BJCP British Journal of Clinical Pharmacology

DOI:10.1111/j.1365-2125.2009.03555.x

Letter to the Editors

Severe toxicity related to a pharmacokinetic interaction between docetaxel and ritonavir in HIV-infected patients

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The treatment of AIDS-related malignancies raises specific pharmacological issues in patients receiving highly active antiretroviral therapy (HAART), particularly when the regimen includes a ritonavir-boosted protease inhibitor. Ritonavir potently inhibits CYP3A4, the main enzyme involved in the metabolism of a number of anticancer agents, including docetaxel [1–3].

We have recently treated three patients receiving ritonavir-based HAART, who experienced severe haematological and skin toxicity shortly after the first infusion of docetaxel. We believe that this toxicity was directly triggered by ritonavir. Hence, despite normal baseline liver function and blood cell counts, our patients experienced early febrile neutropenia, grade 3 mucositis, skin rash and hand-foot syndrome (Table 1). None of the patients had other recognized risk factors for docetaxel-induced febrile neutropenia: albuminaemia and C-reactive protein were normal, and baseline lymphocyte count was >700 g l^{-1} [2, 4].

Docetaxel is approved in the treatment of non-AIDS-defining malignancies such as breast, prostate and lung cancers, but also displays clinical activity in Kaposi's sarcoma [5]. In a Phase II study, docetaxel administered weekly was active and well tolerated in Kaposi's sarcoma patients, with moderate haematological toxicity [5]. However, patients included in this study received HAART without ritonavir pharmacoenhancement, and therefore did not experience toxicity in the same range as that observed in our case series.

Preclinical reports indicate that ritonavir-induced inhibition of CYP3A4 causes a significant increase in exposure to docetaxel [6]. In a similar way, concomitant administration of docetaxel and ketoconazole, another potent inhibitor of CYP3A4, resulted in a major reduction in plasma clearance of docetaxel [7]. Therefore, we assume that ritonavir-induced inhibition of CYP3A4 may decrease the plasma clearance of docetaxel, and subsequently lead to severe docetaxel-related toxicity (mainly haematological and cutaneous).

Another three cases [8, 9] of severe toxicity following co-administration of docetaxel and ritonavir were found in the literature (Table 1). As well, toxicity occurred after the first cycle of treatment, even with moderate doses of docetaxel (25–60 mg m^{-2}). According to the drug interaction probability scale, the event–drug relationship was probable [10].

Among the above-described cases, paclitaxel was substituted for docetaxel in two patients, without recurrence of severe toxicity in the following cycles. However, two cases of severe haematological toxicity (including one fatal outcome) have been reported after the concomitant administration of paclitaxel and ritonavir [11]. Of note, paclitaxel is mainly metabolized by CYP2C8, and to a lesser extent by CYP3A4 [12]. Hence, it remains unclear whether inhibition of CYP3A4 by ritonavir could significantly decrease the plasma clearance of paclitaxel and cause severe haematological toxicity.

In conclusion, these cases strongly support our hypothesis of a pharmacokinetic drug–drug interaction between ritonavir and docetaxel, even in patients treated with low doses of docetaxel. Clinicians should be aware that human immunodeficiency virus-infected patients receiving ritonavir-based HAART must receive anticancer drugs that are not metabolized by CYP3A4 instead of docetaxel.

Table 1

Severe toxicity following co-administration of docetaxel and ritonavir-based highly active antiretroviral therapy (HAART)

Reference	Sex, age (years)	HAART	Cancer, chemotherapy regimen	Toxicity observed	Delay between chemotherapy administration and toxicity, cycle	Outcome
[8]	Male, 40	Lamivudine, tenofovir, lopinavir, **ritonavir**	Kaposi's sarcoma, docetaxel (25 mg m^{-2} weekly)	Febrile neutropenia	8 days, 1st course	Recovery, docetaxel withdrawn
[9]	Male, 30	Zidovudine, lamivudine, saquinavir, **ritonavir**	Kaposi's sarcoma, docetaxel (60 mg m^{-2} q. 3 weeks)	Febrile neutropenia, mucositis	5 days, 1st course	Recovery, ***paclitaxel substituted for docetaxel***
[9]	Male, 38	Lamivudine, abacavir, indinavir, **ritonavir**	Kaposi's sarcoma, docetaxel (60 mg m^{-2} q. 3 weeks)	Grade 4 neutropenia, mucositis	6 days, 1st course	Recovery, ***paclitaxel substituted for docetaxel***
Present report	Male, 43	Tenofovir, emtricitabine, atazanavir, **ritonavir**	Oropharyngeal carcinoma, docetaxel (70 mg m^{-2} q. 3 weeks), 5-FU, carboplatin	Febrile neutropenia, grade 3 mucositis, skin rash, hand-foot syndrome	5 days, 1st course	Recovery, docetaxel withdrawn
Present report	Female, 58	Atazanavir, abacavir, lamivudine, **ritonavir**	Breast carcinoma, docetaxel (100 mg m^{-2} q. 3 weeks)	Febrile neutropenia, grade 3 mucositis, skin rash, hand-foot syndrome	3 days, 1st course	Recovery, docetaxel withdrawn
Present report	Male, 49	Tenofovir, abacavir, lopinavir, **ritonavir**	Kaposi's sarcoma, docetaxel (100 mg m^{-2} q. 3 weeks)	Febrile neutropenia, grade 3 mucositis	7 days, 1st course	Recovery, docetaxel withdrawn

Competing interests

None declared.

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RECEIVED
26 May 2009

ACCEPTED
1 September 2009

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