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Docetaxel (Taxotere®), a review of preclinical and clinical experience. Part II: clinical experience

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Docetaxel, a promising inhibitor of microtubule depolymerization has shown significant anti-cancer activity during phase I and early phase II trials. The recommended dosage for phase II trials is 100 mg/m^2 every 3 weeks which provides optimal activity with tolerable adverse effects. Docetaxel has shown high single agent activity including use as first- or second-line therapy and in anthracycline refractory breast cancer patients. Results have been comparable to that of established treatments for breast cancer. In addition, docetaxel has shown significant activity in non-small cell lung cancer and a range of other tumors, but no activity in renal or colo-rectal tumors. At present it is undergoing further evaluation in combination therapy. The safety profile of docetaxel is well defined. Major adverse effects include hypersensitivity reactions, fluid retention and neutropenia. Peripheral neuropathy is not a significant adverse effect. The aims of phase II trials with regard to counteracting side-effects are therefore 2-fold: firstly, to evaluate the use of premedication with corticosteroids and antihistamines as a means of counteracting hypersensitivity reactions and fluid retention; secondly, to determine whether granulocyte colony stimulating factor may be useful for attenuating neutropenia.

Keywords: Docetaxel, Taxotere®, clinical, efficacy, safety.

Introduction

Following success in phase I studies in which docetaxel (Taxotere®) demonstrated potent anti-cancer activity against a variety of tumors including breast, ovarian and lung cancer, it is currently undergoing phase II development.

The following review will consider the clinical experience with docetaxel to date, including efficacy and safety data in a variety of tumor types.

Early clinical development

The primary aims of phase I studies initiated in 1989 were to determine the optimal dosage schedule for subsequent clinical development, to define the maximum tolerated dose and to characterize the pharmacokinetic profile of docetaxel. Since paclitaxel had demonstrated good activity against breast and ovarian cancer, approximately 50% of patients recruited into phase I studies had one of these two tumor types. The remaining 50% of patients had colorectal (12%), lung (8%), sarcoma (6%), melanoma (4%) and other (20%) cancers.[88]

Dose-ranging studies

In phase I studies patients received i.v. docetaxel at total dosages of 5–130 mg/m^2.[89–95] The infusion time of docetaxel varied between 1 and 24 h (Table 1). In all cases, the dose-limiting adverse effect was neutropenia. Full neutropenic recovery was achieved by administering docetaxel every 3 weeks in all but one study,[92] in which docetaxel was administered every 2 weeks. With the exception of one study[93] for which results are still pending, the maximum tolerated dose was 115 mg/m^2.

Blaney *et al.*[96] administered docetaxel 55–75 mg/m^2 i.v. every 3 weeks to 23 pediatric patients (median age 14 years) with refractory cancer. The authors reported that the maximum tolerated dose of 65 mg/m^2 in these heavily pretreated children was lower than that in a comparable group of adult patients on the same dosage schedule (Table 1).

Clinical pharmacokinetics

Serum docetaxel concentrations are assayed using a highly sensitive HPLC technique. The pharmacokinetics of docetaxel 20–115 mg/m^2 were reported by Extra *et al.*[92] in 23 patients with a variety of tumor types that had failed to respond to standard therapy (Table 2). Docetaxel exhibited linear pharmacokinetics; the area under the concentration–time curve increased in proportion to dose and the total plasma clearance was independent of dose. Between

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Table 1. A summary of dosage schedules and maximum tolerated dose in phase I studies of docetaxel

Schedule	Course interval (weeks)	Maximum tolerated single dose (mg/m^2)	Response rates	References
1–2 h	2–3	115	one PR in each of ovarian, breast, SCLC and unknown primary site; eight subjective response (five ovarian and three with breast cancer)	92
1 h	3	NA	15 responses in patients with cancers of the breast, ovary, bladder and lung (NSCLC) and larynx	94
2 h	3	115	four PR (two adenocarcinoma of the lung, one breast cancer and one cholangiocarcinoma)	91
1 h, days 1 + 8	3	110	five PR in breast cancer and one with adenocarcinoma unknown origin	95
6 h	3	100	one PR in breast cancer	91
24 h	3	90	no partial or complete responses reported	90
1 h × 5 days	3	80	responses in five patients with ovarian cancer and one with breast cancer	93

Abbreviations: SCLC, small cell lung cancer; NSCLC, non-small cell lung cancer.

doses of 20 and 70 mg/m^2 the docetaxel plasma profile was biphasic; however, this changed to a triphasic profile at doses of 85 to 115 mg/m^2, resulting in a longer estimate of the terminal half-life (Figure 1). The authors suggested that observation of the third elimination phase for taxotere may be due to the higher sensitivity of the assay method.

The recommended dosage of docetaxel based on phase I pharmacokinetic and dose-ranging studies for subsequent phase II trials was therefore 100 mg/m^2 as a 1-h infusion every 3 weeks. This dosage schedule combined acceptable tolerability whilst allowing full neutropenic recovery between treatment courses.

Phase I trials also identified docetaxel potency in various tumor types, particularly breast and ovarian cancer (Table 1). In addition, the efficacy of docetaxel in combination with other anti-cancer agents is undergoing evaluation, and further pharmacokinetic studies of docetaxel in this setting are necessary.

Phase II studies

Following very encouraging results in phase I studies, further investigation of docetaxel activity as

Table 2. A summary of the pharmacokinetic data from 23 patients given docetaxel 20–115 mg/m^2 i.v.[92]

	Dose	
	20–70 mg/m^2	85–115 mg/m^2
No. of patients	9	14
Dose (mg/m^2)	20–70	85–115
Infusion duration (h)	1–1.68	2.41–2.68
C_{max} (μg/ml)	0.42–3.8	2.41–2.68
AUC (μg/ml h)	0.67–2.79	4.1–5.19
Elimination half-life (h)	2.2–4.6	9.6–18.5
Clearance ($l/h/m^2$)	20.8–39.9	17.0–22.6
V_{ss} (l/m^2)	12–16	53–95
Renal excretion in 24 h (%)	1.2–9	2.1–3.5

Abbreviations: AUC, area under the concentration–time curve; C_{max}, peak plasma concentration; V_{ss}, volume of distribution at steady state.

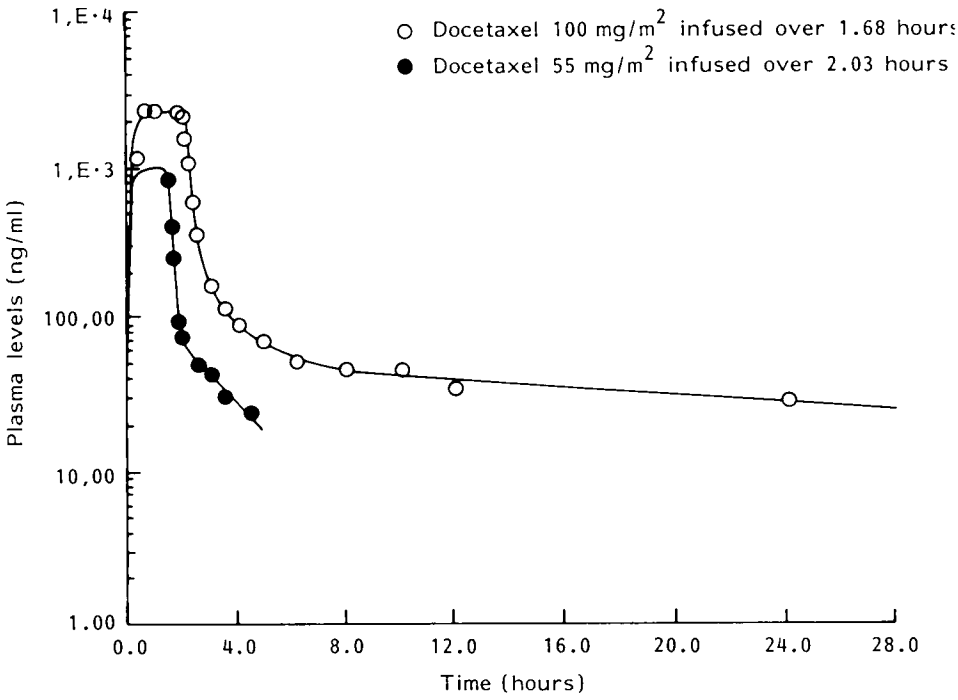

Figure 1. The docetaxel plasma concentration–time curve from two patients following two different single doses of i.v. docetaxel.[92] ©AACR. Graph reproduced with permission from *Cancer Research* 1993; 53 (5)

either a first- or second-line single agent in a variety of tumor types was undertaken in phase II trials.

Breast cancer

Breast cancer is a leading cause of cancer death in women. Each year in the US approximately 180 000 new cases of breast cancer are diagnosed and there are approximately 46 000 breast cancer deaths.[97] Although the incidence of breast cancer appears to increase each year, mortality rates have remained relatively stable. Increased screening and advances in disease management are two possible explanations for this apparent anomaly.

The choice of first-line systemic therapy is largely dependent on the patient's estrogen receptor (ER) status and to a lesser extent on menopausal status. Approximately 30% of patients respond to first-line endocrine treatment[98] and in non-responders chemotherapy may be given as second- or third-line therapy. In contrast, chemotherapy is the first-line choice in ER-negative patients.

At present, the most active single chemotherapeutic agents are the anthracyclines doxorubicin and epirubicin, which produce response rates of 20–40%.[98] Combination chemotherapy is even more effective. Two of the most frequently used regimens—cyclophosphamide, doxorubicin and 5-fluorouracil, and cyclophosphamide, methotrexate and 5-fluorouracil—have produced response rates of 37–82%.[89]

During phase I trials it was observed that docetaxel could produce response rates in breast cancer at doses lower than those which have now been recommended for phase II studies. To date, seven phase II trials have confirmed the efficacy of first- and second-line docetaxel as monotherapy in metastatic breast cancer (Table 3).

First-line therapy. In three studies involving a total of 88 women with metastatic breast cancer, first-line therapy with docetaxel 100 mg/m^2 given every 3 weeks achieved an overall response rate of 57–69% (Table 3).[99–102] Using a similar dosage schedule in 34 patients and a reduced dosage of 75 mg/m^2 every 3 weeks in a further 11 patients, Eisenhauer reported an overall response rate of 67%. A lower response rate of 38% achieved in one study may be considered unrepresentative because of the small number of patients involved (n = 8).[102]

Second- and third-line therapy. Five phase II studies have assessed the efficacy of docetaxel 100 mg/m^2 i.v. every 3 weeks as second-line therapy.[102–106] The overall response rate in a total of 135 evaluable patients in these studies ranged between range 54 and 58% (Table 3).

Table 3. Summary of phase II studies of docetaxel in metastatic breast cancer

Investigators (reference)	No. of patients enrolled/ evaluable	Prior chemotherapy	Dosage regimen	Complete Response	Partial Response	Response rate (%)
Fumoleau *et al.*[99]	35/32	first-line	100 mg/m^2 over 1 h every 3 weeks	4	18	69
	40/31		75 mg/m^2 over 1 h every 3 weeks	2	14	52
Seidman *et al.*[100]	18/14	first-line	100 mg/m^2 over 1 h every 3 weeks	2	6	57
Eisenhauer *et al.*[101]	51/45	first-line	100 mg/m^2 over 1 h every 3 weeks (n = 34) then all patients received 75 mg/m^2 thereafter	—	—	67
Ten Bokkel Huinink *et al.*[102]	39/32	first-line (n = 8)	100 mg/m^2 over 1 h	1	2	38
		second-line (n = 24)	every 3 weeks	1	13	58 overall: 53
Ravdin *et al.*[103]	28/26	second-line	100 mg/m^2 over 1 h every 3 weeks	3	11	54
Valero *et al.*[104]	35/33	second- or third-line	100 mg/m^2 over 1 h every 3 weeks	—	18	55
Piccart *et al.*[105]	70/52	second-line	50 mg/m^2 on days 1 and 8 every 3 weeks	1	17	34
Taguchi *et al.*[106]	51/50[a]	advanced and recurrent	60 mg/m^2 over 1 h every 3–4 weeks	2	19	42
	155/133[b]			—	—	46 and 55 in two studies

CR, complete response; NA, not available; PR, partial response.
[a] Early phase II.
[b] Late phase II.

Further analysis of combined data from two phase II studies of 68 evaluable breast cancer patients who were refractory to treatment with anthracyclines or anthracenediones showed a better than expected response to docetaxel.[104] The overall response rate was 55% (three complete and 35 partial responses). Responses were also seen in all metastatic sites, including chest wall, liver and lung.

Other docetaxel regimens in first- and second-line therapy. Following phase I investigations in Japan, which determined the maximum tolerated dose to be 70 mg m^2, one study investigated second-line docetaxel at a dose of 60 mg m^2 every 3–4 weeks in patients with advanced or recurrent breast cancer.[106] Details on prior chemotherapy are not provided; response rates were very good (55 and 46% in two independent studies), but not as high as those achieved with docetaxel 100 mg m^2.

Fumoleau *et al.*[99] administered a reduced dosage of docetaxel (75 mg m^2 i.v. every 3 weeks) as first-line therapy to 31 patients. The response rate (52%) was lower than that observed in the 32 patients who received full-dose docetaxel (69%) and there was no parallel improvement in the safety profile. Preliminary evaluation of a regimen comprising docetaxel 50 mg/m^2 on days 1 and 8 every 3 weeks has shown an even lower response rate of 34%; final results of this study are pending.[107]

Duration of response. For many studies it is still too early to determine the median duration of response. In one study comparing first-line docetaxel 100 mg/m^2 with docetaxel 75 mg/m^2 every 3 weeks, the median duration of response was 44 (range 12–69) and 34 (range 11–42) weeks, respectively.[99] An overall median duration of response of 38 weeks was reported in 32 patients receiving docetaxel 100 mg m^2 every 3 weeks as first- or second-line therapy.[102]

Response rates in metastatic sites. The median survival time associated with liver metastases is lower than that associated with other sites of metastases

such as bone or soft tissue.[107] Sixteen women with advanced breast cancer and liver metastases (four with single and 12 with multiple lesion sites) have been enrolled in an ongoing trial of first-line docetaxel 100 mg/m^2 every 3 weeks. An overall response rate of 75% (four complete and eight partial responses) has been obtained with regard to liver metastases to date. The complete responses were obtained in single (n = 1) and multiple metastatic sites (n = 3). A greater proportion of patients with isolated liver metastases responded compared with those who had more widespread disease.[108] Other groups have also reported high mean response rates for liver metastases of 45[104] and 50%.[109]

Survival data is still scarce, although one group has reported a combined median duration of survival for patients with liver or soft tissue metastases of more than 5 months.[105]

Lung cancer

Lung cancer is the most common form of neoplastic worldwide. Approximately 900 000 new cases occur each year and in 1994 an estimated 172 000 of these will have occurred in the US.[110,111] Most lung cancer deaths are attributed to metastatic non-small cell lung cancer (NSCLC).[112] First-line monotherapy with cisplatin, ifosfamide, mitomycin and the vinca alkaloids produces response rates of 18–22% in inoperable NSCLC.[113,114] Combination therapy with these agents in advanced NSCLC achieves response rates in the order of 30–51%.[115]

Preliminary results with first-line docetaxel 100 mg/m^2 every 3 weeks in recent phase II studies with first-line docetaxel 100 mg/m^2 every 3 weeks have been particularly promising (Table 4).[91, 116–118] In particular, a response rate of 38% achieved with docetaxel in a study of 29 patients with pathologically confirmed NSCLC is greater than the maximum response expected with any other single agent in current clinical use.[118] Furthermore, docetaxel has produced comparable response rates in patients who are refractory to cisplatin therapy (Table 4).[91,117]

Ovarian cancer

More women die from ovarian cancer than any other gynecological cancer and it is the fourth most common cause of cancer death in women.[119]

Three phase II studies of treatment with docetaxel in ovarian cancer have yielded data for 200 patients (Table 5).[120] All patients had received prior plati-

Table 4. A summary of open phase II studies with docetaxel as first-line and second-line treatment in NSCLC

Study (reference)	No. of evaluable patients	Response rate (%)	Median duration of response (months)
MSKCC[118]	29	38	≥5
EORTC-ECTG[116]	37	23	9
MDACC[117]	39 (41)	33 (27)	≥5
UTHSC[91]	14 (14)	21 (20)	ongoing

Figures in parentheses indicate patients refractory to cisplatin; MSKCC, Memorial Sloan-Kettering Cancer Center; EORTC-ECTG, European Organization for Research and Treatment of Cancer—Early Clinical Trials Group; MDACC, MD Anderson Cancer Center; UTHSC, The University of Texas Health Science Center at San Antonio.

Table 5. Summary of response rates from three phase II trials with docetaxel 100 mg/m^2 i.v. for advanced ovarian cancer[120]

Parameter	Study		
	ECTG pooled data[a]	MDACC	Total
No. of evaluable patients	160	40	200
Complete response (CR)	9	1	10 (5%)
Partial response (PR)	40	13	57 (28.5%)
Progressive disease	43	3	46 (22%)
CR + PR	49 (31%)	14 (35%)	67 (33.5%)

[a] Pooled EORTC results consists of data from the Early Clinical Trials Group and the Clinical Screening Group.

num therapy and were stratified according to their previous response to platinum therapy, ranging from patients who were refractory to those who had shown some sensitivity. All patients received docetaxel 100 mg/m^2 i.v. every 3 weeks. Preliminary data are also available for a further 24 platinum-refractory patients; results to date show a partial response rate of 33%.[121]

It is still too early to assess the duration of response fully; nevertheless, docetaxel shows significant activity in the treatment of ovarian cancer. Present data show that approximately a third of patients respond to docetaxel irrespective of response to previous platinum therapy. However, its precise role in the management of advanced ovarian cancer will not be ascertained until the results of ongoing phase II trials with cisplatin/docetaxel combinations are complete.

Other tumors

In addition to breast cancer, NSCLC and ovarian cancer, phase II studies have demonstrated various degrees of activity with docetaxel in the following cancers: melanoma,[122–124] head and neck cancer,[124,126] gastric cancer,[127] urothelial cancer, soft tissue sarcomas,[128] pancreatic cancer[129,130] and small cell lung cancer.[131] In addition two phase II studies in urothelial cancer are still ongoing; preliminary results have given response rates of up to 50% (Figure 2).[132]

The response rate with docetaxel in head and neck cancer (34%) is particularly impressive compared with that obtained with current standard therapy using methotrexate (18%).[133] Furthermore, encouraging results with docetaxel in gastric cancer suggest that investigation into combination therapy regimens for gastric cancer would be valuable. This is especially important following the results of a recent study which showed that a combination of 5-fluorouracil with other conventional agents failed to improve upon survival rates obtained with 5-fluorouracil monotherapy.[134]

Docetaxel may also prove to be a valuable therapeutic option in metastatic malignant melanoma and soft tissue sarcomas, which do not respond well to conventional chemotherapy. The reported response rates for melanoma with dacarbazine vary between 0 and 30%; hence response rates with docetaxel of 8[124] and 17%[125] are encouraging. Only three drugs are presently available to treat soft tissue sarcomas—doxorubicin, dacarbazine and ifosfamide, and these produce a response rate of more than 15%.

Colorectal[135–137] and renal cancer[138,139] showed no response to docetaxel.

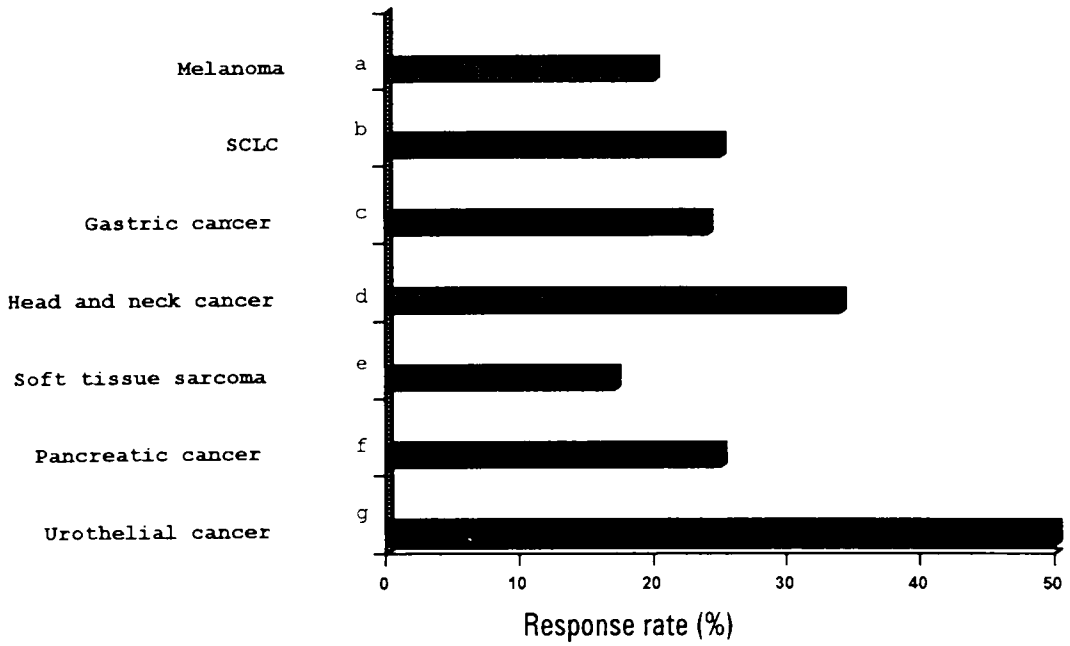

Figure 2. The average response rates obtained in phase II studies of docetaxel in various tumor types. [a] Aamdal *et al.*,[122] Bedikian *et al.*,[123] Einzig *et al.*;[124] [b]Smyth *et al.* 1994;[131] [c]Sulkes *et al.*;[127] [d]Catimel *et al.*,[125] Dreyfuss *et al.*;[126] [e]Van Hoesel *et al.*,[128] [f]De Forni *et al.*,[129] Ducreux *et al.*,[130] [g]De Wit *et al.*[131]

Extended pharmacokinetic data

Combination therapy. Various combination regimens of docetaxel and cisplatin are currently being evaluated in phase I and early phase II studies, and initial results have shown promising activity in NSCLC[140] and other solid tumors.[141] The pharmacokinetic profile of docetaxel in these regimens appears to be unaffected by the sequence of drug administration. However, there may be clinical implications regarding the reduced DNA–adduct levels of cisplatin when this is administered after docetaxel; this is undergoing further investigation.[142] Furthermore, the tolerability of chemotherapy may also be affected by the sequence of drug administration.[141]

Impaired hepatic metabolism. Measurements of pharmacokinetic and pharmacodynamic parameters have been undertaken in patients with metastatic cancer of the breast, ovary and colon.[143] Decreased clearance and increased toxicity indicate that a reduced dosage of docetaxel may be necessary in patients with liver metastases and abnormal liver function.[143]

Safety

Docetaxel has now been used in many hundreds of patients and the safety profile is well characterized. Accumulation of data is still ongoing, with the results of many studies only available in abstract form. Results from the first 450 evaluable patients in phase II trials are summarized in Figure 3.

Nausea and vomiting can be very distressing and debilitating, and is associated with many anticancer agents.[145] Importantly, docetaxel is not highly emetogenic. In 46 breast cancer patients receiving docetaxel 100 mg/m^2 every 3 weeks, 35% of patients experienced grade I or II vomiting. However, nausea was easily prevented using standard antiemetics.[144] Other gastrointestinal effects included diarrhea (70%) and stomatitis (63%).[101]

Neutropenia was the dose-limiting toxicity identified in phase I trials. Although it was uncommon at doses below 70 mg/m^2, at higher doses 70–100% of patients experienced myelosuppression. The occurrence of fever and mucositis appeared to be independent of dose and was associated with longer infusion schedules.[88]

The combined results of these phase II studies with 104 patients identified grade IV neutropenia as the most common major adverse event in patients with NSCLC, affecting 70% of patients.[117] Severe neutropenia (greater than grade II) occurred in 76% of all the MSKCC study group patients, but recovery occurred after 21 days.[114]

In the largest study to date in breast cancer patients (n = 46), 98% of patients experienced grade III or IV neutropenia. Ten of the 11 patients requiring hospitalization for febrile neutropenia had been

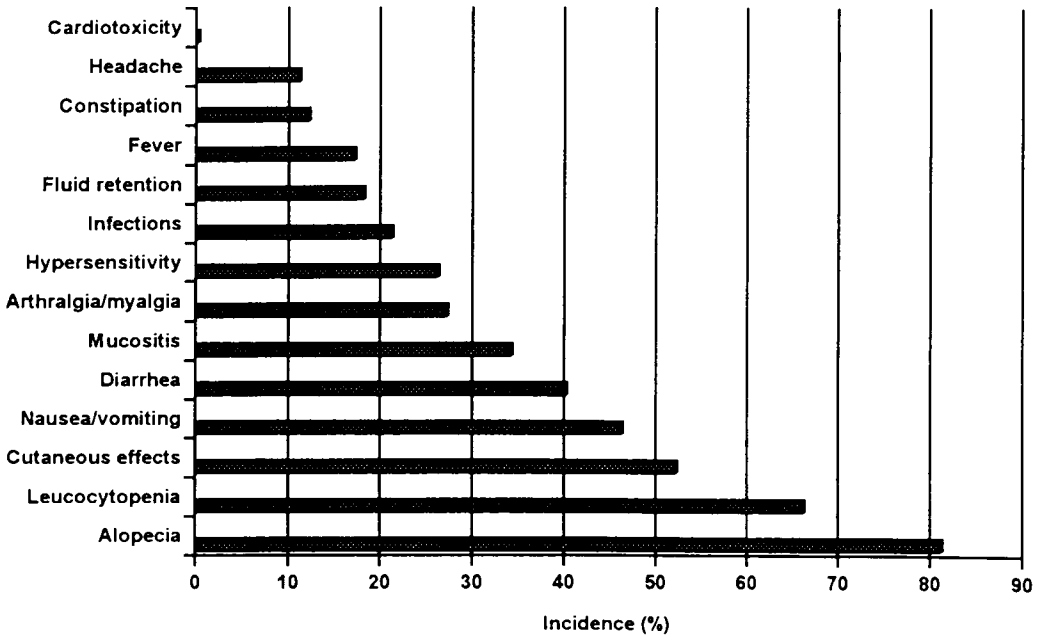

Figure 3. Adverse effects reported in the first 450 evaluable patients in phase II trials of docetaxel.[144]

treated with docetaxel 100 mg/m^2. However, severe infection only occurred in one patient.[146] Another study also showed that although grade III–IV neutropenia occurs frequently, the incidence of febrile episodes is below 10%.[120] The neutropenia associated with docetaxel therapy has an early onset, with the nadir occurring at day 5–8;[144] however, neutrophil recovery is sufficiently rapid to allow retreatment at 21 days.[102] Other hematological adverse effects (e.g. thrombocytopenia, anemia) have rarely been reported.

The occurrence of fluid retention appears to be related to the cumulative dose of docetaxel. The reported incidence rapidly increases at cumulative doses above 400 mg/m^2.[147] Fluid retention occurred in 50% of breast cancer patients receiving 75–100 mg/m^2 every 3 weeks without premedication.[101] Generally, fluid retention is peripheral, although it may also cause pleural effusions and ascites.[144] The problem is particularly troublesome in patients with ovarian cancer where development of ascites is generally associated with disease progression.[120] In most patients natural resolution occurs slowly when docetaxel is discontinued. Fluid retention can also be controlled by using premedication (discussed later), treating with diuretics, delaying retreatment and reducing docetaxel.[118]

The majority of hypersensitivity reactions (HSRs) occur within minutes of initiating an infusion.[148] HSRs have been reported in 33[100] and 57%[101] of breast cancer patients, and can largely be controlled using premedication regimens of corticosteroids and H_1- and H_2-histamine antagonists.[148] A premedication regimen of methylprednisolone 32 mg, cetirizine 10 mg and ketotifen 1 mg completely blocked the HSR to docetaxel in all but one of 14 patients.[149] Other studies have also sought to evaluate various premedication regimens.[150,151] Although the results are still preliminary and the optimal regimen has not yet been defined, they are nonetheless very encouraging. Furthermore, prophylactic management with steroids is showing promise in the prevention of fluid retention.[149–151]

Mild to moderate peripheral neuropathy has been reported with docetaxel but this is not not dose limiting and may be reversible.[152]

In common with many anticancer agents, alopecia almost always occurs with docetaxel therapy, although it is fully reversible once therapy ceases.[144] Skin reactions are common and occasionally severe, manifesting as erythema, rash and nail changes.[146] They can be treated with an ointment of glycerin and chlorhexidine.[149] Other adverse effects of lesser clinical relevance include arthralgia, myalgia and headache.[144] Importantly, docetaxel is not associated with any cardiac, renal, liver or endocrine dysfunction.[144]

Conclusion

Docetaxel is a new anticancer agent with significant single agent activity in a broad spectrum of tumor types. It has shown particular activity as a single agent in breast and lung cancer where it has similar efficacy to established anticancer therapy. The dosage schedule which provides optimal benefit/risk ratio is well-defined, at 100 mg/m^2 every 3 weeks in all indications.

The safety profile of docetaxel has been established in phase I and II studies. Furthermore, the use of premedication to counteract those effects most frequently implicated in withdrawal from therapy (i.e. skin toxicity, HSRs and fluid retention) has produced promising results.

Future studies, some of which are already underway, should aim to achieve the following: further define the optimal premedication regimen required to combat fluid retention; establish the role of docetaxel in combination regimens; and define the role of granulocyte-colony stimulating factors in minimizing the complications of neutropenia with higher doses of docetaxel.

Clearly, docetaxel is a very promising new anticancer agent and the results of further clinical studies are anticipated with optimism.

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