Netherlands
The Journal of Medicine

CASE REPORT

Early onset of oral aphthous ulcers with weekly docetaxel

E. Göker*, S. Rodenhuis

Department of Oncology, Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, the Netherlands, *corresponding author: Department of Clinical Oncology, Leiden University Medical Centre, Leiden, the Netherlands, tel.: +31 (0)71-526 34 64, fax: +31 (0)71-526 67 60, e-mail: e.goker@lumc.nl

ABSTRACT

Two patients with metastatic breast cancer developed oral aphthous ulcers after only two administrations of weekly docetaxel without any other toxicity. A treatment delay and dose reduction appears to be an effective management strategy.

KEYWORDS

Docetaxel, oral aphtous ulcer

INTRODUCTION

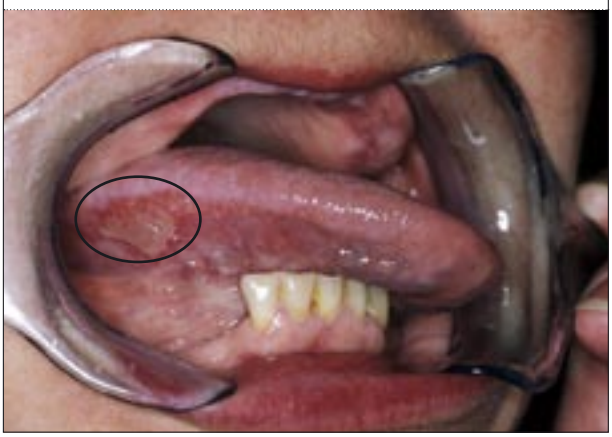
Weekly administration of docetaxel can be effective in the treatment of metastatic breast cancer and has a relatively low toxicity in comparison with docetaxel given once every three weeks. Grade 3/4 myelosuppression is uncommon (percentages of 14 to 20% have been reported). Fatigue and asthenia are the most frequent nonhaematological toxicities (also observed in 14 to 20% of the patients). Grade 3/4 mucositis is seldom described in weekly docetaxel.[1,2] We report two patients with unusual oral aphthous ulcers after only two applications of weekly docetaxel.

CASE REPORT

Patient A

A 73-year-old woman who presented with breast cancer and skeletal metastases in 2000 was treated with pamidronate and tamoxifen. In 2001, radiotherapy was administered because of progressive disease with compression of the spinal cord. Simultaneously, she developed liver metastases, for which first-line palliative chemotherapy consisting of six cycles of doxorubicin and cyclophosphamide was given. This therapy led to regression of the liver metastases. Subsequently, treatment with anastrozole was started as consolidation therapy. After four months the patient developed progressive liver metastases. Laboratory findings showed grade 2 hepatic dysfunction: bilirubin 24 μmol/l (<16 μmol/l), alkaline phosphatase 595 U/l (40 to 120 U/l), serum glutamic oxaloacetic transaminase (SGOT) 178 U/l (<40 U/l) and serum glutamic pyruvic transaminase (SGPT) 76 U/l (<45 U/l). Second-line treatment with weekly docetaxel for three weeks, followed by a one-week rest, was initiated. Because of the hepatic dysfunction the dose was reduced to 25 mg/m²/week (normal dose is 36 to 40 mg/m²/week). After only two applications of docetaxel grade 3, painful, grey aphthous ulcers developed on the lateral aspects of the tongue (*figure 1*). There were no other signs of mucositis. There was no bone marrow suppression either, or any other toxicity. The patient had not experienced stomatitis aphtosa or oral herpes before. Diagnostic polymerase chain reaction for herpes simplex virus was negative. The cultures of oral lesions showed only a trace of *Candida albicans*. Treatment with acyclovir and fluconazole had already been started but did not lead to any noticeable improvement, also suggesting docetaxel-associated oral toxicity. The next chemotherapy course was delayed for one week, in which time the aphthous ulcers improved. Weekly docetaxel applications were

Figure 1 *Aphthous ulcer on the lateral side of the tongue*



continued in a reduced dose of 15 mg/m², without recurrence of aphthous ulcers. Evaluation by CT abdomen after six weeks and 12 weeks showed a reduction in the liver metastases. Because of the development of meningitis carcinomatosa, the docetaxel therapy was discontinued after a total of 16 weeks of treatment.

Patient B

A 45-year-old woman was found to have breast cancer T2N1M0 in 2002. She was treated with breast-conserving therapy and adjuvant chemotherapy with doxorubicin and cyclophosphamide. After the fifth course, progressive cancer infiltration of the chest wall was observed and loco-regional radiotherapy was given. In 2003, a local relapse in the breast was treated with salvage surgery followed by radiotherapy and hyperthermia. Subsequently, she developed progressive disease in the contralateral breast, with metastases in lymph node, pleura and lung. Laboratory findings showed a grade 1 liver dysfunction: bilirubin 11 µmol/l (<16 µmol/l), alkaline phosphate 240 U/l (40 to 120 U/l), SGOT 65 U/l (<40 U/l) and SGPT 81 U/l (<45 U/l). The standard dose of weekly docetaxel of 40 mg/m² was started, because the bilirubin was not elevated. Following the second administration of docetaxel, the patient developed grade 3, painful, grey aphthous ulcers covered with white plaques, which she had never experienced before. Acyclovir and miconazole were administered for supposed fungal or viral infection. A third application of docetaxel was given in a slightly lower dose of 35 mg/m²/week. Six days later, the patient was admitted to the hospital with severe ulcerative pharyngitis. The docetaxel was suspended; the patient developed neutropenic fever and was treated with parenteral ceftriaxone, fluconazole and valaciclovir. Cultures were negative for herpes simplex and for candida. In two weeks the oral lesions had improved. Docetaxel was reintroduced at a lower weekly dose of 25 mg/m²/week. Seven weekly doses of docetaxel were administered without recurrence of the aphthous ulcers. Evaluation after six applications of docetaxel showed regression of pleuritis carcinomatosa and stable disease of liver metastases. After a total of 11 weeks of therapy, the docetaxel was stopped because of progression, which manifested as cerebral metastases.

DISCUSSION

Weekly docetaxel therapy is an active regimen that is generally well tolerated by patients with metastatic breast cancer.[1,2] The usual dose of weekly administration of docetaxel ranges from 36 to 40 mg/m². Hepatic dysfunction may cause a significant reduction in docetaxel clearance, which can result in a higher risk of toxicity. A 25% dose reduction is commonly recommended if there are abnormalities in the alkaline phosphatase (>2.5 x upper limit of normal (ULN)) and transminase values (>1.5 x ULN), even in the presence of normal bilirubin levels.[3] Stomatitis is seen in about 5 to 20% of patients receiving docetaxel in a three-weekly schedule. With weekly docetaxel use, stomatitis is infrequent and less severe.[3-9] In stomatitis the mucosa initially becomes diffusely reddened and swollen, followed by ulceration which may be covered with fibrinous exudate. In these two cases the patients only developed solitary oral aphthous ulcers, with otherwise normal mucosa. There are a number of reasons why we suppose that these oral aphthous ulcers were caused by the docetaxel treatment. First, in both cases there is a clear relation in time between the start of docetaxel administration and the development of the oral ulcers. Second, there were no signs of other causes of oral ulcers in either of the patients. Neither of the patients had history of aphthous ulcers or herpes infection. The cultures for candida and herpes were negative. Moreover antifungal and antiviral therapy gave no improvement. Third, in both cases the oral ulcers disappeared in only two weeks after cessation of docetaxel and after reintroduction of docetaxel in a lower dose there was no recurrence of the aphthous ulcers. Remarkable is that the grade 3 oral aphthous lesions developed in these two patients with only mild hepatic dysfunction and even though the dose of docetaxel was reduced in patient A. To our knowledge, early onset of severe solitary oral aphthous ulcers without any other toxicity has not been reported before in patients on weekly low-dose docetaxel. Physicians treating patients with weekly docetaxel should be aware of the possibility of this side effect developing, even with mild impairment of liver function. A treatment delay and dose reduction appears to be an effective management strategy. We are curious whether other physicians have also noticed this toxicity of docetaxel.

REFERENCES

1. Aihara T, Kim Y, Takatsuka Y. Phase II study of weekly docetaxel in patients with metastatic breast cancer. Ann Oncol 2002;13(2):286-92.
2. Hainsworth JD, Burris III HA, Yardley DA, Bradof JE, Grimaldi M, Kalman LA Sullivan T, et al. Weekly docetaxel in the treatment of elderly patients with advanced breast cancer: A Minnie Pearl Cancer Research Network Phase II Trial. J Clin Oncol 2001; 19(15):3500-05.
3. Bruno R, Vivier N, Veyrat-Follet C, Montay G and Rhodes R. Population pharmacokinetics and pharmacokinetic-pharmacodynamic relationships for docetaxel. Invest New Drugs 2001;19:163-9.
4. Burstein HJ, Manola J, Younger J, Parker LM, Bunnell CA, Scheib R, Matulonis U, et al. Docetaxel administration on a weekly for metastatic breast cancer. J Clin Oncol 2000; 18(6):1212-9.
5. Clarke SJ and Rivory LP. Clinical Pharmacokinetics of Docetaxel. Clin Pharmacokinet 1999 Feb; 36(2):99-114.
6. Wildiers H and Paridaens R. Taxanes in elderly breast cancer patients. Cancer Treat. Rev. 2004;30:333-42.
7. Bruno R, Hille D, Riva A, Vivier N, Ten Bokkel Huinink WW, Van Oosterom AT, Kaye SB and et al. Population Pharmacokinetics/ Pharmacodynamic of Docetaxel in Phase II Studies in Patients With Cancer. J Clin Oncol 1998;16(1):187-96.
8. Esteva FJ. The Current Status of Docetaxel for Metastatic Breast Cancer. Oncology 2002;6(S):17-26.
9. Coleman RE, Howell A, Eggleton SPH, Maling SJ and Miles DW. Phase II study of docetaxel in patients with liver metastases from breast cancer. Ann Oncol 2000;11:541-46.