Cutaneous adverse reactions to chemotherapy with taxanes. The dermatologist's point of view

Efeitos colaterais cutâneos de quimioterapia com taxanos. O ponto de vista do dermatologista

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Abstract: Chemotherapy with taxanes has recently become part of the treatment for many advanced neoplastic diseases, specially breast and lung cancer. Their main noncutaneous adverse reactions include neutropenia and mucositis, which eventually lead to drug discontinuation. Cutaneous adverse reactions are frequent and significantly interfere with the patient's quality of life. Treatments are poorly effective, but special recommendations may improve symptoms and prevent relapses requiring drug rechallenge.
Keywords: Drug Eruptions; Drug Therapy; Cutaneous adverse reactions; Paclitaxel; Taxoids

Resumo: Taxanos são drogas quimioterápicas cada vez mais utilizadas no tratamento adjuvante de um grande número de cânceres, principalmente câncer de mama e de pulmão. Os efeitos colaterais não cutâneos mais importantes e limitantes do uso destas drogas são neutropenia e mucosite. Os efeitos colaterais cutâneos, além de muito frequente, interfere de forma importante na qualidade de vida dos doentes. Não existem tratamentos totalmente eficazes, mas algumas orientações podem diminuir os sintomas e prevenir recidivas em novas sessões de quimioterapia.
Palavras-chave: Erupção por droga; Paclitaxel; Quimioterapia; Taxóides; Toxicidade de drogas

INTRODUCTION

Taxanes (TX) are drugs used to treat several types of neoplasias, such as breast and lung cancer. There are 2 types of TX in Brazil: paclitaxel (PC) (Taxol®) and docetaxel (DC) (Taxotere®). The most common side effects of these drugs are neutropenia and mucositis. They present a similar mode of action but a distinct profile regarding cutaneous adverse reactions.[1] With the purpose of making dermatologists more familiar with this kind of reaction, which will become more frequent with greater utilization of TX, we report below 4 cases that were followed in a dermatology office.

CASE REPORT

1 – Female patient, 54 years old, after 4 years of breast cancer treatment with mastectomy and chemotherapy (CTH) with other drugs, presented bone and liver metastases; a new CTH series was started with PC and carboplatin. Two months later she presented erythema and hyperchromia on the back of hands and on the face, accompanied by dysesthesia with local burning sensation (Figure 1). She wore a moisturizer and photoprotector, and was oriented to avoid sun exposure. Two months later, in view of the intensity of cutaneous adverse reactions, PC was replaced by DC, with great improvement of symptoms. After 2 cycles of the new drug, she developed phlebitis at the place of infusion with linear hyperpigmentation following the venous pathway (Figure 2). The elementary lesions of this second episode were similar to those observed in the first. She was treated with creams composed of tretinoin/hydroquinone/fluocinolone on the face and

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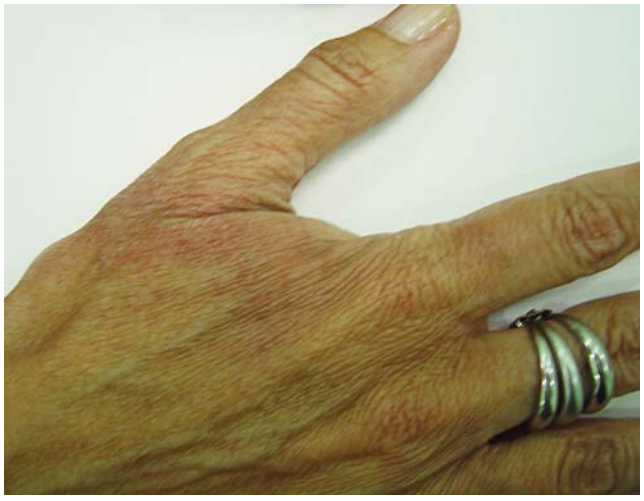

Figure 1: Erythema, hyperchromia and dysesthesia on back of hand after 2 months of chemotherapy with paclitaxel and carboplatin

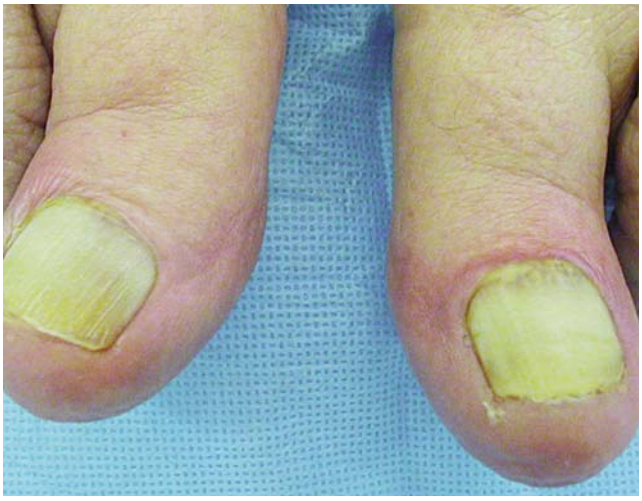

Figure 3: Thickened and yellowed nail plates associated with onycholysis and inflammation of the nail bed and periungual tissue after 3 months of chemotherapy with paclitaxel and carboplatin

glycolic acid/hydroquinone/ heparinoid on the forearm, in addition to photoprotection. Thirty days later she reported great improvement. With the new cycle of DC the facial condition was reactivated, with erythema, peeling and hyperpigmentation. She was oriented to continue the same treatment until the end of CTH. Eleven months after this last visit she mentioned that CTH with TX had been suspended. She presented melasma and mottled hyperpigmentation on the face, supposedly a residual effect of previous processes.

2 – Male patient, 84 years old, presented paronychia on both halluces after 3 months of CTH with PC and carboplatin to treat lung cancer. Onycholysis and inflammation of nail bed and subjacent periungual tissue were observed. The plates were thickened and yellowed (Figure 3). Nail avulsion was carried out, as they were loose in most of their area. Erythema and granulation tissue were observed on the nail bed. Forty days after surgery he returned to the office mentioning that he had completed CHT. The nails and periungual tissue did not present any phlogistic signs and it was already possible to observe that the nails were growing. The patient was discharged.

3 – Female patient, 49 years old, two months after mastectomy due to breast cancer was subjected to CHT with DC, adriamycin and cyclophosphamide. After the 4th chemotherapy session she presented erythema and dysesthesia of the burning sensation type on the hands, that greatly improved in 2 weeks. After the next session there was recidivation of symptoms and the heels were also involved (Figures 4 and 5). She was treated with prednisone 0.2 mg/kg/day for 7

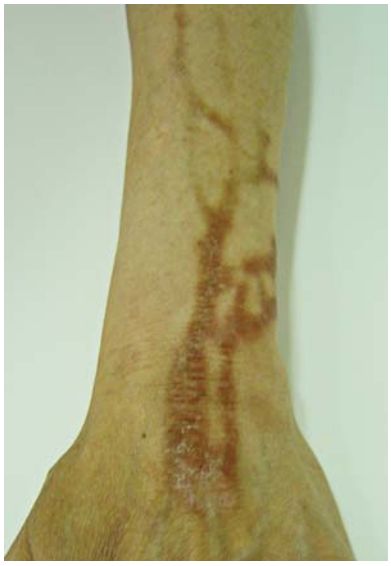

Figure 2: Hyperpigmentation on phlebitis that occurred after 2 docetaxel cycles

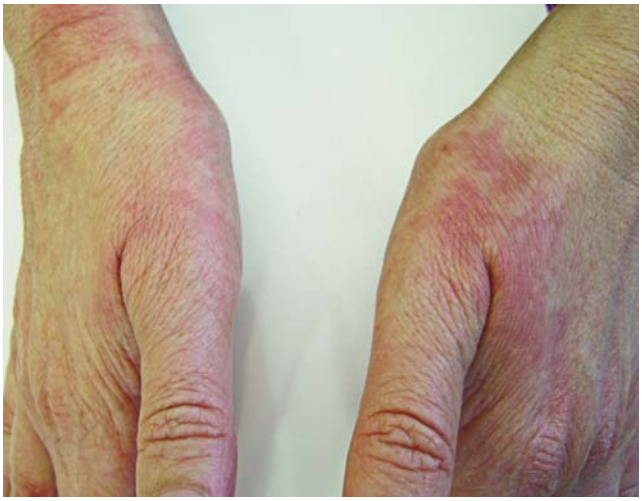

Figure 4: Erythema and dysesthesia on hands after 4 docetaxel, adriamycin and cyclophosphamide cycles

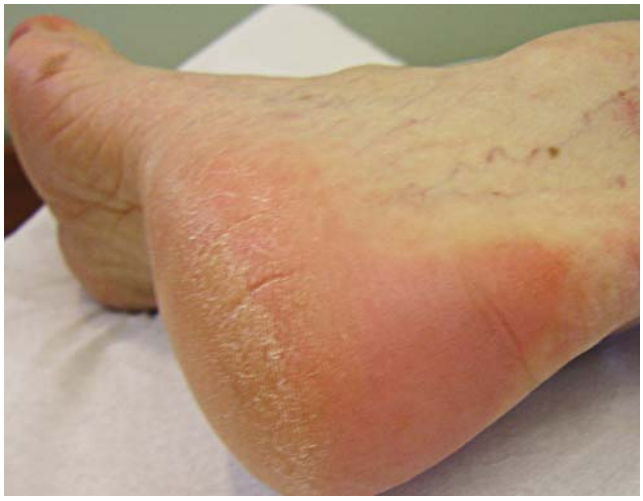

Figure 5: Erythema and dysesthesia present also on heels (same patient as in figure 4), worsening with each chemotherapy cycle

days, mometasone cream and moisturizers. There was partial improvement of symptoms. At each new CHT session she presented the same symptoms with greater intensity and less expressive improvement with the treatment.

4 – Female patient, 44 years old, presented breast cancer with liver metastasis and chemotherapy with PC was started at the same time. After 4 months she presented infiltrated maculae and hyperpigmentation on back of hands and periungual pain on hands and feet. The condition evolved with a subungual abscess on the 3rd left digit and local onycholysis; the patient was treated with prednisone 10mg/d, glycolic acid/hydroquinone bleaching cream, moisturizers and opioid analgesics. She presented discreet improvement of symptoms, but a few days later paronychia appeared on the 3rd and 4th right digits and the erythema worsened, this time on back of hands and on the face, with local burning sensation (Figure 6). The

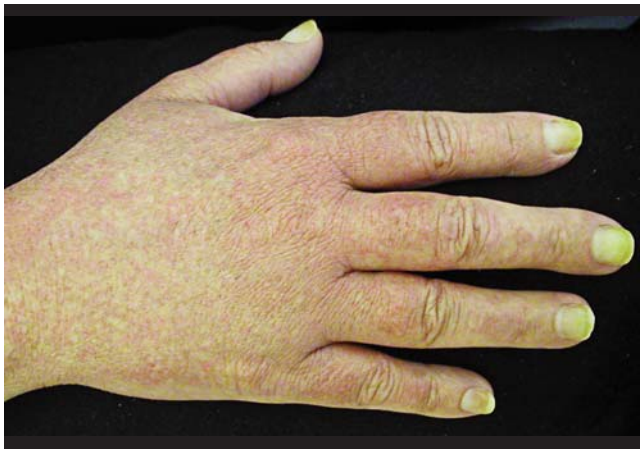

Figure 6: Erythema and dysesthesia on back of hands, accompanied by subungual inflammation on several digits after 4 months of chemotherapy with paclitaxel

symptom complex continued progressing with the onset of similar new lesions on toenails and on other fingers. The remission occurred only gradually, after suspension of CHT.

DISCUSSION

There are 2 types of TX in the domestic market: PC and DC. The difference between them is found in their origins: PC is extracted from the bark of the *Taxus brevifolia* tree, while DC is obtained from the *Taxus baccata* leaves. Although their mechanism of action is similar (microtubule stabilization during mitosis, blocking their ability to disaggregate and leading to cellular death), their indication and side effects are distinct.[2] This may be due to the fact that DC is better absorbed by cells and is within the intracellular environment for a longer time. [3]

Signs of dermatological toxicity are observed in around 65% of cases and include alopecia, hypersensitivity reactions and ungual alterations.[4] Most cases are treated by the oncologist, therefore many studies on the theme do not reflect the dermatological vision of the clinical picture, briefly described as "cutaneous reaction".

Among the papers published in dermatology journals one from 2008 stands out, where a list of all reactions already described as secondary to taxanes is found.[5] Other texts are reports or series of cases focusing only on a facet of cutaneous adverse reactions, such as a "photo recall" phenomenon, generalized pustular dermatosis, scleroderm-like reactions, fixed pigmented erythema and erythrodysesthesia, [3,6,7,8,9]

Acral or palmar-plantar erythrodysesthesia (PPE) is a peculiar cutaneous and neurological symptom complex associated with the use of TX, mainly DC. It has already been found in patients that made use of PC or other chemotherapeutic agents (cytarabine, doxorubicin and 5-fluorouracil).[10] Clinically, it varies only from erythema to edematous plaques and is especially present in acral regions. Dysesthesia sensations may or may not occur, almost always painful and of varying intensity.[11] Residual hyperchromia is frequent and may be treated with bleaching creams. Histology reveals spongiotic epidermis with lichenoid alterations, such as apoptotic keratinocytes and interface activity. A discreet superficial perivascular inflammatory lymphohistiocytic infiltrate is seen on the dermis. Unspecific glandular alterations, such as neutrophilic eccrine hidradenitis, necrosis of the secretory epithelium and syringosquamous metaplasia are also described.[3,4,12]

The cause of PPE is unknown, although there is a theory concerning the affinity of these drugs to eccrine sweat glands.[4] The immunocytochemical characteristics of the inflammatory infiltrate and lack of a con-

sistent response to corticosteroids and antihistaminics go against an allergic origin of the reaction.[3]

There are no known risk factors for development of PPE, nor characteristics that predict its intensity. The reactions usually occur after the 1st treatment cycle and are dose-dependent, with relief of discomfort during relapses when the quantity of the drug being given is decreased. There usually is spontaneous resolution of PPE after 2 weeks, with recurrence when the drug is reintroduced. The use of topical or systemic corticosteroids, elevation of legs and application of cold compresses is recommended for incapacitating pain.[11] Preventive treatment with pyridoxine was reported as beneficial in one study. It is recommended to apply local hypothermia to acral regions during medication infusion to decrease local drug perfusion.[13]

Another characteristic cutaneous adverse reaction is ungual infection.[14] The most prevalent alteration is onychomelanosis, although onycholysis, as reported here, is the most studied finding. The hallux nail is the most affected, but there are cases of multiple infection or where all nails are infected. The use of DC, the PC/anthracycline association and prolonged PC use (>12 weeks) are considered risk factors.

In some cases, in addition to onycholysis there is inflammation of the skin close to the hyponychium and it is believed that the greater sensitivity of this portion of the nail apparatus to ultraviolet rays may be part of onycholysis physiopathology.[15] The exact role of UV radiation as a trigger is not totally clear, but an increase in the incidence of this cutaneous adverse reaction is observed in the summer. Moreover, nail sun protection by physical methods is able to prevent lesion recurrence in subsequent treatment cycles.

Cutaneous adverse reactions are very common with the use of TX. There are no exact numbers, as there are no epidemiological studies of such drugs used isolated, but a 65% incidence is estimated. These reactions have variable intensity and may significantly alter quality of life; the relief of symptoms and prevention of reactions are fundamental. There are few studies regarding treatment, which leaves dermatologists without much scientific evidence. Among the skin alterations that make patients seek a dermatologist are PPE and onycholysis. Preventive orientation is useful to avoid suspension of treatment, and many times it is the only way to treat the restricting symptoms of PPE triggered by TX._❑

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