Docetaxel (Taxotere) Associated Scleroderma-Like Changes of the Lower Extremities

A Report of Three Cases

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Background. **Docetaxel (Taxotere) is a microtubule-stabilizing agent that is potentially important in chemotherapy for a variety of malignancies.**

Methods. **A clinical study of the cutaneous reactions experienced by a group of patients receiving docetaxel chemotherapy was undertaken. Patients were examined before initiation of therapy, before and after each cycle of therapy, and were followed subsequent to the completion of docetaxel chemotherapy.**

Results. **Three patients developed diffuse lower extremity edema (3–18 kg) and subsequent scleroderma-like changes after receiving multiple cycles of docetaxel therapy. These patients had different underlying malignancies and dissimilar prior therapy. Rheumatoid factor, antinuclear antibodies, anticentromere, and topoisomerase antibodies were not present in any patient. The diffuse lower extremity edema did not resolve with diuretic therapy. Cutaneous biopsies in two patients revealed diffuse sclerosis. One patient had a normal lymphangiogram during the edematous phase. Discontinuation of docetaxel correlated with resolution of edema and softening of the skin.**

Conclusion. **The etiology of the scleroderma-like skin changes is unclear but appears to be either a toxic effect of docetaxel or an effect of polysorbate 80 (Tween 80), the vehicle for docetaxel. *Cancer* 1995;76:110–5.**

Key words: docetaxel, Taxotere, toxicity, scleroderma, scleroderma-like.

Docetaxel (Taxotere; RP 56976; NSC 628503; N-debenzoyl-N-tert-butoxycarbonyl-10-deacetyl taxol) (Rhone Poulenc Rorer, Collegeville, PA) is a microtubule stabilizing agent that is obtained by hemisynthesis from a noncytotoxic precursor extracted from the needles of the European yew tree, Taxus baccata-L.[1] Docetaxel is a potentially important chemotherapeutic agent that has produced a substantial number of responses in patients with refractory malignancies reported in Phase I trials.[2–5] Unlike many plant-derived antimicrotubule agents (e.g., colchicine, podophyllotoxin, or the vinca alkaloids) that inhibit microtubule assembly, taxanes, such as docetaxel and paclitaxel (Taxol, Bristol-Meyers Squibb Co., Princeton, NJ), promote the assembly of tubulin and stabilize the formed polymers against depolymerization. Bundles of microtubules thus accumulate, interfering with cell division and resulting in cell death.[6,7] Neutropenia has been the dose-limiting effect experienced with the use of docetaxel, with mucositis reported in some schedules.[2–5] Acute cutaneous reactions and alopecia have also been described with docetaxel.[8] In the current study, we report three cases of scleroderma-like changes of the lower extremities observed in patients receiving multiple cycles of docetaxel therapy (Table 1).

Case Reports

Patient 1

A 46-year-old white male was diagnosed with leiomyosarcoma of the duodenum in 1984. He underwent a Whipple's procedure, and there was no clinical or histologic evidence of metastasis. Since surgery, he has required daily insulin injections and oral pancreatic enzyme supplementation. In November 1991, biopsy-proven metastases in the liver were doc-

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Table 1. Patient Profiles

	Patient 1	Patient 2	Patient 3
Age/sex/race	46/male/white	63/male/white	67/female/white
Tumor	Leiomyosarcoma	Melanoma	Bronchoalveolar lung
Prior treatment	Whipple's procedure; adriamycin, dacarbazine	Local radiation therapy	Right middle lobectomy
Total taxotere courses	13	7	7
Cutaneous reactions	C1, alopecia, erythrodysesthesia C2, onycholysis C5, lower extremity edema C7, sclerodermatous change of lower extremities	C1, alopecia, erythrodysesthesia C3, onycholysis, lower extremity edema C5, sclerodermatous change of lower extremities	C1, alopecia, erythrodysesthesia C2, onycholysis C4, lower extremity edema C5, sclerodermatous change of lower extremities
Baseline motion of knees and ankles	Knee flexion to 135° Ankle dorsiflexion to 20°	Knee flexion to 135° Ankle dorsiflexion to 20°	Knee flexion to 135° Ankle dorsiflexion to 20°
Joint motion impairment on taxotere	Knee flexion to 110° Ankle dorsiflexion to 10°	Knee flexion to 90° Ankle dorsiflexion to 10°	Knee flexion to 120° Ankle dorsiflexion to 10°
Residual impairment off taxotere	Knees, none Ankles, dorsiflexion to 10° Skin, moderate sclerodermatous change of the lower extremities	Knees, none Ankles, none Skin, moderate sclerodermatous changes of the lower extremities	Knees, none Ankles, none Skin, none
Laboratory evaluation*	Normal/negative	Normal/negative	Normal/negative
Skin biopsy	Consistent with scleroderma	Consistent with scleroderma	Not performed

* Complete blood count, chemistry panel, urinalysis, Westergren sedimentation rate, C-reactive protein, thyroid panel, serum complement levels, rheumatoid factor, and antinuclear, extractable nuclear, antitopoisomerase, anticentromere, anticardiolipin, smooth muscle, and mitochondrial antibodies.

umented. A chemotherapeutic regimen of doxorubicin and dacarbazine was initiated, but imaging studies performed after the sixth course revealed that the hepatic metastases had enlarged. In June 1992, the patient consented to enrollment in a Phase I docetaxel trial.

The patient received a total of 14 courses (2-hour infusions) of docetaxel, with the first 11 courses being given at a dose of 100 mg/m^2 and the remaining three courses at 80 mg/m^2. Docetaxel courses were given every 21 days. The hepatic metastases remained the same size throughout the 14 courses of docetaxel. The patient experienced several side effects (which did not require a change in the dose of docetaxel), including chemotherapy-induced acral erythema (erythrodysesthesia),[8] mucositis, neutropenia, nail changes, arthralgias, myalgias, and severe fatigue. He also developed persistent paresthesias of the feet after the first docetaxel course and a mild peripheral neuropathy confirmed by nerve-conduction velocities. Pedal edema began after the fifth course of docetaxel and was cumulative, despite the addition of hydrochlorothiazide (50 mg/day) and the lengthening of infusion intervals from 3 to 4 weeks. Three-plus pitting edema progressed to the level of the knees and was treated empirically with spironolactone (100 mg twice daily). A trial of dexamethasone (40 mg on days 1 and 2) during the 10th course was given without improvement of the edema. The edema progressed to the level of the sacrum associated with a 3.1 kg weight gain, and the dose of docetaxel was decreased to 80 mg/m^2. Despite the dose change, severe edema/induration gradually evolved into diffuse skin tightening of the legs (Fig. 1, top left). Renal, cardiac, hepatic, and endocrine functions were normal by physical examination and laboratory testing. Besides fatigue and the lower extremity symptoms, review of systems was negative for Raynaud's phenomenon or any other organ involvement. An incisional full-thickness biopsy of the left thigh (Fig. 1, top right and bottom left) was performed after the 12th course of docetaxel, revealing marked sclerosis of the dermal collagen and fibrous septae of the subcutaneous fat consistent with scleroderma. Results of direct immunofluorescence of the skin were negative.

Physical examination revealed hidebound skin of the lower extremities without edema and generalized alopecia secondary to docetaxel. The skin was red-brown and warm to touch. Forced flexion of the lower extremity resulted in blanching of the knee and notable linear induration of the proximal thigh (Fig. 1, bottom right). There were no tendon friction rubs, telangiectasia, or calcific deposits. Capillary refill of the feet was minimally delayed, and nail-fold capillaroscopy was normal. The upper extremities were normal, and the remainder of the examination was unremarkable except for a mild lower extremity neuropathy.

The leukocyte count was 5.8×10^3, hemoglobin was 10.5 g/dl, and the platelet count was 341×10^3. Serum chemistry results were within normal limits, and urinalysis results were unremarkable. Erythrocyte sedimentation rate was 38 mm/hour (normal, <30 mm/hour), and the C-reactive protein was 1.2 mg/dl (normal, <0.8 mg/dl). Thyroid function tests and serum complement levels (C3 and C4) were normal. Serology results were negative for antitopoisomerase, anticentromere, antinuclear, extractable nuclear, and anticardiolipin antibodies. Mitochondrial antibodies were reactive at 1:40 titer, and smooth muscle antibodies were reactive at 1:20 titer. Rheumatoid factor was negative.

The 13th course was held for 8 weeks, with marked

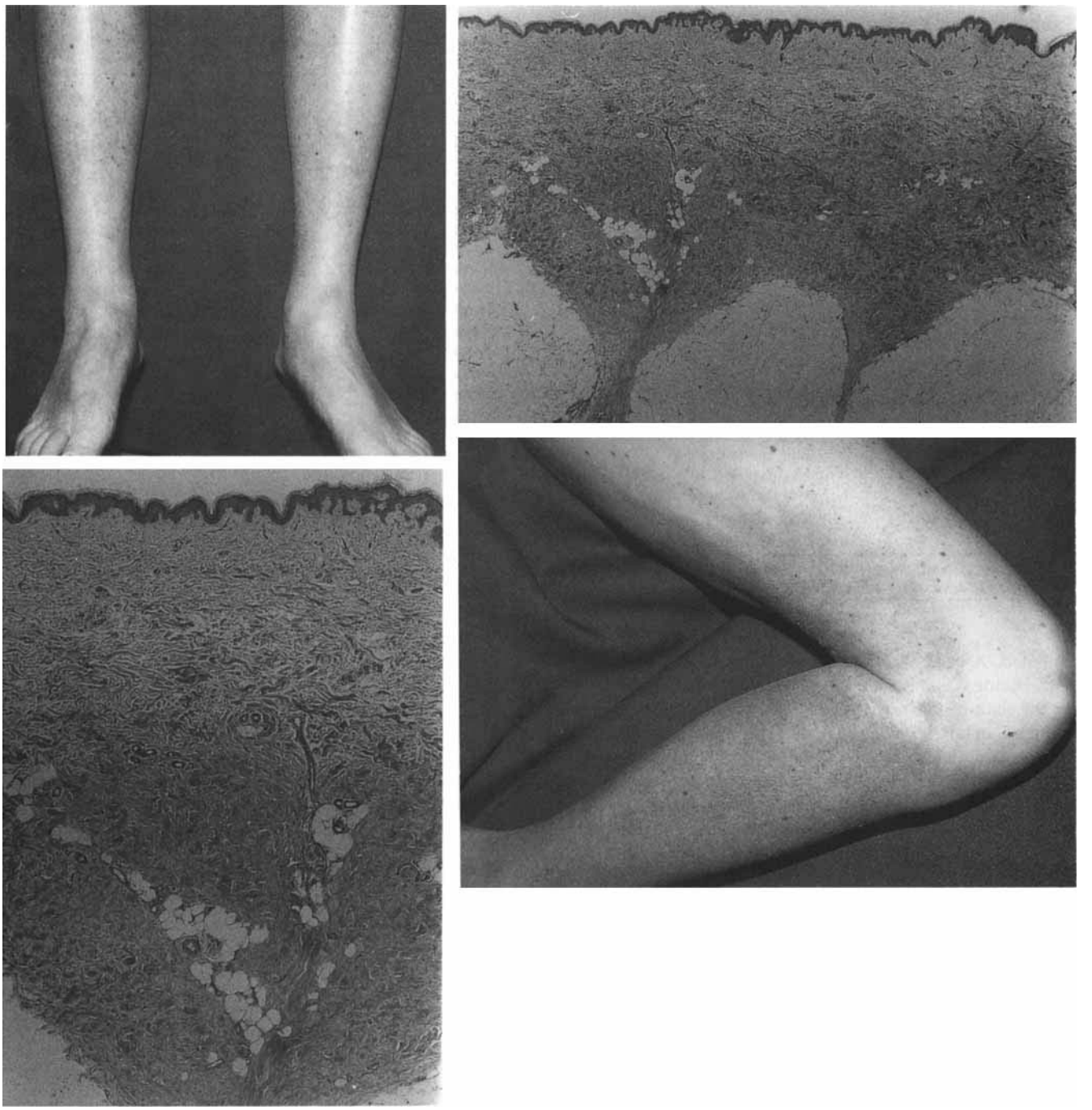

Figure 1. (Top left) The loss of hair and the shiny skin of the lower extremities resulted from the taut bound-down character of the skin of Patient 1 noted on physical examination. (Top right) An incisional biopsy of the left thigh of Patient 1 revealed collagen deposition resulting in a widened dermis (H & E, original magnification ×20). (Bottom left) Collagen deposition resulting in the appearance of widened hyalinized collagen bundles is noted in a close-up view of the biopsy shown in the top right panel (H & E, original magnification ×40). (Bottom right) The diffuse red-brown skin color corresponds to the thickened skin, although the extent of the fibrosis/thickening was difficult to visualize. When the lower extremity was forcibly flexed at the knee, visual changes were obvious, with blanching at the knee and linear areas of induration in the proximal thigh of Patient 1.

improvement of the edema but with persisting hidebound skin of the lower extremities. The liver metastases enlarged despite docetaxel therapy, and treatment was discontinued due to subcapsular hepatic hemorrhage. One year later, the hidebound skin of the legs has shown marginal improvement with subsequent skin softening. The patient currently has full flexion of both knees and can dorsiflex the feet 10 degrees.

Patient 2

A previously healthy 63-year-old white male was diagnosed as having metastatic melanoma of facial skin in June 1991. A primary melanoma was not discovered. Initially, he underwent local cutaneous radiation therapy but was switched to a Phase II docetaxel melanoma study when new facial metastases appeared. The patient was administered seven courses of docetaxel at a dose of 100 mg/m^2 intravenously for 1 hour every 21 days. The patient experienced chemotherapy-induced acral erythema (erythrodysesthesia) of both hands and feet with each course of docetaxel. He developed lower extremity edema after the third course. The edema progressed to waist level, with a remarkable weight gain of 18.1 kg despite empiric diuretic therapy. He also developed paresthesias and stereoagnosia of the feet after the fifth course of docetaxel, which subjectively improved with pyridoxine (50 mg three times/day).[9] Finally, he developed noncardiogenic pulmonary edema after the seventh course, and docetaxel was discontinued. Renal, cardiac, hepatic, and endocrine function were normal at the onset of the pulmonary edema. The skin of the lower extremities evolved from an edematous/indurated state to a leathery texture by the last course of docetaxel.

At the time of the rheumatology evaluation, the patient was only concerned about his thickened skin changes. He still had residual paresthesias of the feet but did not have cardiac or pulmonary symptoms, and the remainder of the review of systems was negative. A 4-mm punch biopsy of the right leg was performed 12 months after the initiation of docetaxel and at a time when the skin was clinically softening. Histologically thickened collagen bundles in a widened dermis were noted (Fig. 2). Immunofluorescence results were negative.

Physical examination results were normal except for numerous darkly pigmented cutaneous nodules over the face. The upper extremities were normal. Cardiac and pulmonary examination results were normal. The skin of the lower extremities was warm and diffusely thickened on palpation but not hidebound. Capillary refill of the feet was decreased, but capillaroscopy was normal. There were no tendon friction rubs, telangiectasia, or calcific deposits. A mild decrease in vibratory and light touch sensations of the lower extremities was present. The remainder of the examination was unremarkable.

Serology results and routine laboratory tests were all unremarkable. There is persistent residual thickening of the skin despite discontinuance of docetaxel 1 year ago. The patient currently has full range of motion of the lower extremities with residual paresthesias of the soles and toes of the feet.

Patient 3

A 67-year-old white female was diagnosed in October 1992 with a well differentiated, bronchoalveolar carcinoma extending to but not including the pleura. She underwent a right middle lobe lobectomy without complications and was doing well until February 1993, when new bilateral alveolar metastases were detected. Selected lesions from both lungs were measured and serially followed. In March 1993, she was enrolled in a Phase II study, and docetaxel therapy was initiated at 100 mg/m^2 and given intravenously over 1 hour every 21 days. She tolerated the first three infusions without difficulty, but then reported painful acral erythema (erythrodysesthesia) of the palms, which resolved before each subsequent dose of docetaxel. Dexamethasone (20 mg orally) was given empirically for prevention of the cutaneous lesions on the day before and the day of the fourth course, but this was of no benefit. After the fourth course, she developed lower extremity edema, which progressed to the knees by the fifth course (Fig. 3). The dosage of docetaxel was decreased to 75 mg/m^2. Hydrochlorothiazide and eventually spironolactone were prescribed for treatment of cumulative edema and weight gain (4.1 kg) with only mild improvement. The dosage interval was increased to 28 days without improvement in symptoms. Pain in the feet secondary to edema persisted without paresthesias and progressed to presacral pitting edema after the sixth course of docetaxel. Renal, cardiac, hepatic, and endocrine functions were normal, and the review of symptoms was negative. The dosage interval was increased to 35 days, but docetaxel had to be discontinued due to severe mucositis, blis-

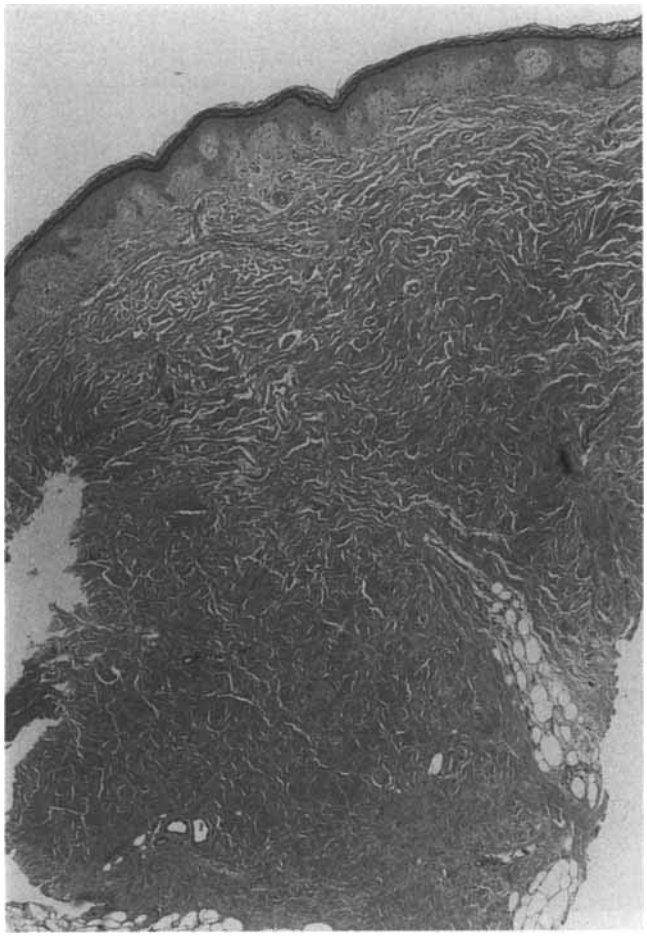

Figure 2. A punch biopsy of the right leg of Patient 2 revealed hyalinized collagen bundles resulting in widening of the dermis, with markedly thickened collagen bundles (H & E, original magnification ×40).

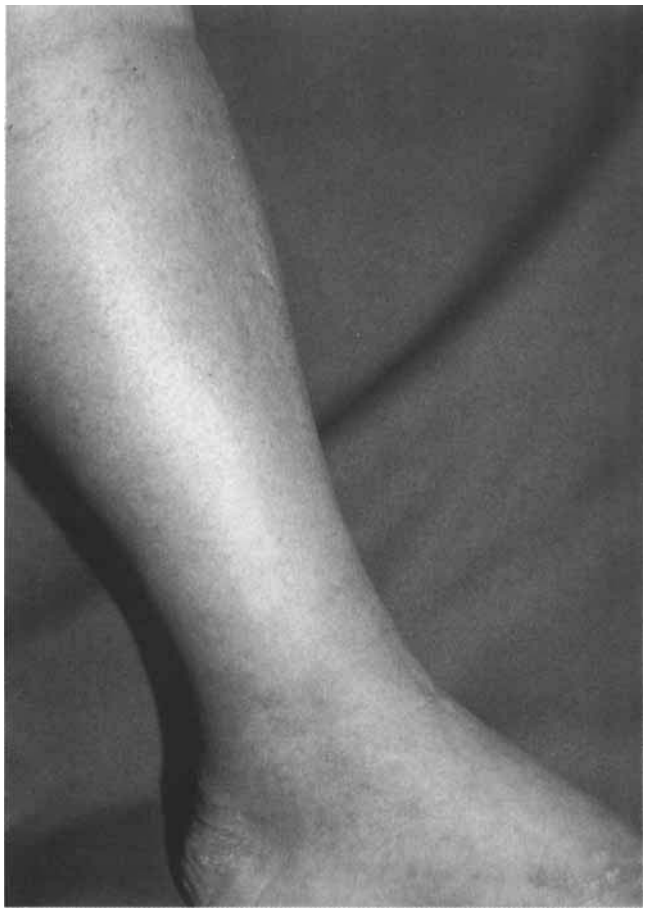

Figure 3. The shiny distended skin with a cobblestone appearance corresponds to the clinically thickened edematous skin of the lower extremity noted for Patient 3.

tering erythrodysesthesia of the feet, and persistent lower extremity edema. The patient did not consent to skin biopsies. A lymphangiogram revealed patent lymphatics of the lower extremities.

Physical examination was notable for pitting edema and induration of the lower extremities extending to the sacrum. The skin was thickened but not hidebound. There were no tendon friction rubs, telangiectasias, or changes of calcinosis cutis. Nail-fold capillaroscopy of the feet was normal. The remainder of the examination was normal.

Laboratory analysis revealed a leukocyte count of 4.2×10^3, hemoglobin of 13.1 gm/dl, and platelet count of 276×10^3. Serum chemistries, creatinine phosphokinase, and thyroid function test results were normal. Erythrocyte sedimentation rate and C-reactive protein were 20 mm/hour and 0.6 mg/dl, respectively. Serum complement for C3 and C4 were normal. Rheumatoid factor was 1:80 titer. Serology results for antinuclear, anticardiolipin, antitopoisomerase, anticentromere, antiextractable nuclear antigens, anticardiolipin, and mitochondrial and smooth muscle antibodies were negative. Five months after the discontinuation of docetaxel, the edema resolved and there are no residual scleroderma-like changes.

Discussion

The clinical observations described in the current paper are very similar to patients with cutaneous toxicity mentioned in a previous Phase I study of docetaxel.[4] In that study, the five patients who received the highest cumulative doses of docetaxel experienced diffuse subcutaneous edema and weight gain ranging from 2 to 15 kg. There was no evidence of fluid retention syndrome in these patients, and the authors stated that the edema was highly responsive to diuretic therapy. Four patients had cutaneous biopsies, and histopathologic examination was consistent with nonspecific toxidermic cutaneous reaction, and scleroderma-like changes were found in two patients. Antihistamine and corticosteroid therapy was ineffective in preventing this cutaneous toxicity.

The three patients described in the current paper demonstrated three phases of dermal involvement similar to that seen in patients with systemic sclerosis.[10] All three patients experienced an initial edematous phase restricted to the lower extremities followed by induration and hardness of the skin and finally a softening phase. Unlike systemic sclerosis, however, the rapid transition from the edematous phase to the softening phase was observed within 1 year, and there was no evidence of an endothelial injury on biopsy specimens. The finding that the softening phase began only after discontinuance of docetaxel treatment supports a direct correlation to drug toxicity or vehicle toxicity. Another unusual observation was that the skin involvement was limited to the lower extremities, even though intravenous access in all three patients was in the upper extremities.

The other taxane, paclitaxel (Taxol), with its own unique vehicle, polyoxyethylated castor oil (Cremophor EL), has been reported to cause skin changes described as erythematous rashes and fluid retention, but we could not find any reports of morphea/scleroderma-like changes with paclitaxel.[11,12] The labeling for paclitaxel indicates that 21% of all patients develop edema.[11] A recent presentation on docetaxel involving 837 patients revealed that 47% of the patients experienced fluid retention (mild, 15%; moderate, 23%; severe, 9%).[13] The vast majority of edema in these patients involved the lower extremities, and docetaxel treatment was discontinued in 9% due to fluid retention. Although skin toxicity associated with docetaxel was discussed, morphea/scleroderma-like changes were not listed as an adverse event for any patients. Docetaxel has up to four times greater potency than paclitaxel on preclinical trials,[6] thus it is unclear whether fluid retention is related to the potency of the parent compound or the vehicle.

Clinical variants of systemic sclerosis have been described in patients after exposure to certain organic solvents (i.e., vinyl chloride, benzene, toluene), drugs (i.e., bleomycin, carbidopa, pentazocine, cocaine), and miscellaneous substances (i.e., rapeseed oil/aniline, silicone implants, L-tryptophan).[14,15] We believe that docetaxel should be added to this list of drugs. The etiology of the scleroderma-like skin changes appears to be either a direct toxic effect of docetaxel or an effect secondary to polysorbate 80 (Tween 80), the vehicle for docetaxel.

References

1. Bissery MC, Guenard D, Gueritte-Voegelein F, Lavelle F. Experimental antitumor activity of taxotere (RP 56976, NSC 628503), a taxol analogue. *Cancer Res* 1991;51:4845–52.
2. Burris H, Irvin R, Kuhn J, Kalter S, Smith L, Shaffer D, et al. Phase I clinical trial of taxotere administered as either a 2-hour or 6-hour intravenous infusion. *J Clin Oncol* 1993;11:950–8.
3. Bissett D, Setanoians A, Cassidy J, Graham MA, Chadwick GA, Wilson, et al. Phase I and pharmacokinetic study of taxotere (RP 56976) administered as a 24-hour infusion. *Cancer Res* 1993;53:523–7.
4. Extra JM, Rousseau F, Bruno R, Clavel M, LeBail N, Marty M. Phase I and pharmacokinetic study of taxotere (RP 56976; NSC 628503) given as a short intravenous infusion. *Cancer Res* 1993;53:1037–42.
5. Pazdur R, Newman RA, Newman BM, Fuentes A, Benvenuto J, Bready B, et al. Phase I trial of taxotere: five-day schedule. *J Natl Cancer Inst* 1992;84:1781–8.
6. Ringel I, Horwitz SB. Studies with RP 56976 (taxotere): A semisynthetic analogue of taxol. *J Natl Cancer Inst* 1991;83:288–91.
7. Blume E. Agreement to develop taxotere expected in April. *J Natl Cancer Inst* 1992;84:673.
8. Zimmerman GC, Keeling JH, Burris HA, Cook G, Irvin R, Kuhn J, et al. Acute cutaneous reactions to docetaxel (RP 56976), a new chemotherapeutic agent. *Arch Dermatol* 1995, 131:202–6.
9. Vukelja SJ, Baker WJ, Burris HA, Keeling JH, Von Hoff D. Pyridoxine therapy for palmar-plantar erythrodysesthesia associated with taxotere. *J Natl Cancer Inst* 1993;85:1432.
10. Silver RM. Clinical aspects of systemic sclerosis (scleroderma). *Ann Rheum Dis* 1991;50:846–53.
11. Taxol (Paclitaxel) [package insert]. Princeton, NJ: Bristol-Myers Squibb Company, 1994.
12. Kohler DR, Goldspiel BR. Paclitaxel (Taxol). *Pharmacotherapy* 1994;14:3–14.
13. Rhone Poulenc Rorer Oncology Drug Advisory Committee Presentation. Food and Drug Administration, December 13, 1994, Rockville, MD.
14. Perez MI, Kohn SR. Systemic sclerosis. *J Am Acad Dermatol* 1993;28:525–47.
15. Yoshida S, Gershwin ME. Autoimmunity and selected environmental factors of disease induction. *Semin Arthritis Rheum* 1993;22:399–419.