were also evaluated using these covariates, number of chemotherapy cycles administered and cumulative dose of docetaxel. All P values were two-sided, with <0.05 indicating statistical significance.

**RESULTS**

Of a total of 86 patients who entered the study, two patients were excluded because they did not receive protocol therapy owing to rapid deterioration of general condition. The baseline and treatment characteristics are listed in Table 1. Forty-one patients were treated with 3-weekly docetaxel plus cisplatin, whereas 43 patients were treated with weekly docetaxel plus cisplatin. The median number of chemotherapy cycles administered to the whole patients was 297 (median, 3; range, 1–6) and median treatment duration was 2.8 months (95% CI, 2.1–3.6 months). Patients in the 3-weekly regimen received a median of four (range, 1–6) cycles and weekly regimen received a median of three (range, 1–6) cycles.

Twenty-two patients (26%) were diagnosed with nail changes during treatment: 13 patients had grade 1 or 2 and 9

<table>
<thead>
<tr>
<th>Table 1. Patient and treatment characteristics</th>
<th>All patients</th>
<th>Nail changes</th>
<th>P value</th>
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<tbody>
<tr>
<td></td>
<td>Yes (n = 22)</td>
<td>No (n = 62)</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
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<tr>
<td>Male</td>
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<tr>
<td>Female</td>
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<td>Adenocarcinoma</td>
<td>53</td>
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<tr>
<td>Squamous cell carcinoma</td>
<td>31</td>
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<tr>
<td>Stage</td>
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<tr>
<td>IIIb</td>
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<td>2</td>
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<tr>
<td>Weekly</td>
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(11%) had grade 3 nail changes. Overall, 33 patients discontinued chemotherapy owing to toxicity: 23 patients without nail changes and 10 with nail changes. Nine patients who developed grade 3 nail changes (7 of whom received weekly docetaxel) were not able to complete the planned six cycles of chemotherapy. Management of all patients with nail changes was conservative. Only minor debridement procedures were attempted to reduce pain and accompanying infections. Topical antiseptics and/or oral analgesics were recommended and, in some patients, oral and/or transdermal narcotics were prescribed. Seven patients with grade 3 nail changes received oral antibiotics. Treatment with antibiotics resulted in transient improvement, but only one patient showed sustained improvement of nail changes after a week of antibiotic treatment. The other six had persistent nail changes, resulting in a nail extraction.

There was no association of the development of nail changes with gender ($P = 0.57$), age ($P = 0.33$), histologic diagnosis ($P = 0.28$), stage ($P = 0.90$), or ECOG performance status ($P = 0.66$). Most occurrences of nail changes were diagnosed in patients who were treated with weekly docetaxel plus cisplatin ($P = 0.02$). Interestingly, only two out of 41 patients (5%) who received 3-weekly docetaxel developed grade 3 nail changes. Chemotherapy cycles and cumulative docetaxel doses were strongly associated with the development of nail changes (Table 2). Patients who developed nail changes received a median number of five cycles (range, 1–6), whereas the respective number for patients without nail changes was three cycles (range, 1–6; $P = 0.01$). The association of nail changes with time of chemotherapy duration showed a marginal statistical significance (3.5 versus 2.4 months; $P = 0.18$).

Figure 1 shows the time to the occurrence of nail changes for all patients. The cumulative hazard of developing nail changes increased above 10% after 2.8 months, up to 40% at 6 months. For type of docetaxel administration schedules, we compared the cumulative hazard rates between patients who received 3-weekly docetaxel versus those who received weekly docetaxel. The chance of developing nail changes was significantly higher in the weekly regimen ($P = 0.02$; Fig 2). The likelihood was 5% within the first month of treatment, increasing to 60% at 6 months for weekly docetaxel; whereas the likelihood among the 3-weekly regimen was 0% for the first month, increasing to only 21% after 6 months of treatment.

A multivariate analysis of factors associated with the occurrence of nail changes identified the following to have independent adverse significance: weekly docetaxel administration (odds ratio, 0.084; 95% CI, 0.014–0.510; $P = 0.01$) and the number of chemotherapy cycles (odds ratio, 0.232; 95% CI, 0.067–0.805; $P = 0.02$).

**DISCUSSION**

Docetaxel has been approved for the treatment of a variety of solid tumors, including those arising from head and neck, esophagus, stomach, breast and lung (9–13). In particular, docetaxel is the only agent that is approved for

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**Table 2. Incidence of nail changes related to docetaxel administration**

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Nail changes</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes ($n = 22$)</td>
<td>No ($n = 62$)</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy cycle</td>
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</tr>
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<tr>
<td>Range</td>
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<td>1–6</td>
<td>1–6</td>
</tr>
<tr>
<td>Chemotherapy duration, months</td>
<td>2.8</td>
<td>3.5</td>
<td>2.4</td>
</tr>
<tr>
<td>95% CI</td>
<td>2.7–4.2</td>
<td>1.7–3.0</td>
<td></td>
</tr>
<tr>
<td>Docetaxel doses, mg/m²</td>
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<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Median</td>
<td>263</td>
<td>345</td>
<td>218</td>
</tr>
<tr>
<td>Range</td>
<td>35–573</td>
<td>70–561</td>
<td>35–573</td>
</tr>
</tbody>
</table>

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**Figure 1.** Time to the occurrence of nail changes among 84 patients treated with docetaxel plus cisplatin.

**Figure 2.** Cumulative hazard of developing nail changes according to treatment schedules (solid line, 3-weekly administration of docetaxel; dotted line, weekly administration of docetaxel).
first- and second-line chemotherapy for NSCLC. The efficacy of docetaxel for the treatment of advanced NSCLC was well established by several randomized clinical trials (14–17). In early phase I studies, the most frequent dose-limiting toxicity with docetaxel therapy was myelosuppression, primarily neutropenia (2). Non-hematologic toxicities included neuropathy, fatigue, gastrointestinal disturbances, mucositis, hypersensitivity, fluid retention and skin/nail changes. To reduce docetaxel-induced fluid retention and hypersensitivity, corticosteroid premedication is frequently administered (18).

In the mid 1990s, studies have demonstrated that the weekly administration may alter the toxicity profiles of docetaxel (19,20). The underlying presumption is that, with lower doses more frequently, toxicity may be decreased while maintaining the dose intensity necessary for antitumor activity. With weekly docetaxel, acute toxicities, in particular myelosuppression, are uncommon. In contrast, cumulative toxicities are much more prominent. The most frequent adverse events are fatigue, alopecia, excessive tearing and skin/nail changes (21).

Docetaxel-induced nail changes, which include paronychia, onycholysis and pyogenic granuloma formation, were initially considered mild and merely bothersome adverse events. However, currently it is recognized to be a complaint that can particularly affect quality of life (QOL), leading to treatment discontinuation (22,23). It should be noted that, in acknowledgment of the severe impact on patients’ QOL, the latest version of the NCI CTCAE (version 3.0) included grade 3 nail changes (interfering with daily life) whereas version 2 only included rating up to grade 2. It is likely that the previously reported severity of nail changes is underestimated as a result of the lack of more specific rating. Nail changes are usually asymptomatic and will improve with drug withdrawal, but may persist in some patients (24). In a review by Minisini et al. (25), who performed a Medline search of the literature, the overall incidence of taxane-induced nail changes is as high as 44%. Recently, Scott et al. reported that docetaxel-induced nail changes might be reduced by using an Elasto-Gel frozen glove during docetaxel infusion (26). However, once developed, treatment includes only conservative measures. The risk of developing taxane-induced nail changes may be related to the dosing schedule and the cumulative dose (25,27,28). Although these reports make the association of weekly docetaxel administration and the development of nail changes likely, the true incidence and risk factors are unknown. We attempted to evaluate docetaxel-induced nail changes prospectively in a randomized clinical trial. Currently, there are several randomized clinical trials which have compared weekly and 3-weekly docetaxel for either metastatic breast cancer or prostate cancer and which have reported on difference incidences of nail changes between the two treatments. For instance, Tabernero et al. (23) reported that although the incidence of low grade nail changes was not different for weekly or 3-weekly docetaxel in metastatic breast cancer patients, nail changes substantially affected the QOL in the weekly treatment regimen and were the major reason for withdrawal. Similarly, in the prostate cancer phase III trial (22), major reasons for treatment withdrawal also included fatigue and nail changes.

The incidence of nail changes in patients treated with docetaxel was 26%, and severe (grade 3) nail changes in 11% of patients. Our analysis indicated that more frequent and prolonged exposure to the drug, regardless of the dose, is the most significant risk factor for the development of docetaxel-induced nail changes. Furthermore, patients who were treated with weekly docetaxel experienced more severe forms of nail changes. The difference in the hazard between 3-weekly and weekly docetaxel was significant, indicating that nail changes might be prevented or minimized with 3-weekly administration of docetaxel.

Apart from docetaxel schedule, the duration of chemotherapy exposure have been implicated in the development of nail changes. Most patients developed nail changes after treatment of three cycles or more. Randomized trials suggested that the duration of chemotherapy in advanced NSCLC should be brief (3 or 4 cycles) and that prolonged therapy could lead to cumulative toxicity, without no proven advantage in efficacy (29,30).

One may argue that all patients in the current study were treated with docetaxel and cisplatin combination chemotherapy, and we could not statistically distinguish which agent induced the toxicity. Randomized studies and meta-analysis have shown that cisplatin-containing regimens are significantly more toxic than those without cisplatin, owing to excessive non-hematologic toxicity of cisplatin (31,32). Our study is also limited in that we perform toxicity evaluation (i.e. clinic visits) once per chemotherapy cycle in the 3-weekly regimen (on day 1) and twice in the weekly regimen (on days 1 and 15). Lower incidence of severe nail toxicity was in part owing to the fact that weekly clinic visits were not done for the 3-weekly regimen.

In conclusion, nail toxicity is a complication that is correlated with frequent and prolonged use of docetaxel. Recently, because of less severe myelosuppression, weekly docetaxel has become an attractive option in the management of advanced NSCLC. Several randomized trials showed similar efficacy and significantly less myelosuppression with weekly docetaxel (3–7). However, this benefit comes at the cost of cumulative increase in late toxicities including nail changes and no trials have directly compared docetaxel schedules in first-line setting. In view of data reported here, caution is required for prolonged use of weekly docetaxel. Furthermore, the requirement for frequent infusion schedule necessitates frequent patient visit to oncology clinics, which may result in a reduced compliance and compromised QOL. Treatment with weekly docetaxel should only be considered as an alternative for patients who are unlikely to tolerate the standard 3-weekly schedule.
Acknowledgment

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Conflict of interest statement

None declared.

References