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Original Paper

Efficacy and Safety of Docetaxel (Taxotere™) in Heavily Pretreated Advanced Breast Cancer Patients: the French Compassionate Use Programme Experience

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The aim of this investigation was to assess retrospectively docetaxel safety and efficacy in advanced breast cancer patients in a French compassionate use programme. Patients had received >1 prior chemotherapy regimen for advanced disease, were either anthracycline-resistant (that is progressed within 6 months after anthracycline-based chemotherapy) or had received the maximum cumulative dose. The recommended docetaxel dose was 100 mg/m^2/cycle (75 mg/m^2 in case of liver function impairment: transaminases >1.5×upper limit of normal (ULN), alkaline phosphatases >3×ULN). Between August 1993 and December 1995, 889 patients were treated in 67 French centres, of whom 870 were evaluable for safety and 825 were evaluable for patient and treatment characteristics and efficacy. 20.5% (of the 825 patients evaluable for baseline characteristics) had poor performance status (PS≥2), 49.3% liver metastasis and 9.6% biological liver dysfunction. 98.4% had been previously treated by anthracyclines, 50.8% had resistant disease and 37.1% had received >2 prior palliative chemotherapy lines. The most frequent severe toxicity, febrile neutropenia (reported in 223/870 (25.6%) patients evaluable for safety), caused 10 deaths, 6 of these being patients with severe liver impairment before inclusion. Fluid retention syndrome and other common non-haematological toxicities were well tolerated. 3.1% (28/889) of all patients and 11.4% of those with liver dysfunction, died from treatment-related causes. The overall response rate in 825 assessable patients was 22.9% (95% confidence interval (CI): 20.2–26.2%). Median time to treatment failure was 4 months (95% CI: 3.6–4.3) and median survival was 9.8 months (95% CI: 8.8–10.7). This report on the largest series of unselected advanced breast cancer patients treated with docetaxel, supports previous phase II studies, confirming docetaxel's utility in patients relapsing after failing anthracycline-containing palliative chemotherapy. © **1999 Elsevier Science Ltd. All rights reserved.**

Key words: advanced breast cancer, docetaxel, compassionate use, anthracycline, liver metastasis, liver impairment
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INTRODUCTION

ANTHRACYCLINES, INTRODUCED over 20 years ago, have contributed to the improvement of survival and quality of life of metastatic breast cancer patients [1]. The cyclophosphamide/5-fluorouracil/anthracycline combination was until recently the standard first-line treatment of metastatic disease. However, the median time to progression is generally less than 18 months [1], and median survival has only slightly improved in the last 10 years [2]. In patients relapsing after first-line

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metastatic treatment with anthracyclines, other standard agents have proven to be poorly active. In recent studies, the overall response rate (ORR) to the second line mitomycin C/vinblastine combination [3] and to vinorelbine [4, 5] was less than 20%.

Docetaxel (Taxotere™; Rhône-Poulenc Rorer, Antony, France), is a recently available anticancer agent of the taxane class. It has shown a high level of activity against advanced breast cancer in several phase II studies. Similar response rates have been observed in first- and second-line metastatic treatment (52–67% and 44–58%, respectively) [6–15], even in anthracycline-resistant patients [12, 13, 15], or in patients with liver metastases [6–15]. In phase I and II studies, the principal dose-limiting toxicity of docetaxel at 100 mg/m^2 per cycle was severe neutropenia, occurring in nearly all cycles. However, it was generally short-lived and rarely complicated by fever or infection. A fluid retention syndrome characterised by peripheral oedema, weight gain and, sometimes, non-malignant serous effusions was related to the cumulative dose of docetaxel administered. During early clinical studies, this syndrome led to the withdrawal from treatment of a number of patients. A 3-to-5-day steroid regimen, starting the day before docetaxel administration, reduces its incidence and severity [16]. The other main non-haematological toxicities are reversible alopecia, sensitive neuropathy, nail disorders and asthenia.

Hepatobiliary extraction is the major route of elimination of docetaxel [17]. In a pharmacokinetics/pharmacodynamics analysis, a 27% decrease in docetaxel clearance was observed in patients with concomitant elevations of transaminases $>1.5\times$the upper limit of normal (ULN) and of alkaline phosphatase $>2.5\times$ULN [18]. Patients presenting these liver dysfunctions and treated at the dose of 100 mg/m^2 per cycle are at a higher risk of developing febrile neutropenia, thrombocytopenia and severe stomatitis [19]. Therefore, an initial 25% dose reduction is currently recommended in such patients.

Positive results in the initial clinical studies led Rhône-Poulenc Rorer (RPR) to submit a marketing authorisation dossier for docetaxel to the European Medical Agency on 19 July 1994. From this date, RPR and the French Medical Agency made docetaxel available to practising oncologists through a compassionate use programme, 'Autorisation Temporaire d'Utilisation' (ATU), which lasted until the drug was approved by the European Medical Agency on 27 November 1995. The aim of this programme was to provide docetaxel to patients with chemotherapy-resistant advanced breast cancer who could not be entered in ongoing clinical trials with the drug, and for whom no standard salvage treatment was available. In this paper, the serious and unexpected adverse events reported in this patient cohort are reported. In addition, the safety and antitumoral efficacy of docetaxel are further characterised, in these patients who most closely reflect the population actually treated in daily practice.

PATIENTS AND METHODS

Between 8 August 1993 and 19 July 1994, docetaxel was exceptionally supplied by RPR for humanitarian treatment. From 19 July 1994 to 27 November 1995, docetaxel was provided through the ATU programme. Docetaxel continued to be supplied until its effective marketing in France on 31 December 1995. This study reports on all the advanced breast cancer patients treated in France with docetaxel outside clinical trials between 8 August 1993 and 31 December 1995.

Patient population

The ATU allowed the use of docetaxel in patients with advanced progressive breast cancer who had received at least one standard chemotherapy regimen for advanced disease. Patients were required to be ineligible for anthracycline treatment because of resistant disease (that is progressive disease within 6 months of completion of an anthracycline-based regimen), medical contraindication, or having received a maximum permitted cumulative dose. Moreover, patients had to be ineligible for inclusion in an ongoing docetaxel study. Other inclusion criteria were: age between 18 and 75 years; performance status (PS) ≤ 2; adequate bone marrow function (absolute neutrophil count $\geq 2\times10^9$/l, platelet count $\geq 100\times10^9$/l), adequate renal function (creatinine level ≤ 1.25 ULN), and adequate hepatic function (serum bilirubin ≤ 1.5 ULN and transaminases ≤ 5 ULN). The protocol did not require measurable or evaluable tumour sites.

Patients were considered ineligible for the ATU if they were pregnant or breast-feeding, had serious illnesses (such as active infection, uncontrolled hypertension, congestive heart failure, or recent myocardial infarction), had a prior history of significant neurological or psychiatric disorders that would interfere with the intention of informed consent. Patients who were receiving concomitant treatment with other experimental agents, or who had received previous treatment within a clinical trial less than 30 days prior to study entry were also ineligible. The protocol recommended not to include patients with active cerebral or leptomeningeal disease, but it was not an absolute exclusion criterion.

Docetaxel was supplied by RPR on an individual case request basis and its use was the sole responsibility of prescribers, who had to establish the eligibility of each patient for inclusion. All of the patients who entered the ATU gave written informed consent.

Treatment

The recommended dose of docetaxel was 100 mg/m^2 as a 1-h intravenous infusion every 3 weeks. However, a 25% dose reduction (that is 75 mg/m^2) was recommended in the case of abnormal liver function tests: grade 3 bilirubin, transaminases $>3\times$ULN, or transaminases $>1.5\times$ULN associated with alkaline phosphatanes $>2.5\times$ULN. Premedication with dexamethasone was recommended before each administration (4 mg twice daily from day -1 to day 4).

Treatment was to be given for a maximum of six cycles to patients presenting stable disease, and for a maximum of nine cycles to patients presenting an objective response. Treatment was to be discontinued in the case of progressive disease, unacceptable toxicity or upon the patient's request. Treatment was to be delayed for 1 or 2 weeks if the neutrophil count was less than 1.5×10^9/l or if the platelet count was less than 100×10^9/l. If no recovery was observed after 2 weeks, treatment was to be discontinued. Dose adjustments in the case of severe toxicities were as follows: if the prior dose level was 100 mg/m^2, the dose for all subsequent cycles was to be 75 mg/m^2, if it was 75 mg/m^2, the subsequent dose was to be 55 mg/m^2. Treatment had to be discontinued if severe toxicity still occurred at 55 mg/m^2. Dose reductions had to be maintained for all subsequent cycles. Severe toxicities requiring dose reduction were: neutrophil nadir

$<0.5\times10^9$/l lasting more than 7 days, febrile neutropenia, platelet nadir $<25\times10^9$/l, nausea-vomiting and/or diarrhoea graded 3 or 4 according to the National Cancer Institute-Common Toxicity Criteria (NCI-CTC), and grade 2 or more peripheral neurotoxicity. According to the protocol, an assessment of tumour response had to be performed at the beginning, and at least once more at the end of treatment, employing the appropriate tests. Blood cell counts had to be performed at least before each cycle.

Study assessment and quality control

The treating physicians had to use specific case report forms to report information concerning patient identification (whilst respecting patient confidentiality), docetaxel treatment, and safety. The serious adverse events (SAE) occurring during treatment or within 30 days after the last docetaxel infusion had to be reported on specific report forms. SAEs encompassed events which were fatal or life-threatening and/or required or prolonged patient hospitalisation, whether or not considered as drug related. This data collection was carried out with a pharmacovigilance objective. From July to October 1996, a second, retrospective data collection was undertaken via examination of clinical records, with the aim of assessing docetaxel efficacy in the ATU population. This involved retrospectively collecting and analysing in greater detail patient characteristics, treatment and efficacy parameters, based on clinical source record verification. Safety data were also verified, completed and analysed from the initial case report forms. In particular, the SAEs were source verified, and classified according to their causality relationship to docetaxel (possibly/probably, remotely, or not related). For reasons of review feasibility, patients treated in centres having recruited fewer than 5 patients were excluded from the retrospective clinical record review, except when an SAE had been reported in this centre. In this case, the SAE was source verified and all the cases in the centre were reviewed.

Before each new cycle, clinical or laboratory abnormalities arising since the previous treatment were recorded by the treating physicians, and toxicities were graded according to either National Cancer Institute (NCI) criteria, or clinically, as mild, moderate, or severe. For data analysis, adverse effects graded following NCI criteria were converted into the three-level clinical system: toxicities graded as 1 were considered as mild, grade 2 as moderate and grades 3 and 4 combined together as severe.

Response was assessed according to World Health Organization (WHO) criteria [20]. No patient with bone metastases as their only disease site was considered a complete responder. Isolated variations in the level of tumour markers (Ca 15.3 and carcino-embryonic antigen (CEA)) were never used to determine tumour response category, but were considered of corroborative value for response assessments obtained via objective clinical or imaging methods. Given the lack of guidelines in the protocol on the periodicity of tumour evaluation, patients could be defined as having complete response (CR), partial response (PR) or stable disease (SD), even if only one assessment had shown a decreased or unchanged tumour size.

Patients were considered as anthracycline-resistant if they relapsed or showed disease progression within 6 or 3 months after the completion of adjuvant or palliative anthracycline treatment, respectively. Such patients were further considered to have anthracycline-refractory disease, if tumour progression was the best response to first-line chemotherapy with an anthracycline for advanced disease, or if they relapsed during anthracycline-based adjuvant treatment. Patients never treated with anthracyclines, or progressing more than 6 months after adjuvant chemotherapy, or more than 3 months after palliative chemotherapy, were classified as non-resistant. We defined liver dysfunction as AP $>3\times$ULN associated with transaminases $>1.5\times$ULN.

Statistical analysis

Patients registered in the ATU but not treated with docetaxel were excluded from all analyses. The safety analysis was performed on all patients who had received at least one cycle of docetaxel and for whom the initial data collection realised by treating physicians was available. Analyses of inclusion characteristics, safety, treatment and efficacy were carried out on patients who had received at least one cycle of docetaxel and whose clinical records were reviewed. Efficacy parameters were Response Rate (RR), time to treatment failure (TTF), and overall survival (OS). All cases of early treatment discontinuation (before the fourth cycle) without evidence of progressive disease were classified as early treatment failure, whatever the reason for discontinuation (toxic death, unacceptable toxicity, patient's request, lost to follow-up). The response rate was calculated with 95% confidence intervals. Time to treatment failure was the time between the first day of treatment and the date of the first event considered as treatment failure. Such events could be progression, early discontinuation whatever its cause, or death. Survival was the time between the first day of treatment and the date of death, patients being censored at the date they were last known to be alive. TTF and OS curves were obtained using the Kaplan–Meier method [21]. The statistical analysis was performed using Statistica (version 5.1, Statsoft Inc., Tulsa, Oklahoma, U.S.A.) and SPSS software (version 6.1, SPSS Inc., Chicago, Illinois, U.S.A.). Preliminary results have been reported previously in abstract form [22–25]. The cohort follow-up was closed on 30 June 1997.

RESULTS

From 8 August 1993 to 31 December 1995, 945 patients were registered in the ATU programme. 56 of them did not receive docetaxel treatment so only 889 patients who received at least one cycle of docetaxel were included in this report. 864 of them were registered during the ATU period (between 19 July 1994 and 27 November 1995), whilst 25 patients were treated outside those dates. 19 patients were excluded from the adverse event and efficacy analysis because insufficient data could be collected from the initial case report form or the source records. 870 patients (97.9% of the 889 treated patients) were, therefore, evaluated and analysed for adverse events. 45 additional patients, not having experienced a SAE and treated in centres having recruited less than 5 patients, were excluded from the clinical source record review. The analyses of patient characteristics, treatment and efficacy were, therefore, carried out on 825 patients (92.8%). Patients were treated in 67 French institutions and 48% were in the six centres accruing more than 50 patients each.

Patient characteristics

825 patients, for whom the clinical source data review was carried out, were analysed for pretreatment characteristics (Table 1). 9 men treated with docetaxel for metastatic breast

cancer were included in the analysis. The median age of patients at inclusion was 51 years (range: 25–77 years). 169 (20.5%) patients had a performance status of 2 or 3 at the start of docetaxel treatment. At initial diagnosis, 59.6% of the 478 patients for whom hormonal receptor status was reported had positive oestrogen or progesterone receptors. The median number of involved organs by patient at inclusion was three (range: 1–9). 605 patients (73.5%) had visceral involvement, with liver metastases present in 404 (49.1%), brain metastases in 52 (6.3%) and meningeal metastases in 17 (2.1%). At inclusion, liver dysfunction (transaminases >1.5 ULN, alkaline phosphatases >3 ULN) was recorded in 74 patients (9.6%) and 28 patients had increased bilirubin levels (>1.5×ULN). 640 patients (77.5%) were previously treated by hormonotherapy and all 825 patients by chemotherapy: 410 patients (50.4%) had received adjuvant chemotherapy and 736 (89.3%) at least one line of chemotherapy for advanced disease. A median of two previous lines of palliative chemotherapy (range: 0–9) had been administered. Of the 800 patients who had received anthracyclines or mitoxantrone, 413 (50.8%) were retrospectively classified as anthracycline-resistant and, among them, 87 as anthracycline-refractory. The median interval between the first relapse and inclusion was 22 months (range: 0–334).

Table 1. *Patient characteristics*

Characteristics	Patients	
	Number evaluated	*n* (%)
Age at inclusion	823	
Median (range)		51 (25–77) years
Sex	889	
Male		9 (1)
Female		880 (99)
Oestrogen receptors in initial breast cancer	478	
Positive		285 (59.6)
Negative		193 (40.4)
Performance status at inclusion (WHO)	822	
0		267 (32.5)
1		386 (47.0)
2		140 (17.0)
3		29 (3.5)
Number of organs involved by patient	820	
Median (range)		3 (1–9) organs
Site of disease*	823	
Bone		437 (53.1)
Metastatic nodes		325 (39.5)
Breast		299 (36.3)
Skin/soft tissue		280 (34.0)
Visceral		605 (73.5)
Liver		404 (49.1)
Lung		283 (34.4)
Pleura		182 (22.1)
Brain		52 (6.3)
Meningea		17 (2.1)
Biochemical liver tests at inclusion		
Liver dysfunction†	774	74 (9.6)
Hyperbilirubinaemia	759	28 (3.7)
Prior systemic anticancer therapy		
Hormonotherapy	825	640 (77.5)
Chemotherapy	825	825 (100)
Adjuvant chemotherapy	814	410 (50.4)
Chemotherapy for advanced disease	824	736 (89.3)
Number of previous palliative chemotherapy lines	824	
Median (range)		2 (0–9) lines
1–2		430 (52.2)
>2		306 (37.1)
Prior treatment including anthracyclines	813	800 (98.4)
Anthracycline resistant	813	413 (50.8)
Anthracycline refractory	813	87 (10.7)
Interval between advanced disease status and inclusion	790	
Median (range)		22 (0–334) months

*Total higher than 100% because most patients had more than one site. †AST, aspartate transaminase, and/or ALT, alumine transaminase, >1.5 upper limit of normal (ULN) and alkaline phosphatanes >3 ULN.

Table 2. Maximum haematological toxicities per patient (amongst 870 evaluable patients)

	Total incidence	Mild	Moderate	Severe	SAE related to treatment
Toxicity	Pts (%)	Pts (%)	Pts (%)	Pts (%)	Pts (%)
Leucopenia	176 (20.2)	9 (1.0)	22 (2.5)	145 (16.7)	0
Neutropenia	395 (45.4)	13 (1.5)	44 (5.1)	338 (38.9)	0
Anaemia	86 (9.9)	18 (2.1)	37 (4.2)	31 (3.6)	21 (2.4)
Thrombocytopenia	73 (8.4)	17 (2.0)	26 (3.0)	30 (3.4)	15 (1.7)
Febrile neutropenia	223 (25.6)	NA	NA	NA	164 (18.9)

NA, not available; SAE, serious adverse events.

Treatment

A total of 4146 cycles were given to the 825 source reviewed patients. Patients received between 1 and 20 cycles of docetaxel, with a median of five cycles; 267 patients (32.4%) received fewer than four cycles. The median docetaxel dose by cycle was 100 mg/m^2 (range: 30–175). Three thousand one hundred and fifty-six cycles (76.1%), including 691 first treatment cycles (84%) were administered at a 100 ± 10 mg/m^2 dose. The median cumulative dose by patient was 460 mg/m^2 (range: 50–1700). 11 patients were treated with a dose below 55 mg/m^2 in at least one cycle, 5 of these patients having a liver dysfunction. 2 patients were treated with a dose higher than 110 mg/m^2. One patient was overdosed by mistake with 175 mg/m^2 in the first cycle and developed febrile neutropenia with severe mucositis. Another received four cycles at 135 mg/m^2 without any SAE. 35 of the 74 patients with liver dysfunction were treated at an initial dose higher than 75 mg/m^2, despite protocol recommendations. Two thousand six hundred and sixty-two cycles (80.6% of 3303 evaluable cycles) were administered according to the recommended 3-week interval, and 628 (19%) were delayed. The most frequent reasons for treatment discontinuation were tumour progression (47.5% of 819 assessable patients) and non-lethal toxicity (14.1%).

Safety

870 patients were evaluable for safety. Toxicity is summarised in Tables 2 (haematological toxicities) and 3 (non haematological toxicities) on a worst grade per patient basis. Overall, 353 patients (40.6% of the 870 patients) experienced an SAE which was able to be source verified, whilst one SAE was reported among the 19 unassessable patients. Only SAEs considered as probably, possibly or remotely related to docetaxel treatment are described in this analysis.

Table 3. Maximum non-haematological toxicities per patient (amongst 870 evaluable patients)

	Total incidence	Mild	Moderate	Severe	SAE related to treatment
Toxicity	Pts (%)	Pts (%)	Pts (%)	Pts (%)	Pts (%)
Gastro-intestinal					
Nausea	135 (15.4)	96 (11.0)	30 (3.4)	9 (1.0)	0
Vomiting	119 (13.7)	26 (3.0)	70 (8.0)	23 (2.6)	6 (0.7)
Diarrhoea	176 (20.2)	74 (8.5)	84 (9.7)	18 (2.1)	7 (0.8)
Constipation	48 (5.5)	27 (3.1)	16 (1.8)	5 (0.6)	5 (0.6)
Mucositis	256 (29.4)	98 (11.3)	114 (13.1)	44 (5.1)	24 (2.8)
Hepatic	32 (3.7)	6 (0.7)	4 (0.5)	22 (2.5)	3 (0.3)
Acute hypersensitivity reaction	1 (0.1)	0	1 (0.1)	0	1 (0.1)
Infection without neutropenia	139 (16.0)	42 (4.8)	56 (6.4)	41 (4.7)	16 (1.8)
Fever without infection	164 (18.7)	52 (6.0)	96 (11.0)	16 (1.8)	8 (0.9)
Fluid retention	363 (41.7)	149 (17.1)	150 (17.2)	64 (7.4)	18 (2.1)
Alopecia	351 (40.3)	90 (10.3)	157 (18.0)	104 (12.0)	0
Skin	182 (20.9)	117 (13.4)	52 (6.0)	13 (1.5)	4 (0.5)
Nail disorder	176 (20.2)	87 (10)	51 (5.9)	38 (4.4)	0
Ocular disturbances	66 (7.6)	51 (5.9)	14 (1.6)	1 (0.1)	0
Local toxicity	4 (0.5)	3 (0.3)	1 (0.1)	0	0
Asthenia	376 (43.2)	82 (9.4)	195 (22.4)	99 (11.4)	5 (0.6)
Neurotoxicity					0
Sensory	322 (37.0)	204 (23.4)	98 (11.3)	20 (2.3)	0
Motor	56 (6.4)	18 (2.1)	14 (1.6)	24 (2.8)	2 (0.2)
Headache	40 (4.0)	25 (2.9)	14 (1.6)	1 (0.1)	0
Mood	8 (0.9)	4 (0.5)	1 (0.1)	3 (0.3)	0
Arthralgia	69 (8.0)	34 (3.9)	31 (3.6)	4 (0.5)	0
Myalgia	81 (9.3)	44 (5.1)	35 (4.0)	2 (0.2)	0
Heart failure	NC				7 (0.8)
Renal impairment	NC				3 (0.3)

NC, not collected in CRF, case report form; SAE, serious adverse events.

The most frequent haematological toxicities were severe leucopenia (145 patients) and neutropenia (338 patients). Febrile neutropenia, the most frequent SAE reported, occurred in 223 patients (25.6% of the 870 patients), leading to hospitalisation, with intravenous antibiotics prescribed, in 164 patients (18.9%). Other frequently reported SAEs were severe anaemia and thrombocytopenia, occurring in 31 (3.6%) and 30 (3.4%) patients, respectively, and requiring hospitalisation, mainly for transfusion, in 21 and 15 patients, respectively. Gastro-intestinal toxicity was generally mild. Nausea and/or vomiting, diarrhoea and ileus were reported as SAEs related to treatment in less than 1% of patients. 30 patients presented biochemical liver test abnormalities during treatment, and in 3 patients liver insufficiency led to hospitalisation. 256 patients (29.4%) presented at least one episode of mucositis. Severe mucositis was reported as a serious adverse event in 24 patients, 23 of whom concomitantly experienced febrile neutropenia. One patient experienced a hypersensitive reaction with erythema and dyspnoea which spontaneously resolved after stopping docetaxel infusion. No further docetaxel treatment was administered to this patient. 16 patients experienced episodes of severe infection (reported as an SAE) outside a neutropenic period. 363 patients (41.7%) presented fluid retention syndrome, which was graded as severe in 64 patients (7.4%). In 18 patients, severe oedema and/or symptomatic serous effusion (pleural in 7 patients, pericardial in 4 patients) led to hospitalisation, the median cumulative docetaxel dose at the onset of this type of SAE being 240 mg/m^2 (range 100–700 mg/m^2). Alopecia was reported in 351 patients (40.3%). Skin toxicity, nail disorders and ocular disturbances (consisting of lacrimation or conjunctivitis) occurred in 182, 176 and 66 patients, respectively. 376 patients (43.2%) presented asthenia considered as related to treatment. Neurotoxicity was generally mild or moderate and consisted mainly of subjective sensitivity signs or alterations of deep tendon reflexes. Objective alterations of sensitivity or strength (graded as severe neurotoxicity) were recorded in 20 and 24 patients, respectively. Arthralgia and myalgia occurred in 69 and 81 patients, respectively, but were seldom graded as severe. 6 patients presented acute heart failure considered as possibly or remotely related to docetaxel. However, 1 patient presented a prior history of ischaemic heart failure, another presented a reduced initial myocardiac function, and 3 patients had been previously treated with anthracyclines. In addition, an asymptomatic myocardial infarction was considered remotely related. 3 patients experienced renal function impairment, for which the relationship to docetaxel was assessed as possible by the treating physician. Two events were related to simultaneous dehydration, and one to malignant hypercalcaemia.

Overall, 120 patients experienced a fatal SAE (listed in Table 4). 19 deaths were possibly or probably related to docetaxel. Among them, 10 deaths were related to severe sepsis during a neutropenic period. Of interest, 6 of these patients had presented with severe liver impairment before starting docetaxel, and 3 of them had received a dose higher than 75 mg/m^2, despite protocol recommendations. In addition, 2 deaths occurring during febrile neutropenia, and for which the main causal event was liver insufficiency and progressive disease, respectively, were considered possibly related. One death occurred in a context of severe fluid retention syndrome with bilateral pleural effusion and was related to treatment. The main causal event of 6 other deaths considered related to treatment by the treating physician was liver insufficiency (1 patient), infection outside of a neutropenic period (2 patients), acute heart failure occurring in a context of arterial hypertension (1 patient), respiratory distress syndrome of imprecise cause (1 patient) and acute renal failure related to hypercalcaemia (1 patient). 9 deaths were considered remotely related to docetaxel. In 6 patients, the

Table 4. *Fatal serious adverse events: deaths occurring during treatment or within* 30 *days after the last infusion of docetaxel*

Relationship with docetaxel	Main causal event (and possible associated events)	*n* of pts
Deaths probably/possibly related		19
	Sepsis during neutropenic period	10
	Liver insufficiency (+ febrile neutropenia in 1 patient)	2
	Progressive disease (+ febrile neutropenia)	1
	Fluid retention syndrome	1
	Infection outside of a neutropenic period	2
	Acute heart failure	1
	Respiratory distress syndrome of imprecise cause	1
	Acute renal failure	1
Deaths remotely related		9
	Progressive disease	6
	(+ myelosuppression	2
	Pleural and peritoneal effusion	1
	Respiratory distress syndrome	1
	Gastrointestinal haemorrhage + liver insufficiency + myelosuppression	1
	Gastrointestinal haemorrhage)	1
	Undetermined cause (one of them during a febrile neutropenia episode)	3
Deaths not related		92
	Progressive disease	88
	Other causes	4
	Septic shock outside a neutropenic period	
	Acute pulmonary oedema	
	Coma	
	Pulmonary embolism	

main causal event was progressive disease, associated with possibly related docetaxel treatment events (see Table 4 for details). The causes of 3 deaths were undetermined and they were also considered as remotely related. One of them occurred during febrile neutropenia without septic shock and was treated with appropriate antibiotics. Twenty-eight deaths, representing 3.1% of the ATU population, were therefore related to docetaxel. Among them, 13 deaths occurred during febrile neutropenia (1.5% of patients). 9 out of 74 patients with liver dysfunction (12.2%), and 19 out of 700 patients without liver dysfunction (2.7%) experienced fatal SAE related to treatment. 92 deaths occurring during treatment were not related to docetaxel, being due to progressive disease in 88 patients.

Efficacy

Among the 825 source reviewed patients, we observed 13 CR, 176 PR, 305 SD and 294 outright disease progressors. In addition, treatment was stopped before the fourth cycle without evidence of progressive disease in 30 patients who were classified by the reviewers as experiencing early treatment failure (toxic death, unacceptable toxicity, patient's request, lost to follow-up). 7 patients who received more than three cycles, but who were not evaluated for tumour response, were considered non-evaluable. The objective RR was therefore 22.9% (95% CI: 20.2–26.2%). A more extensive and detailed subgroup analysis of the response data wil be published elsewhere [30].

At the time of the close of follow-up assessment on 30 June 1997, the median follow-up for the 192 patients still alive was 17.9 months (0–32.7). The median time to treatment failure was 4 months (95% CI: 3.6–4.3 months) among the 825 source reviewed patients (Figure 1a). 633 patients had died and median survival was 9.8 months (95% CI: 8.8–10.7 months) (Figure 1b).

DISCUSSION

Given their nature, compassionate use programmes cannot substitute for prospective clinical research. Clinical trials are essential for assessing the efficacy and tolerability of a new drug before and during market availability. Restrictive eligibility criteria in formal clinical trials exclude a significant proportion of advanced breast cancer patients with poor prognosis. Study populations with age restrictions, performance status limitations, normal major organ function, prior treatment limitation, and disease measurability requirements allow for valid data, yet are not always representative of the situation that prevails in routine clinical practice. The aim of this compassionate use programme was to provide docetaxel to heavily pretreated patients with no salvage treatment available. Consequently, the eligibility criteria were only moderately restrictive, and measurable disease was not a requirement. Moreover, as the ATU prescription was the responsibility of the participating physicians, eligibility criteria and protocol requirements concerning treatment adjustments and surveillance were not always strictly respected. Thus, the present ATU analysis offered an opportunity to gather additional safety and efficacy data on docetaxel when used in unselected patients, under prescription and surveillance conditions similar to those of routine oncological practice when a new, active agent is initially available to prescribing physicians.

This is the largest reported series of advanced breast cancer patients treated by docetaxel, the data from this series having undergone intensive source record review. Clinical factors associated with poor prognosis were frequent among patients included in the ATU, many of which would lead to patient exclusion from most clinical trials (see Table 1) (e.g. poor performance status, brain metastasis, having received more than two previous palliative chemotherapy lines, etc.). Anthracyclines had previously been given to 98.4% of patients, and 50.7% of patients were retrospectively classified by an external, independent medical oncology team as anthracycline-resistant following a rigorous assessment of their clinical records.

Most patients were treated according to ATU protocol requirements: 80.6% of cycles were given at 3-week intervals, and 76.1% of cycles were given at $100 \pm 10\,mg/m^2$. This fact underlines the adequacy of current docetaxel dosing recommendations in patients without liver dysfunction.

The principal toxicity encountered in this cohort was febrile neutropenia. 223 patients (25.6% of 870 evaluable patients) presented at least one episode and 10 patients died from sepsis during a neutropenic period. In clinical trials of docetaxel at $100\,mg/m^2$/cycle, the incidence of febrile neutropenia was generally between 10 and 20% of patients [3, 8, 10, 13, 14], and toxic deaths were exceptionally reported. Liver dysfunction before treatment, associated with decreased docetaxel clearance and a higher risk of febrile neutropenia, was reported in 3.9% of 1365 patients treated in phase II trials [19], but in 9.6% of patients treated in the ATU programme. Thus, the higher proportion of patients

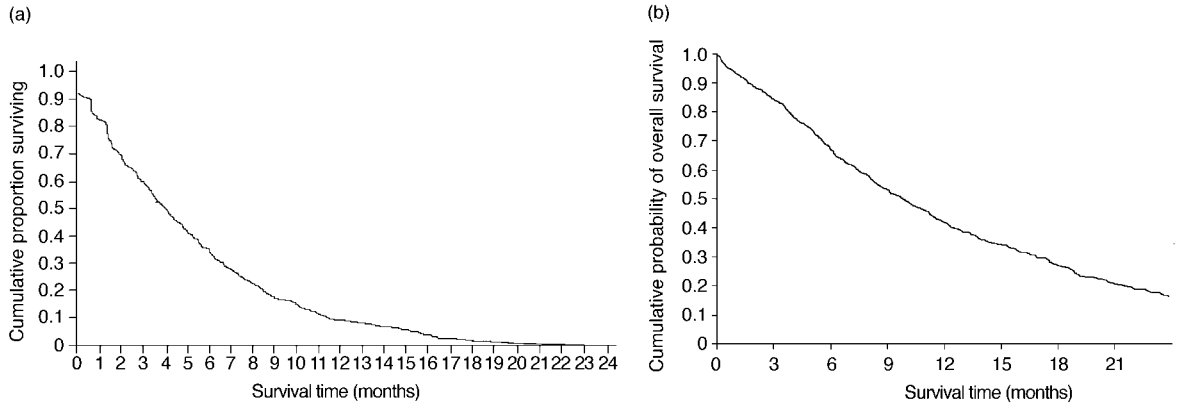

Figure 1. (a) Time to treatment failure, (b) overall survival.

with liver impairment in our analysis could explain the higher incidence of febrile neutropenia observed. 9 patients presenting liver dysfunction (12.2% of 74 patients) experienced a fatal SAE related to docetaxel; 6 of them died from sepsis during a neutropenic period. Nearly half of the patients presenting liver dysfunction received a dose higher ($>75\,mg/m^2$) than that recommended, and 3 of these patients died from febrile neutropenia. These observations confirm that the therapeutic index of docetaxel is decreased in patients with liver dysfunction. Close surveillance and respect for dosage adjustment recommendations should, therefore, be maintained in this patient subpopulation. The overall severe neutropenia incidence was lower than in previous clinical trials, but ATU toxicity monitoring guidelines for haematological parameters were much less stringent than in previous phase II experiences (where weekly blood counts were performed), explaining the lack of nadir detection and the under-reported incidence. The incidence of non-haematological toxicities was similar to that observed in previous studies with docetaxel. The low incidence of reported severe fluid retention is probably due to the routine use of corticosteroid medication and confirms the clinical relevance of the latter [16]. Alopecia, asthenia, neurosensory symptoms and nail disorders were common but usually manageable.

Although this was not the objective of the ATU protocol, 825 patients were evaluable for response. We observed an overall response rate (ORR) of 22.9%, with 13 complete responses. It is not surprising that the reported ORR is less than in previous phase II studies, given the high prevalence of poor prognostic factors and anthracycline resistance among the ATU population. Moreover, the lack of measurable disease or frequent and regular tumour evaluation in many patients lowered the number of reported objective responses. However, the median TTF was 4 months which is similar to that of phase II studies in previously treated patients. This result is of particular interest for at least two reasons. Firstly, TTF may be a better efficacy endpoint than response rate in cancer trials [26]. Secondly, this result confirms that docetaxel provides efficient palliation, even in poor prognosis, heavily pretreated patients. The median overall survival was 9.8 months. This result is a reassuring and important benchmark, given the fact that median time since first diagnosis of advanced disease was nearly 2 years. However, a long time since first relapse or a high number of previous palliative chemotherapy lines are not always associated with decreased survival in metastatic breast cancer patients. In particular, it is well known that survival of patients with advanced disease confined to the skeleton and/or the soft tissues is often extended [27]. However, this is not the case for most patients in our analysis, given the high prevalence of visceral disease. Thus, our review provides further support for docetaxel as a valid and useful option for patients relapsing after anthracycline-containing palliative chemotherapy. An in-depth analysis of prognostic factors for safety and efficacy will be the subject of a further paper.

The results of two compassionate use programmes of taxanes in advanced breast cancer have already been published and are summarised in Table 5. Leonard and associates [28] reported a 40.1% ORR and a 6.5 month overall survival in 377 patients treated by docetaxel in the U.K. However, the patients included in that analysis had received a lower number of previous palliative chemotherapy lines than in our analysis (Table 5). Moreover, data about previous treatment and disease characteristics at inclusion were less precise than in our cohort. 225 patients were treated by paclitaxel through a compassionate use programme in North America [29]. A $175\,mg/m^2$/cycle dosing was used in a 24-h infusion, whereas a 3-h infusion is currently recommended. Patients included in that study had previously received at least two palliative chemotherapy lines. ORR, TTF and OS were close to our own results. However, only 174 patients with measurable disease were evaluated for objective response. Febrile neutropenia occurred in 45% of patients, and 38% of patients who received more than one treatment cycle required dose reductions. The authors concluded that in spite of anticancer activity, the dose and schedule of paclitaxel used would not be acceptable in the palliative setting, owing to the high incidence of febrile neutropenia.

Table 5. *Main results of taxane compassionate use programmes in advanced breast cancer*

	Docetaxel: British extended access programme [28]	Paclitaxel: National Cancer Institute ($175\,mg/m^2$ over 24 h) [29]	Docetaxel: French 'ATU'
n treated patients/*n* evaluable for efficacy	377/377	225/174	889/825
Main patient characteristics			
PS ≥2 (%)	ND	17	20.5
Liver metastasis (%)	ND	31	49.1
Brain metastasis (%)	ND	3	6.3
Liver dysfunction (*n*)	ND	ND	74
Hyperbilirubinaemia (*n*)	0	0	28
Previous anthracycline-based chemotherapy (%)	91	>90	98.5
First-line chemotherapy for metastatic disease (%)	20	0	9.6
More than two previous palliative chemotherapy lines (%)	14	60	37.1
Efficacy			
Overall response rate (%)	40.1	23	22.9
Time to treatment failure/to progression (ms)	ND	4	4
Overall survival (ms)	6.5	9.5	9.8
Febrile neutropenia (% pts)	ND	45	25.6
Deaths related to treatment	11 (2.8%)	5 (2.2%)	28 (3.1%)

PS, performance status; ND, not determined.

This analysis in heavily pretreated breast cancer patients supports results from phase II studies. Severe toxicities occur mainly when dosage adjustment recommendations and docetaxel contraindications are not respected, especially in patients with liver function impairment. We also confirm that docetaxel provides good palliation and probably increases survival in patients relapsing after anthracycline-based chemotherapy, even in routine clinical practice.

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