A Phase I Trial of the Novel Farnesyl Protein Transferase Inhibitor, BMS-214662, in Combination with Paclitaxel and Carboplatin in Patients with Advanced Cancer

Grace K. Dy,1 Laura M. Bruzek,1 Gary A. Croghan,1 Sumithra Mandrekar,1 Charles Erlichman,1 Prema Peethambaram,1 Henry C. Pito,1 Lorelei J. Hanson,1 Joel M. Reid,1 Alfred Furth,1 Shinta Cheng,2 Robert E. Martell,2 Scott H. Kaufmann,1 and Alex A. Adjei1

1Department of Oncology, Mayo Clinic and Foundation, Rochester, Minnesota and 2Bristol Myers, Wallingford, Connecticut

ABSTRACT

Purpose: This phase I study was conducted to determine the toxicities, pharmacokinetics, and pharmacodynamics of BMS-214662, a farnesyl transferase inhibitor, in combination with paclitaxel and carboplatin, in patients with advanced solid tumors.

Experimental Design: Patients with solid tumors received one of six escalating dose levels of BMS-214662 infused over 1 hour given following paclitaxel and carboplatin on the first day of a 21-day cycle. Toxicities were graded by the National Cancer Institute common toxicity criteria and recorded as maximum grade per patient for each treatment cycle. Inhibition of farnesyl transferase activity in peripheral blood mononuclear cells (PBMCs) was evaluated. Accumulation of unfarnesylated HDJ-2 in PBMCs of patients was evaluated as a marker of farnesyl transferase inhibition by BMS-214662.

Results: Thirty patients received 141 cycles of treatment through six dose levels. Dose-limiting toxicities were neutropenia, thrombocytopenia, nausea, and vomiting. There was no pharmacokinetic interaction between BMS-214662 and paclitaxel. The maximum tolerated dose was established as BMS-214662 (160 mg/m2), paclitaxel (225 mg/m2) and carboplatin (area under the curve = 6 on day 1), every 21 days. Inhibition of HDJ-2 farnesylation in PBMCs of patients was shown. One measurable partial response was observed in a patient with taxane-resistant esophageal cancer. There was partial regression of evaluable disease in two other patients (endometrial and ovarian cancer). Stable disease (> 4 cycles) occurred in eight other patients.

Conclusions: The combination of BMS-214662 with paclitaxel and carboplatin was well tolerated, with broad activity in solid tumors. There was no correlation between dose level and accumulation of unfarnesylated HDJ-2 in PBMCs nor tumor response.

INTRODUCTION

Recent years have seen a flourish of mechanism-based, target-directed anticancer therapies, with multiple agents currently undergoing active clinical testing. Paclitaxel, the prototype taxane in the antimicrotubule class of cancer chemotherapeutic agents, is a cell cycle phase–specific agent that has shown impressive single-agent activity against advanced tumors of the lung, breast, esophagus, head and neck, ovary and bladder (1). This prompted its use in combination with platinum compounds such as cisplatin and carboplatin. Carboplatin is a second-generation platinum analogue that has comparable activity to, yet is less nephrotoxic and neurotoxic than cisplatin. Although it is not cell cycle–specific, cell-killing effects can be maximized if cells are in S phase upon exposure to carboplatin (2). It is currently the most commonly used platinum-containing agent in the clinical setting. The combination of paclitaxel and carboplatin has shown broad antitumor activity and is a front-line therapy in various cancers, such as non–small cell lung cancer and ovarian cancer (3).

BMS-214662 is a potent benzodiazepine-like nonthiol, nonpeptide, competitive farnesyl transferase inhibitor that has completed several phase I clinical studies (4–7). Farnesyl transferase inhibitors belong to a novel class of relatively nontoxic agents whose development was largely prompted by the pivotal role of farnesyl transferase in facilitating the membrane attachment and subsequent functioning of Ras proteins. These Ras proteins transduce upstream signals to cytoplasmic and nuclear processes, resulting in enhanced proliferation and angiogenesis as well as inhibition of apoptosis (8). However, the clinical activity of farnesyl transferase inhibitors subsequently has been shown to be independent of ras mutation status. BMS-214662 produces rapid tumor regression and cures in various human xenograft models independent of ras mutation status (9). This dose-dependent cytotoxicity is primarily attributed to induction of apoptosis even at submicromolar concentrations, with a majority of the apoptotic tumor cells arising from G1 and S phases of the cell cycle in tumor cells with activated H-ras (9). Both the p.o. and i.v. forms of BMS-214662 have been evaluated in previous phase I studies, demonstrating the single-agent clinical activity of this compound. Because of considerable gastrointestinal toxicities encountered with the p.o. preparation (10), i.v. infusion has been the formulation utilized in subsequent studies.
Preclinical cancer models have shown synergy between farnesyl transferase inhibitors and taxanes (11, 12). This enhanced antitumor activity is seen with both peptidomimetic and nonpeptide farnesyl transferase inhibitors, suggesting an effect of farnesyl transferase inhibitors as a class rather than related to a specific drug structure (11, 13). Moreover, it has been shown that farnesyl transferase inhibitors singly have some activity in tumors previously resistant to paclitaxel (14), and in combination with paclitaxel, can sensitize these tumors to the effect of the latter (11). The combination of BMS-214662 and paclitaxel exhibited sequence-dependent synergy in preclinical studies, when paclitaxel was given before BMS-214662 (6). Farnesyl transferase inhibitors have been reported to exhibit sequence- and cell line-dependent additive or synergistic effects when combined with platinum-based agents (15). Based on these preclinical data, we undertook a phase I trial to define the maximum tolerated dose, toxicities, pharmacokinetics, clinical activity, and farnesyl transferase inhibition after treatment combination of BMS-214662, and paclitaxel and carboplatin.

MATERIALS AND METHODS

Patient Selection. Patients with histologic or cytologic evidence of metastatic or locally advanced cancer for which no effective or proven treatment exists, or who were unresponsive to currently available therapy, and had measurable or evaluable disease, were eligible for this study. Other inclusion criteria were age ≥18 years; expected survival of at least 3 months; Eastern Cooperative Oncology Group performance status ≤1; adequate bone marrow (platelets ≥100 × 10⁶ cells per liter, absolute neutrophil count ≥1.5 × 10⁹ cells per liter; hemoglobin ≥9.0 g/dL), hepatic (total bilirubin ≤1.5 mg/dL; ALT ≤1.5 times the upper limit of reference range), and renal (stable serum creatinine ≤1.8 mg/dL) functions; no chemotherapy, hormonal, or investigational drug therapy to >30% of the bone marrow; history of stem cells for hematopoietic reconstitution; radiation therapy elapsed after nitrosourea, mitomycin C, or platinum-based chemotherapy; patients who had significant pulmonary or cardiovascular disease; ≥ grade 1 peripheral sensory or motor neuropathy; prior treatment with regimens requiring the use of stem cells for hematopoietic reconstitution; radiation therapy to >30% of the bone marrow; history of ≥ grade 3 hypersensitivity to paclitaxel or its vehicle; active brain metastasis; or an active infection requiring therapy were excluded from this trial. Written informed consent was obtained according to federal and institutional guidelines.

Treatment and Clinical Care of Patients. Each patient received sequential i.v. infusions of paclitaxel, carboplatin, and BMS-214662 according to the assigned dose level (Table 1). Paclitaxel was supplied in vials of either 6 mg/mL or 100 mg/17 mL formulated with mannitol and sodium acetate as a sterile lyophilized powder. This was reconstituted with normal saline to make a solution containing 10 mg/mL paclitaxel. Carboblatin was supplied as a 1 mg/mL aqueous solution in 50 and 100 mg vials for injection. The total dose was diluted in 750 mL of 5% dextrose in 1/2 normal saline containing 25 g of mannitol. BMS-214662 was supplied by Bristol-Myers in 100 mg vials containing 20 mg/mL BMS-214662 as the free base. This was diluted with 5% dextrose to a maximum concentration of 2.5 mg/mL. After appropriate premedication as prophylaxis against anaphylactoid reactions to paclitaxel or the cremophor vehicle, paclitaxel was given over a period of 3 hours. Fifteen minutes after completion of this infusion, carboplatin was given over a period of 30 minutes. The 1-hour infusion of BMS-214662 was then started 15 minutes after completing the carboplatin infusion.

BMS-214662 was given as a fixed i.v. dose weekly (days 1, 8, and 15) for the first two dose levels. Cycles were repeated every 21 days. At least three new patients were entered at each dose level in a standard “cohorts of three” phase I design (16). Dose escalation was not allowed in individual patients. However, because BMS-214662 will most likely be used in combination regimens rather than as a single agent, the study protocol was simplified by omitting the administration of BMS-214662 on days 8 and 15 from the schedule of all patients upon enrollment from the third dose level onwards. This change was likewise implemented among the few patients in the earlier dose levels who were receiving ongoing treatment at the time the protocol amendment took effect.

Complete patient histories, physical examinations, complete blood cell counts, serum electrolytes, chemistries, urinalysis, and electrocardiograms were done at baseline and prior to each course of treatment. Laboratory studies were repeated weekly while patients were on study. Ophthalmologic examination, including retinal photography, was done at baseline and prior to the third cycle of treatment. Radiologic studies (roentgenograms, computed axial tomographic scans, and magnetic resonance imaging) were done at baseline and after every two cycles of therapy to assess tumor response. A partial response required at least a 50% reduction in the sum of the products of bidimensional measurements, separated by at least 4 weeks. A complete response was defined as the disappearance of all evidence of tumor on two measurements separated by a minimum of 4 weeks. Progressive disease was the appearance of new lesion(s) or an increase in the sum of the bidimensional products of all known disease by at least 25%. Stable disease was documented when there was persistence of disease without meeting the criteria for progression, partial response, or complete response. Evaluable disease refers to lesions that could not be accurately measured in at least one dimension or whose longest diameter is <20 mm with conventional techniques of <10 mm with spiral CT scan (such as peritoneal carcinomatosis, effusions, etc.). A complete response in this situation was defined as the disappearance of all lesions and normalization of tumor marker levels. Significant regression of disease in patients with evaluable disease alone required either normalization of tumor marker level or disappearance of all visualizable lesions in the presence of tumor marker levels above the normal limit.

Table 1 Dose escalation scheme

<table>
<thead>
<tr>
<th>Dose level</th>
<th>BMS-214662 (mg/m²)</th>
<th>Paclitaxel (mg/m²)</th>
<th>Carboplatin (AUC = 6)</th>
<th>Cycles</th>
<th>Dose-limiting toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>80</td>
<td>135</td>
<td>6</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>80</td>
<td>175</td>
<td>6</td>
<td>30</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>120</td>
<td>175</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>160</td>
<td>175</td>
<td>6</td>
<td>31</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td>160</td>
<td>225</td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td>6</td>
<td>9</td>
<td>225</td>
<td>175</td>
<td>6</td>
<td>35</td>
</tr>
</tbody>
</table>

Downloaded from clin-cancerres.aacrjournals.org on October 15, 2017. © 2005 American Association for Cancer Research.
**Dose-Limiting Toxicity.** All toxicities were graded according to the National Cancer Institute common toxicity criteria (version 2.0). The maximum tolerated dose was defined as one dose level below the dose that induced dose-limiting toxicities in more than one-third of patients (at least two of a maximum of six patients). Severe or life-threatening National Cancer Institute common toxicity criteria grades 3 or 4 nonhematologic toxicity (with the exception of fatigue, myalgias/arthralgias, alopecia, nausea, vomiting, grade 3 injection site reactions, and hypersensitivity reactions) were considered dose-limiting. National Cancer Institute common toxicity criteria grade 3 or 4 nausea and vomiting in patients who had received prophylactic treatment with an optimal antiemetic regimen was considered dose-limiting. An absolute neutrophil count of less than 0.5 x 10^9 cells per liter associated with fever or lasting for more than 5 consecutive days, a platelet count of less than 25 x 10^9 cells per liter of any duration or between 25 and 50 x 10^9 cells per liter associated with hemorrhage requiring blood transfusion, and treatment delay of more than 1 week because of failure of adequate recovery from the previous cycle were also considered dose-limiting.

**Blood Sampling.** Plasma pharmacokinetics of BMS-214662 and paclitaxel, when given in combination with carboplatin, was evaluated during the first cycle. Fourteen blood samples per patient were collected, prior to and after, the administration of paclitaxel within the first 24 hours. Peripheral blood mononuclear cells (PBMCs) were collected from blood samples serially in the first 24 hours in order to characterize farnesyl transferase enzyme inhibition as well as the feasibility of using unfarnesylated HDJ-2 protein as a surrogate marker of farnesyl transferase inhibition.

**Pharmacokinetics.** Noncompartmental pharmacokinetic analysis methods were applied to paclitaxel and BMS-214662. Area under the plasma concentration-time curve was calculated using the linear trapezoidal method. Data obtained for paclitaxel given alone were compared with those given in the presence of BMS-214662.

**Toxicities**

**Hematologic Toxicity.** The hematologic effects of BMS-214662 in combination with paclitaxel and carboplatin and the number of patients experiencing various grades of toxicity are shown in Fig. 1A. Neutropenia was the most common dose-limiting toxicity. Out of 141 treatment courses, neutropenia of varying severity was seen in 77 courses, 49 (64%) of which were severe (grades 3 and 4). Twenty-five patients had some degree of neutropenia along the course of therapy. Grade 4
neutropenia occurred in 60%, 75%, and 78% of patients in
dose levels 4, 5, and 6, respectively, compared with 0%, 50%,
and 0% for dose levels 1 to 3. Thrombocytopenia, which was
not as frequent, occurred in 35 treatment courses and was severe
in 4 (11%). Severe anemia (1 of 29, 6%) was less common
(Fig. 1A).

Gastrointestinal Toxicity. Diarrhea (common toxicity
criteria grades 1 and 2) was common, observed in over half of
all patients (Fig. 1B). This was largely related to BMS-214662,
having been reported in prior phase I single-agent studies (4, 10).
Anorexia, nausea, and vomiting, mostly common toxicity criteria
grades 1 and 2, were also frequently reported symptoms (20 of 30,
24 of 30, 14 of 30 patients, respectively) and occurred at all dose
levels. The dose of carboplatin was fixed throughout the six dose
levels (see Table 1). These findings therefore suggest that BMS-
214662 did not contribute substantially to the known emetogenic
effects of carboplatin. In most instances, nausea and vomiting
were controlled with aggressive prophylaxis with granisetron and
dexamethasone. Whereas the severity and frequency of nausea
and vomiting were not clearly related to the dose level, one patient
at dose level 6 had severe grade 3 symptoms in spite of optimal
antiemetic premedication. Dose-related BMS-214662-induced
elevation in liver enzymes has been variably reported in earlier
studies (4, 5), but was not seen in this cohort of patients.

Constitutional Symptoms. Fatigue, arthralgias, and myalgias were also common symptoms that were typically mild to
moderate in severity. These were attributable to paclitaxel and
carboplatin. One patient (dose level 1) had grade 3 fatigue that
required withdrawal from the study.

Other Toxicities. Alopecia was universal. Mild to moder-
ate peripheral sensory neuropathy with a glove-and-stocking
distribution was reported by approximately two thirds of the
patients. These were expected with respect to the standard
agents used in this regimen. Mild rash was seen in a few
patients (5 of 30). Based on the toxicities that precluded
further dose escalation, the maximum tolerated dose was
established as BMS-214662 (160 mg/m²), paclitaxel (225 mg/
m²) and carboplatin (area under the curve = 6 on day 1), every
21 days.

Antitumor Activity. Four out of 30 patients were
withdrawn from therapy after ≤2 cycles as previously mentioned,
prior to initial assessment for antitumor activity (Table 3). One
partial response was observed after the fourth cycle of treatment in
a patient with metastatic esophageal adenocarcinoma previously
treated with two cycles of CPT-11 and docetaxel. He was enrolled
at dose level 1 of this combination and received a total of 13
cycles. His intra-abdominal disease showed continued disease
response immediately prior to the 13th cycle, although the
presence of brain metastases was documented shortly thereafter.
Significant regression of evaluable disease occurred in two
patients. Both were enrolled at dose level 2. The first one was seen
in a patient with endometrial cancer whose disease progressed
earlier through a cisplatin- and paclitaxel-containing regimen.
This response was maintained for five additional cycles after the
demonstrable response was first documented in the second cycle.
The second was observed in a patient with ovarian cancer who had a
relapse a year after completing six cycles of adjuvant
treatment with carboplatin and paclitaxel. After one cycle
of chemotherapy at dose level 2, her CA 125 levels normalized.
This was demonstrable regression of the peritoneal implants
radiographically as well. She completed eight cycles of treatment.
Her response was sustained for 11 months after elective cessation
of therapy. Eight other patients had stable disease for > 4 cycles of
treatment.
Inhibition of Farnesyl Transferase in Peripheral Blood Mononuclear Cells. The effect of BMS-214662 on farnesyl transferase activity was assessed by measuring activity in extracts from isolated PBMCs. Farnesyl transferase enzyme activity reached a nadir immediately at the end of the BMS-214662 infusion. The degree of farnesyl transferase enzyme inhibition was dose-dependent (Spearman correlation of dose and farnesyl transferase activity was \( P = 0.0001 \)) and reversible, with full recovery of enzyme activity by the 20th hour relative to the start of BMS-214662 administration (Fig. 2A). Immunoblot assays (Fig. 2B) revealed a general trend towards accumulation over time of unfarnesylated HDJ-2 protein which seemed to persist longer in patients receiving a higher dose of BMS-214662. However, unfarnesylated HDJ-2 was present in certain samples even prior to the administration of the farnesyl transferase inhibitor (Fig. 2B).

Pharmacokinetics

The potential for a pharmacokinetic interaction between paclitaxel and BMS-214662 was determined. Regardless of the dose of BMS-214662, plasma concentrations of paclitaxel achieved during infusion were not altered by administration of this farnesyl transferase inhibitor (Fig. 3A). Steady-state plasma concentrations of BMS-214662 increased as dose increased from 80 to 225 mg/kg (Fig. 3B). Plasma clearance and \( t_{1/2} \) were not significantly changed at the various dose levels, confirming linearity of BMS-214662 pharmacokinetics over this dose range as well as the apparent absence of interaction with paclitaxel.

For paclitaxel, no significant difference between any pharmacokinetic estimate was seen when comparing with and without BMS-214662 administration.

DISCUSSION

The evaluation and clinical use of farnesyl transferase inhibitors as a class continues to evolve as a promising small molecule inhibitor of dysregulated cell signaling in malignancies. The pharmacology and clinical activity of the farnesyl transferase inhibitors have been comprehensively reviewed recently (21–25). Like other specific target–directed agents, farnesyl transferase inhibitors may be more effective in combination with cytotoxic chemotherapy because of the heterogeneous and multistep nature of carcinogenesis. Preclinical studies have shown sequence-dependent cytotoxic synergy when cultured human cancer cell lines were exposed to paclitaxel and farnesyl transferase inhibitors in vitro (6). In addition, synergy between farnesyl transferase inhibitors and cisplatin has been observed in vitro (15). Multiple regimens combining various farnesyl transferase inhibitors and platinum or taxane analogues have been tested (7, 26–28). In this phase I trial, we studied the safety and efficacy of BMS-214662 in combination with one of the most effective combination regimens in wide clinical use. The maximum tolerated dose was determined to be BMS-214662 (160 mg/m²) infused over 1 hour, paclitaxel (225 mg/m²) and carboplatin (area under the curve = 6 on day 1), every 21 days.

Overall, the toxicities observed were expected from the known effects of the individual agents in this combination. Neutropenia was the main dose-limiting adverse effect. The severity of neutropenia seemed to be dependent on the dose level of BMS-214662 in addition to that contributed by the combination of paclitaxel and carboplatin in general.

It has been shown that the processing of certain proteins, such as prelamin A or HDJ-2, in easily obtainable tissue specimens from patients could be utilized as a surrogate marker of farnesyl transferase activity in vivo (18). The degree of expression of unfarnesylated HDJ-2 protein in PBMCs is

![Fig. 2 Pharmacodynamic markers of BMS-214662 activity in PBMCs. A, median farnesyl transferase activity in PBMCs over time per dose level showing dose-dependent reversible farnesyl transferase enzyme inhibition. Time in hours/minutes relative to the onset of paclitaxel infusion. 3:58 is the time point at the end of the carboplatin infusion, before the start of the BMS-214662 infusion. 4:58 is the time point at the end of the BMS-214662 infusion. B, inhibition of HDJ-2 farnesylation in peripheral blood mononuclear cells. Peripheral blood mononuclear cells were prepared and processed for SDS-PAGE immunoblotting with anti-HDJ-2 antibody are described in Materials and Methods. F, farnesylated HDJ-2; U, unfarnesylated HDJ-2. Anti Histone H1 antibody was used as a loading control. A549 cells treated with 1 μmol/L BMS-214662 or vehicle for 24 hours serve as positive and negative controls.](http://cancerres.aacrjournals.org/content/1881)
In this study, we confirmed that BMS-214662 inhibited farnesyl transferase enzyme in a dose-dependent fashion in clinical samples. This inhibition was reversible within 24 hours, and confirms the earlier results of Mackay et al. (7). Nevertheless, it is important to note that a biological threshold of farnesyl transferase inhibition that can be utilized as a surrogate marker to correlate with clinical outcome has not been established. In contrast to other farnesyl transferase inhibitors that are given p.o. daily, differences in pharmacodynamic effects may in part be schedule-dependent as BMS-214662 was delivered intermittently at longer intervals. Although the optimal timing of farnesyl transferase inhibition within tumors for antitumor effect and synergy with taxanes and/or platinum agents is not well elucidated, and the clinical relevance of prolonged farnesyl transferase inhibition in normal tissues is unclear, weekly schedules of administration may provide a more consistent plasma exposure as well as a more sustained pharmacodynamic effect that may be required for optimal activity. It is interesting to note that the two patients in our study who had tumor responses were among the five patients who received weekly BMS-214662 prior to protocol modification.

Many of the cases of disease stabilization that occurred in non–small cell lung cancer were in either taxane- or platinum-naïve patients. Moreover, the patient with ovarian cancer who achieved both radiographic regression of peritoneal disease and tumor marker (CA-125) normalization had platinum-sensitive disease. The antitumor activity reported in this study thus has to be interpreted with caution for two reasons. First, this study represents a combination of a farnesyl transferase inhibitor with a regimen that by itself is clinically effective. Second, the trial was not designed to evaluate the efficacy of antitumor activity of this combination.

In conclusion, this study has shown that clinically relevant doses of all three agents can be safely combined to treat patients. Not only is the BMS-214662 dose effective in inhibiting farnesyl transferase, but the paclitaxel and carboplatin doses recommended for future studies are also within the therapeutic range. Because the antitumor activity of BMS-214662 is dependent on the cumulative dose given other than the schedule used (9), re-examining the feasibility of its weekly administration might be considered.

ACKNOWLEDGMENTS

We thank Sue Steinmetz and Melanie Kassner for excellent data management, Sara Felten for statistical programming support, Sacha Nelson for protocol management, and Raquel Ostby for secretarial assistance.

REFERENCES

A Phase I Trial of the Novel Farnesyl Protein Transferase Inhibitor, BMS-214662, in Combination with Paclitaxel and Carboplatin in Patients with Advanced Cancer

Grace K. Dy, Laura M. Bruzek, Gary A. Croghan, et al.


Updated version  Access the most recent version of this article at: http://clincancerres.aacrjournals.org/content/11/5/1877

Cited articles  This article cites 23 articles, 10 of which you can access for free at: http://clincancerres.aacrjournals.org/content/11/5/1877.full#ref-list-1

Citing articles  This article has been cited by 6 HighWire-hosted articles. Access the articles at: http://clincancerres.aacrjournals.org/content/11/5/1877.full#related-urls

E-mail alerts  Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions  To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions  To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.