Addition of Verapamil and Tamoxifen to the Initial Chemotherapy of Small Cell Lung Cancer

A Phase I/II Study

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Based on experimental observations that verapamil and tamoxifen reverse multiple drug resistance, the authors investigated the feasibility of combining both agents with the initial chemotherapy of extensive small cell lung cancer. Overall, in a consecutive series of 58 patients the most important toxicity was myelosuppression, and there was a 24% rate of severe infections. Therapeutic results included 24% complete and 34% partial response rates, median time to disease progression of 32 weeks, and median survival of 46 weeks. In three consecutive cohorts of patients the dose of either tamoxifen or verapamil were escalated by 25% and 33%, respectively. The cohort of patients receiving verapamil 360 mg/day and tamoxifen 100 mg/day (level 2) had slightly more toxicity but also more responses than the other groups. Therefore, the authors recommend that these doses be used in controlled trials to confirm the promising results of their study.
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THE SPONTANEOUS occurrence of resistant tumor cell mutants is a significant obstacle to further improvements in the management of patients requiring chemotherapy.[1,2] The multiple drug resistance (MDR) phenotype is of major importance since it leads to resistance to a group of chemically dissimilar but highly active drugs such as doxorubicin, etoposide, and the Vinca alkaloids.[3–6] The MDR is associated with poor cellular uptake and retention of the cytotoxic drugs. This impairment appears to be related to membrane alterations, including overexpression of the drug transport P-glycoprotein by amplification of the *mdr-1* gene.[3–6] Laboratory investigations led to the discovery of various of compounds, collectively known as resistance modifiers (RM), capable of reversing MDR when used in conjunction with antitumor agents.[3,7–18a] The RM include calcium-channel blocking agents such as verapamil[7–16] and triparanol derivatives such as tamoxifen.[17–18a] A current hypothesis[3] states that RM act by competitive binding with the active P-glycoprotein sites, inhibiting the efflux of cytotoxic drugs. An alternative hypothesis[19] indicates that RM, which share an amphophilic structure, may interact with membranes, modifying the solubility of cytotoxic drugs in resistant cells.

Since most RM are available for other clinical uses, early clinical application of these laboratory findings is possible. This attractive approach is, however, associated with a number of problems. The optimal concentrations of RM required to cause reversal of MDR *in vitro* are within the range of clinical toxicity. There is concern that RM may enhance some chemotherapy toxicities as the P-glycoprotein occurs in normal hepatic, renal, and intestinal epithelia;[5,6] however bone marrow toxicity may not be enhanced.[31] Although patients with clinically resistant tumors might appear to be the best population to investigate, this group of patients will, in general, be pretreated, and have a large tumor burden. Only three clinical studies report in detail the results of adding RM to chemotherapy.[20–22]

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To overcome some of these problems we tested the combination of two RM and chemotherapy in a consecutive group of previously untreated patients with extensive small cell lung cancer (SCLC). Doxorubicin, vincristine, and etoposide were chosen as induction therapy because these drugs are very active in SCLC but also commonly select for MDR or develop cross-resistance. Two RM, verapamil and tamoxifen, were used with the expectation that they might have an additive effect in overcoming resistance at nontoxic doses. The RM were combined with chemotherapy from the outset, when the resistant population is expected to be small and more nearly approximates experimental conditions where this approach worked.[7,9,12] In addition, patients with refractory disease or who relapsed after responding to initial therapy were treated with cyclophosphamide and cisplatin, two cytotoxic agents not known to be affected by MDR. The hypotheses to be tested were that chemotherapeutic agents known to select for MDR can be combined with RM without undue toxicity, that extensive SCLC has such a uniformly poor prognosis that a significant interaction between chemotherapy and RM would be seen as a clinically important improvement in survival, and that significant cross-resistance would not develop to drugs that do not select for MDR. To this end, a Phase I/II study was done with increasing doses of RM to determine the feasibility of this approach.

Materials and Methods

Selection of Patients

Between November 1985 and July 1987 consecutive patients presenting to the Hamilton Regional Cancer Centre with the diagnosis of extensive stage SCLC were considered for entry into this study. Extensive stage was defined by the presence of pleural or pericardial effusion, lymphadenopathy beyond the ipsilateral neck, or disease beyond the thoracic cavity. Patients were excluded because of prior chemotherapy, age > 80 years, Eastern Cooperative Oncology Group (ECOG) performance status <3, leukocyte count $<3.0 \times 10^9$/l, platelet count $<100 \times 10^9$/l, serum bilirubin >34 mmol/l, serum creatinine >160 mmol/l, myocardial infarction within the past 3 months and/or congestive heart failure or arrhythmia under treatment with digoxin, beta-blockers, quinidine, procainamide, or calcium-channel blockers.

The study was approved by the ethical review boards of the participating institutions, and all patients gave informed consent.

Chemotherapy

Doxorubicin 50 mg/m^2 intravenously (IV) and vincristine 1 mg/m^2 IV were administered on day 1 and etoposide 100 mg/m^2 IV on days 1 to 3. Treatment was given every 3 weeks for six cycles.

Both verapamil and tamoxifen were given in oral daily doses starting 3 days before each primary chemotherapy course and continuing to include day 4 of each cycle. The starting doses (Level 1) were verapamil 120 mg orally three times a day and tamoxifen 80 mg daily. The escalated daily doses were as follows: Level 2, verapamil 120 mg three times a day and tamoxifen 100 mg daily; Level 3, verapamil 120 mg four times a day and tamoxifen 100 mg daily. The dose escalations were done in three successive cohorts of patients, each receiving the same dose of RM throughout the six courses of primary chemotherapy. Doses were escalated when the previous drug dose level did not require reduction of therapy dose (see Dose Reduction).

Patients with residual disease after completion of initial chemotherapy and those who subsequently relapsed after initial response were treated with cyclophosphamide 1000 mg/m^2 IV on day 1 and cisplatin 25 mg/m^2 IV on days 1 to 3 at three-week intervals for four cycles.

Radiation Treatment

Palliative radiation therapy was given for brain metastases, residual primary disease, or symptomatic distant metastases. Prophylactic cranial irradiation was administered to some patients who had a complete response from initial chemotherapy.

Dose Reduction

The dose of all myelosuppressive chemotherapy was reduced by 25% for treatment-day granulocyte counts between 1.5 and 1.9×10^9/l or platelet counts between 100 and 150×10^9/l. All drugs were withheld for 1 week for more severe grades of myelosuppression or ulcerative stomatitis. The dose of doxorubicin was reduced by 25% for serum bilirubin levels ≥15 to 34 mmol/l. The dose of vincristine was reduced by 50% in the presence of severe paresthesias or constipation and withheld for marked muscular weakness. The dose of verapamil was reduced by 33% in the presence of a PR interval of >0.20 seconds, other arterivenous conduction defects, or hypotension. Tamoxifen was discontinued in the presence of retinopathy or corneal disorders.

Assessment

Patients were evaluated for toxicity every 3 weeks, using ECOG criteria, and for response after six cycles of initial chemotherapy and at completion of secondary chemotherapy. Responses were assessed by standard criteria. In brief complete responses required the complete disappearance of all evidence of disease and partial responses >50% decrease in initial lesions without appearance of new lesions. To be classified as a complete or a partial response, these criteria must have been met for at least 4

weeks. Nonresponders included all patients with less than a partial response and those with early deaths from whatever cause, even if the patient had signs of response. Time to progression and survival were dated from the onset of treatment.

Investigations

Investigations before study entry included: pathology review; clinical examination and ECOG performance status; complete blood counts; blood urea, creatinine, electrolytes, albumin, bilirubin, liver enzymes, and carcinoembryonic antigen; electrocardiogram; chest radiograph; liver ultrasound or computed tomographic (CT) scan; isotope brain scan; and CT scan of the brain. If all clinical and imaging investigations were negative for metastases, a bone marrow examination was done.

Testing before each chemotherapy included: clinical examination and performance status, blood counts, chemistry, and chest radiograph.

Analysis

Data was analyzed using algorithms of the BMDP (BMDP Statistical Software Inc, Los Angeles, CA). Quoted response rates are shown with 95% confidence intervals. Contingency tables were analyzed using Pearson's chi-square test for 2×2 tables and Armitage's chi-square test for linearity. Toxicity is reported in two ways: (1) as percentage of patients with ECOG Grade 3 or worse toxicity during all courses of each chemotherapy and (2) as mean and maximal toxicity scores. The mean toxicity scores are either for each category of ECOG toxicity or globally for all toxicities in each patient. The maximal toxicity score is the worst score of any toxicity in each patient. The mean and maximal toxicity scores are used to screen for minimal differences in treatment effect and not for their clinical relevance. Toxicity score distributions between prognostic groups were compared using the Mann-Whitney test for two groups and analysis of variance with linear contrast where there were more than two groups. Survival data (response duration, time to progression, and survival) were expressed as Kaplan-Meier curves, and comparisons between survival were analyzed by the Mantel-Cox test. Patients who died of toxicity (4) or of causes unrelated to their disease (3) were censored in the analysis of response duration and time to disease progression, but all deaths were included in the survival analysis. All P values were two tailed.

Results

Fifty-eight eligible patients were entered into the study. All patients are evaluable for response, survival, and toxicity. Patient characteristics are shown in Table 1. In 13 patients the disease was relatively localized, confined to the chest wall, pleura, pericardium, or contralateral cervical lymph nodes without evidence of more distant spread. Five patients had initial brain metastases.

TABLE 1. Patient Characteristics

	Dose level of response modifiers		
	1	2	3
No. of patients	15	25	18
Male/female	8/7	14/11	12/6
Mean age (yr)	61.5	60.6	58.4
Performance status			
0	2	4	1
1	6	8	10
2	5	11	2
3	2	2	5
Sites involved by disease			
Liver	4	7	7
Bone	7	11	5
Brain	2	2	1
Pleura-pericardium	5	13	8
Cervical lymphadenopathy	4	9	8
Other sites	4	5	7

Treatment Administered

Thirty-nine patients completed all six courses of initial chemotherapy; three completed five; four completed four; and 12 completed three or less courses. The reasons for stopping therapy in the 19 patients who did not complete treatment were early death in six patients, refusal of further treatment in five, progressive disease in seven, and one death due to a ruptured abdominal aneurysm. The average chemotherapy dose ± standard deviation (SD) per course to each patient was 91% (±11). The dose of vincristine was reduced in 14 patients, doxorubicin in seven patients, and etoposide in five patients.

According to the dose escalation of RM, 15 patients were entered at Level 1, 25 at Level 2, and 18 at Level 3. The mean number of cycles of initial chemotherapy at the three dose levels of RM was five.

Secondary chemotherapy was given to 27 patients. Fifteen patients were treated for refractory or residual disease and 12 for recurrent disease. All patients with recurrent disease received the intended four courses, but only nine of the patients with refractory disease completed treatment.

Prophylactic cranial irradiation was given to eight patients considered to be in complete remission. Palliative radiation therapy was given to 28 patients, including 13 with brain metastases appearing before, during, or after chemotherapy.

Toxicity

Toxicity grades during the primary therapy are shown in Table 2. Bone marrow suppression was the most common severe (ECOG Grade 3–4) toxicity observed. Trans-

TABLE 2. Percentage of Patients Who During All Cycles of AVE Chemotherapy had ECOG Grade 3 or More Toxicity

Toxicity	Dose levels of response modifiers		
	1 (n = 15)	2 (n = 25)	3 (n = 18)
Nadir leukopenia	79*	87*	86*
Nadir neutropenia	100*	100*	86*
Nadir thrombocytopenia	7*	27*	14*
Anemia	40	48	29
Infections	20	28	22
Nausea and vomiting	27	4	11
Stomatitis	13	0	6
Constipation	7	0	0
Peripheral neurotoxicity	13	0	11

AVE: doxorubicin, vincristine, etoposide.
The differences among the three dose levels were not significant ($P > 0.10$).
* Considers only patients who had weekly blood counts (level 1 = 14, level 2 = 15, and level 3 = 14).

fusions were required for severe anemia in 40% of patients and for severe thrombocytopenia in 11% of patients. The leukocyte and neutrophil nadirs were recorded in 43 patients having weekly blood counts; ECOG Grade 3–4 leukopenia and neutropenia were observed in most patients. Severe infections, requiring hospitalization and intravenous antibiotics, occurred in 14 of 58 (24%) patients. Five of these 14 episodes of febrile neutropenia contributed to death and, in one other patient, to refusal of further therapy. Peripheral neurotoxicity was symptomatic in 44% of patients and led to vincristine dose reductions in 24% of patients.

By contrast, no major specific toxicity due to verapamil or tamoxifen was observed. The electrocardiograms in the first 30 patients indicated prolongation of the PR interval up to (but no more than) 0.20 seconds and no other arrhythmia. No symptomatic decrease in blood pressure was observed. Ocular toxicity due to tamoxifen was not apparent.

The global toxicity scores of initial therapy in relation to some host and treatment factors are shown in Table 3. These global scores are used as more sensitive indices of drug action, but their clinical relevance is unproved. Increased global toxicity was associated with advanced age, liver involvement, and higher tamoxifen dosage. In Table 4 the consistently higher mean toxicity scores with higher tamoxifen doses is contrasted to the lack of this effect with higher verapamil doses.

The worst toxicity during second-line chemotherapy with cyclophosphamide and cisplatin was mainly myelosuppression. Nadir neutropenia ECOG Grade 3 or 4 was observed in 65% of patients, but no episodes of severe infection were observed. Anemia requiring blood transfusions occurred in 38% of patients. Serum creatinine levels increased significantly in 30% of patients.

Therapeutic Response

Data on final evaluation for response to initial chemotherapy are shown in Table 5. The overall response rate was 34/58 (59%) with a 95% confidence interval of 45% to 71%. The 24 patients classified as nonresponders included 12 patients with progressive disease, two patients with stable disease, seven patients with early death due to toxicity or intercurrent illness, and three patients who refused further treatment.

The modification of response by age, sex, performance status, disease site, and doses of RM was investigated. The most important factors in decreasing response were involvement of liver ($P = 0.16$), brain ($P = 0.09$) and low performance status ($P = 0.17$). There was no difference in response rates with verapamil dose ($P = 0.82$), but there was a 10% higher response rate for patients receiving the higher tamoxifen dose ($P = 0.44$). However, there was insufficient power in this study to pick up small differences in response rates, and the RM dose ranges explored were relatively small.

The response rate to secondary chemotherapy is also shown in Table 5. Six of 15 (40%) patients with residual refractory disease had a response, as did ten of 12 (83%) patients with recurrent disease. When the six responses obtained in patients with residual disease are counted together with the 34 responders after primary therapy, the overall response rate to chemotherapy was 40/58 (69%, 55–80%) and the complete response rate was 17/58 (29%, 18–43%). Two further patients became clinically disease free by the addition of palliative locoregional radiotherapy, but they have not been included in the estimated response rate to chemotherapy.

TABLE 3. Global Toxicity Scores of Initial Therapy in Relation to Some Host and Treatment Factors

Patient group	Mean toxicity		Maximum toxicity	
	Score	*P* value	Score	*P* value
Age (yr)				
<50	0.90		2.70	
50–60	0.59	0.02	2.4	0.05
>60	1.03		3.20	
Liver metastases				
No	0.76		2.53	
Yes	1.05	0.02	3.50	0.002
Verapamil dose (mg/day)				
360	0.85		2.90	
480	0.88	0.64	2.78	0.50
Tamoxifen dose (mg/day)				
80	0.50		2.47	
100	0.98	0.002	3.0	0.18
Dosage level				
1	0.50		2.47	
2	1.05	0.04	3.16	0.43
3	0.82		2.78	

TABLE 4. Mean Toxicity Scores According to Verapamil and Tamoxifen Doses

Toxicity (mean score)	Verapamil dose			Tamoxifen dose		
	Low	High	*P* value*	Low	High	*P* value*
Myelosuppression						
Hemoglobin	0.83 (1.32)	1.11 (1.28)	0.18	0.07 (0.25)	1.21 (1.39)	0.003
Platelets	0.28 (0.99)	0.22 (0.94)	0.80	0.00 (0.00)	0.35 (1.11)	0.23
Leukocytes	1.83 (1.96)	1.33 (1.91)	0.55	1.07 (1.87)	1.88 (1.94)	0.11
Infections	1.55 (2.00)	1.61 (1.91)	0.77	0.87 (1.81)	1.81 (1.97)	0.08
Gastrointestinal						
Stomatitis	0.65 (1.63)	0.67 (0.91)	0.65	0.47 (0.99)	0.72 (0.98)	0.23
Nausea/vomiting	1.63 (1.05)	1.17 (1.04)	0.12	1.53 (1.19)	1.47 (1.03)	0.81
Diarrhea	0.13 (0.40)	0.50 (0.69)	0.16	0.00 (0.00)	0.33 (0.65)	0.08
Constipation	0.30 (0.65)	0.50 (0.79)	0.28	0.20 (0.56)	0.42 (0.73)	0.27
Neurologic						
Central	0.35 (0.74)	0.39 (0.70)	0.63	0.00 (0.00)	0.49 (0.80)	0.017
Peripheral	0.93 (1.00)	1.33 (0.91)	0.11	0.80 (0.94)	1.14 (0.99)	0.23

Standard deviations are given in parentheses. Verapamil dose: low, 360 mg/day in 40 cases; high, 480 mg/day in 18 cases. Tamoxifen dose: low, 80 mg/day in 15 cases; high, 100 mg/day in 43 cases.
* Mann-Whitney test.

Response Duration and Time to Disease Progression

Median follow-up as of November 1988 was 48 weeks (range, 1–96). For the 40 patients with chemotherapy responses, the median response duration was 28 weeks. All but two responding patients relapsed. Factors associated with length of response duration were absence or the presence of central nervous system metastases at presentation (5 weeks *versus* 28 weeks, $P = 0.003$). Median time to disease progression (Fig. 1) was 32 weeks, and only central nervous system metastases predicted time to disease progression (14 weeks *versus* 33 weeks, $P = 0.056$). The median response duration for patients receiving cyclophosphamide and cisplatin was 12 weeks.

Overall Survival and Disease Progression

Overall survival is shown in Figure 1. The median survival for the whole group was 46 weeks (0.95 confidence limits: 37, 55 weeks). In patients without initial brain metastases, the median survival was 50 weeks (0.95 confidence limits: 40, 60 weeks). The group of patients with only thoracic disease or contralateral lymphadenopathy was compared with patients with distant metastases: the survival curves were almost identical ($P = 0.42$). Similarly, there was no significant survival difference among the three groups of different dose levels of verapamil and tamoxifen ($P = 0.39$).

Discussion

Our primary objective was to test the feasibility and safety of combining two RM with a chemotherapeutic regimen which was likely to select for MDR. As a model we chose patients with SCLC because a major cause of eventual treatment failure in this disease is the development of chemoresistance, demonstrable both clinically

TABLE 5. Therapeutic Responses

Chemotherapy	RM Dose levels	Disease present	No. of patients	Responses (%)		
				Complete	Partial	None
Primary AVE	1	Initial	15	3 (20)	5 (33)	7 (47)
	2	Initial	25	7 (28)	9 (36)	9 (36)
	3	Initial	18	4 (22)	6 (33)	8 (44)
Secondary CP	—	Residual	15	3 (20)	3 (20)	9 (60)
	—	Recurrent	12	4 (33)	6 (50)	2 (17)

AVE: doxorubicin, vincristine, etoposide; CP: cyclophosphamide, cisplatin.

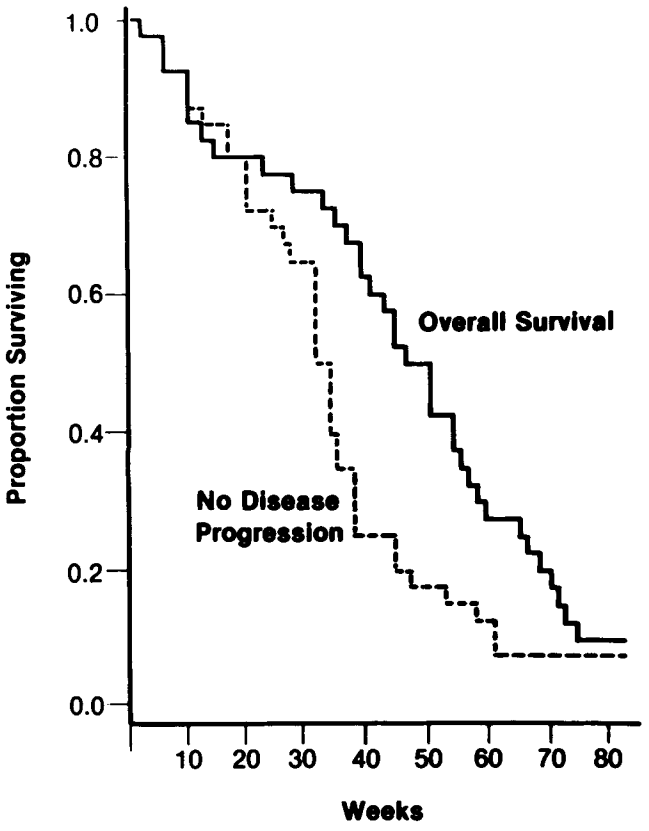

FIG. 1. No disease progression (---) and overall (—) survival of 58 patients with extensive small cell lung cancer.

and *in vitro*.[23,24] At the time this study was developed, verapamil and tamoxifen showed the greatest potential as RM, and their pharmacokinetics at the dose levels proposed were well described.[25,26]

The chemosensitizing effect of verapamil is selective for MDR cells and is dose related. Significant activity is seen at concentrations above 250 ng/ml, although some cell lines require concentrations of up to 3 μg/ml for maximum effect.[7-16] Oral verapamil, at a dose of 240 to 480 mg/day, produces peak serum levels of 100 to 500 ng/ml.[25] These levels are below the optimal but still within the range observed to reverse drug resistance. Intravenous dosing can achieve higher levels, but patients then require hospitalization and cardiac monitoring.[21,27]

Ramu *et al.*,[17,18] investigating the lipid metabolism of MDR cells, found that lipid-active drugs such as tamoxifen also induce this chemosensitizing effect, which is dose related, does not require antiestrogenic action, and occurs to a greater extent in resistant than in sensitive cells. Foster *et al.*[19] recently confirmed these findings. The concentration of tamoxifen at which resistance modification occurs *in vitro* ranges from 0.8 to 2.8 μg/ml. Using an oral dose of 40 mg/m^2 twice daily, within 4 days, serum levels of 400 ng/ml can be achieved, double that amount if tamoxifen metabolites are considered.[26] These concentrations are within the range required for reversal of MDR *in vitro*.[18]

We postulated that verapamil and tamoxifen might have at least additive effects in reversing MDR when used in suboptimal but nontoxic doses. Used in this manner, it would be possible to test the combination of these two RM with chemotherapy in an outpatient setting. More recently Weisenthal *et al.*[28] reported that a combination of five RM, at clinically relevant concentrations, produced *in vitro* reversal of vincristine resistance in human malignant lymphoid cells; the combination of RM also had a more pronounced effect than single exposure to verapamil or lidocaine.

As this was a Phase I/II dose finding study, toxicity was closely monitored. The toxicity observed was mainly related to the chemotherapy used and consisted of nausea and vomiting, peripheral and autonomic neurotoxicity of vincristine, and most prominently, bone marrow depression and severe infections. The rate of neutropenic febrile episodes affected 24% of patients and contributed to death in 9% of patients. Although we observed a similar high rate of febrile neutropenic episodes in a previous study of patients with extensive SCLC during intensive chemotherapy with doxorubicin, vincristine, and cyclophosphamide[29] such rates of infection were not reported in clinical trials using doxorubicin, vincristine, and etoposide without RM[30-32] or in those trials using doxorubicin combined with verapamil.[20,21] The *in vitro* cytotoxicity of doxorubicin, vincristine, and etoposide on human bone marrow cells is not enhanced by the addition of verapamil in the doses used in this study.[15,33,34] On the other hand, we observed higher mean toxicity scores of marrow suppression at higher dose levels of tamoxifen (Table 4). The serious infections observed may be related to more pronounced neutropenia due to the mild myelosuppressive effect of high doses of tamoxifen,[35] added to that of chemotherapy. Whatever its effect, the high rate of infections will require antibiotic prophylaxis during neutropenia as shown in other studies.[36,37]

No significant cardiovascular side effects due to verapamil or visual disturbances related to tamoxifen were observed. There were no unexpected toxicities related to tissues which contain markers of MDR cells, such as renal, hepatic, or intestinal epithelia.

Although toxicity is a major component in the determination of the feasibility and safety of a treatment, the therapeutic results are also important. Even if nontoxic, an experimental treatment would not be considered for further use if the therapeutic results were inferior to those expected from standard therapy. We observed a 24% complete response rate, a median response duration of 28 weeks, a median time to progressive disease of 32 weeks, and a median survival time of 46 weeks (50 weeks

for those without central nervous system metastases). These results compare favorably with those reported for patients with extensive SCLC treated with an induction regimen of doxorubicin, vincristine, and etoposide but without RM. Abbratt *et al.*[30] administered these drugs for six cycles to 28 patients and obtained a complete response rate of 21% and a median survival of only 24 weeks. Timothy *et al.*[31] treated 48 patients with six cycles of the same regimen and observed a complete response rate of 12% and a median survival of 18 weeks. Robinson *et al.*[32] administered these drugs for four cycles and then used high-dose cyclophosphamide in responding patients: among 63 patients, the complete response rate was only 16%, the median time to progression was 20 weeks, and the median survival was 26 weeks.

In a multivariate analysis RM dose levels were not a significant factor in response occurrence; however, higher tamoxifen doses produced a 10% higher response rate. The change in verapamil dose did not have that effect.

The early use of RM with chemotherapy is not likely to change the response rate substantially because of the initially low proportion of resistant cells in the tumor. On the other hand, we postulate that a relatively small decrease in the resistant tumor cell population might subsequently become apparent as a prolongation of time to progression and survival. A number of investigators[38-41] commented on the reported homogeneity of patient survival in extensive SCLC treated with combination chemotherapy. We confirmed these observations in an extensive review of 64 studies, including 6365 patients, reported between 1976 and 1987.[42] These studies used various drugs, doses, and schedules with additional radiation therapy. The reported values for median survival ranged from 19 to 53 weeks (mean, 31 weeks; SD, 6 weeks). Thus, the median survival of 46 weeks obtained in our study is within the upper range of that generally reported. It is possible that favorable selection of patients may have affected our results. We attempted to avoid this bias by investigating a relatively large series of consecutive patients and using standard criteria for inclusion and exclusion of patients.

A second objective of our study was to investigate whether the administration of cyclophosphamide and cisplatin, subsequent to the combination of doxorubicin, vincristine, and etoposide, would produce further responses indicating lack of cross-resistance. In 15 patients whose disease was refractory to initial chemotherapy, the response rate was 40%, while in 12 patients relapsing after an initial response, 83% responded. These results suggest that the two cytotoxic regimens are only partially cross-resistant.

The investigation of chemotherapy and RM has been reported in detail in a few published studies. Presant *et al.*[20] used oral verapamil, in doses of 480 to 960 mg/day, combined with doxorubicin, in patients with various chemoresistant tumors. Response was seen in a few patients, and the higher doses of verapamil caused an increased rate of emesis, arrhythmias, and hypotension. Ozols *et al.*[21] treated eight patients with refractory ovarian carcinoma with doxorubicin and high-dose intravenous verapamil. No responses were observed, and patients had considerable, but reversible, cardiotoxicity due to verapamil. More recently, Miller *et al.*[22] reported on the use of trifluoperazine, a calmodulin antagonist, combined with doxorubicin in 36 patients with tumors clinically resistant to the anthracycline. There were no responses in 15 patients with intrinsic resistance, but seven responses occurred in 21 patients with acquired resistance to the anthracycline.

In these studies[20-22] patients with resistant disease were treated with a single chemotherapeutic agent, in standard dose, combined with a single RM in high doses. The clinical efficacy was measured by the occurrence of otherwise unexpected tumor responses. By contrast, we investigated the combination of chemotherapy and RM in the initial treatment of patients with chemosensitive tumors who later develop resistant disease. Our results indicate that this therapeutic approach is feasible as the initial outpatient treatment of extensive SCLC patients; it is not associated with unexpected toxicity and the survival results are encouraging. Higher doses of tamoxifen will induce a more complete reversal of MDR,[17-19] and we have suggestive evidence that these higher doses also increase clinical response and toxicity. Controlled clinical trials will be needed to establish the degree to which the addition of RM modulate the effects of chemotherapy on both tumors and normal tissues. At present we would suggest further investigating our Level 2 doses of RM or possibly escalating further the dose of tamoxifen.

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41. Unpublished observations. Data available on request from A. Figueredo.