original article

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A multicenter phase II study of XRP6258 administered as a 1-h i.v. infusion every 3 weeks in taxane-resistant metastatic breast cancer patients

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Background: XRP6258 is a novel taxoid with a low affinity for P-glycoprotein. This multicenter phase II study assessed the activity of XRP6258 in the treatment of taxane-resistant metastatic breast cancer (MBC).
Patients and methods: XRP6258 was administered as a 1-h i.v. infusion every 3 weeks at 20 mg/m^2 (then, in the absence of severe toxicity, at 25 mg/m^2 from cycle 2). The primary end point was the objective response rate (ORR) assessed according to response evaluation criteria in solid tumours (RECIST) guidelines.
Results: Seventy-one patients were enrolled. The median relative dose intensity was 0.98. The ORR was 14% (two complete, eight partial responses). Eighteen patients (25%) had stable disease of >3 months duration. At a median follow-up of 20.0 months, the median time to progression was 2.7 months, and the median overall survival 12.3 months. The most common grade 3/4 adverse events (AEs) were neutropenia (73%) and leucopenia (55%), with a low febrile neutropenia rate (3%) and infrequent grade 3/4, treatment-related, non-hematological AEs (<5% patients for any AE). Two deaths were reported, one related to study drug and one to unknown cause.
Conclusions: XRP6258 was active and well tolerated in this group of MBC patients with taxane-resistant disease. These results support the further clinical development of this agent.
Key words: chemotherapy, metastatic breast cancer, resistance, taxane, taxoid, XRP6258

introduction

While breast cancer is generally not overtly metastatic at presentation (~6% cases), ~30% of women with early stage lesions eventually develop advanced disease [1]. Metastatic breast cancer (MBC) remains essentially incurable, with median survival in the range of 2–4 years [2]. In this clinical situation, systemic therapies are palliative, aiming primarily at controlling disease symptoms, improving survival and preserving quality of life [3]. Regimens containing anthracyclines and taxanes as first-line treatment in MBC have demonstrated their potential to prolong patient survival [1, 4, 5]. When disease progression occurs after the completion of first-line treatment, additional lines of chemotherapy may be administered, with the capecitabine–docetaxel combination being an important treatment option for women with anthracycline-pretreated MBC [6, 7], However, if metastatic disease becomes resistant to anthracycline and/or taxanes, effective treatment options are limited. With the growing use of anthracycline/taxane-containing regimens in adjuvant therapy, there remains an unmet clinical need for effective compounds to treat patients with MBC developing or having developed resistance to taxanes.

For this reason, a program of medicinal chemistry was undertaken to identify new taxoid compounds with a broader spectrum of activity than the marketed taxanes, paclitaxel and docetaxel. XRP6258 and larotaxel (XRP9881) are new taxoids efficient in stabilizing microtubules against cold-induced depolymerization, the mechanism of action which is unique to the taxane class [8]. While the commercially available taxanes are substrates for P-glycoprotein, encoded by the multidrug resistance gene *ABCB1*, XRP6258 and larotaxel were selected for their low affinity for this drug efflux pump [9, 10]. This optimization suggested that both could be clinically effective in tumors expressing a multidrug resistance phenotype as a consequence of high-level expression of P-glycoprotein. Preclinical studies demonstrated that XRP6258 was cytotoxic for cell lines with acquired resistance to doxorubicin, vincristine, vinblastine, paclitaxel or docetaxel

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[11]. Similarly, both agents showed an *in vivo* spectrum of antitumor efficacy on most docetaxel-sensitive, -refractory or -resistant models, such as B16/TXT melanoma [9, 11]. Interestingly, both compounds showed the ability to cross the blood–brain barrier, a characteristic which may be a consequence of their low affinity for P-glycoprotein [12, 13].

Weekly and every 3-week schedules of administration of XRP6258 were tested in phase I trials [14, 15]. In one study, XRP6258 was given on a weekly schedule as a 1-h i.v. infusion on days 1, 8, 15 and 22 every 5 weeks. For the weekly regimen, the recommended dose was 10 mg/m^2 and the dose-limiting toxicity was diarrhea. Two studies have been carried out with XRP6258 administered as a 1-h i.v. infusion every 3 weeks. For this regimen, the maximum tolerated dose (MTD) was reached at the 30 mg/m^2 dose level, at which dose-limiting adverse events (AEs) such as febrile neutropenia and grade 4 neutropenia >5 days occurred. The recommended dose for phase II and III studies was 20 mg/m^2.

Originally, a three-arm study was initiated which was designed to compare the relative efficacy and safety of the two new taxoids, XRP6258 and larotaxel. However, due to low recruitment during the first 6 months, the protocol was amended to a single-arm phase II study exploring the activity of XRP6258 given every 3 weeks in patients with taxane-resistant MBC, as summarized in Figure 1. Consequently, only the data from this arm are reported.

patients and methods

This open-label phase II study was conducted in 39 study centers in Europe, Northern America and Southern America from August 2002 to January 2005 (cut-off date). The protocol complied with recommendations of the 18th World Health Congress (Helsinki, 1964) and all relevant amendments and was approved by the ethics committee of each participating institution. All patients gave their written informed consent.

main eligibility criteria

Eligibility criteria included the following: age ≥18 years, with histologically confirmed human epidermal growth factor receptor 2 (HER2)-negative (or HER2-positive previously failing trastuzumab) metastatic breast adenocarcinoma, Eastern Cooperative Oncology Group performance status (PS) zero to two and adequate hematological (granulocytes ≥2 × 10^9/l, platelet count ≥100 × 10^9/l), renal [creatinine ≤upper limit of normal (ULN) or creatinine clearance ≥60 ml/min] and liver (total bilirubin ≤ULN, serum aspartate aminotransferase/alanine aminotransferase and alkaline phosphatase ≤2.5 × ULN) functions. Patients were required to have at least one measurable lesion according to RECIST guidelines [16]. Resistance to previous taxane-containing chemotherapy was required. This resistance was defined as: for advanced disease; progressive disease (PD) as the best overall response after first- or second-line treatment; or, PD within 4 months following discontinuation of first- or second-line treatment after an initial objective response or disease stabilization; or, stable disease (SD) as the best overall response if first- or second-line treatment with a taxane-containing regimen had been administered for at least 3 months; or, for patients who had received an adjuvant or neo-adjuvant taxane-containing regimen, a disease-free interval (DFI) ≤12 months from the end of treatment.

Patients were excluded if they had concurrent cancer, received more than two lines of chemotherapy for metastatic disease, hypercalcemia, grade 2 or 3 neuropathy, brain or leptomeningeal symptomatic involvement or uncontrolled significant comorbid conditions.

treatment assignment and schedule

Patients in the analyzed experimental arm received XRP6258 at 20 mg/m^2, given as a 1-h i.v. infusion on day 1 every 3 weeks. Intrapatient dose escalation to 25 mg/m^2 was permitted in patients who did not experience a significant AE during cycle 1. Patients received i.v. antihistaminic anti-H1 premedication 30 min before study drug administration. No prophylactic antiemetic drugs were allowed at the first cycle. In case of nausea/vomiting, patients could receive preventive antiemetic treatment in compliance with the conventional antiemetic protocol of the center, for subsequent cycles. In the event of a treatment-related severe AE occurring during any cycle, a 20%–25% dose reduction and treatment delay for the individual drug was required on the basis of predefined criteria. Treatment was continued until disease progression, the occurrence of an unacceptable AE or the withdrawal of patient consent.

evaluations before and during therapy

Before registration, a complete medical history was taken and a physical examination was carried out, which included a complete blood count, blood chemistry analyses and tumor assessments.

Tumor measurements were made every 6 weeks by chest, abdominal and brain computed tomography scans or magnetic resonance imaging. Responses had to be confirmed by two evaluations taken at least 4 weeks apart. Complete blood counts were routinely carried out weekly or every day if grade 4 neutropenia occurred (until recovery to grade 3) or in the case of fever. Patients were regularly assessed for potential AEs and disease-related signs and symptoms. Follow-up including physical examination, tumor assessments and survival data were collected every

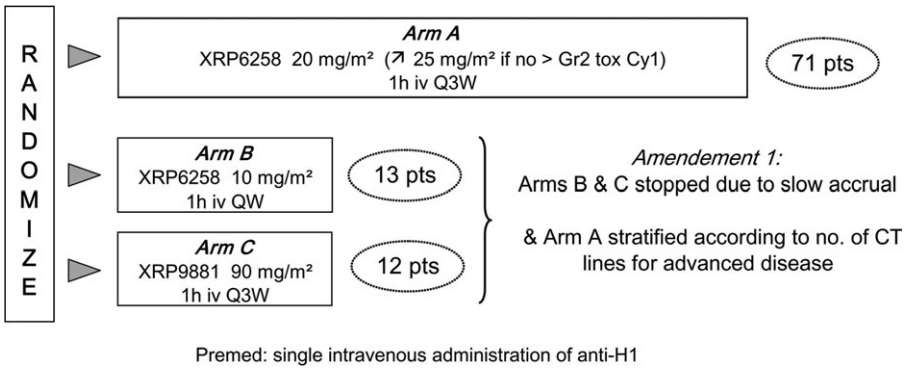

Figure 1. Randomization schedule.

6 weeks for the first 3 months and then every 3 months until the subject's death or until the study cut-off date.

data analysis

Following low recruitment during the first 6 months, the protocol was amended on 21 January 2003. The study consequently became a multicenter, multinational, open-label, single-arm, stratified phase II study in patients with taxane-resistant MBC treated with XRP6258 administered every 3 weeks. Two strata were defined according to the number of lines of taxane-containing treatment previously administered (stratum 1: resistance to an adjuvant/neo-adjuvant or first-line taxane-based regimen for advanced disease versus stratum 2: resistance to a second-line, taxane-based regimen for advanced disease). For each of the strata, a two-stage modified Fleming design was used where accrual was to be stopped if no response was observed after the first 20 per-protocol patients. Within each stratum, if at least one response was observed, 20 additional per-protocol patients were accrued. If at least five responses were observed in the final set of 40 per-protocol patients per stratum, the null hypothesis—that the true response rate was ≤5%—was rejected. Overall, at a significance level of 10%, the procedure had a power of 98%.

The primary end point was defined as the objective response rate (ORR), according to RECIST guidelines, achieved by XRP6258 administered every 3 weeks. Secondary efficacy end points were duration of response, time to progression (TTP) and overall survival (OS). They were analyzed using the Kaplan–Meier method [17]. Efficacy was assessed on the treated (all enrolled patients) and the per-protocol population (comprising patients who were eligible for the study and evaluable for response). Duration of response was measured for patients who had complete response (CR) or partial response (PR) as best overall response and calculated as the time from first documentation of CR or PR (whichever status was recorded first) until the first documented progression or death due to any cause. TTP was defined as the time from first infusion to first documented progression or death due to any cause. OS was calculated from the time of first infusion to death, whatever the cause. Where appropriate, 95% confidence intervals (95% CIs) were calculated following the Clopper–Pearson exact method [18].

The safety population included all treated patients. AEs/signs and symptoms of disease observed by the investigator or reported by the patients were recorded and graded according to the National Cancer Institute—Common Toxicity Criteria version 2 whenever possible, otherwise the Medical Dictionary for Regulatory Activities version 6 was used.

results

patients

Of 71 enrolled and treated patients, four were ineligible for the study: two were considered not to be resistant to taxanes, one did not have a histologically confirmed initial breast cancer and one had only one target lesion, in a previously irradiated area. Forty-seven eligible patients were accrued in stratum 1 and 20 in stratum 2. Six patients were not assessable for response due to the administration of concurrent treatments or early discontinuation due to AE or death. The per-protocol population therefore comprised 61 patients. Patient and disease characteristics are summarized in Table 1.

The median age was 53 years and 89% of patients were PS zero to one. All patients had previously received chemotherapy: 1% as adjuvant and 69% and 27% given as first- and second-line for metastatic disease, respectively. A total of seven patients had detectable metastatic disease at presentation and the median DFI for the remaining patients was 33.3 months. Hormonal receptor status was positive in 52% of tumors and HER2-positive status was scored in 27% of tumors (Table 1). The majority (75%) of patients had visceral metastatic disease, and 79% had multiple organ involvement (two or more).

Table 1. Patient and cancer characteristics

Included patients	$N = 71$
Age, years	
Median (minumum–maximum)	53 (35–77)
ECOG performance status, *N* (%)	
0	30 (42)
1	33 (46)
2	7 (10)
Missing	1 (1)
Hormonal status ER and/or PgR, *N* (%)	
Positive	37 (52)
Unknown	6 (8)
HER2 receptors, *N* (%)	
Positive	19 (27)
Not done	15 (21)
Disease-free interval, months[a]	
Median (minimum–maximum)	33.3 (1.58–214.01)
Number of organs involved	
1	15 (21)
2	26 (37)
3	14 (20)
4 or more	16 (23)
Main organs involved, *N* (%)	
Any visceral	53 (75)
Liver	42 (59)
Lymph nodes	33 (46)
Bone	31 (44)
Lung	22 (31)
Breast	16 (23)
Connective soft tissue	11 (15)
Skin	8 (11)
Brain	7 (10)
Prior chemotherapy exposure	
Adjuvant	1 (1)
Advanced	70 (99)
One line[b]	49 (69)
Two lines	19 (27)
Three lines	2 (3)
Prior anthracycline exposure, *N* (%)	54 (76)
Last taxane exposure, *N* (%)	71 (100)
Docetaxel	46 (65)
Paclitaxel	25 (35)
More than one line of taxane	7 (10)

[a]For 64 patients with nonmetastatic disease at presentation.
[b]Including patients with adjuvant chemotherapy with a DFI < 12 months.
ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; PgR, progesterone receptor; HER2, human epidermal growth factor receptor 2; DFI, disease-free interval.

exposure to study medication

In total, 345 cycles of XRP6258 were administered, with a median of four cycles (range 1–25 cycles). The median relative

dose intensity was 0.98 (range 0.60–1.14). At least one cycle delay of >3 days was observed in 32% of patients and in 14% of cycles, half of those delays being related to technical or personal reasons. At least one dose reduction was required in 10% of patients and in 2% of cycles. The most frequent reasons for treatment discontinuation were PD (75%), no further benefit expected (13%) and AE (6%).

safety

Treatment emergent grades 3–5 hematological and non-hematological AEs possibly related to study medication are listed by patient and cycle in Table 2. Neutropenia was the most common grade 3/4 hematological AE occurring in 73% of patients and 43% of evaluable cycles. Treatment-related febrile neutropenia or neutropenic infections were observed in 3% and 4% of patients and in <1% of cycles, respectively. Grade 3/4 anemia and thrombocytopenia were rare. Dose escalation up to 25 mg/m^2 from cycle 2, in selected patients, on the basis of their good tolerance in cycle 1, was feasible in 20 patients (28%) with no evident increase in the overall incidence of subsequent AEs in this group.

Treatment emergent grades 3–5 non-hematological AEs probably or possibly related to study treatment were also rare, with the most common including: hypersensitivity (4%), fatigue (3%) and hemorrhagic cystitis (3%). No severe AE occurred for nausea, vomiting, neuropathy sensory, myalgia and fluid retention. The most frequent non-hematological AEs at any grade, occurring in >15% of patients, were fatigue (35%), nausea (32%), diarrhea (30%), vomiting (18%), myalgia (17%), neuropathy sensory (17%) and anorexia (15%).

At cut-off, 52 patients had died, with 50 of those deaths considered to be related to disease progression. Two patients died within 30 days of the last on-study treatment: one patient on day 9 of cycle 1, due to shock with respiratory failure, deemed possibly related to study treatment, and one patient on day 21 of cycle 1, of an unknown cause. A total of four patients were withdrawn from the study due to AEs: three patients for grades 1–2 alteration of liver function tests at cycle 1 for one patient and cycle 6 for two patients and one for grade 4 allergic reaction at cycle 2.

efficacy

The investigator-determined ORR was 14% (95% CI 7% to 24%) in the treated patient population (Table 3). Interestingly, two patients achieved a complete response. The median response duration was 7.6 months (range 2.6+ to 18.7+).

Table 2. Grades 3–5 hematological and non-hematological toxic effects possibly or probably related to study treatment

NCI CTC term, *N* (%)	Patients, *N* = 71		Cycles, *N* = 345	
Hematological	All grades	Grade 3/4	All grades	Grade 3/4
Neutropenia[a]	67 (94)	52 (73)	254 (78)	141 (43)
Leukopenia[b]	69 (97)	39 (55)	248 (76)	95 (29)
Anemia[b]	64 (90)	2 (3)	243 (75)	4 (1)
Thrombocytopenia[b]	7 (10)	3 (4)	13 (4)	3 (1)
Neutropenic complications		*N* = 71		*N* = 325
All grade 4 neutropenia		35 (49)		67 (21)
Lasting >5 days		19 (27)		26 (8)
Febrile neutropenia		2 (3)		2 (0.6)
Neutropenic infection		3 (4)		3 (1)
Non-hematological	All grades	Grades 3–5	All grades	Grades 3–5
Hypersensitivity reaction	4 (6)	3 (4)	5 (1)	3 (1)
Infection (neutropenic)	3 (4)	3 (4)	3 (1)	3 (1)
Fatigue	25 (35)	2 (3)	68 (20)	3 (1)
Hemorrhagic cystitis	2 (3)	2 (3)	5 (1)	3 (1)
Diarrhea	21 (30)	1 (1)	66 (19)	1 (0.3)
Headache	7 (10)	1 (1)	16 (5)	1 (0.3)
Peripheral edema	6 (8)	1 (1)	16 (5)	1 (0.3)
Infection without neutropenia	3 (4)	1 (1)	4 (1)	1 (0.3)
Arrhythmia supraventricular	1 (1)	1 (1)	1 (0.3)	1 (0.3)
Cyanosis	1 (1)[c]	1 (1)[c]	1 (0.3)[c]	1 (0.3)[c]
Dyspnea	1 (1)[c]	1 (1)[c]	1 (0.3)[c]	1 (0.3)[c]
Incontinence	1 (1)	1 (1)	1 (0.3)	1 (0.3)
Injection site reaction	1 (1)	1 (1)	2 (0.6)	2 (0.6)
Irregular menses	1 (1)	1 (1)	7 (2)	7 (2)
Pleural effusion	1 (1)	1 (1)	2 (0.6)	2 (0.6)
Thromboembolism	1 (1)	1 (1)	1 (0.3)	1 (0.3)

[a]*N* = 325 evaluable cycles.
[b]*N* = 326 evaluable cycles.
[c]Death (grade 5).
NCI CTC, National Cancer Institute Common Toxicity Criteria.

Table 3. Best overall response rate (modified ITT and per-protocol populations)

	Treated population ($N = 71$)	Per-protocol population ($N = 61$)
Response, N (%)[a]		
Overall response rate	10 (14)	8 (13)
Complete response	2 (3)	2 (3)
Partial response	8 (11)	6 (10)
No change/stable disease	27 (38)	27 (44)
Progressive disease	29 (41)	26 (43)
Response duration, median (minimum–maximum)	7.6 mo (2.6 ± 18.7+)	7.6 mo (2.6 ± 18.7+)
TTP, median (95% CI)	2.7 months (1.45–4.07)	2.8 months (1.45–4.07)
OS, median (95% CI)	12.3 months (9.49–15.05)	–

[a]Response/disease stabilization confirmed by analyses at least 1 month apart.
TTP, time to progression; OS, overall survival; CI, confidence interval.

In addition to the objective responses, 27 patients (38%) had SD with a median duration of 4.2 months (95% CI 3.71–5.42), including 18 (25%) with tumor stabilization >3 months (from 3.4 to 14.6 months). Eight of these patients had experienced PD as the best overall response to the last taxane treatment. The median TTP was 2.7 months (95% CI 1.45–4.07). At a median follow-up of 20.0 months, the median OS was 12.3 months (95% CI 9.49–15.05). Although numbers were small, no marked difference in response rate was apparent for stratum 1 versus stratum 2 (ORR per-protocol population: 14% versus 12%, respectively).

discussion

Increasingly, taxane- and anthracycline-containing regimens are being used as adjuvant treatments and remain the most efficient systemic treatments and consequently the most commonly used worldwide in the treatment of MBC. After failure of these agents, and particularly in the case of resistance of the tumor to taxanes, the prognosis remains poor. Apart from capecitabine [6, 19], active agents that could be used in subsequent treatment lines are lacking.

XRP6258 appears to be active in docetaxel- or paclitaxel-resistant breast cancer, even when the most stringent criterion of resistance (PD on therapy) was used. The ORR was 14% (95% CI 7% to 24%) in the treated population. In addition, 18 patients (25%) had SD lasting for >3 months (range 3.4–14.6 months). Long-lasting SD may be an indicator of activity, especially in heavily pretreated patients, who did not respond or had responses of short duration to the previous line of chemotherapy. The 14% ORR reported is comparable to that described by Dieras et al. [20] for larotaxel in a similar population. This larotaxel phase II study was conducted in 130 patients with MBC and was designed to assess the efficacy of larotaxel administered every 3 weeks at 90 mg/m^2 in populations of patients with taxane-resistant and nonresistant disease. The different response rates in these groups (taxane-resistant, 20% versus nonresistant, 42%) highlighted the need to establish a clinical definition of taxane resistance comparable to the model reported for anthracycline breast cancer resistance.

Several drugs have recently been reported to be potentially effective in the treatment of breast cancer patients following the failure of anthracycline- or taxane-based treatment. These include fluoropyrimidines such as capecitabine [21] and combinations including 5-fluorouracil (5-FU) plus oxaliplatin [22] and 5-FU plus eniluracil [23], but also gemcitabine [24] and vinorelbine [25]. The definitions of taxane resistance across these studies were different and often not restrictive. Only capecitabine was extensively assessed in stringently defined taxane-resistant patients (PD while on therapy). Although no responses were observed with gemcitabine, response rates between 10% and 26% were observed for the other agents/combinations (20% for capecitabine), which are comparable to the 14% rate observed for XRP6258 in this study. Median TTP and median OS times achieved with XRP6258 were also similar to those achieved in these earlier studies. Finally, the semisynthetic epothilone, ixabepilone, has recently been reported to have achieved response rates of 12% in two separate phase II studies in patients with taxane-resistant MBC [26–28], albeit against a background of difficult-to-manage neurotoxicity.

The safety profile of XRP6258 was very favorable when compared with the known safety profile of the marketed taxanes or other compounds under development. No severe AE occurred for nausea, vomiting, neuropathy sensory, myalgia or fluid retention. The most frequent grade 3/4 non-hematological AEs were allergic reaction (4%), fatigue (3%) and diarrhea (1%). The hematological AE profile was also favorable, with rare grade 3/4 anemia and thrombocytopenia. Only grade 3/4 neutropenia was common, occurring in 73% of patients and 43% of cycles. Treatment-related febrile neutropenia occurred rarely. Therefore, the biological mechanism of cytotoxicity coupled with the evidence of activity in taxane-resistant MBC patients and the tolerability of this agent justify further clinical testing.

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conflict of interest

SA is salaried employee of Sanofi Aventis

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