Modulation of Vinblastine Resistance in Metastatic Renal Cell Carcinoma with Cyclosporine A or Tamoxifen: A Cancer and Leukemia Group B Study


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ABSTRACT

Multidrug resistance mediated by P-glycoprotein may be an important cause of chemotherapy failure. Renal cell carcinoma is a disease known to demonstrate a high degree of intrinsic chemotherapy drug resistance, and this has been shown to be related to intrinsic overexpression of P-glycoprotein. Cyclosporine A and tamoxifen have been shown to reverse multidrug resistance in renal cell carcinoma cell lines in vitro. Phase I studies have defined appropriate doses of cyclosporine A and tamoxifen that can be combined with continuous-infusion vinblastine and safely achieve serum levels associated in vitro with resistance reversal. A randomized Phase II study was carried out by the Cancer and Leukemia Group B to evaluate the potential of high doses of cyclosporine A or tamoxifen to modulate clinical vinblastine resistance in patients with advanced renal cell carcinoma. Patients were treated initially with continuous-infusion vinblastine alone (1.2 mg/m²/day for 4 days or 1.5 mg/m²/day for 5 days); patients with stable or progressive disease were then treated with the same vinblastine regimen, combined with a high-dose regimen of either cyclosporine A (12.5 mg/kg/day for 5 days) or tamoxifen (400 mg/m² as a loading dose and 300 mg/m²/day for 13 days). Sixty-three patients were randomized to each arm. Eighty patients on both arms were evaluable for response to vinblastine alone; of these, only one patient achieved a partial response. Thirty-three patients went on to be treated with vinblastine and high-dose cyclosporine A. No responses were observed, although four patients with progressive disease on prior vinblastine achieved stabilization of disease after cyclosporine A was added. Addition of cyclosporine resulted in more leukopenia (5% versus 25%) and in transient hyperbilirubinemia (24%) and neurocortical changes (11%). No significant azotemia was observed. Thirty-five patients received high-dose tamoxifen with continuous-infusion vinblastine. One complete remission was seen in a patient who had stable disease only with prior vinblastine alone; no other responses were observed. Leukopenia was not more severe with the addition of tamoxifen to vinblastine, nor was hyperbilirubinemia observed. However, 9% of patients developed transient ataxia with or without neurocortical changes as a result of high-dose tamoxifen therapy, and 11% developed phlebitis. We conclude that advanced renal cell carcinoma is a highly chemoresistant tumor, that continuous-infusion vinblastine has no appreciable activity in the therapy of this disease, and that addition of high doses of cyclosporine A or tamoxifen was not able to modulate this resistance in these patients. Suggestions regarding study design for future drug resistance modulation trials were made based on the design and conduct of this study.

INTRODUCTION

It has become widely accepted that chemotherapy drug resistance, either inherent or acquired, is one of the major reasons for the relatively limited efficacy of chemotherapy treatment in most advanced solid tumors.

Many mechanisms of drug resistance have been described, including several that result in resistance to multiple chemotherapeutic agents, such as Vinca alkaloids, epipodophyllotoxins, anthracyclines, trimetrexate, and paclitaxel, simultaneously (1–3). One of the first mechanisms of multidrug resistance to be described was that due to increased expression of the mdrl gene encoding P-glycoprotein (4–6). This transmembrane glycoprotein causes increased active efflux of many lipid-soluble chemotherapeutic agents from the cell, with consequent decreased intracellular accumulation of the agent and decreased antitumor efficacy (6). Increased P-glycoprotein expression has been observed at the time of relapse in chemotherapy-sensitive tumors, such as leukemias (7–9) or lymphomas (10, 11), and at the time of diagnosis in other tumor types such as renal cell carcinoma (12–14). Modulation of multidrug resistance has been shown to be clinically important in the treatment of patients with relapsed
multiple myeloma and lymphoma. However, it is not yet clear whether clinical modulation of P-glycoprotein-mediated multidrug resistance will have an impact on the therapy of drug-refractory solid tumors.

Renal cell carcinoma has long been known to be highly refractory to chemotherapy treatment, with reported response rates of only 5–20% (15–23). Of the extensive list of chemotherapeutic agents tested, response rates for the Vinca alkaloid vinblastine are among the highest reported (24, 25). Renal cell carcinoma has been shown to have a high prevalence of constitutive high-level expression of P-glycoprotein (12). Goldstein and colleagues (13) found increased P-glycoprotein expression in 40 of 50 renal cell carcinomas, and Fojo et al. (14) found high levels in 7 of 8 renal cell cancers. This de novo expression of P-glycoprotein may be related to the increased expression normally found in epithelial cells lining the lumina of excretory organs, such as the cells lining the proximal renal tubule (12, 26). Renal cell carcinomas arise from the proximal renal tubule (27); hence, the constitutive expression of P-glycoprotein. It is likely that, at least in part, the clinical resistance of renal cell carcinoma to chemotherapy is related to its overexpression of P-glycoprotein (28). Clinically, P-glycoprotein overexpression has been reported to correlate with a poor outcome of chemotherapy treatment in patients with leukemias (29), sarcomas (30), and neuroblastomas (31).

Many noncytotoxic agents have been found to compete with chemotherapeutic agents for binding to P-glycoprotein, resulting in increased intracellular accumulation of the chemotherapeutic agent and circumvention of drug resistance (32, 33). These agents have been used to modulate multidrug resistance both in vitro and in vivo. The prototypical modulating agent is verapamil (34), but other calcium channel blockers and drugs from many other classes have been effective in preclinical models (32, 35–38). Several clinical trials have evaluated verapamil as a modulator of multidrug resistance (39–42), but the high doses of verapamil required have caused unacceptable toxicity (43). In vitro, drug resistance to vincristine and doxorubicin in renal carcinoma cells and other lines has been shown to be modulated by quinidine (14, 44), cyclosporine A (38, 45, 46), and tamoxifen (47).

Because the nature of the modulation is competitive inhibition of drug binding to P-glycoprotein, the degree of modulation of resistance to a natural product drug, such as vinblastine, is related to the concentration of the modulating agent relative to that of the chemotherapeutic drug. In general, the higher the concentration of modulator, the greater the degree of reversal of resistance. It is likely, therefore, that high levels of modulating drugs would be required to achieve clinically relevant reversal of renal cell carcinoma resistance to vinblastine. High drug concentrations may be associated with increased toxicity due to the modulating agent itself or to the interaction of the modulating agent and the chemotherapeutic agent. Phase I studies have recently been completed evaluating continuous-infusion vinblastine in combination with high-dose cyclosporine A (48) and with high-dose tamoxifen (49). In these studies, plasma concentrations of cyclosporine A and of tamoxifen and N-desmethyl tamoxifen were achieved that corresponded with concentrations demonstrated to be able to reverse multidrug resistance in vitro. Mean plasma cyclosporine A levels were found to be 0.97 ± 0.44 μM at a dose of 12.5 mg/kg/day, where concentrations of 1 μM are sufficient to reverse multidrug resistance in vitro (48). Mean plasma tamoxifen levels were 4 μM, and N-desmethyl tamoxifen levels were 6 μM at a dose of 150 mg/m² twice daily, within the range of concentrations of each compound shown to reverse multidrug resistance in vitro (49).

We therefore used the recommended Phase II dose combinations from these studies in a randomized Phase II trial to determine whether clinical resistance of renal cell carcinoma to vinblastine can be modulated by high doses of cyclosporine A or tamoxifen.

PATIENTS AND METHODS

This was a multi-institutional, groupwide, randomized, Phase II trial conducted by the Cancer and Leukemia Group B.

Eligibility Criteria. Eligibility criteria for the trial included histologically documented advanced renal cell carcinoma, either metastatic or unresectable; the tumor could be either measurable or evaluable. Patients could not have received previous chemotherapy, but prior immunotherapy was allowed. If central nervous system metastases were present, patients were required to have had adequate radiation therapy or surgical resection. Patients were required to have adequate bone marrow function (hemoglobin ≥10 gm/dl, absolute neutrophil count ≥1800/mm³, and platelets ≥100,000/mm³), renal function (serum creatinine ≤2.0 mg/dl or creatinine clearance ≥50 ml/min), and hepatic function (bilirubin ≤2.0 mg/dl). Patients were also required to have a normal QTc interval on a baseline electrocardiogram. In addition, patients were required to have completely recovered from the effects of prior therapy, to be at least 16 years old, to have an adequate performance status (Cancer and Leukemia Group B level 0–2), and to have a life expectancy ≥2 months. Institutional Review Board approval was obtained for the study at each participating institution, and each patient was required to give written, informed consent.

Study Design. The Phase I studies that formed the basis of this trial used doses of vinblastine with cyclosporine or tamoxifen of 1.2 mg/m²/day for 4 days (48) and 1.5 mg/m²/day for 5 days (49), respectively. Patients were randomized to either regimen A, with high-dose cyclosporine A, or regimen B, with high-dose tamoxifen. The randomization was stratified according to whether patients had measurable or evaluable disease. To define clinical vinblastine resistance, they were then treated with continuous-infusion vinblastine alone at 1.2 mg/m²/day for 4 days, if they were randomized to regimen A, or with continuous-infusion vinblastine alone at 1.5 mg/m²/day for 5 days, if randomized to regimen B. Vinblastine infusions were repeated every 28 days. Following two cycles of vinblastine alone, patients with stable disease continued treatment with vinblastine plus the modulating agent to which they had originally been randomized. Patients who had documented tumor progression at any time or patients responding to single-agent vinblastine who later had disease progression then continued on vinblastine plus the modulating agent from the time of documentation of tumor progression. Patients were evaluated for response after every two cycles of treatment.

When the modulating agent was added to the regimen, the vinblastine infusion was administered every 28 days, as before.
On regimen A, the cyclosporine A infusion was administered at a dose of 12.5 mg/kg/day, beginning 12 h before vinblastine and ending 12 h after the end of the vinblastine infusion. Cyclosporine A was administered either in glass or polyolefin containers, because the Cremophor vehicle can cause stripping of phthalates from polyvinylchloride. For patients on regimen B, tamoxifen was administered p.o. Because of the long plasma half-life of tamoxifen (42 h), administration began 8 days prior to the start of the vinblastine infusion, to achieve steady-state plasma levels. A loading dose of 400 mg/m² was given in three divided doses on the first day, followed by 300 mg/m²/day given in two divided doses, which continued through the end of the vinblastine infusion at day 13. Vinblastine was administered via an implanted venous access port because of its potential vesicant effects. After addition of the modulating agent to the regimen, two cycles of therapy were administered at 28-day intervals before evaluation for response was performed. Patients with tumor responses or stable disease were continued on therapy until disease progression. Patients were evaluated for toxicity 2 weeks after the start of each treatment cycle. Toxicities were determined by patient interview; physical examination; and weekly measurement of creatinine, sodium, magnesium, and bilirubin levels and complete blood count. Doses of vinblastine were reduced to 80% of baseline for grade 3 or 4 hematological toxicity, and doses of tamoxifen were reduced to 50% of baseline for central nervous system toxicity. Phenothiazines and steroids were prohibited as antiemetics because of their potentially confounding effect as modulators of drug resistance. Calcium channel blockers were not used to control cyclosporine-induced hypertension for the same reason; however, patients already receiving calcium channel blockers, steroids, cimetidine, and other drugs known to affect cyclosporine A pharmacokinetics at study entry were permitted to continue this medication. No measurements of vinblastine or modulator plasma levels were attempted in this study, because data were available from prior studies and because of the difficulties in obtaining reliable samples from multiple institutions in a cooperative group setting.

Tumor Response Criteria. For patients with measurable disease, complete response was defined as the total disappearance of all evidence of tumor by physical examination and appropriate laboratory and radiological studies for a minimum of 4 weeks, during which time no new lesions could appear. Partial response was defined as a greater than 50% reduction in tumor mass, calculated by the sum of the products of two perpendicular dimensions of all measurable lesions, for a minimum of 4 weeks, during which time no new lesions could appear and no existing lesions could enlarge. Stable disease was defined as a less than 50% reduction in tumor mass or a less than 25% increase in tumor mass, calculated by the sum of the products of two perpendicular dimensions of all measurable lesions, for a minimum of 8 weeks, during which time no new lesions could appear.

Progressive disease was defined as a greater than 25% increase in any lesion calculated by the sum of the products of two perpendicular dimensions, or the appearance of new lesions.

For patients with evaluable disease at enrollment, regression of disease was defined as a definite decrease in tumor size, as agreed on by two independent investigators for a minimum of 4 weeks, during which time no new lesions could appear and no existing lesions could enlarge. Stable disease was defined as the absence of a clear-cut change in tumor size for a minimum of 8 weeks. Progressive disease was defined as a definite increase in size of the tumor, or the appearance of new lesions.

Statistical Methods. McNemar's test (50) was used to compare toxicity from vinblastine alone with toxicity from vinblastine-plus-modulator therapy among those patients who received both therapies. Table 4 shows toxicity experienced by all patients, rather than just those who received both single-agent vinblastine and vinblastine-plus-modulator therapy. Survival in each cohort was calculated from the day of study entry until the date of death or last date known alive. The Kaplan-Meier product-limit method was used to estimate survival distributions (51), and CIs4 for median survival were computed using the method of Brookmeyer and Crowley (52).

RESULTS

A total of 126 patients were enrolled in the study between July 3, 1992, and December 12, 1993. Their demographic characteristics are listed in Table 1. Fifteen patients were not evaluable for toxicity or response due to ineligibility and/or major protocol violations. Thus, 111 patients were potentially evaluable. Of these, the majority (100; 90%) had measurable disease at study enrollment. Clinical response determination and evaluation of regimen efficacy were carried out only in the popula-

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4 The abbreviation used is: CI, confidence interval.
tion with measurable (as opposed to evaluable only) tumor at study enrollment, whereas toxicity evaluation was carried out in the entire group of 111 patients who did not have protocol violations. Of the 100 fully evaluable patients with measurable disease, a total of 68 received the modulation regimen to which they would have been originally randomized following initial therapy with vinblastine alone. Because this was a randomized Phase II study, the two arms were essentially independent, and the results will therefore be described separately. Table 2 outlines the reasons why patients dropped out of the study prior to addition of the modulator, by study cohort.

Regimen A (Vinblastine and Cyclosporine A)
Sixty-three patients were randomized to this arm. Eight patients were not evaluable for either toxicity or tumor response because of ineligibility or protocol violations, leaving 55 patients evaluable for toxicity. Of these remaining 55 patients, 8 were not evaluable for response because they did not have measurable tumor at study entry.

Response Data. Thus, 47 patients were potentially evaluable for response. Of these, 38 completed the first part of the study with vinblastine therapy alone and had measurable disease reevaluated. These patients are evaluable for response to single-agent vinblastine therapy. No complete or partial responses were observed after therapy with single-agent vinblastine by continuous i.v. infusion at 1.2 mg/m²/day for 4 days; 16 patients (42%) had stable disease, and 22 (58%) had progressive disease.

Of the evaluable patients completing therapy with vinblastine alone, 33 went on to receive vinblastine with high-dose cyclosporine A modulator therapy. No complete or partial responses were observed. Fourteen patients (42%) had progressive disease, and 19 (58%) had stable disease for a median of 1.8 months (range, 0.2–22.4 months). Of the 19 patients with stable disease, 4 (21%) had been observed to have progressive tumor when treated with vinblastine alone. These four patients had a time to treatment failure ranging from 3.2 to 9.1 months. Responses of those patients who received both parts of the planned regimen to each separate part of the regimen are shown in Table 3.

Toxicity Data. Toxicity data for vinblastine with and without cyclosporine A are found in Table 4. No significant thrombocytopenia was noted, but leukopenia was more severe when cyclosporine A was added (grade 3 or 4 leukopenia was 5 versus 25%; P = 0.01 for patients receiving both therapies). Despite this, the incidence of infection requiring i.v. antibiotics was similar (10 versus 14%), and no life-threatening infections were reported. There was no significant increased azotemia following the addition of cyclosporine (no grade 4 increases in creatinine and 4 versus 14% incidence of grade 3 increases), but 5% of patients had hypertension requiring therapy. Significant, although transient, increases in serum bilirubin level were seen in 24% of patients receiving vinblastine and cyclosporine A compared with none with vinblastine alone (P = 0.02 for patients receiving both therapies). Severe, although transient, neurocortical changes were reported in 11% of patients on cyclosporine and vinblastine and 4% of patients on vinblastine alone.

Regimen B (Vinblastine and Tamoxifen)
Sixty-three patients were randomized to this arm. Seven patients were not evaluable for either toxicity or tumor response because of ineligibility or protocol violations, leaving 56 patients evaluable for toxicity. Of the remaining 56 patients, 3 were not evaluable for response, because they did not have measurable tumor at study entry.
**Response Data.** Thus, 53 patients were potentially evaluable for response. Of these, 42 completed the first part of the study with vinblastine therapy alone and had measurable disease reevaluated. These patients are evaluable for response to single-agent vinblastine therapy. One partial response (2%) was observed with therapy with single-agent vinblastine by continuous i.v. infusion at 1.5 mg/m²/day for 5 days; 23 patients (55%) had stable disease, and 18 (43%) had progressive disease. The patient who achieved a partial response received two additional cycles of therapy with single-agent vinblastine before developing progressive disease.

Of the evaluable patients completing therapy with vinblastine alone, 35 went on to receive vinblastine with high-dose tamoxifen modulator therapy. In this group of patients, one complete response was observed (3%) in a patient who had stable disease on vinblastine alone; 15 patients (43%) had progressive disease, and 19 (54%) had stable disease for a median of 3.0 months (range, 0.2–26.7 months). One patient with stable disease on the modulation regimen had progressive disease previously on vinblastine alone; this patient withdrew from the study after two cycles of the modulation regimen and progressed at 4.8 months. The patient who achieved a complete response remains in clinical complete remission at 42+ months. This patient was a 66-year-old white female with a biopsy-proven, 4.5-cm solitary pulmonary metastasis diagnosed 9 months following radical nephrectomy for a stage II renal cell carcinoma. She had a best response to stable disease with vinblastine therapy alone. Responses of those patients who received both parts of the planned regimen to each separate part of the regimen are shown in Table 3.

**Toxicity Data.** Toxicity data for vinblastine with and without tamoxifen are found in Table 4. Again, no significant thrombocytopenia was noted; leukopenia after vinblastine alone (9%) was similar to regimen A. When tamoxifen was added, there was little change in the incidence of leukopenia (12%). One episode of life-threatening infection was reported after the addition of tamoxifen. More severe anorexia was reported after tamoxifen was added (2 versus 11%), but the incidence of both nausea and vomiting was similar. There was no significant azotemia as a result of the addition of tamoxifen and no increases in serum bilirubin level. Patients on vinblastine alone had severe, although transient, neurocortical (4%), sensory (2%) or cerebellar (2%) toxicities compared with 9% who, on vinblastine and tamoxifen, developed the transient ataxic syndrome reported previously with administration of high-dose tamoxifen (49). There were more patients with phlebitis on tamoxifen (11%) than on vinblastine alone (4%). One patient receiving tamoxifen had grade 4 phlebitis.

**Single-Agent Infusional Vinblastine**
When the data for the initial phases of Regimens A and B are considered together, 80 patients with measurable disease at enrollment were treated with one of two continuous-infusion vinblastine regimens and were evaluable for tumor response. No complete responses and only one partial response were documented in these 80 patients.

**Survival**
Overall survival for patients in both regimens is shown in Fig. 1. The median survival for patients on modulation regimen A was 7.36 months (95% CI, 6.41–11.07); on regimen B, median survival was 6.18 months (95% CI, 4.80–11.11).

**DISCUSSION**
A randomized Phase II trial design (53) was chosen to evaluate two potential methods of clinical modulation of multidrug resistance in the same population of patients with advanced renal cell carcinoma. Vinblastine was chosen as the chemotherapeutic agent, because it was shown in previous reports to have the most, albeit limited, activity in this setting (24). The drug was given by continuous i.v. infusion, because there were already some published data regarding the efficacy of continuous-infusion vinblastine in renal cell carcinoma (24, 25). There are also data suggesting that vinblastine might be more effective when used in this schedule (54). In addition, Phase I toxicity data were available for continuous-infusion vinblastine with multidrug resistance modulation using both cyclosporine A and tamoxifen (48, 49). modulation of vinblastine resistance using high-dose cyclosporine on an intermittent bolus schedule has subsequently been reported to be ineffective (55). It was also decided that it would not be appropriate to modify the recommended Phase II doses for the combinations derived from Phase I studies to make the dose and schedule of vinblastine the same.

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**Table 4 Grade 3 and 4 toxicities by treatment cohort**

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Arm A (VBL + CSA)</th>
<th>Arm B (VBL + TAM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VBL alone (%)</td>
<td>VBL + CSA (%)</td>
</tr>
<tr>
<td></td>
<td>gr 3 gr 4</td>
<td>gr 3 gr 4</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>5 0 11 14</td>
<td>7 2 9 3</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
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<td>0 0 0 0</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>5 4 27 3</td>
<td>6 0 14 0</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>0 0 16 8</td>
<td>0 0 6 0</td>
</tr>
<tr>
<td>Hepatic enzymes</td>
<td>6 0 3 5</td>
<td>6 0 3 0</td>
</tr>
<tr>
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<td>4 0 14 0</td>
<td>7 0 3 0</td>
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</tr>
<tr>
<td>Neurocortical</td>
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<td>2 2 0 0</td>
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<tr>
<td>Ataxia</td>
<td>0 0 0 0</td>
<td>2 0 9 0</td>
</tr>
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* VBL, vinblastine; CSA, cyclosporine A; TAM, tamoxifen; gr, grade. Values shown are percentages of patients with toxicity.
in both arms. The rationale for this was that in a randomized Phase II design, formal comparison of the two arms would not be performed. Moreover, the modulation regimens were derived from evaluation of various dose combinations of the component drugs, which might well have complex pharmacokinetic and pharmacodynamic interactions. We therefore felt that the modulation regimens should each be regarded as a unitary whole and evaluated in that fashion.

In the initial phase of the study, vinblastine was administered as a single agent by extended continuous i.v. infusion for 4 or 5 days. Of the 80 patients evaluable for response in this part of the study, there were no complete responses, and only one partial response was seen. When given by continuous infusion, recommended Phase II doses of vinblastine have ranged from 1.5 to 2.0 mg/m²/day (54). Although the doses in the single-agent vinblastine part of the study are toward the low end of this range, this is the largest study of single-agent vinblastine in advanced renal cell carcinoma in recent years and the largest of infusional vinblastine. The fact that virtually no responses were obtained in a large series of patients should cast doubt on the traditional wisdom that vinblastine has an approximately 10% response rate in this disease. We conclude that continuous-infusion vinblastine has no significant activity in advanced renal cell carcinoma. This phenomenon, in which modern-day studies, perhaps carried out under more stringent conditions, fail to verify response rates obtained in earlier trials, is well documented and has recently been reviewed by Poplin and Baker (56).

When patients randomized to regimen A had no response to, or disease progression on vinblastine, they were treated with the combination of vinblastine and cyclosporine A at doses previously demonstrated to produce plasma cyclosporine levels of approximately 1 μM (48); on regimen B, they were treated with the combination of vinblastine and tamoxifen at doses demonstrated previously to produce tamoxifen and N-desmethyl tamoxifen plasma concentrations ≥4 μM (49). It was hoped that the addition of a known modulator of multidrug resistance at effective concentrations would produce responses in a proportion of patients with clinical resistance to vinblastine. In fact, only one complete response and no partial responses were seen. Fifty-eight% of the patients on modulation regimen A and 54% on regimen B had stable disease, more than might be expected after failure of single-agent vinblastine, although 33 (87%) of the stable disease patients were patients who had had stable disease, rather than progressive disease, on prior single-agent vinblastine therapy. Thus, we could not demonstrate any clinically important modulation of resistance to vinblastine therapy in patients with advanced renal cell carcinoma through the addition of either high-dose cyclosporine A or high-dose tamoxifen, although a small minority of patients may have derived some benefit from the addition of a modulating agent to the vinblastine regimen. We recognize that P-glycoprotein levels were not actually measured in the tumors of patients treated on this study. Although other studies have demonstrated that most renal cell carcinomas overexpress P-glycoprotein, other mechanisms of chemotherapy drug resistance could also exist in these tumors. Thus, it is possible that the failure of multidrug resistance-modulating agents to improve the response to vinblastine therapy could have been due to other mechanisms of resistance being operative, rather than a failure to clinically modulate multidrug resistance. Nevertheless, neither regimen can be recommended for additional testing in this disease.

Although clinically relevant modulation of vinblastine resistance was not demonstrated, we believe that this study has identified important considerations for the design of future clinical studies of drug resistance modulation. In the initial design of this study, we felt that it was important to be certain that patients who were treated with a multidrug resistance-
modulating regimen were, in fact, demonstrated to be clinically resistant to vinblastine. For this reason, initial therapy was with vinblastine alone and only patients with stable or progressive disease went on to receive the modulator regimen. In retrospect, virtually no responders were seen with vinblastine alone, but delay of the modulator regimen meant that a significant proportion of patients who were enrolled did not go on to receive the modulator regimen, for a variety of reasons. This resulted in more patients being enrolled than had originally been planned, because the dropout rate was greatly underestimated. Only 53% of all patients enrolled were finally evaluable for response to a modulation regimen. The time required to complete the study was also extended. Thus, this two-phase study design, although scientifically sound and scientifically desirable, was not clinically practical. Future studies of modulation regimens in inherently drug-resistant tumors should have a simpler study design, in which the modulator regimen is studied immediately, without a preceding course of treatment with the chemotherapy drug alone. This would be feasible in situations in which there are already data regarding the efficacy the chemotherapy drug in question, in treating the disease of interest, without modulation. If there is a significant effect of the modulating agent on the response to chemotherapy, the effect is likely to be suggested by comparison of the data with historical controls treated with the same chemotherapy regimen without modulation. Regimens that show significant promise could then be evaluated further in randomized studies, comparing the chemotherapy plus modulator to chemotherapy alone. There are clear and well-documented problems in the use of historical controls (57); however, modulation of clinical drug resistance is unlikely to be clinically meaningful unless the effect is large, so that effective modulators suitable for additional, randomized trials should be identifiable by these means. Such a two-step approach is unlikely to fail to demonstrate a clinically significant modulation effect but should provide a more efficient and practical strategy for the clinical evaluation of drug resistance modulation. It is to be hoped that more potent modulators of multidrug resistance, such as the nonimmunosuppressive analogue of cyclosporine A, PSC 833, might be more effective in the clinical inhibition of P-glycoprotein-mediated drug resistance than cyclosporine itself or tamoxifen. As such new modulators are developed, we recommend that they be tested using the study design that we have proposed.

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Modulation of vinblastine resistance in metastatic renal cell carcinoma with cyclosporine A or tamoxifen: a cancer and leukemia group B study.

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