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Optimal use of docetaxel (Taxotere®): maximizing its potential

HA Burris
Cancer Therapy & Research Center, Suite 1000, 8122 Datapoint Drive, TX 78229 San Antonio, USA.

The safety of docetaxel (Taxotere®) has been evaluated in the safety overview population consisting of 1070 patients recruited to phase II trials. These patients received a total of 4989 cycles of therapy (median four cycles per patient). Since docetaxel is known to be metabolized in the liver, hepatic impairment was predicted to be a risk factor for increased toxicity and was studied prospectively, comparing the 42 patients in the overview population with moderate hepatic impairment with the 1028 patients with liver function within normal limits. Hepatic dysfunction was associated with an increase in the percentage of cycles of therapy during which febrile neutropenia occurred and the number of patients suffering documented infection and severe (grade 3/4) stomatitis. The incidence of toxic death was also increased in patients with moderate hepatic impairment. The severity of fluid retention, a cumulative toxicity of docetaxel, was found to be reduced, and its onset delayed, by prophylactic treatment with corticosteroids for 5 days, starting 1 day before docetaxel administration. Treatment with corticosteroids was also recommended to reduce the incidence and severity of hypersensitivity reactions and cutaneous toxicities. The most frequent severe non-haematological toxicity of docetaxel was asthenia. Other non-haematological toxicities were generally mild or moderate.

Keywords: Docetaxel (Taxotere®), hepatic impairment, fluid retention, corticosteroids.

Introduction

Docetaxel (Taxotere®) is an important novel therapy indicated for use in patients with locally advanced or metastatic breast cancer who have previously been treated with a cytotoxic regimen containing an anthracycline, and have recurrent disease, disease resistant to therapy, or have relapsed during an adjuvant therapy.

The recommended dose and schedule for administration of docetaxel is 100 mg/m^2, given intravenously over 1-h every 3 weeks. The patient population that has been used for the safety overview of docetaxel consists of 1070 patients recruited during phase II studies. These patients were suffering from a variety of solid tumours. A total of 4989 cycles of therapy were administered, with a median of four cycles per patient (range 1–25+). The median cumulative dose administered was 399 mg/m^2, with some patients receiving more than 1600 mg/m^2.

Risk factors can be predicted to a considerable extent by consideration of the known characteristics of the drug. Because docetaxel is metabolized in the liver, reduced hepatic function was recognized as a factor which could increase the toxicity of the drug, and has been studied prospectively. Since patients with severe hepatic impairment are excluded from phase II studies, pharmacokinetic studies were conducted in patients with hepatic function within normal limits and in patients with moderate hepatic impairment. The clearance of docetaxel by the liver was found to be reduced by 25–30% in patients who had liver transaminase levels more than 1.5 times the upper limit of normal (ULN) associated with alkaline phosphatase levels more than 2.5 times ULN [1]. This degree of impairment of hepatic function has proved to be a predictive factor in the incidence of febrile neutropenia, mucositis and toxic death, and these data will be reviewed here.

Moderate hepatic impairment and the safety of docetaxel

Treatment with docetaxel induced grade 4 neutropenia in 76% of patients in the safety overview population, and in 57% of cycles of therapy. This severe neutropenia was, however, short-lived. Figure 1 shows a typical neutrophil count profile after treatment with docetaxel, 100 mg/m^2. The median time to nadir was 8 days and the median nadir count was 0.4×10^3 cells/mm^3. The neutrophil count recovers quickly from this nadir, with the median time for recovery to 1.5×10^3 cells/mm^3 being 7 days. Since most patients have recovered adequate neutrophil counts by day 15 after treatment, the 3-week interval between doses is usually adequate and the intended dose intensity can be achieved.

Febrile neutropenia was recorded in 12.9% of the 1028 patients with liver function tests (LFTs) within the normal range in the safety overview population, and 23.8% of the 42 patients with elevated LFTs. The incidence of febrile neutropenia, expressed per cycle

Correspondence to HA Burris

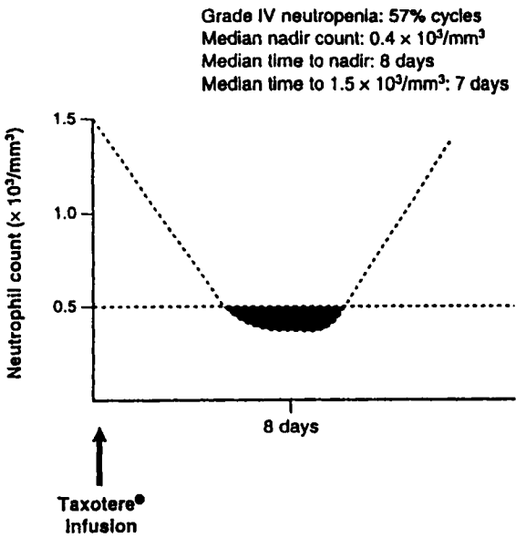

Figure 1. Typical neutrophil count profile following a 1-h intravenous infusion of docetaxel (n = 2407 evaluable cycles).

of treatment, in the overview population, in patients given docetaxel as second-line treatment, and in patients with anthracycline-resistant disease, is shown in Table 1 for patients with normal LFTs and patients with elevated LFTs. The impact of impaired hepatic function was statistically significant in all three patient groups. These results indicate that, although docetaxel induced severe neutropenia in 76% of evaluable patients and 57% of evaluable cycles of treatment in the safety overview population, neutropenia was complicated by fever in only 13% of patients and 3% of cycles, in patients with hepatic function within normal limits. When patients with impaired hepatic function are considered, it is apparent that impaired hepatic function increases the probability of fever developing in association with neutropenia. The incidence of documented infections is also increased in

Table 1. Febrile neutropenia by cycle (grade 4 with fever >38°C with antibiotics and/or hospitalization) following treatment with docetaxel

Patient population	Liver function tests		p
	Normal, events/total (%)	Elevated, events/total (%)	
Overall RPR*	155/4865 (3.2)	12/124 (9.7)	< 0.001
Breast second-line	49/1436 (3.4)	7/52 (13.5)	0.003
Anthracycline-resistant	30/758 (4.0)	4/28 (14.3)	0.029

*Integrated Safety Summary, data on file, Rhône-Poulenc Rorer (RPR); p values calculated using Fisher's exact test.

Table 2. Severe infections following treatment with docetaxel

Patient population	Liver function tests		p
	Normal, events/total (%)	Elevated, events/total (%)	
Overall RPR*	53/1028 (5.2)	7/42 (16.7)	0.007
Breast second-line	18/286 (6.3)	4/15 (26.7)	0.017
Anthracycline-resistant	9/127 (7.1)	4/7 (57.1)	0.002

*Integrated Safety Summary, data on file, Rhône-Poulenc Rorer (RPR); p values calculated using Fisher's exact test.

patients with impaired hepatic function, as summarized in Table 2.

Severe (grade 3/4) stomatitis was encountered in only 5.5% of patients with normal hepatic function in the safety overview population, and in 16.7% of the 42 patients with reduced hepatic function. The incidence of stomatitis in patients with elevated LFTs rose sharply for patients receiving second-line therapy (40%), and for patients with anthracycline-resistant disease (57%) (Table 3).

It is evident from these results that patients with moderately impaired hepatic function have an increased incidence of some severe toxicities. These patients are effectively being given an increased dose of docetaxel, since their clearance of the drug is reduced, and toxicities such as febrile neutropenia and stomatitis are dose-related. Toxic death is the ultimate consequence of such elevated toxicities, and the incidence of toxic death in the safety overview population, shown in Table 4, illustrates the significant impact of moderately impaired liver function on the safety of docetaxel. This vulnerable patient population can easily be identified before the start of docetaxel therapy, and treated at a reduced dose to avoid this increased toxicity. The population of patients with hepatic function within normal limits shows an incidence of toxic death of less than 2%, which supports the contention that docetaxel, at the recommended dose of 100 mg/m^2, has a good therapeutic index in patients who are severely ill with advanced breast cancer.

Preventative measures and the toxicity of docetaxel

Fluid retention was an unexpected cumulative toxicity of docetaxel treatment and caused significant numbers of withdrawals from phase II trials in which no prophylactic corticosteroid regimens were employed. The use of prophylactic corticosteroids to delay the

Table 3. Stomatitis (grade 3/4) following treatment with docetaxel

Patient population	Liver function tests		*p*
	Normal, events/total (%)	Elevated, events/total (%)	
Overall RPR*	57/1028 (5.5)	7/42 (16.7)	0.01
Breast second-line	27/286 (9.4)	6/15 (40.0)	0.003
Anthracycline-resistant	11/127 (8.7)	4/7 (57.1)	0.003

*Integrated Safety Summary, data on file, Rhône-Poulenc Rorer (RPR); *p* values calculated using Fisher's exact test.

Table 4. Toxic deaths following treatment with docetaxel

Patient population	Liver function tests		*p*
	Normal, events/total (%)	Elevated, events/total (%)	
Overall RPR*	18/1028 (1.7)	5/42 (11.9)	0.001
Breast second-line	4/286 (1.4)	3/15 (20.0)	0.003
Anthracycline-resistant	1/127 (0.8)	2/7 (28.6)	0.007

*Integrated Safety Summary, data on file, Rhône-Poulenc Rorer (RPR); *p* values calculated using Fisher's exact test.

onset and reduce the incidence of fluid retention was introduced during some phase II trials. A retrospective analysis of the occurrence of fluid retention in patients involved in phase II studies which have been completed is presented in Table 5 [2]. A 5-day course of prophylactic corticosteroids, starting the day before each treatment with docetaxel, delayed the onset and reduced the severity of fluid retention, compared with patients given no prophylactic medication. The median cumulative dose to the onset of moderate or severe fluid retention was increased from 490 mg/m^2 to 746 mg/m^2 and the incidence of severe cases of fluid retention was reduced from 20 to 6%. The number of patients discontinuing treatment because of this side effect was reduced from 32 to 3%. An interim analysis of data from 201 patients in ongoing phase II trials has confirmed these observations [2] with only half the patients showing any, and only 6% severe, fluid retention, and only 3/201 (1.5%) patients withdrawing from treatment because of this side effect of docetaxel. The prophylactic regimen of 5 days of corticosteroid treatment, starting the day before the docetaxel infusion, is now recommended for all patients in whom corticosteroid use is not contraindicated. The use of prophylactic steroids starting the day before the administration of docetaxel also reduces the incidence and severity of hypersensitivity reactions [3–5], and may reduce the severity of cutaneous toxicities [5,6].

Table 5. The influence of a 5-day course of prophylactic corticosteroids on fluid retention following treatment with docetaxel, 100 mg/m^2

	Without prophylactic steroids	With prophylactic steroids
Number of patients	60	32
Fluid retention		
All grades	76.7%	43.8%
Severe	20%	6.3%
Median cumulative dose		
At onset	490 mg/m^2	746 mg/m^2
Withdrawals due to		
Fluid retention	32%	3.1%

Overview of non-haematological toxicities of docetaxel

The most frequent severe non-haematological toxicity of docetaxel reported in the safety overview population was asthenia, with 69% of patients reporting some degree of asthenia, 30% of patients reporting moderate asthenia, and 11% reporting severe asthenia. Severe myalgias were reported in only 1% of patients. Arthralgias of any grade were infrequent (9%) with only 0.2% of patients reporting severe arthralgias.

Significant neuropathy was rarely observed. Nausea and vomiting are very generally mild or moderate with docetaxel therapy and anti-emetic prophylaxis is not routinely required.

Conclusions

In conclusion, a population with increased risk of toxicity due to reduced liver function has been identified, and limiting the exposure of that population to docetaxel improves the overall risk–benefit ratio for docetaxel. In addition, the cumulative toxicity of fluid retention can be reduced by prophylactic use of corticosteroids. Attention paid to these well defined toxicity prevention measures will help to optimize the use of this important novel treatment for advanced breast cancer.

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