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Safety of repeated administrations of ixabepilone given as a 3-hour infusion every other week in combination with irinotecan in patients with advanced malignancies

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ABSTRACT

Epothilones are active tubulin-interacting agents that warrant combinations in clinical studies. This phase I combination study explored ixabepilone administered as a 3-h infusion followed by a 90-minute infusion irinotecan, on days 1 and 14 of every 28-day cycle. Forty-one patients received doses of ixabepilone and irinotecan ranging from 15–30 mg/m^2 and 120–180 mg/m^2 every 2 weeks for a total of 173 cycles, respectively. Dose limiting toxicities reported at doses $\geqslant$25 mg/m^2 ixabepilone and 180 mg/m^2 irinotecan consisted of acute grade 3 diarrhoea and asthenia, eventually associated with neutropenia and sepsis, and/or delayed grade 3 peripheral neuropathy. Therefore, the recommended doses were 20 mg/m^2 ixabepilone and 180 mg/m^2 irinotecan. At this dose level, acute side effects were neutropenia, anaemia, nausea-vomiting, diarrhoea, asthenia, and alopecia. Delayed neuropathy was mostly restricted to reversible grade I–II. Pharmacokinetic data suggested no drug–drug interaction. Five objective responses were observed in four patients with lung cancer and one unknown primary epidermoid carcinoma patient. In conclusion, toxicity including peripheral neuropathy was manageable at the recommended doses of 20 mg/m^2 ixabepilone combined with 180 mg/m^2 irinotecan on days 1 and 14 every 28 days. Promising antitumour activity was observed in patients with platinum-pretreated lung cancer.

1. Introduction

Epothilones belong to a new class of non-taxane tubulin-interacting agents obtained from myxobacteria *Sorangium cellulosum*, stabilising microtubule polymerisation,[1] and thereby resulting in mitotic arrest and potent cytotoxic activity. Although epothilones and taxanes share closely related mechanisms of action, ixabepilone (BMS-247550), a semi-synthetic analogue of epothilone B (BMS-205535), appears to remain active against various paclitaxel-resistant cell lines, encompassing either p-glycoprotein-related multidrug-resistance in colon HCT116/VM46 or tubulin-mutations in ovarian A2780Tax carcinomas, both in cell lines and mouse xenografts.[2–5] In murine models, ixabepilone caused

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gastrointestinal toxicity, bone marrow depletion and peripheral neuropathy characterised by axonal degeneration similar with that observed with paclitaxel at pathological examination. Rodent data have suggested that ixabepilone-induced neuropathy could be related to peak plasma concentrations, 3-h infusion inducing less severe sciatic nerve degeneration than shorter bolus infusions. Phase I clinical trials investigated ixabepilone given once[6] and daily for 3–5 days every 3 weeks[7,9] at doses ranging from 7.5–59.2 mg/m^2/cycle. Given every 3 weeks, dose limiting toxicities included peripheral neuropathy, asthenia, abdominal pain, diarrhoea, and neutropenia leading to the recommended dose of 40 mg/m^2. Peripheral neurotoxicity was commonly observed at doses $\geqslant$50 mg/m^2 and consisted of cumulative sensory loss and pain in the extremities. In phase I/II studies, objective responses were observed in patients with taxane-refractory ovarian and breast tumours.[6–8]

Irinotecan, a potent topoisomerase-I inhibitor,[10] displays a manageable toxicity profile,[11] demonstrated clinical antitumour activity in a number of patients with various solid tumours,[12–14] and is currently approved in combination with 5-fluorouracil plus leucovorin as a first line treatment for colorectal cancer.[15] As mentioned above, ixabepilone and irinotecan are both active drugs in a number of solid tumours with different mechanism of action. This led us to design a dose escalation study using an every 2 weeks schedule aiming to fit usual administration schemes of irinotecan. To limit potential neurotoxicity associated with the ixabepilone-peak plasma concentration, the duration of infusion was extended to 3-h. Considering peripheral neuropathy as the main dose-limiting event of ixabepilone, we attempted to identify characteristics associated with the risk of toxicity to provide guidance in the dosing of repeated administrations of ixabepilone.

2. Patients and methods

2.1. Patient selection criteria

Patients with histologically/cytologically confirmed malignancy for whom no standard therapy exists were eligible if the following criteria were met: age $\geqslant$18 years; $\leqslant$three previous lines of chemotherapy; measurable/evaluable disease; adequate haematological (granulocytes count $\geqslant$2000/μl, platelet count $\geqslant$125,000/μl), hepatic (bilirubin level of $\leqslant$1.5 times the upper limit of normal-xULN; AST/ALT levels $\leqslant$2.5 $\times$ ULN or $\leqslant$5.0 $\times$ ULN in the case of liver metastasis), and renal functions (creatinine $\leqslant$1.5 times the upper limit of normal); no chemotherapy within 3 weeks prior to study entry (6 weeks for carboplatin or mitomycin C); ECOG performance status of 0–2; life expectancy of $\geqslant$3 months; written informed consent and the use of contraception for women of childbearing age and fertile males. Specific exclusion criteria included pre-existing grade $\geqslant$1 peripheral neuropathy, severe hypersensitivity to Cremophor® EL, history of severe diarrhoea or hypersensitivity reaction to one of the excipients of camptothecin, and chronic inflammatory bowel disease and/or bowel obstruction. This trial was approved by our Institutional Review Board and an independent ethical review committee.

2.2. Pretreatment and follow-up examination

Baseline and weekly follow-up investigations included medical history, physical exam, complete blood cell count with differential, chemistry (sodium, potassium, chloride, bicarbonate, calcium, phosphorus, magnesium, coagulation, creatinine, urea, uric acid, glucose, bilirubin, AST, ALT, alkaline phosphatase, LDH, total protein, and albumin), electrocardiogram, urinalysis by dipstick, and chest X-rays. Evaluation of drug-related toxicity was assessed according to the Common Toxicity Criteria, Version 2.0. In patients with measurable disease, response evaluation was performed every two cycles according to the RECIST criteria.[16] Treatment was continued until evidence of disease progression or occurrence of an unacceptable toxicity.

2.3. Drug administration

Ixabepilone and irinotecan were supplied by Bristol Myers Squibb (Rueil-Malmaison, France). After dissolution in the lyophile solvent (ethanol + Cremophor® EL mixture 1:1), ixabepilone was further diluted with Ringer Lactate to obtain a final solution of 0.4–0.6 mg/mL, and given as an intravenous infusion over 3 h, followed 30 min later by irinotecan given intravenously over 90 min. Both drugs were administrated on day 1 and 15 of a 28-day cycle. One-hour prior to ixabepilone, premedication consisted of 8 mg ondansetron combined with 80 mg methylprednisolone, 5 mg dexchlorpheniramine, and 300 mg cimetidine.

2.4. Dose-escalation procedures

Doses of ixabepilone/irinotecan were escalated as follows: 20/120; 15/150; 15/180; 20/180; 25/180; and 30/180 mg/m^2. No intrapatient dose escalation was allowed. Dose limiting toxicity (DLT) was defined as any of the following events: grade 4 neutropenia lasting more than 7 days and/or grade 3–4 neutropenia associated with fever $\geqslant$38.5 °C; grade 4 thrombocytopenia or bleeding episode requiring platelet transfusion; grade 2 progressive painful paresthesia or grade 3 neuropathy; grade 3–4 non-haematological toxicity (excluding alopecia, nausea/vomiting); and persistence of non-haematological toxicity (excluding alopecia) of grade >2 at the scheduled retreatment. For each dose level, if one of the initial three patients showed a limiting toxicity at cycle 1, then further evaluation was performed by treating three additional patients. The maximum tolerated dose (MTD), based on acute toxicity evaluated on the number of DLT at cycle 1, was defined as the dose level at which at least 2/3 or 3/6 patients experienced DLT. During the first dose level, one DLT occurred at cycle 1 among the first three patients, consisting of a grade 3 neutropenia, leading to the inclusion of three additional patients (six patients in total). This observation led us to consider, for safety reasons, decreasing the dose of ixabepilone from 20 to 15 mg/m^2 until we reached the recommended dose of irinotecan, allowing us to further resume escalation of ixabepilone at the dose of 20 mg/m^2 and higher. Given the occurrence of cumulative toxicity during the trial, the recommended dose (RD) was defined as the dose level that induces less than 30% DLT at any cycle in an expanded cohort of 14 patients.

2.5. Pharmacokinetic study

Pharmacokinetic parameters of ixabepilone, irinotecan and SN-38 were analysed in plasma during cycle 1. Blood samples (5 mL) were collected in heparinised tubes immediately before drug administration, and 1h30, 2h58, 3h10, 3h28, 4h, 4h30, 4h58, 5h10, 5h30, 6h, 7h, 8h, 12h and 24 h from the start of ixabepilone infusion. Whole blood samples were centrifuged immediately (2000 × g for 5 min at 0–5 °C) and plasma was separated for each compound (1 mL each) and frozen at −80 °C until assayed. Liquid chromatography/mass spectrometry mass method for quantification of ixabepilone in 0.2 mL of human EDTA plasma was developed by Bristol Myers Squibb and described elsewhere.[7] The lower limit of quantification was 2 ng/mL. The area under the plasma BMS-247550 concentration-time curve (AUC) was calculated using the trapezoidal method and extrapolated to infinity.

Quantitative analysis of irinotecan and its metabolite SN-38 was performed using a reverse-phase high-performance liquid chromatography with fluorescence detection (HPLC) as described elsewhere.[17] Lower limits of quantifications were 10 ng/mL for irinotecan and 2.5 ng/ml for SN-38. Maximal plasma concentration and area under the plasma concentration-time curve (AUC) were determined by non-compartimental analysis using WinNonlin software (Scientific Consulting, Inc, Cary, NC).

3. Results

3.1. General

Among 43 patients included, two patients were not evaluable for toxicity because of early study withdrawal related to tumour progression (one patient went off study after been treated on day 1 of cycle 1 and another patient did not receive any treatment). As a result, a total of 41 patients, whose characteristics are summarised in Table 1, were treated through 6 dose levels and 173 cycles. Most patients had received prior chemotherapy, including neurotoxic drugs such as cisplatin (22 patients), paclitaxel (eight patients) and/or oxaliplatin (four patients). The median number of cycles administered was three (ranging 1–20).

Dose escalation proceeded up to dose level VI until occurrence of two episodes of acute dose-limiting toxicities at cycle 1 that met criteria for defining the MTD (Table 2). Unlike haematological toxicity and fatigue, which were readily reversible, sustained grade 2–3 peripheral neuropathy, occurring after cycle 1, frequently required treatment discontinuation and was therefore considered as a primary concern for dose recommendation. This led us to consider that at least four patients treated for at least four cycles should be evaluable to properly define the recommended dose for future phase II trials. While three patients were initially treated at dose level VI with no DLT occurring during cycle 1, further evaluation of patients treated at that dose level with repeated cycles revealed that this dose level was associated with two subsequent cases of dose-limiting peripheral neuropathy, thereby confirming that the dose of 30 mg/m^2 ixabepilone was not feasible using this schedule. Dose level V was associated with only one episode of febrile neutropenia at cycle 1. However, subsequent cycles of ixabepilone at the dose of 25 mg/m^2 were also associated with episodes of unacceptable peripheral neuropathy that led us to consider lower doses for defining the recommended dose. Occurrence of cumulative ixabepilone-induced neurotoxicity led us to explore the dose of 20 mg/m^2. Among a total of 14 patients treated at dose level IV, seven patients were treated for $\geqslant$4 cycles and four (28%) patients experienced DLTs that mainly consisted of febrile or severe neutropenia and septic diarrhoea. At this dose level, only one patient developed grade 3 neuropathy at cycle 4. Based on those data, the dose of 20 mg/m^2 ixabepilone was considered as the recommended dose for repeated every other week administrations of ixabepilone in combination with 180 mg/m^2 irinotecan. At the recommended doses, the median overall dose intensity in 14 patients and 55 cycles was 87.8 mg/m^2/week (range 76.4–91.2) for irinotecan and 9.6 mg/m^2/week (range 8.0–10.1) for ixabepilone.

Table 1 – Patient characteristics

Number of patients evaluable (included)	41 (43)
Male / female	24 / 17
Median age, year (range)	51 (25–71)
Performance Status:	
0	23
1	18
Prior chemotherapy treatment:	
No of previous line	
0	1
1	8
2	19
3	13
Type of chemotherapy	
Cisplatin-based	22
Paclitaxel-based	8
Oxaliplatin-based	4
Primary tumour type:	
Lung	9
Ovarian	6
Upper gastrointestinal	5
Colon	3
Breast	3
Neuroendocrine tumour	3
Cervix	2
Thyroid	2
Carcinoma of unknown primary	2
Sarcoma	1
Bladder	1
Mesothelioma	1
Anal	1
Thymus	1
Melanoma	1

3.2. Haematological toxicity

Haematological toxicity consisted of grade 1–2 neutropenia in 32% of patients (22% of cycles) and grade 3–4 neutropenia in 51% of patients (31% of cycles) that lasted less than 7 days. Most patients presented grade 1–2 anaemia (78% of patients,

Table 2 – Dose-escalation scheme

Dose level	Ixabepilone / irinotecan (mg/m^2/ 2 weeks)	No of patients Evaluable/ entered for DLT	Number of cycle	DLT Cycle 1	DLT Any cycle	Type of DLT	Onset of DLT
I	20 / 120	6 / 6	15	1	1	Grade 3 neutropenia 3	Cycle 1
II	15 / 150	3 / 3	14	0	2	Grade 3 diarrhoea Grade 3 diarrhoea and grade 3 vomiting	Cycle 2 Cycle 7
III	15 / 180	6 / 6	41	1	2	Febrile grade 3 neutropenia and grade 4 anaemia Grade 3 diarrhoea and grade 3 vomiting	Cycle 1 Cycle 2
IV	20 / 180	14 / 14	55	2	4	Grade 4 neutropenia Grade 3 diarrhoea and grade 4 septicaemia with toxic death Febrile grade 4 neutropenia, grade 4 anaemia, and grade 4 diarrhoea Grade 3 neuropathy	Cycle 1 Cycle 1 Cycle 3 Cycle 4
V	25 /180	6 / 7	14	1	5	Febrile grade 3 neutropenia Progressive grade 2 neuropathy Grade 3 neuropathy Grade 3 neuropathy Grade 3 neuropathy	Cycle 1 Cycle 2 Cycle 3 Cycle 5 Cycle 4
VI	30 / 180	6 / 7	18	2	4	Progressive grade 2 neuropathy Grade 3 diarrhoea, vomiting, asthenia, and grade 4 septicaemia with toxic death Grade 3 neuropathy Grade 3 neuropathy	Cycle 1 Cycle 1 Cycle 4 Cycle 5

DLT: Dose limiting toxicity.

Table 3 – Worst haematological toxicities

Dose levels	I (20/120)		II (15/150)		III (15/180)		IV (20/180)		V (25/180)		VI (30/180)		Total	
No of patients	6		3		6		14		6		6		41	
No of cycles	15		14		41		55		14		18		173	
Grade of toxicity	1–2	3–4	1–2	3–4	1–2	3–4	1–2	3–4	1–2	3–4	1–2	3–4	1–2	3–4
Neutropenia														
Per patient	4	1	1	1	1	4	5	6	–	5	2	4	13	21
Per cycle	10	1	6	2	2	26	15	12	–	7	5	5	38	53
Thrombocytopenia														
Per patient	–	–	–	–	2	1	2	–	2	–	2	–	8	1
Per cycle	–	–	–	–	2	1	2	–	2	–	3	–	9	1
Anaemia														
Per patient	4	–	3	–	5	1	10	4	5	1	5	1	32	7
Per cycle	8	–	15	–	37	1	38	5	14	2	11	1	123	9

71% of cycles) whereas grade 3–4 anaemia was restricted to 17% of patients (5% of cycles). In contrast, thrombocytopenia was uncommonly reported with only one patient previously treated with pelvic irradiation for cervical cancer who developed grade 3 thrombocytopenia during cycle 1 at dose level III. Transient grade 1–2 thrombocytopenia occurred in eight patients and nine cycles. Table 3

3.3. *Non-haematological Toxicity (Table 4)*

Nausea-vomiting frequently restricted to grade 1–2 occurred in 85% of patients (62% of cycles) with only five patients experiencing transient episodes of grade 3 vomiting despite an intensive metoclopramide, ondansetron, and steroid treatment.

Table 4 – Worst non-haematologic toxicities

Dose levels	I (20/120)		II (15/150)		III (15/180)		IV (20/180)		V (25/180)		VI (30/180)		Total	
No of patients	6		3		6		14		6		6		41	
No of cycles	15		14		41		55		14		18		173	
Grade of toxicity	1–2	3–4	1–2	3–4	1–2	3–4	1–2	3–4	1–2	3–4	1–2	3–4	1–2	3–4
Nausea/Vomiting														
Per patient	6	–	2	1	5	1	11	2	6	–	5	1	35	5
Per cycle	15	–	4	1	29	1	35	2	13	–	11	1	107	5
Diarrhoea														
Per patient	4	–	–	2	5	1	12	1	5	–	5	2	31	6
Per cycle	9	–	–	3	34	2	35	1	11	–	12	2	101	8
Mucositis														
Per patient	1	–	1	–	3	–	2	–	1	–	3	–	11	–
Per cycle	2	–	1	–	3	–	3	–	3	–	3	–	15	–
Alopecia														
Per patient	6	–	3	–	5	–	12	–	5	–	5	–	36	–
Per cycle	15	–	14	–	35	–	45	–	11	–	17	–	137	–
Neurotoxicity														
Per patient	4	–	1	–	2	–	6	1	1	3	2	3	16	7
Per cycle	11	–	2	–	15	–	24	1	3	3	3	3	58	7
Myalgia/arthralgia														
Per patient	–	–	1	–	1	–	3	–	1	–	2	–	8	–
Per cycle	–	–	1	–	3	–	6	–	2	–	2	–	14	–

Irinotecan-induced diarrhoea was generally mild to moderate (grade 1–2: 76% of patients, 58% of cycles) and infrequently severe (grade 3–4: 15% of patients, 5% of cycles). In most cases neutropenia did not coincide with diarrhoea since diarrhoea began between day 3 and 5, followed later by neutropenia onset around days 10–12. In two patients, severe grade 3 diarrhoea was associated with sepsis that led to toxic death. One patient with liver metastasis from oesophagus cancer previously treated with three chemotherapy regimens and treated at dose level IV was hospitalised at day 24 of cycle 1 with grade 2 nausea-vomiting and grade 3 diarrhoea and developed gram negative sepsis leading to death on day 25. The other patient with bone, lung and liver metastasis of thyroid adenocarcinoma previously treated with three chemotherapy regimens received ixabepilone/irinotecan at dose level VI and presented grade 3 nausea-vomiting, diarrhoea and asthenia followed by Gram-negative septicaemia at day 20 of cycle 1 leading to death on day 26.

Grade 1–2 asthenia was reported in 78% of patients and 70% of cycles. Grade 3 asthenia was observed during the two lethal sepsis episodes described above. Transient grade 1–2 elevation of transaminases was observed in 22 patients with only one patients experiencing reversible grade 3 transaminase elevation at dose level V. Complete alopecia was observed in most patients (88%). Grade 1–2 mucositis and myalgia/arthralgia were reported in 27% and 19% of patients, respectively. One case of nail disorder (onycholysis) was observed in a patient that received six cycles of the combination.

3.4. *Peripheral neuropathy*

Painful paresthesia were reported in several patients receiving $\geqslant 3$ cycles. Overall, neuropathy occurred in 23/41 (56%) of patients over 66 cycles. Among these 23 patients, 16 had previously been treated with cytotoxic agents known to induce peripheral neuropathy including cisplatin (ten patients), paclitaxel (six patients), and oxaliplatin (three patients). This suggests that ixabepilone may worsen pre-existing sub-clinical neuropathy. The majority of severe grade 3 neuropathy was observed among patients treated at doses of ixabepilone $\geqslant 25 mg/m^2$ (seven patients) contrasting with only one patient experiencing neuropathy at dose $\leqslant 20 mg/m^2$. In a total of eight patients, progressive grade 2–3 neuropathy resulted in study withdrawal. Neuropathy occurred after repeated cycles, most of grade 3 being observed after a median number of four cycles (range 1–5). Fig. 1 shows the probability of occurrence of the peripheral neurotoxicity from the date of the first ixabepilone administration for all patients treated in this study. As shown, patients receiving doses ranging from 15–20 mg/m^2 could receive 6 months of treatment with about 50% risk of grade 1 neurotoxicity allowing maintaining therapy and <20% risk of developing grade 2–3 neuropathy requiring treatment discontinuation. Conversely, patients receiving doses $\geqslant 25 mg/m^2$ more rapidly developed grade 2–3 neuropathy in >75% of cases after the second month of treatment. These data suggest that ixabepilone given at doses $\leqslant 20 mg/m^2$ can be safely combined with irinotecan. With a follow-up ranging from 6–12 months, 6/8 patients with grade 3 neurotoxicity recovered either partially or completely.

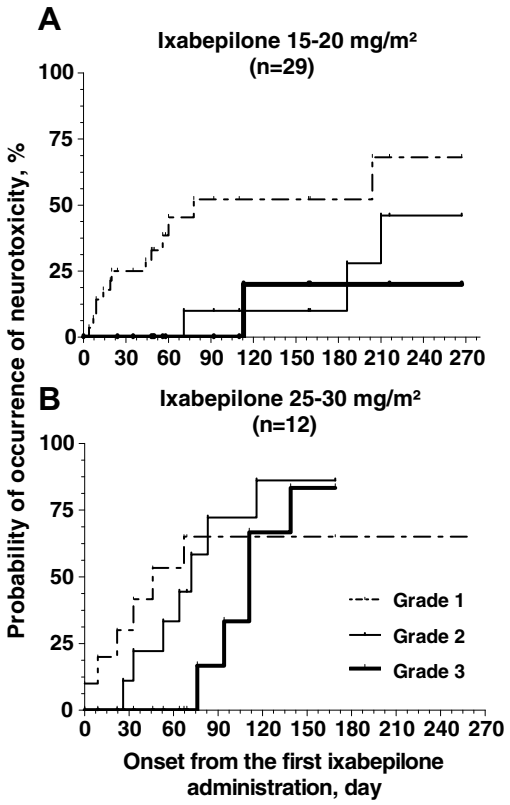

Fig. 1 – Probability of occurrence of neurotoxicity from the date of the first ixabepilone administration, and according to doses of 15–20 (A) and 25–30 (B) mg/m².

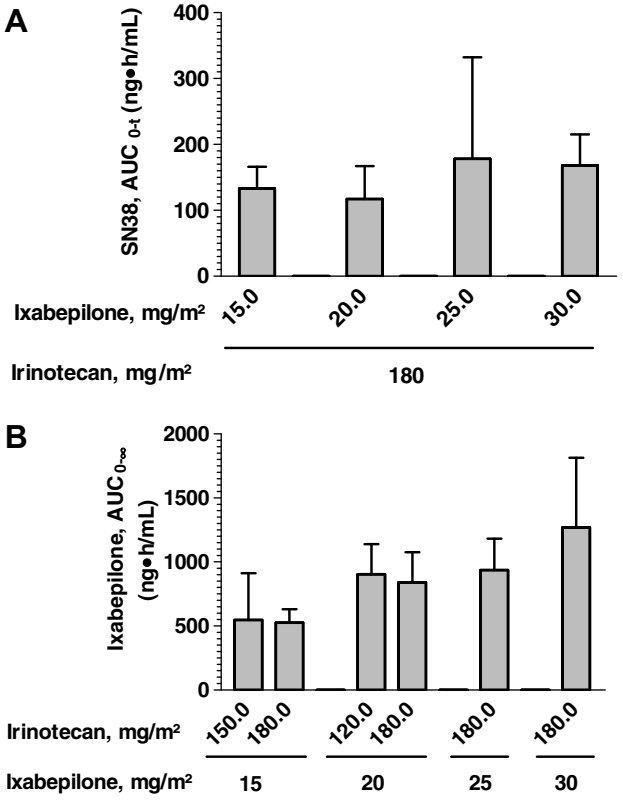

Fig. 2 – Effects of ixapepilone on the exposure of SN38 (A) and effects of irinotecan on the exposure of ixabepilone (B).

3.5. *Pharmacokinetic study*

Plasma samples were obtained from all patients (n = 42) at cycle 1. Irinotecan and SN-38 pharmacokinetic parameters are listed in Table 5. Exposure to irinotecan and SN38 (AUC) ranged from 6798–12,813 and 92.8–178 ng•h/mL, respectively, with high interpatient variability. In patients treated with 180 mg/m² irinotecan, exposure to SN38 was not significantly modified by increasing doses of ixabepilone (Fig. 2A).

Table 6 lists the pharmacokinetic parameters of ixabepilone derived by noncompartimental methods. At all dose levels, ixabepilone displayed a large volume of distribution (>400 L). $T_{1/2}$ and clearance were not significantly different across the various dose levels investigated. Analysis of individual plasma concentrations indicates that both C_{max} and $AUC_{0-\infty}$ values appeared to increase with increasing doses. At the recommended doses (20/180), coefficients of variation of C_{max} and $AUC_{0-\infty}$ were 32% and 30%, respectively. No significant modification of ixabepilone exposure was observed with two different doses of irinotecan (Fig. 2B). The propensity for developing neuropathy was related to dose (Fig. 3A). There was an apparent relationship between ixabepilone exposure ($AUC_{0-\infty}$) and the occurrence of neuropathy (Fig. 3B).

Table 5 – Plasma pharmacokinetic parameters of irinotecan and SN38

Dose levels Ixabepilone/irinotecan in mg/m²(n: number of patients)	Irinotecan		SN38	
	Cmax (ng/mL)	AUC_{0-t} (ng·h/mL)	Cmax (ng/mL)	AUC_{0-t} (ng·h/mL)
	GeometricMean (C.V. %)	GeometricMean (C.V. %)	GeometricMean (C.V. %)	GeometricMean (C.V. %)
Dose level I: 15/150 (3)	1,741 (19)	6,798 (35)	27.7 (32)	134 (35)
Dose level II: 15/180 (6)	2,220 (15)	9,852 (22)	20.1 (26)	133 (25)
Dose level III: 20/120 (6)	1,942 (23)	7,013 (41)	18.0 (38)	92.8 (55)
Dose level IV: 20/180 (14)	2,242 (25)	9,912 (26)	18.0 (36)	117 (43)
Dose level V: 25/180 (6)	2,348 (32)	12,813 (55)	26.2 (89)	178 (87)
Dose level VI: 30/180 (7)	1,962 (15)	9,843 (17)	23.4 (41)	168 (28)

CV: coefficient of variation; SD: standard deviation.

Table 6 – Plasma pharmacokinetic parameters of ixabepilone

Dose levels	Cmax (ng/mL)	AUC_{0-t} (ng·h/mL)	$AUC_{0-\infty}$ (ng·h/mL)	$T_{1/2}$ (h)	Cl_TL/h	Vss (L)
Ixabepilone/irinotecan in mg/m^2 (*n*: number of patients)	GeometricMean (C.V. %)	GeometricMean (C.V. %)	GeometricMean (C.V. %)	Mean (S.D.)	Mean (S.D.)	Mean (S.D.)
Dose level I: 15/150 (3)	114 (46)	547 (67)	728 (88)	12.4 (8.9)	46.3 (31.6)	475 (396)
Dose level II: 15/180 (6)	96 (10)	525 (20)	753 (28)	17.3 (2.9)	37.3 (14.2)	677 (185)
Dose level III: 20/120 (6)	186 (63)	904 (26)	1,237 (27)	13.1 (2.6)	32.8 (9.1)	429 (124)
Dose level IV: 20/180 (14)	193 (32)	841 (28)	1,192 (30)	17.9 (7.7)	30.7 (12.5)	526 (200)
Dose level V: 25/180 (6)	171 (45)	938 (26)	1,524 (28)	24.5 (20.8)	28.9 (8.2)	755 (588)
Dose level VI: 30/180 (7)	261 (30)	1,269 (43)	1,746 (46)	15.6 (2.5)	36.6 (16.2)	595 (271)

CV: coefficient of variation; SD: standard deviation.

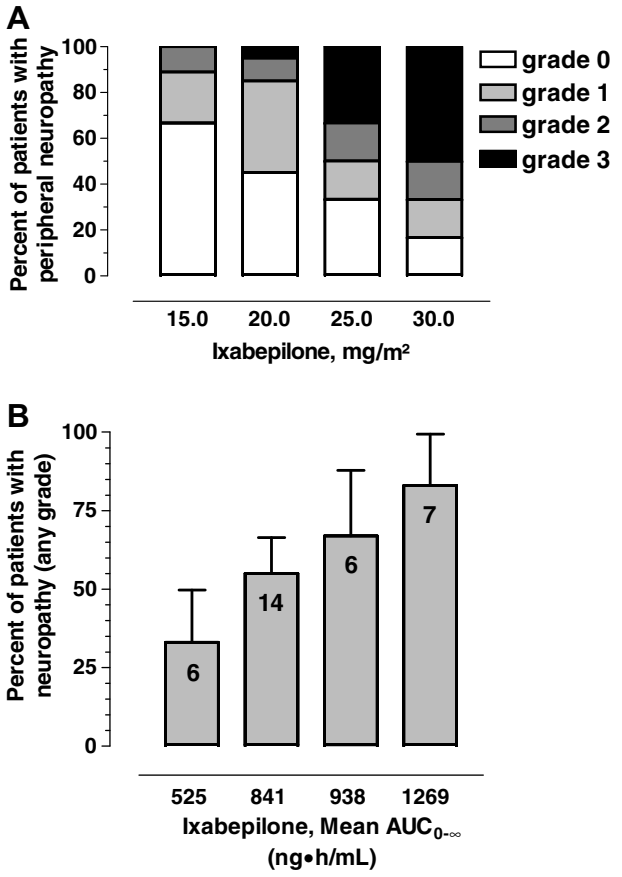

Fig. 3 – Percent of patients with grade 1–3 peripheral neuropathy according to the dose (A) and the $AUC_{0-\infty}$ (B) of ixabepilone.

3.6. *Antitumour activity*

Objective responses were observed in platinum-pretreated patients including two patients with small-cell lung cancer (dose levels IV–V), one patient with non-small-cell lung cancer (dose level V), one patient with bronchiolo-alveolar carcinoma (dose level IV), and in one patient with an unknown primary squamous cell carcinoma (dose level IV). In addition, one patient with taxane-pretreated breast cancer (dose level III) and one patient with platinum-pretreated gastric cancer (dose level III) experienced prolonged disease stabilisation during 11 and 20 months, respectively.

4. Discussion

In this study, the toxicity profile of the combination was very similar to the results of single agent ixabepilone phase I studies, in which DLTs included febrile neutropenia, diarrhoea, asthenia and neuropathy .[6–9] Our data suggested no pharmacokinetic interaction between ixabepilone and irinotecan. Although our trial suggests that ixabepilone did not increase the frequency of irinotecan-induced diarrhoea as compared to previously published data,[18] caution remains mandatory on the management of acute toxicity of this combination since both drugs are susceptible of inducing severe neutropenia and/or diarrhoea.

In this trial, the choice of the 3-h infusion ixabepilone rather than 1-h infusion used in previous studies was motivated by reports suggesting that C_{max} may correlate with neurotoxicity, as observed with other drugs such as oxaliplatin.[19] However, prolonging the duration of infusion did not result in decreasing C_{max} values (but rather seemed to increase exposure as compared to previously published pharmacokinetic data[9]) and was not associated with a decreased incidence of neuropathy. Therefore, prolonging the duration of infusion does not seem to be essential to improve neurological tolerance of ixabepilone.

In our study, neuropathy led us to consider cumulative neurotoxicity, thereby modifying the classical definition of the recommended dose on the basis of multiple ixabepilone administrations. For several neurotoxic anticancer agents, neuropathy that occurs after repeated dosing (i.e. after at least three cycles) is often difficult to explore in the course of classical phase I trials and is not always considered in the final dose recommendation, which in most studies, is primarily based on toxicity at cycle 1. In our experience using oxaliplatin[20] and other compounds with neuromuscular toxicity such as aplidine[21,22] and irofulven,[23] occurrence of delayed neuropathy required redefining the appraisal of the recommended dose based on dose-limiting toxicity occurring not only during cycle 1 but at any cycle in a subset of patients capable to receive at least 3–4 cycles (i.e. the median time to toxicity onset). This approach previously

allowed avoiding critical mistakes in dose recommendation for future phase II–III trials. Considering that approximately one among three patients entering in phase I will be able to finally receive $\geqslant 3$ cycles, this revised definition required extending the number of patients treated at the recommended dose in our study. Our data strongly suggests that the severity and the onset of occurrence of ixabepilone neuropathy are not related to AUC or peak concentration assessed at cycle 1. In contrast, it appears that there is a cumulative toxicity above a threshold dose of ixabepilone per cycle (>25 mg/m^2) while conversely, doses of ixabepilone $\leqslant$20 mg/m^2 per cycle could be maintained in several patients for more than 4 months without inducing severe peripheral neuropathy. In this study, we showed that peripheral neuropathy precluded the use of doses $\geqslant$25 mg/m^2 ixabepilone for more than three cycles, since grade 1 neuropathy rapidly progressed toward grade 2, which ultimately turned to grade 3 in most patients after 2 months of drug administration. Furthermore, discomfort induced by grade 2 peripheral neuropathy combining dysaesthesia and pain, required reconsideration of the individual patient risk-to-benefit equation and necessitated ixabepilone discontinuation before reaching grade 3 toxicity. Taken together, our data suggest avoiding doses $\geqslant$25 mg/m^2 ixabepilone every other week and discontinuing ixabepilone as soon as patients experience grade 2 peripheral neuropathy. Conversely, dose reduction to the recommended dose of 20 mg/m^2 ixabepilone appeared to be feasible with limited occurrence of severe neuropathy. Among fourteen patients treated at the dose of 20 mg/m^2 ixabepilone, seven patients presented a grade 1 neuropathy (that further worsened to grade 2 in only one of those patients) and one patient suffered from grade 3 neuropathy that improved to grade 1 after treatment discontinuation. Based on those data it appears that good adherence to treatment guidelines and careful neurological surveillance should allow maintenance of safe ixabepilone doses (20 mg/m^2) for multiple cycles despite the presence of grade 1 neurotoxicity. Furthermore, the dose-intensity of ixabepilone when given at the recommended dose of 20 mg/m^2 every 2 weeks in this trial was close to that of the dose-intensity reported in a phase I study using ixabepilone as a single agent infusion 3-weeks apart (25 mg/m^2/2-weeks). In addition, combination of ixabepilone with irinotecan retains antitumour activity with objective responses observed in platinum-pretreated patients with lung cancers including small-cell, non-small-cell, and bronchiolo-alveolar carcinoma.

In summary, we showed that ixabepilone combined with irinotecan on an every other week outpatient schedule every 28 days has manageable neurotoxicity. The recommended doses of 20 mg/m^2 ixabepilone with 180 mg/m^2 irinotecan show promising antitumour activity and may warrant further investigations in patients with a variety of tumours known to be sensitive to tubulin-stabilising agents and/or topoisomerase I inhibitors.[24,25]

Conflict of interest statement

Fouad Namouni, Ronald Peck and Marvin Cohen are employed by Bristol Myers Squibb, France and USA respectively.

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