A Randomized Phase II Feasibility Trial of BMS-275291 in Patients with Early Stage Breast Cancer


1Indiana University, Indianapolis, Indiana; 2Green Bay Oncology, Green Bay, Wisconsin; 3Oncology/Hematology Care, Cincinnati, Ohio; 4Bristol-Myers Squibb, New York, New York; 5Albert Einstein University, Bronx, New York; 6Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, Maryland; and 7Rush Presbyterian St. Luke’s Medical Center, Chicago, Illinois

ABSTRACT

Purpose: This pilot trial was performed to evaluate the safety, pharmacokinetics and feasibility of incorporating BMS-275291, a matrix metalloproteinase inhibitor (MMPI), into adjuvant breast cancer therapy.

Experimental Design: Patients with stage I (T1c)-IIIA breast cancer were eligible if planned adjuvant therapy consisted of either tamoxifen alone, doxorubicin + cyclophosphamide every 21 days for four cycles (AC), or AC followed by paclitaxel every 21 days for 4 cycles (AC>T). Patients were stratified by planned adjuvant therapy and randomized (2:1 ratio) to BMS-275291 (1200 mg/day) or matched placebo for 1 year.

Results: Seventy-two patients were recruited from March 2001 to July 2002. Grade ≥ 2 musculoskeletal toxicity, generally reversible arthralgia, was reported by 36.2% of patients receiving BMS-275291 compared with 16.7% of patients receiving placebo; difference = 19.5% (95% confidence interval: -0.06, 0.44; P = NS). Two patients receiving BMS-275291 developed palpable nodules along tendons. Grade ≥ 3 rash was reported by 8.5% of patients receiving BMS-275291 compared with 4.2% of patients receiving placebo; difference = 4.3% (95% confidence interval: -0.18, 0.3; P = NS). Overall, 33% of BMS-275291 patients and 21% of placebo patients discontinued treatment due to adverse events. BMS-275291 trough levels tended to decrease over time; 9 of 47 (19%) had ≥50% of trough concentrations > 124 ng/ml (IC₉₀ for matrix metalloproteinase-9).

Conclusions: The pattern of arthralgia in BMS-275291-treated patients was consistent with matrix metalloproteinase inhibitor toxicity. Although the differential incidence of arthralgia did not reach statistical significance, the trial was terminated. An adjuvant trial in this patient population is not feasible.

INTRODUCTION

Breast cancer remains a devastating disease affecting the lives of 180,000 women and resulting in ~44,000 deaths in the United States each year (1). Improved early detection and advances in systemic therapy of early-stage disease have led to a small decline in overall breast cancer mortality since 1989 (2). Additional advances will require new therapeutic strategies that are firmly rooted in an understanding of breast cancer biology. Inhibition of matrix metalloproteinase (MMP) enzymes provides one such potentially fruitful therapeutic target (3).

MMPs are zinc-containing enzymes that degrade proteins of the basement membrane and extracellular matrix (4). Under normal physiological conditions, the MMPs and their endogenous inhibitors, the tissue inhibitors of metalloproteinases, exist in an exquisite balance. Unbalanced MMP/tissue inhibitors of metalloproteinase expression plays a critical role in cellular movement, invasion, angiogenesis, and metastasis (5–8).

MMP inhibitors (MMPIs) significantly curtail primary breast tumor growth and establishment of metastases in preclinical xenograft models but fail to shrink large, well-established tumors (9–12). Nonetheless, previous MMPIs were tested largely in patients with metastatic disease. Whether administered as monotherapy or in combination with cytotoxic agents, the results were nearly uniform. MMPIs had little activity in advanced disease, leading clinical development of several agents to be terminated (13–18).

The most successful clinical application of MMPIs such as BMS-275291 is likely to be in patients with micrometastatic disease. Successful use in the adjuvant setting will require maintenance of therapeutic drug concentrations above a minimum trough level chronically and safely. Previous MMPIs were limited by musculoskeletal toxicity, making chronic administration of potentially therapeutic doses in the adjuvant setting implausible (19).

BMS-275291 is a rationally designed, peptidomimetic MMPI that contains a chemically novel mercaptoacyl zinc-binding group. BMS-275291 inhibits a broad spectrum of MMPs with IC₅₀ in the low nanomolar range. BMS-275291 does not inhibit the sheddases, which are related metalloproteinases that regulate proinflammatory cytokine and cytokine receptor shedding from the cell surface.
BMS-275291 therapy was not associated with arthralgia or myalgia. Trough levels above the IC_{90} for MMP-2 (261 ng/ml) and MMP-9 (124 ng/ml) were maintained and wound angiogenesis was delayed (21–23). This trial was therefore conducted to determine the feasibility of incorporating BMS-275291 into adjuvant therapy for breast cancer based on safety and pharmacokinetics.

MATERIALS AND METHODS

Patients with histologically confirmed stage I (T1c)-IIIA breast cancer were eligible if planned adjuvant therapy consisted of either tamoxifen alone, doxorubicin (60 mg/m²) + cyclophosphamide (600 mg/m²) every 21 days for four cycles (AC) or AC followed by (paclitaxel 175 mg/m²) every 21 days for four cycles (AC/T). Patients receiving AC or AC/T could receive tamoxifen after completing chemotherapy and radiation if clinically appropriate. All patients had undergone complete surgical excision of the primary tumor. In addition, patients planned to receive tamoxifen alone had completed radiation therapy if indicated before study entry; tamoxifen was not given concurrently with radiation or chemotherapy. All patients had to have adequate renal, hepatic, and hematological function. Left ventricular ejection fraction above the institutional lower limit of normal was required for patients planned to receive doxorubicin. Each local Institutional Review Board approved the protocol, and individual written informed consent was provided before treatment.

After eligibility was confirmed, patients were stratified according to planned adjuvant therapy and randomized (2:1 ratio) to BMS-275291 (1200 mg once daily) or matched placebo for 1 year. The duration of therapy with BMS-275291/placebo treatment was chosen empirically, with the assumption that emergence of treatment-limiting toxicities after 1 year of therapy would be unlikely. Treatment was given orally once daily and was initiated concurrently on the first day of adjuvant systemic therapy. BMS-275291/placebo was held during radiation in those patients requiring radiation therapy if indicated before study entry; tamoxifen was not given concurrently with radiation or chemotherapy. All patients had to have adequate renal, hepatic, and hematological function. Left ventricular ejection fraction above the institutional lower limit of normal was required for patients planned to receive doxorubicin. Each local Institutional Review Board approved the protocol, and individual written informed consent was provided before treatment.

All patients were evaluated every 3 weeks for the first 12 weeks (24 weeks if receiving AC>T), then every 2 months for the remainder of the initial treatment period. Dose-dependent increases in the incidence and titer of positive anti-nuclear antibody (ANA), anti-double-strand DNA, and anti-BMS-275291 antibodies were identified in monkeys during preclinical toxicology studies. Two monkeys developed distal polyarthritis and chronic vasculitis associated with a positive ANA, anti-double-strand DNA, and anti-BMS-275291 antibodies. Although anti-BMS-275291 antibodies had not been reported in the early clinical experience, ANA and anti-BMS-275291 antibody titers were measured at each study evaluation. Patients with prior autoimmune disease, including lupus, scleroderma, or rheumatoid arthritis were excluded.

Chemotherapy doses were adjusted for toxicity based on the investigators’ standard practice. BMS-275291/placebo was not interrupted or modified for chemotherapy-related toxicity. Dose modifications were specified for toxicity potentially related to BMS-275291/placebo. Treatment was held for grade 3 or 4 toxicity and resumed at 600 mg once daily if resolved to less than or equal to grade 1 in 14 days. Treatment could be held for grade 2 toxicity at the discretion of treating investigator and resumed at the same dose if resolved to less than or equal to grade 1 in 14 days. Treatment was interrupted for 3 weeks if surgery was required.

Samples for steady state BMS-275291 levels were obtained every 3 weeks for the first 12 weeks (24 weeks if receiving AC>T), then every 2 months while on therapy; pharmacokinetic samples were not obtained when therapy was interrupted for toxicity, radiation, or surgery. Samples for pharmacokinetic evaluation were collected into plasma collection tubes containing methyl acrylate to stabilize the sulfhydryl group on BMS-275291. The resulting plasma samples contained the BMS-275291-methyl acrylate derivative. Concentrations of BMS-275291 in the plasma samples were determined using liquid chromatography coupled with tandem mass spectrometry. Study samples were analyzed against standard samples prepared at concentrations of 10, 20, 50, 100, 250, 500, 750, and 1000 ng/ml with quality control samples at concentrations of 25, 400, 800, and 5000 ng/ml if dilutions were performed in the run. Each 0.1-ml sample was treated with internal standard and buffer before on-line extraction and chromatography using Waters Oasis HLB extraction columns and Waters Symmetry C-18 (3.9 × 50 mm, 5 μm) chromatography columns. The standard curves were fitted to a 1/x^2 linear regression model. The standard curve and quality control samples confirmed that the assay was precise, accurate, and reproducible.

The primary objectives of the study were to compare discontinuation of BMS-275291 and placebo within 1 year and to determine the percentage of patients receiving BMS-275291 in which at least half of trough concentrations exceeded the IC_{90} for MMP-9 (124 ng/ml). We arbitrarily decided that if 15% more patients discontinued BMS-275291 than discontinued placebo, an adjuvant trial would not be feasible. Assuming a 10% discontinuation rate in the placebo arm, a sample size of 120 was required. This provided >90% power to exclude a discontinuation rate of BMS-275291 that exceeded the discontinuation rate of placebo by ≥15%. An interim analysis to monitor safety was to be conducted by a Data Monitoring Committee after the first 60 patients had either completed 12 months of BMS-275291/placebo therapy or discontinued study drug. After several patients developed arthralgia or hypersensitivity reactions requiring discontinuation, a special Data Monitoring Committee meeting was convened. Although the discontinuation rate did not exceed the prespecified boundaries, the pattern of arthralgias was consistent with MMPI musculoskeletal toxicity and the Data...
Monitoring Committee recommended that the study be terminated. Consistent with the objectives of this study and in recognition of the limitations of the sample size, relapse-free and overall survival data were not collected or analyzed.

RESULTS

From March 2001 to May 2002, 72 patients were enrolled. One patient never began therapy and is not included in this analysis. Characteristics of the 71 treated patients are listed in Table 1.

Musculoskeletal toxicity of any grade was similar in both treatment groups (Table 2). Clinically significant musculoskeletal toxicity (more than or equal to grade 2) was reported by 36.1% of patients receiving BMS-275291 compared with 20.8% of patients receiving placebo (difference 19.5%, 95% confidence interval: -0.06 - 0.44); median time to musculoskeletal toxicity was 5.25 and 3.0 months in BMS-275291- and placebo-treated patients, respectively. The pattern of musculoskeletal toxicity was reminiscent of that seen with other MMPIs; a reversible, proximal tendonitis, and bursitis predominated. Musculoskeletal complaints initially improved with nonsteroidal anti-inflammatory agents, generally resolved within 2 weeks off therapy and recurred when BMS-275291 was resumed. Two patients treated with BMS-275291 developed palpable, nontender nodules along tendon surfaces; nodules persisted for several months after discontinuing therapy.

Four patients (8.5%) treated with BMS-275291 developed grade ≥ 3 hypersensitivity reactions characterized by a diffuse erythematous rash and fever. Symptoms resolved promptly with interruption of therapy but recurred within hours of rechallenge. One patient (4.2%) in the placebo group had a grade 3 hypersensitivity reaction. The incidence of hypersensitivity was not significantly different among treatment groups (difference 4.3%, 95% confidence interval: -0.18 - 0.3).

Other toxicities were uncommon and did not differ between treatment groups. There was no obvious increase in chemotherapy or tamoxifen toxicity with concurrent BMS-275291 therapy. Overall, 33% of patients receiving BMS-275291 and 21% of patients receiving placebo discontinued treatment before completing 1 year of therapy (P/NS). Median treatment duration was 5.26 months for patients on BMS-275291 and 6.01 months for patients receiving placebo. The trial was terminated shortly after the first patient began open-label use of BMS-275291 in year 2; no data from this extension phase of the study is reported.

At least one pharmacokinetic sample was obtained from the 47 patients (100%) treated with BMS-275291. Trough concentrations exceeded the IC90 for MMP-9 (124 ng/ml) on at least half the measured time points in 9 (19%) patients; levels were below the limit of detection (10 ng/ml) at all time points in 3 patients. There was a general trend for concentrations to decrease over time (Fig. 1).

Table 1  Patient characteristics (n = 71)

<table>
<thead>
<tr>
<th></th>
<th>BMS-275291 (n = 47)</th>
<th>Placebo (n = 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in yrs (median 52)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>19 (40%)</td>
<td>10 (42%)</td>
</tr>
<tr>
<td>50–64</td>
<td>22 (47%)</td>
<td>9 (38%)</td>
</tr>
<tr>
<td>≥65</td>
<td>6 (13%)</td>
<td>5 (21%)</td>
</tr>
<tr>
<td>ECOG PS(a)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>41</td>
<td>21</td>
</tr>
<tr>
<td>1</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Not reported</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Stage at diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IC</td>
<td>8 (17%)</td>
<td>6 (25%)</td>
</tr>
<tr>
<td>IIA</td>
<td>23 (49%)</td>
<td>10 (42%)</td>
</tr>
<tr>
<td>IIB</td>
<td>7 (15%)</td>
<td>4 (17%)</td>
</tr>
<tr>
<td>IIIA</td>
<td>9 (19%)</td>
<td>4 (17%)</td>
</tr>
<tr>
<td>Planned adjuvant therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tamoxifen alone</td>
<td>5 (11%)</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>AC</td>
<td>26 (55%)</td>
<td>15 (63%)</td>
</tr>
<tr>
<td>AC &gt; T</td>
<td>16 (34%)</td>
<td>7 (29%)</td>
</tr>
</tbody>
</table>

\(a\) ECOG PS = Eastern Cooperative Oncology Group performance status.

Table 2  Musculoskeletal toxicity

<table>
<thead>
<tr>
<th></th>
<th>National Cancer Institute Common Toxicity Criteria(a)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>BMS-275291 (n = 47)</td>
<td>7 (15%)</td>
</tr>
<tr>
<td>Placebo (n = 24)</td>
<td>11 (46%)</td>
</tr>
</tbody>
</table>

\(a\) Worst grade reported/patient according to the National Cancer Institute Common Toxicity Criteria.

Fig. 1 Mean trough concentration of BMS-275291 over time. Included are lines denoting the IC syncXE90 (bottom line) and IC syncXE99 (top line; 124 ng/ml) for matrix metalloproteinase (MMP)-9. (▲), mean (n = 47).

Downloaded from clincancerres.aacrjournals.org on July 15, 2017. © 2004 American Association for Cancer Research.
DISCUSSION

BMS-275291 was designed to separate potential activity (presumed because of inhibition of MMP-2 and MMP-9) from dose-limiting musculoskeletal toxicity (presumed because of inhibition of the sheddases) to allow adequate testing in the clinic. As predicted from the preclinical data, levels well above the targeted therapeutic range were obtained without arthralgia or myalgia in Phase I trials.

Surprisingly, musculoskeletal toxicity limited BMS-275291 therapy in our patients with early-stage breast cancer. Steady-state trough levels in our patients were similar to those obtained in previous studies with BMS-275291. The mean Cmin level for the Phase I study in cancer patients was 158 ng/ml; obtained in previous studies with BMS-275291. The mean Cmin Steady-state trough levels in our patients were similar to those obtained in previous studies with BMS-275291. Finally, many of our patients developed musculoskeletal toxicity after completing the planned chemotherapy suggesting that corticosteroids, administered as part of a concurrent chemotherapy regimen, may be protective.

Although the rate of arthralgia or myalgia was sufficient to require early termination of the trial, it was nevertheless lower than reported for other MMPIs. In a similar adjuvant trial, marimastat produced significant musculoskeletal toxicity in 45% of patients receiving 10 mg twice daily, although only 18% of patients at this dose achieved even one trough level in the target range (defined as the IC50 for MMP-2 and MMP-9; Ref. 19). Therefore, although the rational design of this MMPI to avoid sheddase release did not eliminate arthralgia, it may have widened the therapeutic window. The critical question, whether it is possible to completely separate inhibition of MMPIs important in cancer progression from those whose inhibition produces joint toxicity, still remains.

The development of the MMPIs, like that of other antiproliferative rather than cytotoxic compounds, poses a challenge in clinical trial design. The cytostatic mechanism of action of the MMPIs implies time to progression rather than objective tumor response as the proper primary end point. Unfortunately, subtle prolongation of time to progression cannot be determined with certainty in uncontrolled trials and may be of minimal clinical benefit in patients with advanced disease. Intuitively, the impact of MMP inhibition is expected to be greatest in patients with micrometastatic disease—an intuition that will require commitment of substantial human and financial resources to a randomized trial in the adjuvant setting to test. A large adjuvant trial should not be initiated if chronic therapy cannot be administered in sufficient doses to support biological activity in the majority of patients treated.

Although a negative trial in the sense that proceeding to a full-scale adjuvant study with BMS-275291 cannot be recommended, we believe this study illustrates the importance of population-specific feasibility trials, especially for agents administered chronically or with a static mechanism of action. Experience gained in patients with advanced disease is meaningful, but even large trials of patients with metastatic disease provide long-term safety data in only a limited number of patients. Population-specific feasibility studies can identify toxicities that might not be acceptable in an otherwise healthy patient population, thereby limiting exposure and avoiding premature closure of a large adjuvant trial (24). Although no small feasibility trial can (or should) eliminate the need for large Phase III studies, promising drugs can be screened rapidly, eliminating those not suitable for Phase III studies, whether due to unforeseen toxicity or unacceptable pharmacokinetics.

REFERENCES

A Randomized Phase II Feasibility Trial of BMS-275291 in Patients with Early Stage Breast Cancer


Updated version
Access the most recent version of this article at:
http://clincancerres.aacrjournals.org/content/10/6/1971

Cited articles
This article cites 23 articles, 12 of which you can access for free at:
http://clincancerres.aacrjournals.org/content/10/6/1971.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/10/6/1971.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.