Clinical case

Taxane-induced nail changes: incidence, clinical presentation and outcome

A. M. Minisini¹, A. Tosti², A. F. Sobrero³, M. Mansutti⁴, B. M. Piraccini², C. Sacco⁴ & F. Puglisi¹*

¹Clinical Oncology, University of Udine, Udine; ²Department of Dermatology, University of Bologna, Bologna; ³Clinical Oncology, San Martino Hospital, Genoa; ⁴Clinical Oncology, General Hospital, Udine, Italy

Received 5 June 2002; accepted 3 July 2002

The clinical characteristics of nail changes in seven patients receiving taxane-containing chemotherapy are described. They include nail pigmentation, subungual hematoma, Beau's lines and onycholysis and subungual suppuration.

The incidence of such changes (ranging from 0% to 44%) is reviewed from a Medline search of the literature.

Key words: chemotherapy, nail changes, side-effects, taxanes

Introduction

The taxanes, paclitaxel (P) (Taxol®; Bristol-Myers Squibb Company; Princeton, NJ, USA) and docetaxel (D) (Taxotere®; Aventis Pharmaceuticals; Collegeville, PA, USA), were introduced in the late 1980s. Since then both drugs have proved to be effective in the treatment of a variety of solid tumors including breast, ovarian, lung and bladder cancers [1, 2]. Taxanes exert their cytotoxic effect by reversibly binding the β-subunit of tubulin, thereby inducing tubulin polymerization and inhibiting microtubule depolymerization [3, 4]. A balance between polymerization and depolymerization is needed for normal microtubule function. Taxanes disrupt this balance, leading to arrest at the G2/M phase of the cell cycle.

P and D are administered intravenously and their pharmacokinetics show a large volume of distribution and a rapid elimination from the plasma with a short terminal half-life of 5 and 12 h, respectively [5, 6]. Both compounds are metabolized by the liver, and require dose adjustment for patients with hepatic dysfunction [7]. They are usually administered every 3 weeks; however, weekly administration is also common. Taxanes have a predictable toxicity profile on an every-3-week basis [8]. The standard dose of P according to this schedule is 175 mg/m² (3-h infusion) with the most common side-effects including myelosuppression, neuropathy, alopecia, hypersensitivity reactions and myalgias/arthralgias.

In women with advanced breast cancer, D is usually administered as a 1-h intravenous infusion at 75–100 mg/m² every 3 weeks. The dose-limiting toxicity is myelosuppression and a 90–95% incidence of grade 3/4 neutropenia is reported in most published series. Other side-effects include asthenia/fatigue, alopecia, skin reaction, stomatitis, hypersensitivity reactions and a fluid-retention syndrome.

Recently, weekly schedules of taxanes have been proposed as a possible therapeutic alternative with the aim of minimizing the acute toxicity while enhancing dose density [9–12]. However, to date results are awaited from randomized trials comparing the clinical effect of every-3-week and weekly schedules. The weekly administration significantly alters the side-effect profile of the agents reducing the incidence and grade of myelosuppression. Neuropathy becomes the most common side-effect of P when administered at 80 mg/m²/week [11]. For weekly D the usual dose ranges between 36 and 40 mg/m² and fatigue/asthenia becomes the dose-limiting toxicity [9].

Cutaneous toxicity has been reported with taxanes and includes erythema and desquamation, involving primarily the hands. Nail changes are described in different series and case reports, but the real incidence of this side-effect is probably underestimated. In addition, a wide clinical spectrum of nail disorders is possible and constitutes the focus of this review.

Case reports

Case 1

At the end of six cycles of adjuvant cyclophosphamide (C), epirubicin (E) and 5-fluorouracil (5-FU) for node-positive breast cancer, a 48-year-old woman developed locoregional relapse and systemic metastases. She received seven courses of weekly 40 mg/m² D producing disease stabilization. Infusional 5-FU was added. After two cycles of this two-drug combination the patient developed onycholysis and subungual hemorrhagic bullae (Figure 1). The treatment was not discontinued and the patient received an additional four courses of D/5-FU. The cumulative dose was 720 mg/m² D and 8400 mg/m² 5-FU.
Nail suppuration with right arm lymphedema occurred about 1 month after the discontinuation of D. A microbiological test showed the presence of *Enterobacter cloacae* and *Staphylococcus aureus*; the patient was treated with ciprofloxacin 500 mg b.i.d. and fluconazole with complete recovery 1 month later.

**Case 2**

After three lines of palliative hormonal treatments and four lines of chemotherapy for advanced breast cancer, a 55-year-old women was treated with D 35 mg/m²/week. After 12 courses of weekly D she presented Beau’s lines and onycholysis with suppuration of fingers and toenails. Microbiological culture demonstrated the presence of infection by *Staphylococcus warnerii*, which was treated with ciprofloxacin 500 mg b.i.d. with full recovery.

**Case 3**

A 55-year-old man with advanced gastric cancer was treated with E/cisplatin/F, receiving a cumulative dose of 585 mg/m² E, 680 mg/m² cisplatin and 50000 mg/m² 5-FU. Because of disease progression he received 40 mg/m² D on days 1, 8 and 15 every 4 weeks. During the third cycle he developed bilateral finger paresthesias and after the following course hemorrhagic onycholysis appeared (Figure 2). Electromyography demonstrated a partial alteration of terminal sensitive fibers with no motor impairment. After discontinuation of D there was a slow and partial improvement of nail changes.

**Case 4**

A 51-year-old female received adjuvant chemotherapy for breast cancer including 120 mg/m² E every 3 weeks for four courses, followed by 100 mg/m² D every 3 weeks for four courses and then four additional courses of C/methotrexate/F. While receiving D she experienced hand and foot paresthesias and developed Beau’s lines of the fingernails. The number of Beau’s lines for each nail corresponded to the number of D courses (Figure 3).

**Case 5**

A 61-year-old female with lung metastases from breast cancer received palliative chemotherapy with 75 mg/m² D, 75 mg/m² E every 3 weeks in combination with trastuzumab 2 mg/kg weekly for eight courses. After five courses she developed paresthesias of the fingers and toes. Electromyography was unremarkable. In addition, Beau’s lines appeared in fingernails with their number corresponding to the total number of D courses.

**Cases 6 and 7**

Two other cases of patients with nail changes during therapy with P were referred to the Department of Dermatology, University of Bologna, Bologna, Italy (Figures 4 and 5).

**Discussion**

Nail abnormalities are a common side-effect of systemic chemotherapy. The clinical presentation of drug-induced nail changes depends on duration and severity of the toxic damage as well as on the nail constituent involved.

In fact the nail consists of a horny product, the nail plate, and four proliferating epithelia, which are responsible for nail plate function.
production and growth correction. These include the nail matrix, the nail bed, the proximal nail fold and the hyponychium.

The nail matrix epithelium is formed by highly proliferating cells that differentiate and keratinize to produce the nail plate. The epithelium contains numerous melanocytes that are normally quiescent. The nail matrix epithelium is very susceptible to toxic noxae. An acute damage of the matrix, as it may occur during systemic chemotherapy, results in a defective nail plate production. The most typical changes are Beau’s lines and onychomadesis (which are signs of an arrest in the epithelial proliferation) or leukonychia, which indicates an abnormal keratinization. Toxicity to the matrix epithelium often results in melanocyte activation with nail plate pigmentation and melanonychia.

The nail bed epithelium is a very thin epithelium that is mainly responsible for the adhesion of the nail plate to the underlying structures. An acute toxic damage to the nail bed causes nail plate detachment with onycholysis.

The proximal nail fold and the hyponychium contribute to maintain correct nail growth and protect the nail matrix from the environment. A toxic damage to the proximal nail fold results in paronychia with subsequent nail matrix exposure and damage.

Taxane probably cause nail changes more commonly than other drugs.

A Medline search of the literature using the terms ‘nail’, ‘docetaxel’ and ‘paclitaxel’ indicated an incidence of nail toxicity ranging from 0% to 44% (Table 1). The majority of studies citing nail changes among drug induced toxicity are related to D use [13–23, 25–30] whereas only two trials describe nail disease as part of P-related side-effects [24, 31].

In addition, several case reports in the literature relate to D- and/or P-induced onycopathy [31–46].

Nail abnormalities related to taxanes include nail pigmentation, splinter hemorrhage and subungual hematoma, Beau’s lines, acute paronychia and onycholysis.

Nail abnormalities occurring during taxane treatments are in most cases not serious but hemorrhagic onycholysis and subungual abscesses can occur producing important morbidity. The latter side-effects are quite exclusive of taxane therapy and can cause potentially severe complications since patients may become neutropenic during chemotherapy, enhancing the risk of sepsis.

Possible explanations for subungual hematoma and hemorrhagic onycholysis are the taxane-induced thrombocytopenia and vascular abnormalities.
Wasner et al. [33] suggest that the integrity of peripheral neural fibers is necessary for the development of nail abnormalities. Two neurotropic mechanisms may be postulated: release of neuropeptides by activation of nociceptive C-fibers, as in the case of neurogenic inflammation, or release of prostaglandins by sympathetic postganglionic fibers. The authors [33] describe a case of nail disorder improved by cycloxygenase-2 inhibitor supporting the second hypothesis. In the third case reported in our work, electromyography showed partial dysfunction of sensitive peripheral nerves with no motor impairment. However, in the fifth case report, electromyography was not considered abnormal.

In conclusion, clinicians should be aware of these important side-effects of taxanes that could lead to substantial subjective toxicity with impairment of quality of life and discontinuation of chemotherapy. Studies are needed to understand better the pathogenesis of taxane-induced subungual hemorrhages and abscesses.

References

Table 1. Incidence of nail changes during treatments with docetaxel or paclitaxel

<table>
<thead>
<tr>
<th>Trial</th>
<th>Chemotherapeutic regimen</th>
<th>No. of patients</th>
<th>Percent with nail changes</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase II trial, metastatic breast cancer</td>
<td>D 40 mg/m²/week</td>
<td>37</td>
<td>27</td>
<td>[13]</td>
</tr>
<tr>
<td>Phase II trial, metastatic breast cancer</td>
<td>A 50 mg/m², C 500 mg/m², D 75 mg/m², q21</td>
<td>54</td>
<td>20</td>
<td>[14]</td>
</tr>
<tr>
<td>Phase II trial, advanced NSCLC</td>
<td>D 100 mg/m² q21</td>
<td>173</td>
<td>20</td>
<td>[15]</td>
</tr>
<tr>
<td>Phase II trial, stage IIIb–IV NSCLC</td>
<td>D 100 mg/m² q21</td>
<td>70</td>
<td>29</td>
<td>[16]</td>
</tr>
<tr>
<td>Phase II trial, stage IIIb–IV NSCLC</td>
<td>D 100 mg/m² q21</td>
<td>27</td>
<td>19</td>
<td>[17]</td>
</tr>
<tr>
<td>Phase I trial, metastatic breast cancer</td>
<td>D 40–55 mg/m² q14</td>
<td>16</td>
<td>44</td>
<td>[18]</td>
</tr>
<tr>
<td>Phase III trial, metastatic breast cancer</td>
<td>D 100 mg/m² q21</td>
<td>140</td>
<td>33</td>
<td>[19]</td>
</tr>
<tr>
<td>Phase II trial, prostate cancer</td>
<td>Estramustine 280 mg × 5 q6h, D 70 mg/m² q21</td>
<td>22</td>
<td>5</td>
<td>[20]</td>
</tr>
<tr>
<td>Phase III trial, metastatic breast cancer</td>
<td>D 100 mg/m² q21</td>
<td>159</td>
<td>44</td>
<td>[21]</td>
</tr>
<tr>
<td>Phase II trial, metastatic breast cancer</td>
<td>D 75 mg/m², A 50 mg/m², C 500 mg/m² q21</td>
<td>54</td>
<td>0</td>
<td>[22]</td>
</tr>
<tr>
<td>Phase I trial, advanced solid tumors</td>
<td>D 60–75 mg/m², ifosfamide 2.5–4 g/m² q21</td>
<td>34</td>
<td>24</td>
<td>[23]</td>
</tr>
<tr>
<td>Phase II trial, metastatic breast cancer</td>
<td>P 90 mg/m²/week × 6 q9 weeks</td>
<td>39</td>
<td>25</td>
<td>[24]</td>
</tr>
<tr>
<td>Phase I trial, advanced solid tumors</td>
<td>D 55–100 mg/m², cisplatin 50–100 mg/m² q21</td>
<td>63</td>
<td>40</td>
<td>[25]</td>
</tr>
<tr>
<td>Phase II trial, advanced NSCLC</td>
<td>D 100 mg/m² q21</td>
<td>29</td>
<td>31</td>
<td>[26]</td>
</tr>
<tr>
<td>Phase II trial, advanced soft tissue sarcomas</td>
<td>D 100 mg/m² q21</td>
<td>28</td>
<td>32</td>
<td>[27]</td>
</tr>
<tr>
<td>Phase II trial, metastatic breast cancer</td>
<td>D 100 mg/m² q21</td>
<td>32</td>
<td>41</td>
<td>[28]</td>
</tr>
<tr>
<td>Phase II trial, metastatic breast cancer</td>
<td>D 35 mg/m²/week × 6 q8 weeks</td>
<td>35</td>
<td>26¹</td>
<td>[29]</td>
</tr>
<tr>
<td>Pool of phase II trials, metastatic breast cancer</td>
<td>D 100 mg/m² as starting dose</td>
<td>228</td>
<td>35</td>
<td>[30]</td>
</tr>
<tr>
<td>Single center experience, metastatic breast cancer</td>
<td>P 100 mg/m²/week, more than six cycles</td>
<td>21</td>
<td>24⁷</td>
<td>[31]</td>
</tr>
</tbody>
</table>

¹No distinction between skin and nail toxicity.
²Only onycholysis reported.
A, doxorubicin; C, cyclophosphamide; D, docetaxel; P, paclitaxel; NSCLC, non-small-cell lung cancer.


