Phase II Clinical Trial Results Involving Treatment with Low-Dose Daily Oral Cyclophosphamide, Weekly Vinblastine, and Rofecoxib in Patients with Advanced Solid Tumors

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Abstract

Purpose: Preclinical studies indicate that conventional chemotherapeutic agents given continuously at low doses (metronomic chemotherapy) may provide an improved therapeutic index. Cyclophosphamide and vinblastine have been best studied in experimental models, where tumor growth inhibition is achieved, at least in part, through antiangiogenic mechanisms.

Experimental Design: Fifty patients with advanced solid tumors were enrolled in this phase II trial, 43 of whom had received at least one prior chemotherapy regimen. Patients were required to have Eastern Cooperative Oncology Group performance status of $\leq$2, a life expectancy of $>$3 months, and at least one measurable lesion. All patients received oral cyclophosphamide (50 mg) and rofecoxib (25 mg) daily in addition to weekly injections of vinblastine (3 mg/m^2). Half of the patients also received minocycline (100 mg) orally twice daily with the intent of further inhibiting tumor angiogenesis. The primary end point of the study was clinical benefit, defined as the percentage of patients experiencing an objective response or exhibiting stable disease for at least 6 months.

Results: For the 47 eligible patients, there were two (4%) complete responses and four (9%) partial responses, for an overall objective response rate of 13%. An additional eight patients achieved disease stabilization (stable disease $\geq$6 months) (17%). The primary end point of clinical benefit was therefore 30%, (95% confidence interval, 16-44%). The median progression-free survival for all patients was 103 days and 289 days for patients experiencing clinical benefit. The incidence of patients experiencing grade 3/4 toxicities were as follows: neutropenia (10/2), anemia (2/0), and thrombocytopenia (1/0). No patients developed grade 3 or 4 nausea, vomiting, mucositis, or alopecia.

Conclusions: This low-dose regimen consisting of daily oral cyclophosphamide and weekly vinblastine injections given concurrently with rofecoxib is associated with minimal toxicity and provides significant clinical benefit to patients with advanced solid tumors. These results are particularly encouraging given the nature of the study population and indicate that this approach merits further investigation in specific disease site studies.

Cancer chemotherapy is typically given periodically at, or near, maximum tolerated doses in an effort to achieve the highest anticancer effect as predicted by a dose-response relationship. In patients with advanced cancers, treatment is often associated with limited response rate, development of drug resistance, and significant toxicity. Recent studies using experimental tumor models have shown improved growth inhibition when anticancer drugs are given more frequently at doses considerably less than the maximum tolerated doses of the tumor-bearing mice. This approach was first studied in two different laboratories using the alkylating agent cyclophosphamide (1) and the *Vinca* alkaloid vinblastine (2). Browder et al. (1) have shown that giving low doses of cyclophosphamide every 6 days to mice bearing transplanted tumors markedly inhibited growth, even in a Lewis lung carcinoma cell line selected *in vivo* for resistance to this agent. This approach was more effective than a more conventional schedule of giving near maximum tolerated doses of cyclophosphamide every 21 days, despite the fact that the latter treatment resulted in higher dose intensity. Klement et al. (2) showed a similar effect of prolonged tumor growth suppression by frequent administration (every 3 days after an initial continuous "induction" phase) of vinblastine in a xenografted human neuroblastoma

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line. Both of these studies provided additional data, which indicated that the mice tolerated treatment without discernible toxicity and that the anticancer effect was principally via an antiangiogenic/antivascular mechanism.

These promising results in experimental models have prompted several clinical trials to determine if this effect can be reproduced in patients with advanced solid tumors. Using the extensive data available on both oral cyclophosphamide and vinblastine, we devised a low-dose protocol, which was expected to be able to be administered to patients for long periods (>6 months) without significant acute or cumulative toxicity. Several experimental studies using metronomic chemotherapy have shown that this treatment is much more effective if combined with an antiangiogenic (1–6) or immunotherapeutic (7) agent. Patients in this study also received concurrent treatment with the cyclooxygenase-2 (COX-2) inhibitor rofecoxib (Vioxx) because several preclinical studies have shown that this class of anti-inflammatory drugs has anticancer activity as a result of its ability to induce tumor cell apoptosis and inhibit angiogenesis. (8–10) Existing clinical data suggested the addition of a COX-2 inhibitor would not result in any significant increased toxicity. Furthermore, half of the patients enrolled in this trial also received the tetracycline antibiotic minocycline. This class of drug inhibits tumor cell invasion (11) and shows antiangiogenic activity in preclinical models as a result of its ability to inhibit matrix metalloproteinase activity (11–13). It was predicted that this multitargeted regimen would have significant anticancer activity without the side effects typically associated with chemotherapy.

Materials and Methods

Patient eligibility. Fifty patients with advanced solid tumors were enrolled in this trial from our institution over the period May 2001 to April 2003. All patients were considered to have incurable disease and minimal anticipated benefit from further treatment with conventional chemotherapy. Eligibility criteria included age >18 years, histologic proof of malignancy, and Eastern Cooperative Oncology Group performance status of 0 to 2, life expectancy of >3 months, and at least a single site of measurable (two-dimensional) disease. Exclusion criteria included treatment with any form of chemotherapy in the past 6 weeks unless there was confirmation of radiographic progression, untreated central nervous system metastases or radiotherapy for this disease <1 month before enrollment, and organ dysfunction characterized by any of the following criteria: hemoglobin (<80 g/L), absolute neutrophil count ($<1.5 \times 10^9$/L), platelet count ($<100 \times 10^9$/L), cardiac (unstable angina, congestive heart failure, or life-threatening dysrhythmia), pulmonary (O_2 dependency), gastrointestinal (chronic diarrhea or recent gastrointestinal bleeding), hepatic (transaminases greater than three times upper limit of normal or elevated bilirubin >1.5 times upper limit of normal), renal (creatinine >150 μm/L or on dialysis), or hypersensitivity to any of the study medications. Patients could not participate if they had received a COX-2 inhibitor or tetracycline antibiotic within 4 weeks before enrollment. All patients were assessed at the start of treatment with history, physical examination, height, weight, and assignment of Eastern Cooperative Oncology Group performance status. Patients submitted to complete blood count, electrolytes, creatinine, liver function tests, tumor marker (when appropriate), and baseline radiographic assessment within 2 weeks of commencing therapy.

Treatment and evaluation. All patients received vinblastine (3 mg/m^2) i.v. weekly, cyclophosphamide (50 mg) orally daily, and rofecoxib (25 mg) orally daily continuously while on study. Half of the patients (25) were assigned (nonrandomized) to receive these three agents (group A) and half to receive the same regimen in addition to minocycline (100 mg) orally twice daily for the duration of the trial (group B). The first 14 consecutive patients were assigned to treatment group A and the next 14 to group B. No further enrollment was permitted in either group until there was confirmation of at least one patient experiencing clinical benefit. This restriction was stipulated in the protocol to limit the number of patients subjected to an ineffective therapy, as no responses would have led to closure of the trial. This approach would have a power of 86% to identify a treatment associated with clinical benefit of at least 20%. The authors felt that this frequency of clinical benefit in such a heavily pretreated population would constitute a significant finding. Once an objective response was observed in the initial cohort, the next 11 consecutive patients (15–25) were assigned to group A and the last 11 patients (26–36) to group B. Treatment was discontinued with development of excess toxicity, disease progression, or clinical deterioration preventing administration of the oral agents (e.g., reduced level of consciousness and intractable vomiting). Patients were permitted to receive all forms of supportive therapy according to physician discretion, including corticosteroids, bisphosphonates, analgesics, antibiotics, transfusions, etc. Palliative radiotherapy could be administered to disease sites, which would not subsequently be used to determine response to systemic therapy. Central venous catheters were inserted for provision of the weekly vinblastine according to patient/physician preference. Patients were assessed for tolerability and compliance with oral medications after 4 weeks and then every 4 or 8 weeks according to physician's discretion. Restaging with quantitative assessment of marker lesions was done every 8 weeks from the time of enrollment. Response criteria were as follows: complete response (disappearance of measurable disease without development of new sites), partial response (at least 50% reduction in tangential product of the sum of measured disease sites), disease progression (at least 50% increase in tangential product of measured disease), and stable disease (if determination did not meet criteria of complete response, partial response, or disease progression). The primary end point of the study was determination of the number of patients deriving clinical benefit (achieving complete response, partial response, or stable disease >6 months). Secondary end points included time to tumor progression and toxicity, which was reported using the National Cancer Institute common toxicity criteria (version 2.0). All participants signed a written informed consent form, and this trial was conducted with the approval of the Sudbury Regional Hospital Research Ethics Board (Sudbury, Ontario, Canada).

Results

Patient characteristics. Fifty patients were enrolled in the trial over the period May 30, 2001 to April 2, 2003 (24 female and 26 male). Review of the data indicated that three patients enrolled in this study were ineligible for participation in the trial (two with active gastrointestinal bleeding at the time of entry and a third with inadequate performance status and life expectancy). The median age of the 47 eligible patients was 61 years (range 24-79). The Eastern Cooperative Oncology Group performance status was 0 in 27 patients, 1 in 18 patients, and 2 in 2 patients. The characteristics of the patient population are summarized in Table 1.

Tumor responses. Initial statistical analysis of the results for treatment groups A and B (i.e., treatment given either with or without concurrent oral minocycline) indicated no significant difference in the primary end point of clinical benefit or time to tumor progression ($P = 0.2$ and 0.2, respectively, χ^2 test). The data sets were therefore pooled and subsequently evaluated using intent-to-treat analysis. For the group of 47 eligible patients, 14 (30%) experienced clinical benefit (95% confidence interval $\pm$ 14%; 4% complete responses, 9% partial

Table 1. Patient characteristics

Age/Gender	Primary tumor	Prior treatment in chronological order (no. cycles)
Group A (23 patients): vinblastine, cyclophosphamide, and rofecoxib		
59/M	Rectum	FUFA (×5), raltitrexed (×5)
24/F	Hodgkin's disease	ABVD (×6), DHAP (×2), cyclophosphamide, carmustine, etoposide (×1)
70/F	Breast	CMF (×6)
77/F	Rectum	FUFA (×1), raltitrexed (×6), irinotecan (×2)
55/M	Hodgkin's disease	ABVD (epirubicin used) (×6), DHAP (×3)
67/M	Lung	Vinorelbine/cisplatinum (×7), carboplatin (×1)
53/M	Melanoma (cutaneous)	None
63/M	Colon	FUFA (×6), IFL (×5)
65/F	Renal cell	IFN (×2)
60/M	Gastric non – Hodgkin's lymphoma	CHOP (×6), ICE (×4), ESHAP (×4), CHOP (×2)
72/M	Non – Hodgkin's lymphoma	CHOP (epirubicin used) (×8)
69/M	Colon	IFL (×2)
79/F	Liver	Doxorubicin (×6)
52/F	Ovary	Paclitaxel/cisplatin (×5)
34/M	Hodgkin's disease	ABVD (×6), mini-BEAM, etoposide (×2)
56/F	Endometrium	None
72/F	Breast	Epirubicin (×12), CMF (×9)
63/F	Leiomyosarcoma	Doxorubicin (×1)
74/F	Endometrium	Paclitaxel/carboplatin (×5)
65/F	Ovary	Paclitaxel/cisplatin (×6), paclitaxel/carboplatin (×6), carboplatin (×3)
46/M	Colon	FUFA (×6), IFL (×5)
61/M	Endometrium	None
55/M	Rectum	FUFA (×12), IFL (×6)
Group B (24 patients): vinblastine, cyclophosphamide, rofecoxib, and minocycline		
63/M	Pancreas	Gemcitabine (×8)
65/F	Rectosigmoid	IFL (×6)
56/F	Cholangiocarcinoma	ECF (×6)
70/M	Colon	IFL (×2)
60/M	Colon	FUFA (×6), CONT FU (×2), irinotecan (×1)
78/M	Rectum	FUFA (×17), irinotecan (×4), CONT FU (×3)
61/M	Colon	FUFA (×11), capecitabine (×3)
69/M	Pancreas	None
71/F	Endometrium	None
43/M	Pancreas	Gemcitabine (×3)
62/M	Rectosigmoid	FUFA (×14), irinotecan (×13), capecitabine (×6)
58/F	Ovary	Paclitaxel/cisplatin (×6), carboplatin\cyclophosphamide (×3), topotecan (×9), doxorubicin (×3)
65/M	Colon	IFL (×2), FOLFOX4 (×6)
59/F	Breast	Paclitaxel (×2), FAC (×6), MMM (×5)
69/F	Pancreas	None
70/F	Peritoneum	Paclitaxel/carboplatin (×6), topotecan (×2)
56/F	Ovary	Paclitaxel/carboplatin (×6), topotecan (×4)
49/M	Colon	IFL (×4), FOLFOX4 (×12)
42/F	Breast	AC (×4), CMF (×5), docetaxel (×4), docetaxel/xeloda (×6)
34/M	Spindle cell sarcoma*	CHOP (×2), ICE (×1)
60/M	Pancreas	Gemcitabine (×8)
49/F	Lung	Vinorelbine/cisplatinum (×2), docetaxel (×4)
60/F	Breast	CEF (×1), FAC (×6), docetaxel (×6)
76/F	Endometrium	None

Abbreviations: FU, 5-fluorouracil; ABVD, adriamycin (doxorubicin), bleomycin, vinblastine, DTIC (dacarbazine); AC, adriamycin (doxorubicin), cyclophosphamide; BEAM, BCNU (carmustine), etoposide, cytarabine, and melphalan; CEF, cyclophosphamide, epirubicin, fluorouracil; CHOP, cyclophosphamide, adriamycin (doxorubicin), vincristine, prednisone; CMF, cyclophosphamide, methotrexate, fluorouracil; DHAP, dexamethasone, ara-C (cytarabine), cisplatin; ECF, fluorouracil, epirubicin, cisplatin; ESHAP, etoposide, solumedrol, cytosine arabinoside, cisplatin; FAC, fluorouracil, adriamycin (doxorubicin), cyclophosphamide; FOLFOX4, oxaliplatin, leucovorin, fluorouracil; FUFA, fluorouracil, leucovorin; IFL, bolus FU/leucovorin, irinotecan; MMM, methotraxate, mitomycin c, mitoxantrone.
*Initially diagnosed as anaplastic non – Hodgkin's lymphoma.

responses, and 17% stable disease >6 months). The median time to tumor progression was 103 days for all patients and 289 days for patients experiencing clinical benefit. The median overall survival for patients was 253 days and 375 days for patients experiencing clinical benefit. The clinical and pathologic characteristics of patients who experienced clinical benefit are summarized in Table 2.

Nonhematologic toxicity. Data related to nonhematologic toxicity indicated that therapy was extremely well tolerated. There was grade 1 alopecia reported in three patients and no grade 3/4 reports for nausea, vomiting, diarrhea, or mucositis. A single case of grade 3 neuropathy was attributable to the cumulative effects of weekly vinblastine. A serious adverse event occurred in one patient who suffered grade 4 hepatitis, renal failure, and myositis, which were attributed to a hypersensitivity to minocycline. After recovery, this patient resumed treatment for a prolonged period with cyclophosphamide, vinblastine, and rofecoxib without recurrent toxicity. Collectively, patients received a total of 850 weeks of treatment, during which there were two venous thromboembolic events (grade 2 and 3) and three reports of gastrointestinal hemorrhaging (all grade 3). One of these was a Mallory-Weiss tear secondary to viral gastroenteritis, and the patient restarted treatment, including daily oral rofecoxib, 2 weeks after this event. Despite the requirement for weekly administration of vinblastine (a vesicant), there was only one incident of extravasation (grade 1), although the majority of patients had a central venous catheter for the purpose of chemotherapy administration.

Hematologic toxicity. The incidences of important hematologic toxicities are presented in Table 3. Neutropenia (any grade) occurred in 25% of the study patients. This frequency indicates that the choice of doses for the two chemotherapeutic agents was appropriate because a significant number of patients experienced grade 3 or 4 severity for this important toxicity. Nonetheless, it should be noted that this value is remarkably low, given the fact that it represents the total incidence of neutropenia observed in our study patients despite the cumulative effects of continuous chemotherapy (with many patients receiving uninterrupted treatment for >6 months). Twelve patients required delay in administration or dose modification of cyclophosphamide and/or vinblastine due to neutropenia and no cases required a second delay or modification for this reason. The study protocol recommended that hematologic toxicity be managed with dose delay or modification; however, the use of hematopoietic growth factors was permitted. Six patients received erythropoietin injections while on the study treatment, and only one patient received filgastim (granulocyte colony-stimulating factor).

Discussion

Established regimens of cytotoxic chemotherapeutic agents are typically given at, or near, maximum tolerated doses in an effort to maximize tumor response. This convention assumes that the dose-response relationship is steep and is an important determinant of clinical outcome. Henderson et al. (14) have reviewed results from clinical trials, which have examined this

Table 2. Characteristics of patients experiencing clinical benefit

Age/Gender	Tumor type	Sites of metastatic disease	Prior chemotherapy in chronological order	Best Response	Time to Progression (d)
55/M	Hodgkin's disease	Cervical, mediastinal, abdominopelvic nodes	ABVD (epirubicin used; 6 cycles), DHAP (3 cycles)	CR	748
34/M	Hodgkin's disease	Lung, liver, pelvis	ABVD (6 cycles), mini-BEAM, oral etoposide (2 cycles)	CR	418
24/F	Hodgkin's disease	Mediastinal adenopathy	ABVD (6 cycles), DHAP (2 cycles), cyclophosphamide, carmustine, etoposide (1 cycle)*	PR	749
78/M	Rectum	Lung	FUFA (17 cycles), irinotecan (4 cycles), CONT FU (3 cycles)	PR	358
56/F	Endometrium	Lung, liver	None	PR	325
69/M	Pancreas	Liver	None	PR	253
59/F	Breast	Lung, cervical nodes	Paclitaxel (2 cycles), FAC (6 cycles), MMM (5 cycles)	SD	391
79/F	Liver	Liver, kidney	Doxorubicin (6 cycles)	SD	344
56/F	Cholangiocarcinoma	Liver, kidney	ECF (6 cycles)	SD	227
69/F	Pancreas	Locally advanced adenocarcinoma	None	SD	226
63/F	Leiomyosarcoma	Liver, abdominal mass, bone, skin	Doxorubicin (1 cycle)	SD	211
71/F	Endometrium	Lung	None	SD	209
70/M	Colon (ascending)	Liver	IFL (2 cycles)	SD	198
53/M	Malignant melanoma	Liver	None	SD	192

Abbreviations: CR, complete response; PR, partial response; SD, stable disease.
*Given as high dose therapy with autologous stem cell rescue.

Table 3. Incidence of worst grade for hematologic toxicities (National Cancer Institute common toxicity criteria version 2.0)

Symptom	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
Anemia	0 (—)	3 (6)	2 (4)	0 (—)
Thrombocytopenia	0 (—)	0 (—)	1 (2)	0 (—)
Neutropenia	0 (—)	0 (—)	10 (21)	2 (4)
Febrile Neutropenia	0 (—)	0 (—)	0 (—)	0 (—)

issue and argue that the available data do not strongly support this conclusion. Furthermore, the narrow therapeutic index of most chemotherapeutic drugs and the fact that dosing calculations are based on only a few variables (usually just height and weight) put many patients at risk of substantial toxicity. These complications are particularly unfortunate when treatment intent is palliative, as toxicity can have a considerable adverse effect on the quality of a patient's limited life expectancy.

A growing number of preclinical studies have shown that the therapeutic index of chemotherapeutic agents can be improved if given more frequently at doses that are minimally toxic. Immunohistochemical analysis of tumor specimens obtained from mice treated in this fashion (1, 2) and results from angiogenesis assays (1, 2, 15) indicate that the anticancer effect is primarily a consequence of lethal damage to proliferating endothelial cells. Observations from recent experimental studies indicate that the antiangiogenic mechanisms produced by low-dose chemotherapy include preferential cytotoxicity to dividing endothelial cells (16), death of circulating endothelial progenitor cells (17), and increased expression of thrombospondin-1 (18). This method of drug scheduling (low-dose, uninterrupted fashion) has been termed "metronomic" chemotherapy and is recognized as an important conceptual advance in cancer therapeutics and has been the subject of several review articles (19–27).

There was a significant clinical benefit observed in patients receiving this low-dose regimen, especially in those with heavily pretreated lymphomas. Patients were allowed participation in this trial regardless of primary tumor type, as preclinical studies have shown that metronomic chemotherapy had activity in a wide variety of transplanted tumors (including carcinoma, sarcoma, and leukemic cell lines; refs. 1–7). Objective responses and prolonged progression-free survival have been reported in patients with Hodgkin's lymphoma who relapsed after high-dose therapy with autologous bone marrow transplantation when treated with vinblastine (4 to 6 mg/m^2) every 1 to 2 weeks (28). Cultured endothelial cells are exquisitely sensitive to the cytostatic effects of vinblastine (29), and this agent has potent antiangiogenic activity when evaluated in a standard *in vivo* assay (29). Results from experimental tumor models confirm that vinblastine exerts a strong antivascular effect (30, 31), and this activity may therefore be involved in the responses achieved in cancer patients. Daily oral cyclophosphamide (50 mg) is extremely well tolerated and has shown significant activity in heavily pretreated patients with metastatic breast (32) or prostate (33) cancers. The mechanism of anticancer activity of the current regimen was not evaluated because imaging methods to assess potential antiangiogenic effects of therapy in patients remain under investigation (34) and were not attempted in our trial. The observed partial responses and prolonged periods of disease stabilization in patients with primary tumors, which are typically chemotherapy resistant [metastatic melanoma (one), leiomyosarcoma (one) and carcinomas of pancreas (two), and endometrium (two)], were unexpected and merit further investigation.

It is not yet known whether modification of the doses and timing of administration of the two chemotherapeutic agents used in this study could significantly improved outcome measures. The selection of a regimen consisting of daily oral cyclophosphamide and weekly vinblastine infusions was based on preclinical efficacy data (1, 2) and the fact that these agents have different modes of action, toxicity profiles, and cellular resistance mechanisms. This study provides data that confirm that cyclophosphamide and vinblastine can be administered to patients for extended periods without significant cumulative toxicity. This was predicted from previous studies, during which some patients received prolonged uninterrupted therapy (>12 months) with either vinblastine (28) or oral cyclophosphamide (32–33). There is no evidence to suggest a small but cumulative potential for cyclophosphamide-induced leukemia (35), and this risk should be discussed with patients considering protracted therapy with this agent. It has not yet been established which is the optimum dosing frequency for either of these two agents when given in metronomic fashion to cancer patients. This variable may very well depend on several factors, including tumor type, growth fraction, the anatomic site of metastases, etc.

The results of this trial do not permit independent assessment of the influence of the COX-2 inhibitor rofecoxib on outcome measures because all patients received this drug. One randomized clinical trial has shown that administration of the nonsteroidal anti-inflammatory indomethacin to undernourished patients with advanced cancer was associated with a significant prolongation in survival (36). Despite the substantial data indicating considerable therapeutic potential for COX-2 inhibitors, there is a paucity of published results from trials examining the effects of these drugs in cancer patients when given as a single agent. Pruthi et al. (37) report that celecoxib can induce significant prostate-specific antigen responses in patients with metastatic prostate cancer. These authors did not provide data about the effects of this agent on more meaningful outcome measures, such as pain scores and quality of life indices. There are now reports from several phase II clinical trials examining the potential benefit of adding celecoxib to conventional chemotherapy in the treatment of patients with breast (38), non–small cell lung (39), colorectal (40), esophageal (41), and pancreatic cancers (42) as well as

malignant gliomas (43) and aggressive non–Hodgkin's lymphomas (44). The preliminary results from these uncontrolled studies indicate that there is promising therapeutic activity with such combinations and little additional toxicity. The COX-2 inhibitor used in our study, rofecoxib, has recently been withdrawn from the market by the manufacturer (45), in light of results obtained from the adenomatous polyp prevention on Vioxx trial (a colon polyposis prevention trial), indicating an increased risk for cardiovascular events in patients receiving this drug for >18 months. It should be noted that there were no cardiovascular events seen in patients who participated in the current study. Future trials in this area will need to examine the therapeutic effects of other COX-2 inhibitors, especially some of the recently identified analogues that have more potent apoptosis-inducing activity (46).

Tetracycline-class antibiotics inhibit metastases formation (47–49) and potentiate chemotherapy effects (50) in experimental tumor models. In the 24 patients who received concurrent therapy with minocycline, there was no apparent improvement in either tumor response rate or time to tumor progression. This drug is generally well tolerated when given over prolonged periods; however, the most serious adverse event in our study (drug-induced hepatitis, myositis, and acute renal failure) was attributable to this antibiotic. The apparent lack of clinical benefit from minocycline observed in this study may be a consequence of the small sample size and trial design. This could also be explained by the fact that patients in this trial had advanced cancer, and the potential anticancer activity of minocycline might only be observed in patients with earlier stage disease.

In summary, this combination of daily cyclophosphamide and weekly vinblastine, given concurrently with daily rofecoxib, provided moderate anticancer activity in a variety of patients with advanced solid tumors. The excellent tolerability of this regimen and infrequency of serious adverse events indicate a favorable therapeutic index and support further evaluation in disease site-specific clinical trials. These future studies might be designed to include concurrent administration of some of the recently developed antiangiogenic agents.

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