Cancer Chemother Pharmacol (2007) 60:203–209
DOI 10.1007/s00280-006-0362-y

ORIGINAL ARTICLE

Phase I trial of oral MAC-321 in subjects with advanced malignant solid tumors

A. C. Lockhart · R. Bukowski · M. L. Rothenberg · K. K. Wang · W. Cooper · J. Grover · L. Appleman · P. R. Mayer · M. Shapiro · A. X. Zhu

Received: 5 May 2006 / Accepted: 27 September 2006 / Published online: 8 November 2006

Abstract
Purpose MAC-321 is a novel taxane that has demonstrated exceptional activity in human xenograft models when administered intravenously and orally. Preclinical studies of MAC-321 have shown antitumor activity in MDR-expressing and paclitaxel-resistant tumors. This phase I dose escalation study was performed to determine the safety, tolerability, and pharmacokinetic profile of orally administered MAC-321 given once every 21 days. Preliminary antitumor activity of MAC-321 was also examined.
Methods Key eligibility criteria included adult subjects with refractory solid tumors or solid tumors for which conventional therapy was unsuitable or did not exist, good performance status (ECOG (2), and adequate hematologic, hepatic, and renal functions. Plasma pharmacokinetic (PK) sampling was performed during the first cycle of therapy.
Results Five dose levels of MAC-321 ranging from 25 to 75 mg/m^2 were evaluated in 18 subjects (four women and 14 men). MAC-321 was well tolerated at the first three dose levels (25, 37, 50 mg/m^2). Two subjects developed dose-limiting toxicities (DLTs) at 75 mg/m^2; one subject with grade 3 and one subject with grade 4 neutropenia with fever. Three subjects treated at an intermediate dose level of 60 mg/m^2 had no DLTs. However, the study was terminated prior to completion of the maximal tolerated dose cohort after subjects treated with intravenous MAC-321 in a concurrent study experienced life-threatening toxicities. Other common toxicities included grades 1–2 fatigue and grades 1–2 diarrhea. There was substantial interpatient variability in the PK parameters. MAC-321 was rapidly absorbed with a mean C_{max} value of less than 1 h. Mean C_{max} and AUC values generally increased in a dose-related manner. The median terminal phase elimination half-life was 45 h (range 20–228 h). Disease stabilization was seen in four subjects with the following tumors: mesothelioma (14 cycles), chondrosarcoma (12 cycles), small cell carcinoma (10 cycles), and prostate carcinoma (6 cycles).
Conclusions MAC-321 can be safely administered orally once every 21 days up to a dose of 60 mg/m^2. The major DLT was neutropenic fever. Four subjects had disease stabilization.

Keywords Phase I · Clinical trial · MAC-321 · Paclitaxel · Docetaxel

A. C. Lockhart (✉) · M. L. Rothenberg · W. Cooper
Division of Hematology/Oncology, Vanderbilt University Medical Center, 777 Preston Research Building, Nashville, TN 37232-6307, USA
e-mail: craig.lockhart@vanderbilt.edu

R. Bukowski
Cleveland Clinic Taussig Cancer Center, Cleveland, OH, USA

K. K. Wang · J. Grover · P. R. Mayer · M. Shapiro
Wyeth Research, Cambridge, MA, USA

L. Appleman · A. X. Zhu
Dana Farber/Harvard Cancer Center, Boston, MA, USA

Introduction

Taxanes are naturally derived small molecules that exert their antitumor actions by inhibiting microtubule function leading to cell division arrest. More recently

described mechanisms of taxane antitumor activity include regulation of gene expression, including those involved in transcription regulation and tumor suppression as well as enzymes governing proliferation, apoptosis, and inflammation [13, 14, 18, 20]. Two taxanes, paclitaxel and docetaxel, have been extensively used to treat ovarian, lung, breast, and upper aerodigestive tract cancers since their FDA approval in the 1990s, and as such both agents have had a significant impact on the treatment of many patients [21]. However, other common tumors, including colon cancer, pancreatic cancer, and melanoma, are unresponsive to taxane therapy and thus limit the universal application of these chemotherapeutic drugs. Many tumors demonstrate de novo taxane resistance, whereas other cancers that initially respond to taxanes eventually develop resistance due to drug efflux pump expression, point mutations in tubulin, or alterations in the machinery that regulates tumor apoptosis [5, 7–9].

MAC-321 (TL 00139; 5β, 20-Epoxy-1, 2α, 4, 7β, 10β, 13α-hexahydroxytax-11-en-9-one 4—acetate 2-benzotae 7-prorionate 13-ester with [2R, 3S]—N-terbutoxycarbonyl-3-[2-furyl] isoserine) is a novel taxane based upon specific modifications of the docetaxel molecule (Fig. 1). Similar to its predecessors, MAC-321 exerts its apoptotic effects by blocking cell division at the G_2-M interface of the cell cycle by promoting tubulin polymerization and microtubule stabilization [22]. However, MAC-321 has demonstrated significant preclinical differences as compared to the other taxanes. First, MAC-321 has demonstrated significant activity in tumor cell lines that are traditionally insensitive to taxanes including colon cancer, pancreatic cancer, and melanoma [22]. Second, MAC-321 demonstrated antiproliferative effects against several human cancer cell lines that were resistant to paclitaxel and docetaxel, which is believed to be attributed to MDR1 (ABCB1) overexpression. Based on experimental IC_{50} values, superior antitumor activity was observed in the cell lines with resistance mediated by MDR1 overexpression [12]. A third advantage for MAC-321 over paclitaxel or docetaxel is that MAC-321 appears to be readily soluble and does not require the use of toxic vehicles that can potentially induce numerous adverse reactions. This improved solubility also allows MAC-321 to be administered orally with acceptable bioavailability in animal models [22]. Oral dosing would improve the convenience of drug administration and reduce the potential complications associated with IV drug administration (i.e., central IV access placement, drug extravasations).

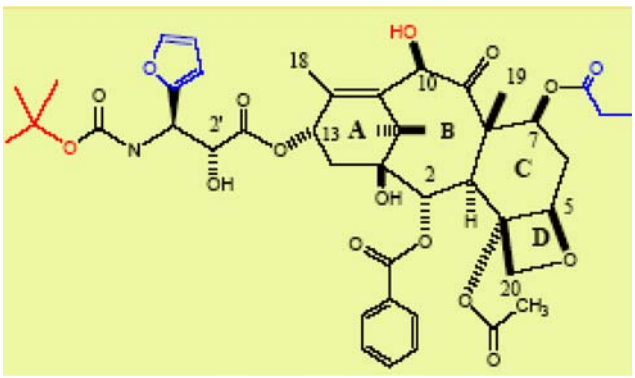

Fig. 1 Chemical structure of oral MAC-321

In animal studies when MAC-321 was administered by gavage, toxicities included increasing body weight, alterations in hematology and chemistry parameters, decreased thymus weight, microscopic alterations in the intestinal tract, bone marrow physiological changes, and some oral irritation [11]. The toxicity profile of oral MAC-321 was similar to the IV formulation. In all species tested (mice, rats, and dogs), MAC-321 showed rapid absorption and rapid clearance from the plasma. The absolute oral bioavailability in animals ranged from 3 to 13% depending on the species. Additionally, MAC-321 was demonstrated to be a competitive inhibitor of CYP3A4, a member of the cytochrome P450 mixed-function oxidase system [11]. The potential for oral MAC-321 to provide effective treatment for tumors that are normally resistant to taxanes, as well as the acceptable toxicity profile in animals, provided the rationale for the phase I dose escalation clinical trial for orally administered MAC-321. A previously performed phase I study of an intravenous formulation of MAC-321 determined a maximal tolerated dose (MTD) of 35 mg/m^2 when administered every 3 weeks and dose-limiting toxicities (DLTs) of neutropenia and myalgia/arthralgia [1]. To assess the safety, tolerability, and pharmacokinetics of oral MAC-321 in comparison to the IV formulation, an every 3-week schedule was evaluated.

Materials and methods

Subject eligibility

Subject inclusion criteria included histologically confirmed malignant solid tumors that had failed to respond to conventional therapy for cancer or a malignancy for which no conventional therapy existed. Subjects must have recovered from all acute adverse effects from prior therapies excluding alopecia and to have a life expectancy of at least 12 weeks, as well as

an Eastern Cooperative Oncology Group performance status of 0, 1 or 2. Subjects had to have measurable disease defined as at least one measurable lesion as specified by the modified RECIST criteria and adequate bone marrow function (a white blood cell count ≥3,000/mm^3, absolute neutrophil count ≥1,500/mm^3, and platelet count ≥100,000 cells/μL); adequate hepatic function (total bilirubin ≤1.5× the upper limit of normal, and alanine aminotransferase and aspartate aminotransferase ≤2.5× the upper limit of normal); adequate renal function (serum creatinine < 2.0 mg/dL); and a signed IRB approved consent form.

Exclusion criteria included subjects with primary central nervous system metastases or symptomatic brain metastases; subjects known to be HIV-seropositive or having acute or chronic hepatitis B or C infections, subjects with concurrent serious infections requiring intravenous antibiotic or antiviral treatment, or subjects with chronic immunosuppression. Additionally, subjects were excluded if they had a known hypersensitivity to ethanol-cremophor, raspberry flavoring, lipid emulsions, egg or egg products. Subjects with a history of unstable angina or recent myocardial infarction (within the previous 6 months), or any other major illness that, in the investigator's judgment, could potentially compromise the subject's safety were also excluded. Because MAC-321 was being administered orally, any condition that could potentially inhibit the oral absorption of MAC-321 also resulted in subject exclusion. Finally, subjects with prior exposure to MAC-321, previous pelvic radiation, grade 2 or greater peripheral neuropathy, and recent major surgery were also excluded. Subjects were discouraged to take concurrent medications known to be cytochrome P450 inhibitors or inducers.

Trial design

This trial was an open-label dose escalation study whose primary objective was to determine the safety, tolerability, and pharmacokinetics of MAC-321 administered orally to subjects with advanced malignant solid tumors. Secondary objectives were to obtain information on the absolute bioavailability of MAC-321 and to obtain preliminary information on the antitumor activity of MAC-321. Subjects were enrolled during dose escalation in three-subject cohorts. Escalation was allowed to proceed after the last subject entered into a cohort that had been evaluated through study day 21, and no DLT had been observed. If a DLT was encountered, the cohort was expanded to a total of six subjects. If a second DLT was observed within the expanded cohort, then dose escalation ceased and one of the prior dose levels would be considered the MTD. To determine the safety of oral MAC-321 in minimally pretreated subjects once the MTD had been determined, at least six minimally pretreated subjects would be treated on the protocol. Minimal pretreatment was defined as fewer than six courses of an alkylating agent-containing chemotherapy regimen or fewer than four courses of platinum chemotherapy. Subjects with prior radiation therapy were permitted to enroll if <25% of their bone marrow was previously irradiated and had fewer than four courses of Mytomycin C or nitrosourea. After the MTD was identified, a bioavailability cohort with eight subjects was to be evaluated for assessing the bioavailability of the oral formulation of MAC-321 at the MTD. Subjects in this cohort were to be given an oral dose of MAC-321 on study day 1 followed by an IV dose of MAC-321 on study day 22 so that the bioavailability with the two methods of administration could be compared.

Treatment of subjects

The subjects underwent a screening that was performed within 2 weeks prior to administration of the first dose of oral MAC-321. During the screening evaluation, the subject signed an IRB approved consent form, had a complete medical history performed, had a complete physical exam including a detailed neurological exam, as well as a chest X-ray, ECG, complete blood counts, comprehensive blood chemistry including liver function tests, coagulation studies an evaluation for ECOG performance status, and a disease assessment by tumor measurement. MAC-321 was administered every 3 weeks.

On study day 1, subjects were administered an oral dose of MAC-321 after an overnight fast and were required to fast for 1 h after drug administration. Treated subjects were monitored for toxicity for at least 1 week before additional subjects could be enrolled at the same dose cohort. Subjects were allowed to receive up to a maximum of six doses of MAC-321 unless continuation was deemed to be medically appropriate by the investigator with agreement of the medical monitor. Since it was anticipated that the bioavailability of MAC-321 administered orally would range from ~3 to 13%, a starting dose of 25 mg/m^2 was recommended for the oral administration of this drug. Dose escalation between cohorts was based on a modified Fibonacci schema and planned as follows: 25, 37, 50, 75, 100, and 125 mg/m^2.

Dose limiting toxicities were defined as any of the following that were possibly related to MAC-321: (1) Any grade 3 or 4 non-hematologic toxicity, except for

grade 3 nausea, vomiting or diarrhea, despite the subjects having received optimal medical therapy; (2) Febrile neutropenia, defined as a fever of unknown origin or microbiologically documented infection and having an absolute neutrophil count of <1,000 cells/mm^3, and an oral or tympanic temperature of at least 38.5°C; (3) Grade 4 thrombocytopenia or grade 4 hematologic toxicity that lasted for at least 5 days; (4) Grade 2 or greater hemorrhage; (5) Grade 2 or greater neurotoxicity that persisted for at least five consecutive days; and (6) Grade 3 or greater neurosensory toxicity.

Drug formulation

Oral MAC-321 powder was provided in a screw-capped amber glass bottle. Diluents needed to prepare oral MAC-321 included anhydrous ethanol in 5 mL glass ampoules, cremophor EL provided as a stock solution in a glass bottle, raspberry flavoring, as well as sterile water for injection. These ingredients were combined in a 1:1:6:12 ratio and adjusted to a total volume of 100 mL.

Response criteria

Tumor response was assessed utilizing the modified RECIST criteria. A complete response (CR) was defined as the disappearance of all target lesions. Partial response (PR) was at least a 30% decrease in the sum of the longest diameter of target lesions when compared to baseline sum of longest diameters. Progressive disease (PD) indicated at least a 20% increase in the sum of the longest diameter when compared to the smallest sum of longest diameter observed after first dose of test article. Stable disease (SD) was recorded when neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. All responses had to be confirmed by repeat assessments performed no less than 4 weeks after the initial response assessment.

Pharmacokinetic analysis

To characterize the plasma pharmacokinetic (PK) of MAC-321, blood samples were taken during cycle 1 at the following time points: 0 (pre-dose), 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 24, 48, 72, 96, and 120 h to measure plasma levels of MAC-321. A high-performance liquid chromatography/tandem mass spectrometry (HPLC/MS/MS) method was validated for the quantification of MAC-321 blood levels [11]. Blood was collected in tubes containing sodium EDTA for pharmacokinetic samples. Plasma (0.5 mL plus an internal standard) was extracted with 5.0 mL of a 50/50 mixture of t-butyl methyl ether/hexane and was taken to dryness under a nitrogen stream. The extract was reconstituted and injected onto a C-18 column with MS/MS detection. The lower limit of MAC-321 detection was 0.2 ng/mL and the accuracy was within 15%, based on quality control samples of 0.5, 10, and 90 ng/mL [11]. Assessment of the stability of MAC-321 in human plasma under various conditions indicated that the compound was stable during short-term storage at ambient temperature or at 4°C up to 24 h [11]. Standard pharmacokinetic variables including C_{max}, t_{max}, AUC, CL/F, and $t_{1/2}$ were determined with model independent methods.

Results

Three institutions participated in the study. Eighteen subjects received 84 complete cycles of oral MAC-321. The median number of administered cycles was 2 (range 1–24). Subject characteristics are listed in Table 1. The study cohort included 14 men and four women with a median age of 60 (range 39–71) years. All of the subjects except one had received prior

Table 1 Subject demographics

Characteristic	Number of subjects
Number of subjects treated	18
Gender: male/female	14/4
Age (years): median (range)	60 (39–71)
Race: Caucasian	18
ECOG	
PS = 0	4
PS = 1	9
PS = 2	3
Number of prior chemotherapy Regimens	1
0	
1	7
2	4
3	2
4	2
5	2
Tumor site	
Colorectal	5
Pancreas	2
Renal	2
Prostate	1
NSCLC	1
Others	1 each
Gastric	
Adenocarcinoma unknown primary	
Chondrosarcoma	
Esophagus	
Mesothelioma	
Small cell undifferentiated carcinoma	
Spindle cell carcinoma	

chemotherapy; the majority of these subjects (eight) had received two or more prior regimens. Median performance status was ECOG 1 (range 0–2). Treatment was well tolerated at the first three dose levels (25, 37, 50 mg/m^2). Three subjects each were treated at the 25 and 37.5 mg/m^2 dose levels. Five were treated at the 50 mg/m^2 dose level after the first two subjects treated at this dose discontinued treatment before day 21 and were replaced. Two of four subjects had DLT of febrile neutropenia at the 75 mg/m^2 dose level. Thus an intermediate dose level of 60 mg/m^2 was explored based on agreement between the investigators and the sponsor. Three subjects were treated at the 60 mg/m^2 dose level and determined to be the MTD. Additional subjects to confirm the MTD were not enrolled at the 60 mg/m^2 dose level because the study sponsor discontinued the study after several cases ($n = 6$) of severe neutropenia associated with life-threatening infection were observed in a concurrent study with intravenous MAC-321. Of note, a case of severe neutropenia with life-threatening infection was observed in this study of oral MAC-321 in a patient with colon cancer who had rapid disease progression and died. Thus, the planned bioavailability cohort to compare the bioavailability of the intravenous and oral formulations of MAC-321 was not completed due to study closure.

Toxicity

Table 2 lists all grade 3/4 toxicities observed during any course of treatment. Dose limiting toxicity for oral MAC-321 was febrile neutropenia. Two of four subjects treated at the 75 mg/m^2 had febrile neutropenia (nadir day 7); one subject had grade 3 neutropenia with fever (3 days duration), the other subject had grade 4 neutropenia with fever (4 days duration). Overall, the grade 3/4 toxicities (Table 2) were neutropenia with fever (two subjects), thrombocytopenia (one subject), neuropathy (one subject), fatigue (one subject), and infection (one subject). Except for the single episode of grade 3 fatigue observed at the 25 mg/m^2 dose level, all other grade 3/4 toxicities were observed at the highest (75 mg/m^2) dose level. Other common toxicities that occurred in ≥25% of subjects included grade 1/2 fatigue, anorexia, nausea, and diarrhea. Importantly, the oral formulation of MAC-321 was not associated with frequent dyspepsia, vomiting, or esophagitis.

Pharmacokinetics and pharmacodynamics

Figure 2 shows the plasma concentration versus time curves for orally administered MAC-321. The measured pharmacokinetic parameters for orally administered MAC-321 by dose group are summarized in Table 3. Oral MAC-321 was absorbed rapidly with a mean C_{max} of less than 1 h at all dose levels. Drug exposure generally increased in a dose-related manner as measured by mean C_{max} and AUC. However, review of the plasma concentration versus time curves at each dose level indicates that toxicity may not be directly related to C_{max}. At the 75 mg/m^2, where two of four patients experienced DLT, the mean C_{max} and AUC were lower than measured at the 60 mg/m^2 dose level which was well tolerated. The substantial intersubject variability in the PK parameters limits the generalizability of the PK observations. Evaluation of the individual data indicates that the elevated mean C_{max} and AUC at the 60 mg/m^2 are driven by one patient with a C_{max} of 113 ng/mL and an AUC of 2,671 ng h/mL. Additionally, both patients who experienced DLT at the 75 mg/m^2 had pathophysiology that may account for their higher exposure. One patient who developed grade 4 neutropenia and grade 4 thrombocytopenia had the highest AUC in the study (3,143 ng h/mL). The patient was found to have a pleural effusion on week 2 of the study, which may have contributed to the higher AUC, based on prolonged drug levels post administration. The second patient had evidence of abnormal liver function at baseline.

The median terminal phase elimination half-life for oral MAC-321 was 45 h (range 20–228). The measured pharmacokinetic parameters for oral MAC-321 were similar to the pharmacokinetics of the IV formulation including substantial intersubject variability in the PK parameters and a similar terminal phase elimination half-life. The small number of subjects treated at the MTD and the lack of bioavailability studies does not

Table 2 Toxicity

Toxicity (≥grade 3)	MAC-321 dose (mg/m^2)					
	25 $n = 3$	37.5 $n = 3$	50 $n = 5$	60 $n = 3$	75 $n = 4$	Total $n = 18$
Neutropenic fever	0	0	0	0	2	2
Fatigue	1	0	0	0	1	1
Infection	0	0	0	0	1	1
Thrombocytopenia	0	0	0	0	1	1
Neuropathy	0	0	0	0	1	1

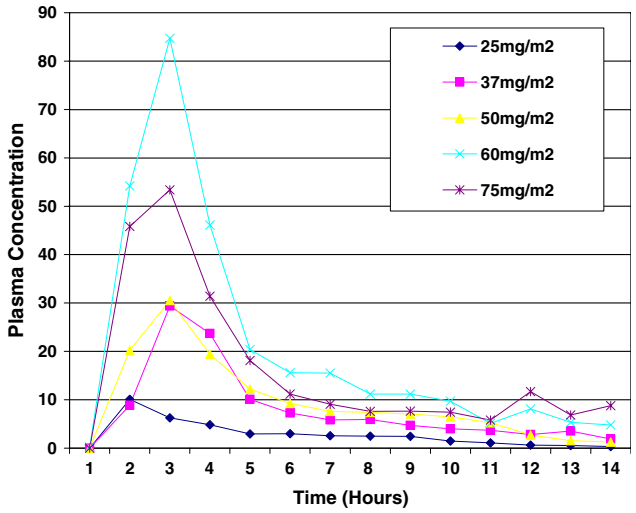

Fig. 2 Plasma concentration versus time curves for each dose level of orally administered MAC-321

allow for final conclusions regarding pharmacokinetics of oral MAC-321.

Antitumor activity

No objective responses (CR + PR) were observed during this trial. The median duration of MAC-321 treatment was 2 cycles (range 1–24). Disease progression was the reason for treatment discontinuation in 14 of 18 subjects. Disease stabilization was seen in four subjects with the following tumors: mesothelioma (24 cycles), chondrosarcoma (12 cycles), small cell carcinoma (11 cycles), and prostate adenocarcinoma (6 cycles). There are no patients that are still being treated with MAC-321 on this study.

Discussion

The taxanes appear to be one of the most successful classes of antitumor drug developed thus far, due at least in part to their broad antitumor activity. The primary mechanism of antitumor activity for the two FDA approved taxanes is through tubulin binding and inhibition of microtubule depolymerization, preventing chromosomal separation and leading to mitotic arrest, and cell death [20]. Taxane treatment has also been reported to induce genes involved in transcription regulation, tumor suppression as well as cellular proliferation, apoptosis, and inflammation [10, 13, 14, 18]. MAC-321 is a docetaxel analogue that can induce tubulin polymerization [22]. MAC-321 also has pharmacological properties that are superior to docetaxel and paclitaxel including higher cytotoxic potency, a weak interaction with MDR1 reducing the potential for MDR1 induced taxane resistance and greater solubility allowing for oral administration.

In this phase I study, oral MAC-321 was administered safely every 21 days at doses up to 60 mg/m^2. The dose limiting toxicity was neutropenic fever. Doses at the MTD and below were very well tolerated. The established MTD for oral MAC-321 was not confirmed in this study as the study was halted after significant toxicity was observed in a concurrent trial of MAC-321 administered intravenously. In that study, six patients developed neutropenic sepsis with three fatalities. In the phase I study of intravenous MAC-321, myelosuppression was also the most common significant toxicity. However, the grade 3 and greater myalgias and dyspnea observed in the intravenous study were not encountered in this study population [1].

Pharmacokinetics of oral MAC-321 was generally linear in the 25–60 mg/m^2 dose range. The C_{max} was highest at the 60 mg/m^2 dose level, indicating that toxicity may not be directly related to C_{max}. The considerable variability in PK parameters suggests that host genetics or other factors such as concurrent medications, or GI system function may contribute to the observed variability in drug disposition. At the MTD, a planned bioavailability cohort to compare the bioavailability of the intravenous and oral formulations of MAC-321 was not completed because the study was terminated. Although no tumor responses were observed, four subjects with refractory tumors had disease stabilization. The tumor types in these subjects who received long-term treatment with oral MAC-321 have all been associated with some level of detectable

Table 3 Summary of pharmacokinetic parameters of MAC-321

Dose group (mg/m^2)	C_{max} (ng/mL)			t_{max} (h)			AUC (ng h/mL)			$t_{1/2}$ (h)			CL/F (L/h)		
	Mean	SD	CV (%)	Mean	SD	CV (%)	Mean	SD	CV (%)	Mean	SD	CV (%)	Mean	SD	CV (%)
25 (n = 3)	11	6	54	1.0	0.9	87	133	43	32	56	23	42	424	132	31
37.5 (n = 3)	32	12	37	1.3	0.6	43	857	972	133	120	96	80	189	137	73
50 (n = 5)	35	27	76	0.8	0.3	31	438	309	71	53	17	31	298	186	63
60 (n = 3)	85	41	48	1.0	0.0	1	1,683	1,399	83	178	–	–	112	95	84
75 (n = 4)	60	48	81	0.8	0.3	39	1,033	1,428	138	27	9	36	640	731	114

MDR1 expression [3, 15, 19, 23]. However, protein and/or mRNA expression levels for MDR1 were not assessed as part of this study; therefore, conclusions about the clinical efficacy of oral MAC-321 in MDR1 expressing tumors cannot be drawn.

Other taxane analogues have been developed with purported ability to overcome MDR1-mediated tumor resistance and have undergone clinical testing [4, 6, 12, 16, 17, 24]. MAC-321 may offer some advantage over these agents based upon availability of a convenient administration route (i.e., oral) and infrequent dosing schedules, but careful patient selection will be required in future studies of this agent. A review of the patients who experienced life-threatening toxicities after intravenous MAC-321 administration indicated that neutropenic sepsis appears to occur in patients with abnormal liver function at baseline. In future planned studies of MAC-321, specific exclusion criteria for patients with abnormal liver function tests will be included. Similar dosing criteria for the administration of docetaxel have been recommended [2]. The convenient route of administration and the observation that subjects can take the drug for prolonged periods of time with tolerable toxicity provide support for further evaluation of oral MAC-321 in select subject populations.

References

1. Brahmer JR, Shapiro M, Carducci K, Beers S, Cameron B, Cohen M, Rubin EH (2003) Phase I trial of a potent novel taxane, TL00139 (MAC-321), in patients with advanced malignant solid tumors. Proc Am Soc Clin Oncol 22 (abstr 527)
2. Burris HA (1996) Optimal use of docetaxel (Taxotere): maximizing its potential. Anticancer Drugs 7(Suppl 2):25–28
3. Campling BG, Young LC, Baer KA, Lam YM, Deeley RG, Cole SP, Gerlach JH (1997) Expression of the MRP and MDR1 multidrug resistance genes in small cell lung cancer. Clin Cancer Res 3:115–122
4. Camps C, Felip E, Sanchez JM, Massuti B, Artal A, Paz-Ares L, Carrato A, Alberola V, Blasco A, Baselga J, Astier L, Voi M, Rosell R, Spanish Lung Cancer G (2005) Phase II trial of the novel taxane BMS-184476 as second-line in non-small-cell lung cancer. Ann Oncol 16:597–601
5. Dumontet C, Sikic BI (1999) Mechanisms of action of and resistance to antitubulin agents: microtubule dynamics, drug transport, and cell death. J Clin Oncol 17:1061–1070
6. Gelmon KA, Latreille J, Tolcher A, Genier L, Fisher B, Forand D, D'Aloisio S, Vernillet L, Daigneault L, Lebecq A, Besenval M, Eisenhauer E (2000) Phase I dose-finding study of a new taxane, RPR 109881A, administered as a one-hour intravenous infusion days 1 and 8 to patients with advanced solid tumors. J Clin Oncol 18:4098–4108
7. Giannakakou P, Gussio R, Nogales E, Downing KH, Zaharevitz D, Bollbuck B, Poy G, Sackett D, Nicolaou KC, Fojo T (2000) A common pharmacophore for epothilone and taxanes: molecular basis for drug resistance conferred by tubulin mutations in human cancer cells. Proc Natl Acad Sci USA 97:2904–2909
8. Gottesman MM (2002) Mechanisms of cancer drug resistance. Annu Rev Med 53:615–627
9. Gottesman MM, Fojo T, Bates SE (2002) Multidrug resistance in cancer: role of ATP-dependent transporters. Nat Rev Cancer 2:48–58
10. Horwitz SB (1992) Mechanism of action of taxol. Trends Pharmacol Sci 13:134–136
11. Investigational Drug Brochure (2002) MAC-321—WAY-179321 (TL 00139)
12. Low JA, Wedam SB, Lee JJ, Berman AW, Brufsky A, Yang SX, Poruchynsky MS, Steinberg SM, Mannan N, Fojo T, Swain SM (2005) Phase II clinical trial of ixabepilone (BMS-247550), an epothilone B analog, in metastatic and locally advanced breast cancer. J Clin Oncol 23:2726–2734
13. Moos PJ, Fitzpatrick FA (1998) Taxanes propagate apoptosis via two cell populations with distinctive cytological and molecular traits. Cell Growth Differ 9:687–697
14. Moos PJ, Fitzpatrick FA (1998) Taxane-mediated gene induction is independent of microtubule stabilization: induction of transcription regulators and enzymes that modulate inflammation and apoptosis. Proc Natl Acad Sci USA 95:3896–3901
15. Ogretmen B, Bahadori HR, McCauley MD, Boylan A, Green MR, Safa AR (1998) Co-ordinated over-expression of the MRP and gamma-glutamylcysteine synthetase genes, but not MDR1, correlates with doxorubicin resistance in human malignant mesothelioma cell lines. Int J Cancer 75:757–761
16. Okuno S, Maples WJ, Mahoney MR, Fitch T, Stewart J, Fracasso PM, Kraut M, Ettinger DS, Dawkins F, Erlichman C (2005) Evaluation of epothilone B analog in advanced soft tissue sarcoma: a phase II study of the phase II consortium. J Clin Oncol 23:3069–3073
17. Ramnath N, Hamm J, Schwartz G, Holden S, Eckhardt SG, Vredenburg MR, Bernacki RJ, Lathia C, Kanter P, Creaven PJ (2004) A phase I pharmacokinetic study of BAY59: a novel taxane. Oncology 67:123–129
18. Rodi DJ, Janes RW, Sanganee HJ, Holton RA, Wallace BA, Makowski L (1999) Screening of a library of phage-displayed peptides identifies human bcl-2 as a taxol-binding protein. J Mol Biol 285:197–203
19. Rosier RN, O'Keefe RJ, Teot LA, Fox EJ, Nester TA, Puzas JE, Reynolds PR, Hicks DG (1997) P-glycoprotein expression in cartilaginous tumors. J Surg Oncol 65:95–105
20. Rowinsky EK, Tolcher AW (2001) Antimicrotubule agents. In: Devita J, Hellman VTS, Rosenberg SA (eds) Cancer principles and practice, 6th edn. Lippincott Williams and Wilkins, Philadelphia, PA, pp 431–452
21. Rowinsky EK (1997) Paclitaxel pharmacology and other tumor types. Semin Oncol 24:S19-11–S19-12
22. Sampath D, Discafani CM, Loganzo F, Beyer C, Liu H, Tan X, Musto S, Annable T, Gallagher P, Rios C, Greenberger LM (2003) MAC-321, a novel taxane with greater efficacy than paclitaxel and docetaxel in vitro and in vivo. Mol Cancer Ther 2:873–884
23. van Brussel JP, Mickisch GH (2003) Multidrug resistance in prostate cancer. Onkologie 26:175–181
24. Wolff AC, Donehower RC, Carducci MK, Carducci MA, Brahmer JR, Zabelina Y, Bradley MO, Anthony FH, Swindell CS, Witman PA, Webb NL, Baker SD (2003) Phase I study of docosahexaenoic acid-paclitaxel: a taxane-fatty acid conjugate with a unique pharmacology and toxicity profile. Clin Cancer Res 9:3589–3597