Cancer Chemother Pharmacol (1999) 44: 461–468

ORIGINAL ARTICLE

Steven M. Grunberg · John Crowley
Kenneth R. Hande · Dori Giroux · Nikhil Munshi
Derick H.M. Lau · Louis E. Schroder
Mark H. Zangmeister · Stanley P. Balcerzak
Harry E. Hynes · David R. Gandara

Treatment of poor-prognosis extensive disease small-cell lung cancer with an all-oral regimen of etoposide and cyclophosphamide – a Southwest Oncology Group clinical and pharmacokinetic study

Received: 27 October 1998 / Accepted: 3 May 1999

Abstract *Purpose*: An all-oral regimen of etoposide and cyclophosphamide was developed for use in poor-prognosis extensive disease small-cell lung cancer. Limited pharmacokinetic sampling was used to derive a pharmacodynamic model predictive of myelosuppression early in the course of therapy. *Patients and methods*: Eligible patients were chemotherapy-naive and had extensive disease small-cell lung cancer with either SWOG performance status 2 or serum albumin <3.5 g/dl. The first cohort ($n = 18$) received etoposide orally at 50 mg daily and cyclophosphamide orally at 50 mg daily days 1–14 every 28 days. Due to good hematologic tolerance, the second cohort ($n = 39$) received both agents orally at 50 mg twice daily days 1–14 every 28 days. Plasma etoposide levels were determined in samples drawn at baseline, and at 1 h, 2 h, and 23.5 h (trough) after the first dose. Linear regression analysis was used to determine pharmacokinetic and demographic parameters predictive of myelosuppression. *Results*: A total of 173 treatment cycles were delivered. Patients on the daily regimen had a 22% response rate (complete and partial), a 22% unconfirmed response rate, and a 5-month median survival, while patients on the twice-daily regimen had a 28% response rate (complete and partial), a 13% unconfirmed response rate, and a 7-month median survival. Granulocytopenia and alopecia were the most common toxicities seen. Significant granulocytopenia could be predicted for the twice-daily regimen according to the formula $\ln(\text{AGC nadir}) = 7.80 - 1.88(\text{trough})$, with an increased incidence of granulocytopenia if the etoposide trough value was ≥ 1.49 μg/ml. *Conclusion*: Oral etoposide and oral cyclophosphamide given days 1–14 every 28 days is well tolerated and results in an acceptable response rate and median survival in poor-prognosis (poor performance status or low serum albumin) extensive disease small-cell lung cancer. A trough etoposide level obtained within 24 h of starting therapy can predict severe granulocytopenia.

Key words Etoposide · Cyclophosphamide · Oral chemotherapy · Pharmacodynamics · Small-cell lung cancer

This investigation was supported in part by the following PHS Cooperative Agreement grant numbers awarded by the National Cancer Institute, DHHS: 1P30CA68485, CA38926, CA32102, CA37981, CA46441, CA35261, CA04920, CA35431. Supported in part by a VA Merit Review research grant, and by a grant from Bristol Laboratories.

Presented in part at the Eighth World Conference on Lung Cancer in Dublin, Ireland, in August 1997.

S.M. Grunberg (✉)[1]
University of Vermont, Burlington, VT, USA

J. Crowley · D. Giroux
Southwest Oncology Group Statistical Center, Seattle, WA, USA

K.R. Hande
Vanderbilt University, Nashville, TN, USA

N. Munshi
University of Arkansas for Medical Science, Little Rock, AR, USA

D.H.M. Lau · D.R. Gandara
University of California at Davis, Sacramento, CA, USA

L.E. Schroder
University of Cincinnati Medical Center, Cincinnati, OH, USA

M.H. Zangmeister
Columbus CCOP, Columbus, OH, USA

S.P. Balcerzak
Ohio State University Health Center, Columbus, OH, USA

H.E. Hynes
Wichita CCOP, Wichita, KS, USA

Contact address:
[1] Fletcher Allen Health Care,
111 Colchester Avenue – Patrick 534,
Burlington, VT 05401, USA
Tel.: +1-802-656-3827, Fax: +1-802-656-5946

Introduction

Recent trends in chemotherapeutic treatment have been influenced both by the traditional goals of increasing response rate and length of survival and by the parallel

goals of maintaining quality of life and maximizing patient time in the outpatient setting, particularly in the treatment of diseases for which cure may be rare. These trends are exemplified by the management of extensive disease small-cell lung cancer. The response rate of this disease to numerous chemotherapeutic agents remains quite high although cure is rarely achieved [2]. However, both comorbid (smoking-related) conditions and decreased performance status due to the disease itself may limit the intensity of treatment that can be delivered. Extended oral administration of chemotherapy would therefore appear to be a reasonable strategy for delivering maximum therapy at tolerable intensity in the outpatient setting.

Several agents with activity against small-cell lung cancer can indeed be administered by the oral route. Oral etoposide has been shown to have significant single-agent activity against small-cell lung cancer even in debilitated patients [14]. The schedule dependence of etoposide [29] and the inverse relationship between oral dose and bioavailability [11] suggest that an extended low-dose oral regimen may even be the preferable method of administration. Cyclophosphamide is another agent with activity against small-cell lung cancer for which significant experience in administration of extended oral courses exists [1]. Use of these two agents as a chemotherapeutic doublet has been attempted in several different tumor types both in vitro and in vivo.

Dombernowsky and Nissen [5] investigated etoposide and cyclophosphamide as one of a series of etoposide-based doublets evaluated for the treatment of murine L1210 leukemia. In this study etoposide and cyclophosphamide were administered by the intraperitoneal route, and increases in both rate of survival and number of cures were noted. Estapé et al. [6–9] performed a series of clinical studies in lung cancer and breast cancer using a combination of intravenous cyclophosphamide and oral etoposide. In two separate studies in lung cancer [6, 8], an overall response rate of 50% in 38 patients with non-small-cell lung cancer and 72% in 22 patients with small-cell lung cancer was noted. Treatment of 27 patients with metastatic breast cancer resulted in a response rate of 41% [7], with a response rate of 50% being seen in 16 additional patients with hepatic metastases from breast cancer [9]. Finally, a combination of oral cyclophosphamide 100 mg per day and oral etoposide 50 mg per day given for 14 days of a 28-day cycle was used by Maulard-Durdux et al. [16] in the treatment of 20 patients with hormone-refractory prostate cancer. Improvement in performance status was seen in 26% of patients, relief of bone pain in 71% of patients, and a 50% decrease in prostate-specific antigen in 35% of patients.

One potential advantage of an extended oral regimen is the ability to modify the duration of therapy during a course of treatment to maximize efficacy while maintaining a tolerable level of toxicity. However, if such dose adjustments are to be made in a prospective manner, a method to predict significant toxicity from data points obtained early in each therapy cycle must be devised. If the convenience of the outpatient regimen is to be maintained, then these data points must be available without extensive sample collection or an extended hospital stay.

We have previously investigated [10] a combination of oral etoposide and oral cyclophosphamide for the treatment of advanced non-small-cell lung cancer and found this regimen to be well tolerated. In the present study, the feasibility, efficacy and toxicity of a similar regimen in a series of patients with poor prognosis (serum albumin < 3.5 g/dl or SWOG performance status 2) extensive disease small-cell lung cancer were investigated. In addition, a limited pharmacokinetic sampling strategy was used to determine whether a predictive model based on etoposide levels obtained during the first 24 h of treatment could be devised for this regimen in this patient population.

Materials and methods

Eligibility criteria

Patients eligible for this study were required to have poor prognosis extensive disease small-cell lung cancer confirmed by histologic or cytologic examination. Extensive disease was defined as the presence of detectable tumor beyond a single hemithorax including mediastinal, hilar or supraclavicular lymphadenopathy or ipsilateral malignant pleural effusion. Poor prognosis patients were defined as those with serum albumin < 3.5 g/dl or SWOG performance status 2. These patients therefore had serum albumin or performance status insufficient for entry into more aggressive SWOG small-cell lung cancer studies. Patients could not have immediately life-threatening complications of malignancy, superior vena cava syndrome, or clinically significant postobstructive pneumonia, and could not have received prior radiotherapy, chemotherapy, hormonal or biologic therapy for this malignancy. Prior surgery was permitted if patients had fully recovered. Measurable or evaluable disease was required. Patients could receive simultaneous cranial radiotherapy if brain metastases were present at diagnosis or palliative radiotherapy for specific painful sites. However, concurrently irradiated areas could not be considered measurable or evaluable sites.

Patients were required to have adequate hematologic reserve (absolute granulocyte count $\geq 1{,}500/\mu l$ and platelet count not less than the institutional lower limit of normal), renal reserve (serum creatinine not more than 1.5 times the institutional upper limit of normal or measured or calculated creatinine clearance > 45 ml/min), and hepatic reserve (bilirubin less than the institutional upper limit of normal and SGOT less than 2.5 times the institutional upper limit of normal). However, SGOT could be up to four times the institutional upper limit of normal if hepatic involvement by tumor had been documented. Patients were ineligible who had had another malignancy within the previous 5 years except for adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer. Pregnant or nursing women could not participate, and women and men of reproductive potential were required to agree to use an effective contraceptive method. All patients were informed of the investigational nature of the study and signed an Informed Consent Form in accordance with institutional and federal guidelines. The protocol was approved by the National Cancer Institute and by the institutional review boards of all participating institutions.

Administration of chemotherapy

The initial study schema specified a treatment plan of oral cyclophosphamide 50 mg daily and oral etoposide 50 mg daily days 1–14 every 28 days. However due to good hematologic tolerance by the first 18 patients, the protocol was amended to increase the doses to cyclophosphamide 50 mg orally twice daily and etoposide 50 mg orally twice daily days 1–14 every 28 days. Chemotherapy could be discontinued after six cycles for patients with a complete response, a stable partial response or stable disease. Patients who were still improving after six cycles of therapy could have chemotherapy continued until a complete or stable partial response was achieved. Patients who demonstrated progressive disease had chemotherapy discontinued. Radiotherapy was allowed for palliation of painful metastases or for treatment of brain metastases at the time of presentation. Prophylactic cranial radiation was also urged for patients achieving complete response after 6 months of chemotherapy.

A new cycle of chemotherapy could not begin until the absolute granulocyte count had recovered to at least 1500/μl and platelet count to at least 100,000/μl. Dose escalation from the daily to the twice-daily regimen was allowed if the granulocyte nadir was 1500/μl or greater and the platelet nadir was 100,000/μl or greater. Dose de-escalation from the twice-daily to the daily regimen was allowed if grade 3 or 4 hematologic or nonhematologic toxicity was noted. Granulocyte colony-stimulating factor could be used for patients who developed grade 4 neutropenia or neutropenic fever on the daily regimen but could not be used prophylactically during the initial cycle.

Definitions of response

Complete response was defined as complete disappearance of all measurable and evaluable disease with the appearance of no new lesions. Partial response of measurable disease was defined as at least 50% decrease under baseline of the sum of the products of perpendicular diameters of all measurable lesions with the appearance of no new lesions. Partial response for nonmeasurable disease was defined as greater than 50% decrease in the estimated area of evaluable tumor as agreed upon by two independent observers. Progressive disease was defined as a 50% increase or an increase of 10 cm^2 (whichever was smaller) in the sum of the products of all measurable lesions over the smallest sum observed, or clear worsening of evaluable disease, or reappearance of lesions that had disappeared, or appearance of any new lesions, or failure to return for evaluation due to death or deteriorating clinical condition (unless clearly unrelated to this cancer). Stable disease was defined as disease that did not meet the criteria for complete response, partial response or progressive disease. Complete or partial response required documentation of response by repetition of all baseline X-ray evaluations and scans on at least two separate occasions (approximately 3–4 weeks apart). If all scans were not repeated or if response could not be confirmed, the patient was considered to have an unconfirmed response.

Etoposide pharmacokinetic measurements

Peak etoposide concentrations occur 1–2 h following oral administration of the drug [11, 12, 32]. In an attempt to identify peak and trough etoposide concentrations, plasma samples were therefore drawn during cycle 1 prior to administration of the first oral dose of etoposide and 1, 2 and 23.5 h following administration of the first oral dose of etoposide. Patients on the daily schedule received day 1 chemotherapy at hour zero and day 2 chemotherapy at hour 24 (after the trough sample had been taken). Patients on the twice-daily schedule received day 1 chemotherapy at hour zero and hour 12 and day 2 chemotherapy at hour 24 (after the trough sample had been taken). Heparinized blood samples (7 ml) were centrifuged within 1 h of collection and the plasma frozen and shipped on dry ice to the reference laboratory.

Plasma samples (50 μl) spiked with teniposide as an internal standard were extracted with 5 ml of an ethyl acetate/dichloromethane (3:2) solution. The organic layer was removed, dried and reconstituted in 70 μl 0.01 *M* sodium acetate/acetonitrile/methanol solution (57:14:29), and 40 μl was used for HPLC analysis. Etoposide was assayed using reverse-phase HPLC on a Zorbox-18 Column at 37 °C with a methanol/acetonitrile/water/acetic acid (30:14:53:3) mobile phase at a flow rate of 1 ml/min. The ultraviolet absorbance (235 nm) of the eluate was monitored using a Hitachi K-42 detector. This assay was sensitive to etoposide concentrations of 0.01 μg/ml and linear over a range of 0.01–10 μg/ml (correlation coefficients of 0.997 or better were obtained for all assays). Inter- and intraassay coefficients of variation were less than 12% for quality control throughout the assay curve.

Pharmacodynamic and statistical analysis

Simple and multiple linear regression analysis with forward stepwise variable selection was used to determine whether predictive models for absolute granulocyte count nadir or platelet nadir based on information available early in the course of therapy could be derived. Potential predictive factors included baseline hemoglobin, radiotherapy, lactic dehydrogenase, gender, performance status, serum albumin, and etoposide levels. Simple linear regression models using trough etoposide levels to predict log granulocyte count nadir and log platelet nadir, respectively, were then used to derive the trough level that predicted severe nadirs. Survival was estimated using the product-limit method [15].

Results

Patient characteristics

A total of 65 patients were registered to this study by 30 Southwest Oncology Group institutions (median 1.5 patients, range 1–6 patients). Of these 65 patients, 57 were considered eligible and analyzable (Table 1). The eight remaining patients included four with SWOG performance status 1 and albumin >3.5 g/dl, one with limited disease small-cell lung cancer, one with non-

Table 1 Patient demographics

	Daily arm (n = 18)	Twice-daily arm (n = 39)
Age (years)		
Median	68.5	68
Range	50–94	46–81
Gender		
Male	13 (72%)	22 (56%)
Female	5 (28%)	17 (44%)
Race		
White	14 (78%)	35 (90%)
Black	1 (6%)	4 (10%)
Hispanic	1 (6%)	0 (0%)
Asian/Pacific	2 (11%)	0 (0%)
Performance status		
0	0 (0%)	1 (3%)
1	4 (22%)	6 (15%)
2	14 (78%)	32 (82%)
Serum albumin (g/dl)		
<3.5	4 (22%)	16 (41%)
≥3.5	14 (78%)	23 (59%)

small-cell lung cancer, one with inadequate staging to determine disease extent, and one who did not receive protocol therapy. The 57 eligible and analyzable patients included 18 of the 21 patients registered to the daily arm and 39 of the 44 patients registered to the twice-daily arm. Patients in both arms were predominantly male and Caucasian with a median age of approximately 68 years. More patients in the twice-daily arm had an elevated LDH (72% versus 50%) and multiple metastases (31% versus 11%). While approximately 80% of patients in both arms were eligible for the study due to poor performance status (performance status 2), eligibility was also established by hypoalbuminemia in 22% of patients in the daily arm and 41% of patients in the twice-daily arm. In the daily arm 6% of patients and in the twice-daily arm 28% of patients had both poor performance status and hypoalbuminemia. No patient in either arm had previously required transfusion.

Treatment and response

Treatment was well tolerated in both arms. In the daily arm, a total of 41 cycles of therapy were delivered with a median of 2 cycles per patient (ranges 0–6 cycles). In the twice-daily arm 132 cycles of treatment were delivered with a median of 3 cycles per patient (range 0–8 cycles). Dose adjustment between the daily and twice-daily regimens was allowed on later cycles based on hematologic and nonhematologic toxicity. Of the 41 cycles delivered to patients entered on the daily regimen, 18 cycles (44%) were escalated to the twice-daily regimen while dose de-escalation to the daily regimen was required in 31 cycles (23%) delivered to patients initially entered on the twice-daily regimen. Only five patients (all in the twice-daily arm) discontinued therapy due to toxicity.

Objective response was commonly noted in both arms of the study (Table 2). Complete or partial response was achieved by 22% of the patients and unconfirmed response was achieved by 22% of the patients entered on the daily regimen. Complete or partial response was achieved by 28% of the patients and unconfirmed response was achieved by 13% of the patients entered on the twice-daily regimen. Survival was slightly longer for patients on the twice-daily regimen. Median failure-free survival was 3 months for the daily regimen and 4 months for the twice-daily regimen while overall survival was 5 months for the daily regimen and 7 months for the twice-daily regimen.

Table 2 Response rates and survival

	Daily arm (n = 18)	Twice-daily arm (n = 39)
Complete response	0 (0%)	2 (5%)
Partial response	4 (22%)	9 (23%)
Unconfirmed response	4 (22%)	5 (13%)
Stable disease	0 (0%)	2 (5%)
Progression or early death	7 (39%)	14 (36%)
Inadequate assessment	3 (17%)	7 (18%)
Median survival (months)		
Failure-free	3	4
Overall	5	7

Adverse reactions

The most common severe adverse reactions (categories in which more than one patient in at least one arm had at least grade 3 toxicity) are listed in Table 3. Alopecia and myelosuppression were the most prominent toxicities seen. However, complete alopecia was considered to be only a grade 2 toxicity. Evaluating the worst toxicity (grade 3 or greater) seen in each patient in all cycles, severe granulocytopenia was seen in 8 patients (44%) on the daily arm and 25 patients (64%) on the twice-daily arm. Severe anemia was seen in two patients (11%) on the QD arm and 8 patients (21%) on the BID arm. Severe thrombocytopenia was not seen on the QD arm but was seen in 5 patients (13%) on the BID arm. Severe respiratory infection was seen in three patients (17%) on the daily arm and five patients (13%) on the twice-daily

Table 3 Common severe adverse reactions (all cycles)

	Daily arm (n = 18)			Twice-daily arm (n = 39)		
	Grade			Grade		
	3	4	5	3	4	5
Anemia	1	1	0	8	0	0
Granulocytopenia	3	5	0	10	15	0
Hypotension	3	0	0	1	0	0
Infection (other)	0	0	1	5	0	1
Leukopenia	6	3	0	10	11	0
Lymphopenia	0	0	0	1	1	0
Nausea	2	0	0	3	0	0
Respiratory infection	2	0	1	4	0	1
Thrombocytopenia	0	0	0	1	4	0
Visual disturbance	0	0	0	2	0	0
Vomiting	2	0	0	1	0	0
Weakness	2	0	0	0	0	0
Weight loss	1	0	0	4	0	0

arm. Other severe infections were seen in one patient (6%) on the daily arm and six patients (15%) on the twice-daily arm, although two patients had both a severe respiratory and other severe infections.

Since potential correlations between etoposide levels and myelosuppression during the first cycle of chemotherapy were being explored, particular attention was paid to hematologic toxicity during the first cycle. On the daily arm one patient (6%) had an absolute granulocyte nadir less than 1000/μl on the first cycle and two patients (11%) had a platelet nadir less than 100,000/μl on the first cycle. Neither of these patients had a platelet nadir of less than 50,000/μl. Myelosuppression was more notable on the twice-daily regimen. Fifteen patients (48%) had an absolute granulocyte nadir less than 1000/μl and five patients (16%) had a platelet nadir less than 100,000/μl. However, only one of these five patients had a platelet nadir less than 50,000/μl.

Etoposide pharmacokinetics and correlations

Etoposide levels were measured at baseline, and 1 h, 2 h, and 23.5 h after the first dose of etoposide (Table 4). Baseline levels were undetectable in 47 of the 55 patients from whom plasma samples were obtained and minimally detectable (below the limits of reliable detection) in four more patients. The four patients with detectable baseline etoposide levels may represent sampling error. Levels at 1 h and 2 h, which reflected only the first dose of etoposide, were similar in both arms. Trough levels samples were drawn at 23.5 h, immediately before the day 2 etoposide doses. Trough levels therefore also reflected the dose of etoposide administered at hour 12 in the twice-daily arm and were higher in patients treated on the twice-daily regimen.

Correlative analyses were performed in patients for whom clinical and pharmacokinetic data were available. Of the 18 patients treated on the daily regimen, analyses could be performed on 17 patients for granulocytopenia and 18 patients for thrombocytopenia. Of the 39 patients treated on the twice-daily regimen, analyses could be performed on 28 patients for granulocytopenia and 30 patients for thrombocytopenia.

Simple and multiple linear regression analyses were used to examine the effects of etoposide levels and descriptive demographic parameters on the natural logarithm of granulocyte and platelet nadirs (natural logarithm transformation provided a more Gaussian distribution) (Table 5). No significant correlation between hematologic nadirs and either demographic parameters or etoposide levels was seen for patients receiving the daily regimen. For the twice-daily regimen there was a marked correlation between the etoposide trough level and granulocytopenia with a weak correlation noted between lactic dehydrogenase and granulocytopenia. Prior radiotherapy did appear to be predictive for thrombocytopenia in the daily regimen. However, this relationship was not maintained in the twice-daily regimen. In the twice-daily regimen, etoposide trough level was significantly correlated with thrombocytopenia with a weaker correlation being suggested for lactic dehydrogenase. When multiple linear regression was performed for granulocytopenia in the twice-daily regimen, etoposide trough level was the only variable selected by forward stepwise analysis. When multiple linear regression was performed for thrombocytopenia in the twice-daily regimen, etoposide trough level was again the first variable selected by forward stepwise analysis with baseline hemoglobin as the second variable to enter the model.

It is therefore possible to derive predictive models for both granulocytopenia [ln(AGC nadir) = 7.80 − 1.88(trough)] and thrombocytopenia [ln(PLT nadir) = 12.60 − 0.55(trough)] in patients receiving the twice-daily regimen using the day 2 etoposide level (trough) as the only predictive variable (Table 6). An etoposide trough level ≥1.49 μg/ml was found to be associated with a granulocyte nadir less than 500/μl with 2 of 4 patients (50%) above this level but only 7 of 24 patients (29%) below this level developing granulocytopenia. In addition an etoposide trough level ≥1.98 μg/ml was found to be associated with a platelet nadir less than

Table 4 Plasma etoposide levels (μg/ml)

	Daily arm	Twice-daily arm
Baseline	0.26 ± 0.90	0.12 ± 0.46
1 h	1.90 ± 1.64	1.35 ± 1.04
2 h	1.75 ± 1.24	1.63 ± 1.07
23.5 h	0.66 ± 0.99	0.85 ± 0.56

Table 5 Univariate analysis for myelosuppression (*P*-values)

	Granulocytopenia		Thrombocytopenia	
	Daily arm	Twice-daily arm	Daily arm	Twice-daily arm
Etoposide level (trough)	0.86	0.007	0.18	0.002
Etoposide level (1 h)	0.40	0.75	0.062	0.63
Etoposide level (2 h)	0.77	0.30	0.076	0.45
Gender	0.44	0.76	0.076	0.75
Performance status	0.79	0.87	0.39	0.99
Serum albumin	0.95	0.70	0.22	0.69
Lactic dehydrogenase	0.98	0.037	0.20	0.049
Hemoglobin	0.45	0.88	0.53	0.12
Radiotherapy	0.98	0.97	0.006	0.49

Table 6 Parameter estimation [ln(blood count) = X + Y(trough)]

	X	SE(X)	Y	SE(Y)	R^2	*P*-value
Daily arm						
AGC nadir	8.06	0.22	0.04	0.25	0.002	0.86
PLT nadir	12.05	0.14	0.17	0.12	0.11	0.18
Twice-daily arm						
AGC nadir	7.80	0.66	−1.88	0.64	0.25	0.007
PLT nadir	12.60	0.16	−0.55	0.16	0.30	0.002

100,000/μl with 1 of 2 patients (50%) above this level but only 4 of 28 patients (14%) below this level developing mild thrombocytopenia. However, the small number of patients with platelet nadirs in this range (and the absence of patients with clinically significant thrombocytopenia using even the twice-daily regimen) limits the usefulness of the predictive model for thrombocytopenia.

Discussion

Both the feasibility and activity of treatment with a regimen of oral etoposide and oral cyclophosphamide in poor-prognosis extensive disease small-cell lung cancer have been demonstrated in this study. The response rate of approximately 45% (including unconfirmed responses) noted in both arms of the study is less than that reported for oral etoposide alone in small-cell lung cancer [3] and the duration of survival was limited. However, in the present study a particularly debilitated (poor-prognosis) population was chosen for first-line treatment. Advanced age has previously been used as a surrogate for debility and poor prognosis [3], but the validity of this surrogate is limited by the fact that baseline health status of an elderly population can be extremely variable. The present study used defined criteria for poor prognosis (low albumin or poor performance status) to identify a patient population at maximum risk for rapid deterioration due to either small-cell lung cancer or comorbid disease. Nevertheless, response was achieved in almost half of the patients without an excessive qualitative or quantitative increase in morbidity. In fact, tolerance of this regimen was sufficient to allow modification of the study schema from the original low dose-schedule (50 mg orally daily) to a full-dose schedule (50 mg orally twice-daily) comparable to that used in our previous study of non-small-cell lung cancer [10] which did not select for a poor-prognosis population. Although an increased level of myelosuppression was seen with the full-dose regimen, myelosuppression was still not excessive and did not prevent continuation of therapy. Overall, duration of therapy was equivalent between the two arms.

A simple model to predict severe granulocytopenia based on a single etoposide level taken 24 h after the first dose of oral etoposide was also successfully derived for the twice-daily regimen. Use of a single trough etoposide level minimizes patient inconvenience while the ability to predict granulocytopenia based on data collected by the second day of therapy could potentially allow adjustment of the duration of a planned 14-day course of oral therapy during the concurrent cycle. However, the positive and negative predictive power of this model are limited, and the value of the model as a patient management tool will need to be prospectively validated.

Several attempts have previously been made to derive predictive models for neutropenia using chemotherapeutic regimens based on extended intravenous administration of etoposide (Table 7). Ratain et al. [26] administered etoposide by intravenous infusion and found that neutropenia could be predicted according to a model that included steady-state concentration of etoposide, serum albumin, performance status, and prior transfusion requirement. Transfusion requirement was considered to be a surrogate for poor hematologic reserve while albumin levels were considered to be significant due to the high level of protein binding of etoposide. Joel et al. [13], examining factors that influenced toxicity of etoposide in an intravenous regimen, have identified serum albumin, performance status, age, and creatinine clearance as significant factors. Minami et al. [24] derived a model for predicting leukopenia after a 14-day etoposide infusion that utilizes a single

Table 7 Predictive factors for myelosuppression during etoposide administration (*IV* intravenous, *IVCI* intravenous continuous infusion, *PO* oral, *AGC* absolute granulocyte count, *HGB* hemoglobin, *PLT* platelet, *WBC* white blood cell count, C_{ss} steady state, C_0 trough level before dose, $C_2/C_4/C_6/C_8/C_{24}$ level 2/4/6/8/24 h after dose, C_{192} level 192 h after start of infusion, *AUC* exposure area under the curve, *NS* not specified)

Reference	Etoposide administration route	Other chemotherapy	Parameters predicted	Etoposide level	Serum albumin	Performance status	Other
26	IVCI	–	WBC	C_{ss}	+	+	Transfusion
13	IV	–	WBC, AGC	AUC	+	+	Age, creatinine clearance
24	IVCI	–	WBC	C_{192}	+	–	Total bilirubin, prior treatment
19	IV	Cisplatin	WBC, AGC, PLT	C_2, C_4	–	–	–
27	IVCI	–	–	–	–	–	–
25	PO	Carboplatin	WBC, AGC, PLT	C_0, C_8, C_{24}	–	–	–
22	PO	–	AGC	C_4, C_6	NS	NS	–
23	PO	Cisplatin	WBC	C_0, C_2	–	NS	–
20	PO	Cisplatin	WBC, AGC, PLT, HGB	C_0	–	–	–
18	PO	Cisplatin	WBC, AGC	C_0	–	–	–
28	PO	–	AGC	C_0	–	–	–
32	PO	–	AGC	C_0	–	–	–
Present study	PO	Cyclophosphamide	AGC, PLT	C_0	–	–	–

etoposide level, serum albumin, total bilirubin, and prior treatment status. However, Miller et al. [19], using a regimen of intravenous etoposide and cisplatin, found that prediction of granulocytopenia and thrombocytopenia requires only peak etoposide levels taken 2 h and 4 h after administration of etoposide and is not dependent upon serum albumin or performance status. By contrast, Robert et al. [27] examined a regimen of etoposide by intravenous continuous infusion and found that none of the above variables effectively predicts myelosuppression.

Attempts to derive predictive models for regimens based on extended oral administration of etoposide have yielded more consistent results. Ohune et al. [25], Millward et al. [22] and Minami et al. [23] all found that leukopenia can be predicted using models derived from multiple peak etoposide levels obtained several hours after administration of oral etoposide. None of these models depends upon serum albumin or performance status. Miller and Tolley [18], Miller et al. [20], Sessa et al. [28], and Zucchetti et al. [32] have identified models similar to ours in which granulocytopenia can be predicted using a single trough etoposide level without inclusion of peak etoposide levels, serum albumin, or performance status. Although serum albumin levels achieved borderline significance in some of our linear regression analyses, it would appear that the effect of this parameter on granulocytopenia produced by an oral etoposide regimen is far overshadowed by the predictive value of the etoposide trough level itself. However, Miller et al. [21] have cautioned that a model highly predictive of population pharmacodynamics may still not have the precision or accuracy necessary for individual dose adjustment.

Miller et al. [20] and Ohune et al. [25] found plasma etoposide levels to be predictive of thrombocytopenia without a confounding effect of performance status. This is consistent with our own results in which a predictive model for thrombocytopenia based upon trough etoposide level could be derived. However, only mild thrombocytopenia was predicted even when a very high trough etoposide level was noted. Since severe thrombocytopenia is not a major problem with this regimen, use of a predictive model for thrombocytopenia may have limited clinical value.

The value of regimens based upon oral etoposide alone in poor-prognosis small-cell lung cancer has recently been questioned. Souhami et al. [30] and the UK Medical Research Council [17] reported studies in which small-cell lung cancer patients were randomized between oral etoposide and standard intravenous infusion chemotherapy. Both studies showed a better response rate and survival in the combination chemotherapy arms. Souhami et al. [30] also reported less tumor-related toxicity but noted increased chemotherapy-related toxicity (particularly nausea and vomiting) with combination chemotherapy. The importance to patients of chemotherapy-related toxicities, such as nausea and vomiting, should not be underestimated. Coates et al. [4] demonstrated that nausea and vomiting are indeed the two toxicities of chemotherapy most feared by patients. Of interest, Tebbutt et al. [31] reported a comparative review of tolerance of small-cell lung cancer chemotherapy in elderly and younger patients. Although similar levels of toxicity were observed in both groups, elderly patients were more likely to have reduction in dose or reduction in number of cycles. Even an expectation of greater chemotherapy-related toxicity may therefore be a determining factor in successful administration of chemotherapy in poor prognosis or fragile patient populations.

Studies using single-agent oral etoposide for small-cell lung cancer are not strictly comparable to the present study in which combination oral chemotherapy was used. As additional oral chemotherapeutic agents with significant activity against small-cell lung cancer are developed, numerous combination oral chemotherapy regimens will become possible. If use of the plasma etoposide concentration obtained early in each course of therapy can be shown to allow optimal dose adjustment to prevent toxicity, then the goals of maximizing patient response and dose intensity while minimizing severe drug-related toxicity during treatment of extensive disease small-cell lung cancer may be realized.

References

1. Bonadonna G, Brusamolino E, Valagussa P, Rossi A, Brugnatelli L, Brambilla C, DeLena M, Tancini G, Bajetta E, Musumeci R, Veronesi U (1976) Combination chemotherapy as an adjuvant treatment in operable breast cancer. N Engl J Med 294: 405
2. Bunn PA Jr, Carney DN (1997) Overview of chemotherapy for small cell lung cancer. Semin Oncol 24 [Suppl 7]: 69
3. Carney DN, Grogan L, Smith EF, Harford P, Berendsen HH, Postmus PE (1990) Single agent oral etoposide for elderly small cell lung cancer patients. Semin Oncol 17 [Suppl 2]: 49
4. Coates A, Abraham S, Kaye SB, Sowerbutts T, Frewin C, Fox RM, Tattersall MHN (1983) On the receiving end – patient perception of the side-effects of cancer chemotherapy. Eur J Cancer Clin Oncol 19: 203
5. Dombernowsky P, Nissen NI (1976) Combination chemotherapy with 4′demethylepipodophyllotoxin 9-(4,6-O-ethylidene-β-D-glucopyranoside), VP 16-213 (NSC 141540) in L1210 leukemia. Eur J Cancer 12: 181
6. Estapé J, Millá A, Agusti A, Sanchez-Lloret J, Palacin A, Soriano E (1979) VP 16-213 (VP 16) and cyclophosphamide in the treatment of primitive lung cancer in phase M1. Cancer 43: 72
7. Estapé J, Cirera L, Millá A, Doncel F (1983) VP 16-213 and cyclophosphamide in advanced breast cancer. Cancer Chemother Pharmacol 10: 154
8. Estapé J, Millá A, Agusti A, Sanchez-Lloret J, Santabarbara P, Rozman C (1983) VP-16 plus cyclophosphamide in the treatment of advanced lung cancer. Cancer 51: 385
9. Estapé J, Daniels M, Viñolas N, Santabarbara P, Grau JJ, Gardella S (1990) Combination chemotherapy with oral etoposide plus intravenous cyclophosphamide in liver metastases of breast cancer. Am J Clin Oncol 13: 98
10. Grunberg SM, Crowley J, Livingston R, Gill I, Williamson SK, O'Rourke T, Braun T, Marshall ME, Weick JK, Balcerzak SP, Martino RL (1993) Extended administration of oral etoposide and oral cyclophosphamide for the treatment of advanced non-

small-cell lung cancer: a Southwest Oncology Group study. J Clin Oncol 11: 1598
11. Hande KR, Krozely MG, Greco FA, Hainsworth JD, Johnson DH (1993) Bioavailablity of low-dose oral etoposide. J Clin Oncol 11: 374
12. Joel SP, Clark PI, Heap L, Webster L, Robbins S, Craft H, Slevin ML (1995) Pharmacological attempts to improve the bioavailability of oral etoposide. Cancer Chemother Pharmacol 37: 125
13. Joel SP, Shah R, Clark RI, Slevin ML (1996) Predicting etoposide toxicity: relationship to organ function and protein binding. J Clin Oncol 14: 257
14. Johnson DH, Greco FA, Strupp J, Hande KR, Hainsworth JD (1990) Prolonged administration of oral etoposide in patients with relapsed or refractory small-cell lung cancer: a phase II trial. J Clin Oncol 8: 1613
15. Kaplan EL, Meier P (1958) Nonparametric estimation from incomplete observations. J Am Stat Assoc 53: 457
16. Maulard-Durdux C, Dufour B, Hennequin C. Chrétien Y, Delanian S, Housset M (1996) Phase II study of the oral cyclophosphamide and oral etoposide combination in hormone-refractory prostate carcinoma patients. Cancer 77: 1144
17. Medical Research Council Lung Cancer Working Party (1996) Comparison of oral etoposide and standard intravenous multidrug chemotherapy for small cell lung cancer: a stopped multicentre randomised trial. Lancet 348: 563
18. Miller AA, Tolley EA (1994) Predictive performance of a pharmacodynamic model for oral etoposide. Cancer Res 54: 2080
19. Miller AA, Tolley EA, Niell HB, Stewart CF, Griffin JP (1992) Pharmacodynamics of three daily infusions of etoposide in patients with extensive-stage small-cell lung cancer. Cancer Chemother Pharmacol 31: 161
20. Miller AA, Tolley EA, Niell HB, Griffin JP, Mauer AM (1993) Pharmacodynamics of prolonged oral etoposide in patients with advanced non-small-cell lung cancer. J Clin Oncol 11: 1179
21. Miller AA, Tolley EA, Niell HB (1998) Therapeutic drug monitoring of 21-day oral etoposide in patients with advanced non-small cell lung cancer. Clin Cancer Res 4: 1705
22. Millward MJ, Newell DR, Yuen K, Matthews JP, Balmanno K, Charlton CJ, Gumbrell L, Lind MJ, Chapman F, Proctor M, Simmonds D, Cantwell BMJ, Calvert AH (1995) Pharmocokinetics and pharmacodynamics of prolonged oral etoposide in women with metastatic breast cancer. Cancer Chemother Pharmacol 37: 161
23. Minami H, Ando Y, Sakai S, Shimokata K (1995) Clinical and pharmacologic analysis of hyperfractionated daily oral etoposide. J Clin Oncol 13: 191
24. Minami H, Ratain MJ, Ando Y, Shimokata K (1996) Pharmacodynamic modeling of prolonged administration of etoposide. Cancer Chemother Pharmacol 39: 61
25. Ohune T, Fujiwara Y, Sumiyoshi H, Yamoaka N, Tsuya T, Hasegawa K, Yamakido M (1994) Phase I and clinical pharmacological evaluation of daily oral etoposide combined with carboplatin in patients with lung cancer (abstract). Proc Am Soc Clin Oncol 13: 143
26. Ratain MJ, Mick R, Schilsky RL, Vogelzang NJ, Berezin F (1991) Pharmacologically based dosing of etoposide: a means of safely increasing dose intensity. J Clin Oncol 9: 1480
27. Robert F, Chen S, Miller AA, Lee BC, Molthrop DC, Wheeler RH (1996) Phase I and pharmacologic study of 7- and 21-day continuous etoposide infusion in patients with advanced cancer. Cancer Chemother Pharmacol 38: 459
28. Sessa C, Zucchetti M, Torri V, Pagani O, D'Incalci M, Gentili D, Martinelli G, de Jong J, Alerci M, Cavalli F (1993) Chronic oral etoposide in small-cell lung cancer: clinical and pharmacokinetic results. Ann Oncol 4: 553
29. Slevin ML, Clark PI, Joel SP, Malik S, Osborne RJ, Gregory WM, Lowe DG, Reznek RH, Wrigley PFM (1989) A randomized trial to evaluate the effect of schedule on the activity of etoposide in small cell lung cancer. J Clin Oncol 7: 1333
30. Souhami RL, Spiro SG, Rudd RM, de Elvira MR, James LE, Gower NH, Lamont A, Harper PG (1997) Five day oral etoposide treatment for advanced small cell lung cancer: randomized comparison with intravenous chemotherapy. J Natl Cancer Inst 89: 577
31. Tebbut NC, Snyder RD, Burns WI (1997) An analysis of the outcomes of treatment of small cell lung cancer in the elderly. Aust NZ J Med 27: 160
32. Zucchetti M, Pagani O, Torri V, Sessa C, D'Incalci M, DeFusco M, de Jong J, Gentili D, Martinelli G, Tinazzi A, Cavalli F (1995) Clinical pharmacology of chronic oral etoposide in patients with small cell and non-small cell lung cancer. Clin Cancer Res 1: 1517