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Interferon Alpha Plus 13-Cis-Retinoic Acid Modulation of BCL-2 Plus Paclitaxel for Recurrent Small Cell Lung Cancer (SCLC):

An Eastern Cooperative Oncology Group Study (E6501)

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Abstract

Background—Patients with recurrent small cell lung cancer (SCLC) have dismal outcomes. The failure of salvage therapy is due to the possible development of resistance mechanisms, such as the upregulation of the anti-apoptosis protein, Bcl-2. We conducted a phase II study to evaluate if modulation of Bcl-2 with 13-cis-retinoic acid (13-CRA) and interferon alpha could improve response rates when combined with paclitaxel in patients with recurrent SCLC.

Methods—Patients with recurrent SCLC and measurable disease were treated with interferon alpha at 6 million units/m² subcutaneously and 13-CRA 1 mg/kg orally on days 1 and 2 and paclitaxel 75 mg/m² intravenously on day 2 of each week for 6 weeks of an 8 week treatment cycle. Treatment was continued until disease progression, development of unacceptable toxicity, or withdrawal of consent. The primary endpoint was response rate with secondary endpoints of progression free survival (PFS) and overall survival (OS). Bcl-2 levels were assessed in peripheral blood mononuclear cells (PBMCs).

Results—37 patients were enrolled; 34 were included in the intention-to-treat analysis as 3 patients were ineligible for the study. There were 3 partial responses (9%) and 5 patients had stable disease (15%) as best response. The median PFS was 2 months and median OS was 6.2 months. Although mean Bcl-2 protein levels decreased with therapy in PBMCs, there was no association between Bcl-2 levels and response rate or survival.

Conclusion—Despite sound pre-clinical evidence, the addition of 13-CRA and interferon alpha to paclitaxel did not improve outcomes for recurrent SCLC.

Keywords

small cell lung cancer; Bcl-2; 13-cis-retinoic acid; interferon alpha

Introduction

Lung cancer remains the leading cause of cancer-related mortality in the United States, with approximately 160,000 deaths predicted in 2013 (1). While the proportion of patients in the United States with small cell lung cancer (SCLC) decreased to 10–15% of all lung cancer for various reasons (2, 3), SCLC remains a virulent disease with few changes in standard therapy for decades. The initial chemotherapy responsiveness and improved survival fueled early optimism that SCLC could potentially be cured with systemic therapy (4, 5). The two-drug regimen, cisplatin plus etoposide, became the most commonly employed systemic therapy due to its favorable toxicity profile and efficacy in comparison to the older CAV or CAE regimens (6, 7). Although the initial response rates seen with frontline therapy for SCLC is high, with 10–20% complete responses (7), most patients subsequently develop recurrent disease and require salvage therapy. Several agents and older regimens have been used in the relapsed setting, including topotecan, irinotecan, etoposide, and paclitaxel (8–11) as well as combination regimens such as CAV and CAE. Paclitaxel was tested as a single agent in recurrent SCLC and showed 29% partial response rate in 24 patients (11). Once SCLC recurs, outcomes are poor, with median duration of survival of less than 6 months. In addition, the timing of disease recurrence with respect to prior chemotherapy portends response rate to salvage chemotherapy; disease relapse within 90 days of completion of first-line therapy is known as ‘resistant’ disease and is associated with a poor response rate in comparison to those cases that relapse after 90 days, considered ‘sensitive,’ predicting response rates of up to 40% (12).

Considering the rapid development of resistance, a better understanding of the mechanisms of resistance may guide interventional approaches to improve the treatment outcomes seen in salvage and possibly first-line treatment of SCLC. One such approach is to design therapies to overcome inherent tumor resistance. One potential target of resistance is the anti-apoptosis protein, Bcl-2. The Bcl-2 family of proteins is overexpressed in many solid tumors, and expression of Bcl-2 may be involved with the development of chemotherapy resistance (13, 14). Prostate cancers which become resistant to hormonal or chemotherapy have a high Bcl-2 expression (14–17). Bcl-2 is frequently overexpressed in small cell lung cancer cell lines, and upregulation of Bcl-2 is seen in chemoresistant small cell lung cancer cell lines (18–20). Developing strategies to decrease Bcl-2 survival signaling could thus potentially overcome the chemoresistance that inevitably develops in small cell lung cancer.

In vitro studies demonstrated that retinoids such as 13-cis-retinoic acid (CRA) and all-trans-retinoic acid inhibit the growth of Bcl-2 overexpressing cancer cells (21–23). Retinoids decrease the levels of Bcl-2 in acute myeloid leukemia cells and can induce apoptosis of Bcl-2 expressing prostate cancer cells (23). The combination of 13-CRA with interferon alpha reduces Bcl-2 levels, enhances sensitivity to other chemotherapy drugs, and results in greater anti-tumor effect than either agent alone (24–27). Based on these observations, phase

I studies combining paclitaxel with interferon alpha and 13-CRA in prostate cancer and other solid tumors were conducted to define safe doses for the combination (27, 28). These studies also demonstrated downregulation of Bcl-2 in peripheral blood mononuclear cells (PBMCs) and tumor tissue as proof of principle (26, 27). We performed a phase II study to determine the efficacy of the combination of interferon, 13-cis-retinoic acid, and paclitaxel in patients with recurrent small cell lung cancer. We also measured levels of Bcl-2 in PBMCs to assess correlation with outcomes.

Methods

This multi-center study was conducted by the Eastern Cooperative Oncology Group (E6501).

Inclusion criteria

Eligibility included histologically or cytologically confirmed, recurrent SCLC with measurable disease, adequate hematologic, hepatic, and renal function, and an ECOG performance status of 0–3. Exclusion criteria were hypertriglyceridemia, pregnancy or lactation, grade 2 or higher depression, prior exposure to paclitaxel or interferon alpha, use of GM-CSF or G-CSF less than 4 weeks before enrollment, or the use drugs with known incompatibility with either 13-cis-retinoic acid or paclitaxel such as carbamazepine, ethanol, tetracycline, doxycycline, minocycline, Retin A containing compounds, vitamin A, cisplatin, ketoconazole, phenytoin or other anti-epileptic drugs. Patients must not have received either chemotherapy or radiation within 60 days of enrollment on study. All patients signed an informed consent form approved by the local institutional regulatory board.

Study treatment

Interferon alpha was dosed at 6 million units/m² subcutaneously and 13-CRA was dosed at 1 mg/kg orally on days 1 and 2 of each week for 6 weeks. Paclitaxel was administered at a dose of 75 mg/m² intravenously on day 2 of each week for 6 weeks. Each treatment cycle consisted of 8 weeks, which included 2 weeks of rest following the 6 weekly doses. Treatment was continued every 8 weeks until the development of progressive disease, unacceptable toxicity, patient withdrawal, or removal from study when considered in the best interests of the patient.

Assessments

Baseline evaluation included complete history and physical examination, assessment of performance status, CBC and comprehensive metabolic panel, triglycerides, pregnancy test in women of childbearing age, and baseline computed tomography (CT) or magnetic resonance imaging (MRI) within 4 weeks of enrollment. Tumor measurement was assessed at baseline and every 8 weeks after each cycle of therapy until progression. Response was assessed using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0. Toxicity was assessed weekly during treatment with history and physical examination and hematology parameters with metabolic profile and triglycerides assessed every 4 weeks; adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE version 2.0).

Laboratory correlative studies were also performed to identify potential biomarkers associated with treatment response. Bcl-2 and actin (control) levels were assessed on pre-treatment, day one of cycle one prior to treatment, and day two cycle one prior to treatment in peripheral blood monocyte samples by immunoblotting and densitometry as previously described (28). This testing was to determine if the regimen resulted in down-regulation of Bcl-2 and to correlate these levels with response and survival.

Statistical methods

The primary endpoint was objective response; secondary endpoints included overall survival (OS) and progression-free survival (PFS). We utilized a standard Simon 2-stage design. In the initial stage, 34 patients were enrolled. If more than 12 objective responses were observed in the first stage, the trial would move on to the second stage and complete enrollment to total of 76 patients. If more than 31 objective responses were observed in the total cohort, the treatment would be considered effective. In order to allow for 10% ineligibility rate for study and evaluable for response, the study plan included 37 patient accruals in the first stage and 46 in the second stage. This study design had a power of 94% to detect an improvement in response from 33% to 50% with a one-sided type I error rate of 0.10. The probability of stopping early under the null hypothesis was 0.55.

The secondary endpoints, OS and PFS, were estimated by Kaplan-Meier method. PFS was defined as the time from study entry to the date of documented progression or death from any cause, whichever occurred first. OS was defined as the time from date of entry on study to the date of death from any cause. Patients without documented progression or death were censored at the last documented disease evaluation. Ineligible patients were excluded from response and survival analyses but included in toxicity analysis, which reports on all patients who received any protocol therapy. A two-sided 90% exact binomial confidence interval for response rate was estimated. 95% confidence intervals for median event times were calculated using the Greenwood formula.

For the correlative studies, median and range values were calculated. Differences between the baseline and treatment BCL-2 and actin levels were assessed with Wilcoxon test.

Results

Patient characteristics

The study was open to accrual in February 2004 and closed early in February 2007 after enrollment of 37 patients to the first stage only. Three patients were ineligible: two patients with target lesions in a previously irradiated field, and one with a lack of biopsy confirmation of recurrent disease (figure 1). These patients were not included in overall analysis for primary and secondary endpoints. In addition, three patients did not receive study treatment; however, they were included in the intent-to-treat analysis, and toxicity assessment. Thus, there were a total of 34 patients in the primary analysis.

Table 1 shows the baseline characteristics of the patients enrolled on study. The median age was 60 (range 39–74 years), included 22 male patients, and 32 (93%) of the patients had an ECOG PS 0–1. All patients received prior chemotherapy, and 24 (71%) had also received

prior radiation therapy. Twenty three (68%) of the 34 enrolled patients received at least one cycle of therapy (range 0–5). The majority (17, 53%) of patients discontinued study treatment due to disease progression. Nine patients (28%) terminated treatment due to adverse events, 3 (9%) died on study, 2(6%) withdrew from the study, and 3 (9%) came off study for unknown reasons.

Efficacy

No complete responses were observed; 3 patients (9%) achieved a partial response (90% CI 2.6–22.5%) and 5 (15%) achieved disease stabilization. Eleven patients (32%) demonstrated a best response of progressive disease. Fifteen patients (44%) were inevaluable for response. The reasons for the inevaluability of response included: death before restaging (4 patients), never starting treatment (2 patients), declining study therapy (1 patient), progressive disease at second cycle based on baseline scan with not all lesions being measurable (1 patient), baseline scan obtained less than 8 weeks from registration (2 patients), and the addition of non-protocol therapy (5 patients).

Toxicity

Among the 34 eligible patients, 27 progressed while 7 died without disease progression. The median PFS was 2.0 months (95% CI 1.8–3.9 months) (figure 2). Median OS was 6.2 months (95% CI 4.7–9.8) (figure 3). All patients had died by the time of data analysis.

Among the 37 patients included in toxicity assessment who started treatment, the most common (grade 3 or higher) toxicities were cytopenias, including leukopenia and neutropenia (Table 2). Fatigue (20.6%) and hypertriglyceridemia (11.8%) were the most common grade 3 non-hematologic toxicities. There was one grade 5 event: a patient who died secondary to pancreatitis attributed as possibly related to therapy.

Translational studies

Protein levels of BCL-2 and actin were assessed by Western blot and measured by densitometry on 12 patients at baseline and day 1 and day 2 of cycle 1 before treatment. The median baseline value of BCL-2 was 15,160 units (range 9,314 to 21,500) and the median change in BCL-2 was –2,529 units (range –6,354 to 402), which was statistically significant ($p=0.001$). As a control, there was no significant change in actin levels (–817.5 units (range –7,450 to 1,992, $p=0.08$). There was also no association between either baseline BCL-2 or actin levels or change in levels with objective response, PFS, or OS.

Discussion

The combination of interferon-alpha, 13-CRA, and paclitaxel lacked sufficient efficacy in patients with relapsed small cell lung cancer to warrant continuation of the study beyond the first futility assessment. Thus, this approach to BCL-2 modulation with interferon alpha and 13-CRA in combination with paclitaxel failed to meet the primary response criteria, was not better than the historic use of paclitaxel alone, nor demonstrated an increase in either PFS or OS in this patient population. Furthermore, the toxicity appeared greater than single agent paclitaxel. Based on all of these findings, the study was terminated for futility.

There are several possible reasons why the combination of interferon alpha and 13-cis-retinoic acid with paclitaxel did not meet the primary endpoint. Firstly, eligibility allowed entry of patients whose disease recurred greater than 60 days from the completion of prior initial therapy. Prior studies demonstrated that recurrence less than 90 days beyond completion of prior chemotherapy demonstrated highly resistant disease (10). This concern is highlighted by the 15 patients (44%) with inevaluable disease, and the 11 with disease progression at the first evaluation at 8 weeks. Consequently, those patients whose disease recurred between 60 and 90 days may have adversely affected the potential outcomes. Another explanation is the choice of interferon-alpha and 13-CRA as the means for testing bcl-2 modulation in a rapidly progressing disease. This combination was previously shown to down-regulate Bcl-2, and showed a decrease of bcl-2 in PBMCs; however, both interferon-alpha and 13-CRA produced considerable toxicity as demonstrated by the nine patients whose therapy was stopped for toxicity, 3 who died on study, 2 who withdrew from study, and 3 who were removed from study for unknown reasons.

Yet another possibility is the potential discordance between bcl-2 modulation in tumor tissue compared to PMBCs. While we measured a decrease in Bcl-2 expression measured in the PBMCs, we did not assess Bcl-2 in the tumor. Assessing bcl-2 in the tumor would have been optimal, but would have required sequential tumor biopsies, which would have been a logistic challenge, at best. Based on these considerations, the combination of interferon-alpha and 13-CRA was not an adequate clinical test of bcl-2 modulation in combination with paclitaxel for recurrent SCLC.

Finally, our present approaches to modulating Bcl-2 signaling may not be adequate to achieve therapeutic benefit in SCLC. We planned this study based on the extensive pre-clinical data that supports Bcl-2 expression association with resistance to chemotherapy and poor outcomes in SCLC (18–20). However, since the close of our study, there have been other more specific Bcl-2 targeting compounds studied in SCLC, which demonstrated limited activity. The combination of oblimersen, an antisense oligonucleotide to bcl-2, with carboplatin and etoposide in the front-line setting failed to improve response rates, and strongly suggested a worse survival compared to standard doublet therapy (hazard ratio for OS = 2.13, $p=0.02$) (29). AT-101 or gossypol, an oral inhibitor of the Bcl family of proteins also failed to improve outcomes; in a phase II study of recurrent small cell lung cancer patients with sensitive relapsed disease, there were no responses seen in any of the 14 evaluable patients (30). The bcl-2 antagonist, obatoclax, in combination with topotecan in the relapsed setting also did not improve response rates compared to topotecan alone (31). Most recently, a newer oral inhibitor of both Bcl-2 and Bcl-xL, ABT-263, was tested for single agent activity in recurrent small cell lung cancer: there was 1 partial response seen in 39 patients (2.6%), and 25.6% of the patients experienced a clinical benefit (32). Interestingly, biomarker analysis of this population did find a correlation between pro-gastrin-releasing peptide (pro-GRP) level, neuron-specific enolase, circulating tumor cell number, and cytokeratin 19 fragment antigen 21-1 and clinical benefit. To date, the use of Bcl-2 blockade as a strategy to overcome chemoresistance of recurrent small cell lung cancer has been disappointing.

Further study is still needed to better understand the role of the Bcl-2 pathway in patients with small cell lung cancer as a potential target for overcoming or preventing treatment resistance. The development of biomarkers to identify patients likely to benefit from Bcl-2 blockade will be integral to the further development of Bcl-2 antagonists.

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Figure 1.
Enrollment and follow-up of patients in the E6501 study.

Figure 2.
Progression-free survival in eligible patients.

Figure 3.
Overall survival in eligible patients.

Table 1

Patient characteristics at baseline.

	Count	Percentage
Age:		
< 65 years	26	76%
65 years	8	24%
Sex:		
Male	22	65%
Female	12	35%
Race:		
White	34	100%
Ethnicity:		
Unknown	4	
Hispanic	1	3%
Non-Hispanic	29	97%
Performance status:		
0	20	58%
1	12	35%
2	2	6%
Weight loss previous 6 months		
<5%	25	76%
5–<10%	7	21%
10–<20%	1	1%
Missing	1	
Pleural effusion:		
No	29	85%
Yes	5	15%
Chronic disease at baseline:		
No	11	32%
Yes	23	68%
Medication for chronic disease:		
No	14	41%
Yes	20	59%
History prior malignancy:		
No	30	88%
Yes	4	12%
Degree of involvement at metastatic sites:		
Single lesion in single site or organ	4	12%
Multiple lesions in single site or organ	8	24%
Multiple lesions in multiple sites or organs	22	65%

	Count	Percentage
Prior radiation:		
No	10	29%
Yes	24	71%
Prior surgery:		
No	34	100%
Yes	0	0%
Prior chemotherapy:		
No	0	0%
Yes	34	100%
Prior other systemic therapy:		
No	33	97%
Yes	1	3%

Table 2

Incidence of significant adverse events.

Toxicity type	Grade 3	Grade 4	Grade 5
Leukopenia	9 (26.5%)	2 (5.9%)	-
Neutropenia	6 (17.6%)	2 (5.8%)	-
Anemia	2 (5.9%)	-	-
Hypotension	1 (2.9%)	-	-
Fatigue	7 (20.6%)	-	-
Dehydration	2 (5.9%)	-	-
Dysphagia	1 (2.9%)	-	-
Pancreatitis	-	-	1 (2.9%)
Vomiting	1 (2.9%)	-	-
Elevated alkaline phosphatase	1 (2.9%)	-	-
Elevated AST	1 (2.9%)	-	-
Elevated ALT	1 (2.9%)	-	-
Febrile neutropenia	1 (2.9%)	-	-
Infection with grade 3 or 4 neutropenia	1 (2.9%)	-	-
Infection without neutropenia	1 (2.9%)	-	-
Elevated amylase	-	1 (2.9%)	-
Elevated lipase	-	1 (2.9%)	-
Hypertriglyceridemia	4 (11.8%)	-	-
Hypokalemia	2 (5.9%)	-	-
Hyponatremia	1 (2.9%)	-	-
Muscle weakness	2 (5.9%)	-	-
Neuropathy: motor	1 (2.9%)	-	-
Cough	1 (2.9%)	-	-
Dyspnea	1 (2.9%)	-	-
Worst degree	18 (52.9%)	2 (5.9%)	1 (2.9%)