Cancer Chemother Pharmacol (1997) 41: 1–8

ORIGINAL ARTICLE

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Pilot study of multiple chemotherapy resistance modulators plus epirubicin in the treatment of resistant malignancies

Received: 1 February 1996 / Accepted: 5 March 1997

Abstract We studied the toxicity and efficacy of adding to epirubicin five resistance modulators in the treatment of resistant solid tumors. Additional drugs were added in successive cohorts of patients, such that cohort 1 patients received two drugs along with their epirubicin, while cohort 4 patients received five modulators along with their epirubicin. Metronidazole, tamoxifen (cohort 1), dipyridamole (cohort 2), ketoconazole (cohort 3) and cyclosporin (cohort 4) were administered with epirubicin. A total of 22 patients were treated. Nausea and vomiting was usually mild to moderate. There was an unexpectedly high incidence of possible cardiac toxicity associated with treatment, although in some patients it was uncertain whether or not observed cardiac events were related to treatment. Granulocytopenia was significant in all four cohorts, but it was unclear whether it was increased by the modulators. There were two febrile neutropenic events in cohorts 1 and 2 successfully treated with antibiotics, and three septic deaths (one in each of cohorts 1, 2 and 4). It was elected to discontinue enrolment on the study prematurely in light of cardiac and other toxicity seen in the first two patients accrued in cohort 4. A single response was observed. While this approach is feasible, the observed toxicity and the difficulty patients experienced in ingesting the large number of prescribed pills will make further exploration of this approach difficult.

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Key words Chemotherapy · Epirubicin resistance modulators · Metronidazole Tamoxifen · Dipyridamole · Ketoconazole · Cyclosporin

Introduction

While some advanced neoplasms are curable by chemotherapy, the majority demonstrate either de novo or acquired resistance to chemotherapeutic agents. The underlying cause of this resistance is likely multifactorial. For anthracyclines, one of the more commonly identified causes of resistance is increased levels of P-glycoprotein resulting from amplification of the *mdr1* gene. P-glycoprotein, enhances the efflux of anthracyclines and other chemotherapeutic agents out of the tumor cells after they have gained entry [1–3]. Other postulated mechanisms of resistance to anthracyclines include high intracellular glutathione levels [1, 2], increased protein kinase C activity [4], and decreased or abnormal topoisomerase II activity [5–7].

As reviewed previously (for example, references 8 and 9), several substances have been identified which can modulate the activity of chemotherapeutic agents in vitro by acting on one or more of the mechanisms of resistance listed above. These resistance modulators include calcium channel blockers (e.g. verapamil [10]), calmodulin inhibitors (e.g. chlorpromazine [11]) and other agents (e.g. quinidine [12], cyclosporin [13], and tamoxifen [14]) which are effective at reversing P-glycoprotein-mediated resistance. The nitroimidazoles (such as metronidazole and misonidazole) may also sensitize cells to some chemotherapeutic agents. They lower intracellular glutathione levels [15], sensitize hypoxic tumor cells to the effect of chemotherapy [16], may inhibit repair of chemotherapy-induced DNA damage [17], and have a direct cytotoxic effect on hypoxic tumor cells [18]. Tamoxifen, an antiestrogen agent used in the treatment of breast cancer, is capable of inhibiting P-glycoprotein [14], protein kinase C [19], and calmodulin [19]. Ketoconazole, an antifungal agent, can

increase the intracellular concentration of some anticancer agents [20], possibly by inhibiting P-glycoprotein [21]. Dipyridamole also appears effective at reversing tumor cell resistance to anthracyclines, but the mechanism by which it does so is not known [22].

Because tumor cells often have more than one mechanism of resistance [7, 23], we initiated studies in which we combined with chemotherapeutic agents several resistance modulators with different mechanisms of action in the hope of overcoming various mechanisms of resistance. Also, since the concentration of resistance modulator required for optimal reversal of resistance is at or above clinically achievable levels in many cases [8, 24], we felt that the addition of several agents with common mechanisms of action, but with different dose-limiting toxic effects, might minimize toxicity while optimizing efficacy. Several preclinical studies have demonstrated that combining two or more modulating agents possessing shared [25–32] or differing [33, 34] mechanisms of action may be more effective in countering chemotherapy resistance than the use of a single modulator.

We have initiated four clinical trials to study the feasibility and toxicity of adding sequentially to a single chemotherapeutic regimen five or six resistance modulators: one study using epirubicin [35], one using etoposide [36], one using carboplatin [37], and one in patients with glioblastomas, using cisplatin, mitomycin-C, and cranial irradiation [38]. We report here the results of our preliminary studies combining epirubicin (an anthracycline with a broad spectrum of activity) with metronidazole, tamoxifen, dipyridamole, ketoconazole plus cyclosporin. These modulators were chosen for their differing mechanisms of action or differing toxicity profiles. Some of the more common or serious toxic effects associated with high doses of these agents when used separately are: myelosuppression, nausea and vomiting, stomatitis, and cardiomyopathy (at high cumulative doses) for epirubicin; nausea, vomiting, and neurotoxicity for metronidazole; nausea, vomiting, hot flushes, and visual changes for tamoxifen; headache, dizziness, restlessness, nausea, bronchospasm, angina, ventricular arrhythmias, and hypotension for dipyridamole; hepatotoxicity and impaired steroid synthesis for ketoconazole; and nephrotoxicity, hepatotoxicity, hypertension, lipoprotein abnormalities, and neurotoxicity for cyclosporin [39].

Patients and methods

Eligibility criteria

All patients gave written informed consent to participate in this study approved by the Research Ethics Committee of the Ottawa Civic Hospital. Only patients with resistant tumors were eligible for entry on this study: patients had to be unlikely to respond to any chemotherapy, and had to have a probability of response to single-agent epirubicin of $<10\%$. Patients were eligible if they had histological proof of glioblastoma, malignant melanoma, carcinoma of the kidney or pancreas with or without prior chemotherapy; non-small-cell lung cancer, or carcinoma of the stomach, colon, rectum, head and neck, esophagus, or cervix refractory to any chemotherapy; or carcinoma of the breast, ovary, prostate, endometrium, adrenal gland, bladder, liver, gallbladder and biliary tree, or small-cell lung cancer, sarcoma, or neuroblastoma demonstrated to be anthracycline resistant. Patients had to be ≥18 years of age, and had to have a performance status <3 (ECOG scale), granulocytes $>1.5\times10^9$/l, platelets $>100\times10^9$/l, bilirubin and creatinine within the normal range, and a left ventricular ejection fraction of $>50\%$.

Study design

Patients received epirubicin 100 mg/m^2 IV over 10–15 min every 3 weeks. In the first cohort of six patients, two resistance modulators were added to epirubicin. In each subsequent cohort, a new modulator was to be added to the previous regimen, provided sepsis or grade 3 or 4 nonhematological toxicity occurred in no more than two of six patients in the previous cohort. (It was elected to accept a relatively high degree of toxicity in this pilot study to maximize the possibility that antitumor activity would be seen if this strategy was indeed active against resistant cancers.)

The scheduling was based on observed effects of scheduling in preclinical systems (reviewed in reference 8), on the desire to ensure that high tissue levels of the agents were present at the time of epirubicin infusion, and on the assumption that most tumor cell uptake and DNA binding of epirubicin will have already occurred by 24 h after drug administration.

Cohort 1 received epirubicin day 0 plus metronidazole (1.5 g/m^2 orally at −12, −0.5 and 24 h; 0.5 g/m^2 per rectum at −12, −0.5, 6 and 24 h; and 0.5 g/m^2 IV at 0.5 h) plus tamoxifen (100 mg/m^2 orally days −1, 0 and 1). Cohort 2 received cohort 1 drugs plus dipyridamole (100 mg/m^2 orally every 6 h days −1, 0 and 1). Cohort 3 received cohort 2 drugs plus ketoconazole (350 mg/m^2 orally days −1, 0 and 1). Cohort 4 received cohort 3 drugs plus cyclosporin (150 mg/m^2 orally at −12, −0.5, 12, 24 and 36 h). (We had planned to also add quinidine as a sixth modulator, but, owing to toxicity, closed the study after initiating patient entry on cohort 4.) For each modulator, the dose chosen was generally at or above the maximum dose recommended when the drug is used for other indications [39]. In some instances, this dose was decreased because of known drug interactions (e.g. cyclosporin; see Discussion), or because of the nature of the toxicity observed in initial patient cohorts.

Complete blood count and serum biochemistry evaluations were performed weekly. Electrocardiograms were done once every 3 weeks. Hematological and nonhematological toxicities were graded according to the National Cancer Insitute of Canada Expanded Common Toxicity Criteria. Cycles were repeated every 21 days provided blood counts had recovered (granulocyte count $>1.0\times10^9$/l, platelet count $>100\times10^9$/l) and other dose-limiting toxicities had resolved. Patients received full supportive care as required. Standard prophylactic antiemetics (generally ondansetron and dexamethasone) were administered. (Note that these antiemetics could also potentially have an effect on chemotherapy efficacy. For example, dexamethasone might potentiate chemotherapy efficacy by inhibiting P-glycoprotein, as it does in some systems [40], but it augments P-glycoprotein expression in other systems [41], and corticosteroids could also potentially antagonize the efficacy of some chemotherapeutic agents by inducing increased production of metallothioneins [42].)

The epirubicin dose was reduced by 25% if granulocyte nadirs were $<0.5\times10^9$/l for >7 days, platelet nadirs were $<30\times10^9$/l for >7 days, or grade 3 stomatitis occurred. A 50% dose reduction was implemented with granulocyte nadirs of $<0.5\times10^9$/l for >14 days, platelet nadirs $<30\times10^9$/l for >14 days, neutropenic fever, thrombocytopenia-related bleeding or grade 4 stomatitis. No hemopoietic growth factors were used. Standard criteria were used to evaluate response to treatment.

Results

Patient demographics

Patient accrual began in April 1991. Pretreatment characteristics of the 22 patients entered on study are listed in Table 1. After discussion with the study chairman, two patients were allowed entry despite a performance status of 3. All patients, except one, had received prior systemic therapy. The median number of regimens received prior to this protocol was one (range none to four). Five patients had received a prior anthracycline-containing regimen.

Toxicity

Six patients were included in cohort 1, seven in each of cohorts 2 and 3, and two in cohort 4. In total, 42 cycles were administered. Table 2 lists the number of patients in whom nonhematological toxicity was observed in each cohort. Nausea and vomiting was usually just grade 1–2, and well controlled with ondansetron plus dexamethasone. Grade 3–4 nausea and vomiting occurred once in each of cohort 1, 2 and 3. Patients generally had difficulty taking the large number of modulator pills by mouth.

Mucositis was also generally grade 1–2. A single episode of grade 3 mucositis was seen in cohort 4. One patient in cohort 3 experienced mucositis during four of his six cycles. Three patients experienced headaches or migraines. In one patient in cohort 2, this occurred on day −1, and was associated with paresthesias in his upper body. Dipyridamole was discontinued and the symptoms resolved. Later that cycle, the patient complained of occasional tinnitus. In another patient in cohort 2, a migraine developed on day 0 and was associated with a sensation of sensitive skin. In a patient in cohort 4, the headache which developed on day 0 was associated with photophobia, and resolved on day +1 after discontinuation of metronidazole and dipyridamole.

Of the 22 patients, 6 (27%) had possible cardiovascular toxicity. Two patients in cohort 1 suffered symptomatic hypotension. One patient developed a blood pressure of 72/48 on day 0 of his first cycle shortly after receiving epirubicin. His blood pressure immediately prior to the epirubicin had been 84/62. He was simply observed and gradually improved after completion of treatment. His blood pressure had not been measured prior to initiation of day-1 modulators, so it could not be stated with certainty that the hypotension was caused by his treatment. His tumor progressed, and he was not rechallenged with study drugs. The second patient had been on a beta blocker, and had a pretreatment blood pressure of 96/60, which then deteriorated to 68/42 over days −1 and 0. She was treated with intravenous fluids, and the beta blocker was discontinued. Her blood pressure returned to normal over the next few days. The

Table 1 Patient Characteristics

Number of patients	22
Gender (males/females)	12/10
Age (years)	
Median	56
Range	21–77
Performance status (ECOG)	
0	2
1	16
2	2
3	2
Primary diagnosis	
Non-small-cell lung cancer	5
Colon cancer	4
Renal cancer	3
Head and neck cancer	2
Breast cancer	2
Neuroblastoma	1
Soft tissue sarcoma	1
Pancreatic cancer	1
Prostate cancer	1
Endometrial cancer	1
Unknown primary	1

Table 2 Nonhematological toxicity

Symptom	Cohort 1 (n = 6)	Cohort 2 (n = 7)	Cohort 3 (n = 7)	Cohort 4 (n = 2)
Nausea and/or vomiting	2	4	4	1
Diarrhea	2	0	0	0
Mucositis	1	0	3	1
Weakness/fatigue	3	2	2	0
Anorexia	1	2	0	1
Alopecia	1	2	0	0
Headache/migraine	0	2	0	1
Peripheral nervous system	0	2	0	0
Febrile neutropenia				
Reversible	1	1	0	0
Fatal	1	1	0	1[a]
Severe hiccups	1	0	0	0
Elevated prothrombin time	0	1	0	0
Heartburn	0	0	0	1
Cardiovascular	2	0	2	2

[a]Suspected (but not confirmed) to be neutropenic

Table 3 Hematological toxicity

Symptom	No. (%) with toxicity			
	Cohort 1 ($n = 6$)	Cohort 2 ($n = 7$)	Cohort 3 ($n = 7$)	Cohort 4 ($n = 2$)
Granulocytopenia ($< 1.0 \times 10^9$/l)	6 (100)	7 (100)	4 (57)	1 (50)
Thrombocytopenia ($< 50 \times 10^9$/l)	1 (17)	0	0	1 (50)
Anemia (< 80 g/l)	1 (17)	0	1 (14)	0

patient subsequently refused further treatment. One patient in cohort 3 developed angina on day +2 of cycle one and day +1 of cycle three, at which time dipyridamole was discontinued. He had no recurrence of angina with three subsequent cycles of treatment. Another patient in cohort 3 had a baseline left ventricular ejection fraction of 57%. After four cycles of therapy, a routine left ventricular gated scan revealed a reduced left ventricular ejection fraction (44%), and therapy was discontinued. She had received a cumulative epirubicin dose of 500 mg/m^2 prior to entry on this study, and received a further 400 mg/m^2 on this study.

Both patients in cohort 4 developed cardiovascular complications. The first developed bradycardia, hypertension, and severe headache on day 0 prior to epirubicin administration. He had no evidence of brain metastases. All medications were held for several hours, and these symptoms resolved. Medications were then restarted with a 50% decrease in the cyclosporin dose, and the treatment course was completed. The second patient in cohort 4 was admitted to hospital 6 days after her first treatment with dyspnea, chest pain, bradycardia, and a decreased level of consciousness. She was felt clinically to be septic. An electrocardiogram demonstrated a sinus rhythm with frequent ventricular premature complexes, abnormal right axis deviation and nonspecific intraventricular conduction block. The patient suffered a cardiac arrest and was not resuscitated, in accordance with her previous request. Autopsy results showed extensive carcinoma, acute bronchopneumonia, and extensive petechial hemorrhages consistent with a coagulopathy. Antemortem laboratory investigation revealed leukopenia, with a white blood cell count of 2.4×10^9/l (although a differential was not done), thrombocytopenia, elevated partial thromboplastin time, prothrombin time, bilirubin, chloride, creatinine, urate and phosphate. In addition, she had a marked reduction in her serum calcium level to 0.8 mmol/l (the normal range being 2.10 to 2.60 mmol/l).

There were two additional treatment-related deaths in addition to this patient. One patient in cohort 1 was admitted to hospital on day 2 of his first treatment with worsening nausea and vomiting. On day 6, he died of neutropenic *E. coli* sepsis. Another, in cohort 2, was admitted to hospital 10 days after her first treatment with dyspnea, chills, febrile neutropenia, and pneumonia. She died on the day of admission. Biochemical evaluation performed antemortem revealed an elevated prothrombin time, bilirubin and transaminases. Two patients with febrile neutropenia recovered with antibiotics.

Table 3 lists the percentages of cycles in which grade 3 or 4 hematological toxicity was observed. Median granulocyte nadirs were ($\times 10^9$/l) 0.4 in cohort 1, 0.6 in cohort 2, 2.2 in cohort 3, and 1.0 in cohort 4. (Only one patient was evaluable in cohort 4). There was no apparent increase in hematological toxicity with each modulator addition. One patient in cohort 1 required platelet and red blood cell transfusions, and another in cohort 2 was given red blood cell transfusion only. In the one patient on cohort 4 suffering a septic death, severe thrombocytopenia was present at the time of death. While she was moderately leukopenic (WBC 2.4×10^9/l), granulocytes were not measured at the time of her death.

Therapy was modified (treatment delayed, dose reduced or drug withheld) because of toxicity in eight patients (two in cohort 1, two in cohort 2, three in cohort 3, one in cohort 4). This was done in response to headaches, nausea and vomiting, neutropenia, chest pain and weakness. One patient received only partial therapy because of urinary retention thought to be unrelated to treatment. One patient in cohort 1 refused further treatment after her first cycle which was complicated with hypotension (as discussed above). Another patient in cohort 4 refused cycle 2 because of the number of oral medications required, and because of toxicity with cycle 1.

In light of the significant rate of complications associated with therapy in this study and other concurrent studies [36–38], and in light of the fact that both patients in cohort 4 developed significant bradycardia, enrolment was closed after the second patient was entered in cohort 4. As noted above, our original intention was to study a fifth cohort of patients in whom quinidine would have been added to the drugs in cohort 4.

Response

A single patient in cohort 3 with breast cancer and a prior response to epirubicin achieved a partial response of chest wall disease which was maintained for 16 weeks. After four cycles of treatment, chemotherapy was discontinued following a drop in her ejection fraction (see toxicity), and the patient was given radiotherapy. No other patient experienced objective tumor regression.

Discussion

Toxicity with the addition of resistance modulators to chemotherapy has previously been documented. Cyclosporin (at doses higher than those employed here) is associated with hyperbilirubinemia [43–46], hypomagnesemia [44, 45], nausea and vomiting [45, 46], and augmentation of chemotherapy-induced myelosuppression [45, 46]. Dipyridamole has been associated with increased toxicity in some clinical trials [47, 48], but not in others [49–51]. One trial found a dose-related increase in myelosuppression [52], and another found persistent nausea and vomiting and neurological toxicity [24] with tamoxifen. Metronidazole has been found to increase the incidence of chemotherapy-induced renal [53] and pulmonary toxicity in some trials [53–55], but has been found to have no apparent effect in others [55, 56]. The toxicity observed with the addition of the modulators could in part be attributed to the direct toxicity of the modulators in these studies, and may have also been due in part to an interaction of these agents with the chemotherapy.

In the present study, we empirically combined multiple potential resistance modulators that have differing presumed mechanisms of action or that have nonoverlapping toxic effects. This study was driven by the assumption that resistance is usually multifactorial in the clinical setting. In keeping with this, there are a number of examples of tumor systems in which different resistance mechanisms coexist [7, 23, 57]. This study was also based on the premise that it would be difficult to give high enough doses of any one resistance modulator to reach a potentially effective concentration [8, 24]. The results of this trial indicate that the combination of moderately high doses of resistance modulators with different mechanisms of action and nonoverlapping toxicity is feasible, but results in substantial toxicity, as was expected from the results of several studies by other investigators using a single resistance modulator. The addition of dipyridamole (in cohorts 2–4) may have increased the incidence of headaches, nausea and vomiting. Dipyridamole is known to cause each of these symptoms when used alone [39]. Nausea and vomiting could be relatively well controlled with ondansetron plus dexamethasone, but despite these antiemetics, patients found it very difficult to ingest the large number of pills prescribed as modulators.

The incidence of cardiovascular events may have been higher than would be expected with epirubicin alone [58, 59]. Two patients in the first cohort experienced hypotension that was either unrelated to treatment, or else was due to the modulators alone, as epirubicin had not yet been administered at the time of detection of the hypotension. One cohort 3 patient experienced angina, thought to be related to the known ability of dipyridamole to cause angina [39]. Both patients in cohort 4 developed bradycardia, suggesting that the bradycardia may have been related to an interaction between cyclosporin and the other modulators, although in the second of these patients, the bradycardia could have resulted either from the patient's terminal sepsis or from an interaction between cyclosporin and epirubicin. Cyclosporin augments cardiac content and cardiac toxicity of anthracyclines in mice [60]. Enrolment was stopped as a consequence of this and other cohort 4 toxicity. A single patient in cohort 3 had a reduction in her ejection fraction, but the cumulative epirubicin dose she had received was high enough for a reduction in ejection fraction not to be unanticipated with the epirubicin alone [58, 59].

Although the degree of myelosuppression did not appear to be substantially greater than would have been expected with epirubicin alone, there was a higher than anticipated rate of septic deaths (14%). The reason for this is unclear.

The effect of the present combination of modulators on epirubicin pharmacokinetics is unknown, as we did not conduct pharmacology studies as part of this trial. If further studies were to be done using this approach, it would be important to assess epirubicin pharmacology. Cyclosporin has previously been found to increase the area under the concentration-vs-time curve of etoposide [61], doxorubicin [46], and other antineoplastic drugs [62], and augments tissue concentrations of doxorubicin in mice [60]. The nitroimidazoles also alter the pharmacology of some anticancer agents [63], and ketoconazole interferes with the metabolism of a wide variety of agents [39].

In any further studies, it would also be important to assess the impact of this combined approach on the pharmacology of each modulator, and to assess whether the blood concentrations attained for each modulator achieve levels that are required in vitro for resistance modulation. Some evidence of drug interactions would be expected. For example, ketoconazole is known to increase plasma concentrations of cyclosporin [64], possibly by inhibiting cyclosporin hydroxylase in hepatic microsomes [65]. Metronidazole [66], tamoxifen [67], and doxorubicin [68] (which is closely related to epirubicin) also may augment cyclosporin blood levels, while cyclosporin may inhibit the metabolism of tamoxifen by cytochrome P450 IIIA [67].

Enhanced expression of P-glycoprotein and increased drug resistance have been reported for refractory hematological neoplasms [43, 69, 70]. In these neoplasms, dipyridamole [69] and cyclosporin [43, 45, 70] appear to enhance drug sensitivity. Solid tumors do not usually express *mdr1* at diagnosis, but some such as sarcomas, and breast, ovarian and small cell lung cancers may become *mdr1* positive at relapse [71]. The benefit of resistance modulators in circumventing resistance in these solid tumors remains uncertain, although several clinical trials have found responses in patients with resistant neoplasms. Cyclosporin may have been effective at partially reversing resistance in some studies involving patients with retinoblastomas [72], breast cancer [73], gynecological cancers [73, 74] and various heavily

pretreated solid tumors [44]. Dipyridamole, however, has been found to be largely ineffective at reversing resistance in renal cell carcinoma [51], and other malignancies [48, 50]. The results obtained with metronidazole are mixed. Somewhat encouraging responses have been observed with metronidazole in non-small-cell lung cancer [55] and head and neck cancer [75], while there appears to be minimal impact on chemotherapy efficacy when it is used in astrocytomas [56], breast cancer [54], renal cell cancer [53] and colorectal cancer [76]. Finally, some clinical trials utilizing ketoconazole or tamoxifen as response modulators have shown modestly promising results in the treatment of small-cell lung cancer [52, 77].

There is limited clinical experience utilizing resistance modulators with epirubicin. Cyclosporin and quinidine fail to augment the efficacy of epirubicin against colorectal cancer [78] and breast cancer [79], respectively.

Overall, while resistance modulators may have some impact in resistant hematological malignancies, their impact in solid tumors has been modest, at best, to date. Since resistance to chemotherapy may well be the result of more than one mechanism in any cell type, the circumvention of this resistance will likely require modulators aimed at a number of different resistance mechanisms.

We have proposed that drug resistance be classified as "active" (from too much of a factor, analogous to competitive inhibition of drug effect) or "passive" (from a deficiency of a factor, analogous to noncompetitive inhibition of drug effect) [80]. As a rule, resistance-modulating agents, such as those employed in this study, modulate active resistance mechanisms, and would not be expected to be of value against passive resistance [80]. Passive resistance (as a result of deficient or mutated drug-uptake systems, drug-activating enzymes, obligate targets, apoptosis mechanisms, essential cofactors, etc) may be quite important in solid tumors [80], and this may partially explain the limited efficacy of most clinical resistance-modulating strategies explored to date, including the strategy used in this study and other studies we have conducted [36–38, 53–56, 75, 81].

We conclude that the addition of metronidazole, tamoxifen, dipyridamole, ketoconazole and cyclosporin to epirubicin at the dose levels used in this protocol can be achieved with increased toxicity. While we saw little activity in this patient population with a variety of resistant solid tumors, further formal efficacy testing would be required before we could state with certainty that efficacy is not enhanced. If this approach were to be tested further, we would suggest that cyclosporin be omitted, and that testing be done in patients with minimal or no prior therapy, or in patients with responsive (but incurable) tumor types. While higher doses might have been attainable for some of the modulators, toxicity and problems with ingesting the large number of pills involved would have made this difficult. Because of the difficulties in delivering these resistance modulators, and because solid tumors may perhaps have passive resistance mechanisms that would not be amenable to this type of approach [80], we have initiated studies to investigate other strategies [82, 83] to overcome chemotherapy resistance.

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