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Predictors of pulmonary toxicity in limited stage small cell lung cancer patients treated with induction chemotherapy followed by concurrent platinum-based chemotherapy and 70 Gy daily radiotherapy: CALGB 30904

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Abstract

Introduction—Standard therapy for limited stage small cell lung cancer (L-SCLC) is concurrent chemotherapy and radiotherapy followed by prophylactic cranial radiotherapy. Predictors of post chemoradiotherapy pulmonary toxicity in limited stage (LS) small cell lung cancer (SCLC) patients are not well defined. Current guidelines are derived from non-small cell lung cancer regimens, and do not account for the unique biology of this disease. Therefore, we analyzed patients on three consecutive CALGB LS-SCLC trials treated with concurrent chemotherapy and daily high dose radiotherapy (70 Gy) to determine patient and treatment related factors predicting for post-treatment pulmonary toxicity.

Methods—Patients treated on CALGB protocols 39808, 30002, 30206 investigating two cycles of chemotherapy followed by concurrent chemotherapy and 70 Gy daily thoracic radiation therapy were pooled. Patient, tumor, and treatment related factors were evaluated to determine predictors of grade 3–5 pulmonary toxicities after concurrent chemoradiotherapy.

Results—100 patients were included. No patient experienced grade 4–5 post-treatment pulmonary toxicity. Patients who experienced post-treatment pulmonary toxicity were more likely to be older (median age 69 vs 60, p=0.09) and have smaller total lung volumes (2565 cc vs 3530

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Conflict of Interest:
The authors have no conflicts of interest to declare

cc, p=0.05).). Furthermore, exposure of larger volumes of lung to lower (median V5=70%, p=0.09, median V10=63%, p=0.07), intermediate (median V20=50, p=0.04) and high (median V60=25%, p=0.01) doses of radiation were all associated with post-treatment grade 3 pulmonary toxicity, as was a larger mean lung radiation dose (median 31 Gy) p=0.019.

Conclusion—Post-treatment pulmonary toxicity following the completion of 2 cycles of chemotherapy followed by concurrent chemotherapy and high dose daily radiation therapy was uncommon. Care should be taken to minimize mean lung radiation exposure, as well as volumes of low, intermediate and high doses of radiation.

Keywords

limited stage; small cell lung cancer; high dose chemoradiotherapy; toxicity predictors; pneumonitis; lung toxicity radiation

Introduction

Small cell lung cancer (SCLC) represents 13% of all lung cancers [1]. Patients with limited stage (LS-SCLC) are potentially curable. Standard therapy for LS-SCLC cancer consists of concurrent multiagent chemotherapy and thoracic radiotherapy (TRT) followed by prophylactic cranial radiotherapy for patients with a good response. The median survival for LS-SCLC patients treated in this manner is 18–22 months with 5-year survival of 15–25%[2,3].

While TRT is integral to the treatment of LS-SCLC, the ideal dose and fractionation is unknown. Intergroup 0096 demonstrated that an accelerated hyperfractionated TRT schedule of 45 Gy in 1.5 Gy twice daily fractions delivered with concurrent and adjuvant cisplatin and etopside improved overall survival compared to 45 Gy in 1.8 Gy daily radiotherapy with the same concurrent and adjuvant chemotherapy [2]. NCCTG demonstrated no difference in overall survival between split course hyperfractionated and conventionally fractionated radiotherapy with cisplatin etopside [3]. Based on these results and the logistics of twice daily radiotherapy, conventionally fractionated radiotherapy is commonly given[4].

A series of studies investigated dose escalated daily radiotherapy for LS-SCLC. CALGB 8837 investigated the maximal tolerated dose of daily and twice daily radiotherapy delivered with concurrent chemotherapy, demonstrating 70 Gy TRT was tolerable[5]. Subsequently, three studies: CALGB 39808 (NCT00003812)[6] (n=57), 30002 (NCT00033696) [7] (n=63), and 30206 (NCT00072527)[8] (n=78) investigated concurrent carboplatin (AUC=5), etopside (100 mg/m^2) and 70 Gy TRT for LS-SCLC, following two cycles of chemotherapy. These studies formed the basis of one of the experimental arms of CALGB 30610 comparing accelerated hyperfractionated radiotherapy to dose escalated conventionally fractionated radiotherapy and also to accelerated concomitant boost radiotherapy all with concurrent cisplatin and etopside.

Few data exist to predict treatment related cardiopulmonary toxicity in the LS-SCLC population. Usually, the same metrics used to evaluate radiotherapy plans for locoregionally advanced non-small cell lung cancer patients are used to evaluate radiotherapy plans for

small cell lung cancer. However, due to differences in the biology of small cell and non-small cell lung cancer, including an increased radiosensitivity of small cell, common presentation with substantial mediastinal adenopathy and a distant primary tumor, as well as more rapid progression, this may not be the correct approach. Additionally, current metrics used are based on heterogeneous and often retrospective patient populations. Therefore, we analyzed pooled patient data from CALGB 39808, 30002, and 30206 to assess cardiopulmonary toxicity in a homogeneously treated population of LS-SCLC patients treated with two cycles of induction chemotherapy followed by concurrent carboplatin, etopside and daily radiotherapy to 70 Gy. Additionally, identified patient, tumor, and treatment related factors associated with grade 3 and higher treatment related toxicity with this regimen.

Materials and Methods

Eligibility

Eligibility criteria for CALGB 39808, 30002, and 30206 have been previously published [6–8]. Briefly, patients with histologically or cytologically confirmed LS-SCLC defined as disease confined to a hemithorax, such that radiotherapy could be given. This included nodal disease limited to the ipsilateral hilum, and bilateral mediastinum, and excluded patients with pleural or pericardial effusions and/or supraclavicular lymphadenopathy. These patients were additionally required to have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2, and normal organ and marrow function. Patients with contralateral hilar lymphadenopathy were eligible for 39808 and 30002, but were excluded from 30206. The trials were approved by the institutional review boards of the participating centers. CALGB 39808 included an initial cohort of patients treated to a total TRT dose of 60 Gy. These patients were not included in this analysis.

Chemotherapy treatment plan

All patients received two induction chemotherapy cycles. On 39808 this consisted of topotecan 1 mg/m^2 days 1–5 and 22–26 and paclitaxel 175 mg/m^2 day 1 and 22 with G-CSF 5 microg/kg day 6 and 27. On 30002, this consisted of etopside 160 mg/m^2 PO d 5–7 and 26–28, paclitaxel 110 mg/m^2 d1 and 22, and topotecan 1.5 mg/m^2 d2–4 and 23–26. On 30206, this consisted of cisplatin 30 mg/m^2 and irinotecan 65 mg/m^2 both on d1,8,22,29. For all three trials, TRT concurrent with carboplatin (AUC=5) d 43, 64, 85 using the Calvert equation and etoposide 100 mg/m^2 d43–45,64–66, and 85–87 was started on day 43. Details of premedication, dose modifications, and chemotherapy treatment delays have been published previously.

Radiation treatment plan

Following induction chemotherapy all patients underwent computed tomography (CT) based radiation treatment planning. Gross tumor volumes of the primary (GTV-P) and pathologically involved lymph nodes (GTV-N) were contoured based on the post-chemotherapy volume. For the first phase of treatment, the primary tumor and pathologically involved adenopathy (those with a necrotic center, biopsy proven, PET avid, or measuring > 1 cm in short axis diameter) were contoured on each slice of the planning CT

as gross tumor volume (GTV1). Clinical target volume 1 (CTV1) included GTV-P, GTV-N, and elective nodal coverage of the ipsilateral hilum, as well as lymph node stations 3, 4R, 4L, and 7. Stations 5 and 6 were included for left lung primary tumors as part of this elective nodal coverage. Planning target volume 1 (PTV-1) included CTV-1 with a 1 cm margin. These trials predated the utilization of 4D CT imaging and the creation of internal target volumes to account for respiratory and organ motion. Clinical target volume 2 included only GTV-P and GTV-N. Planning target volume 2 (PTV-2) included CTV-2 with a 1 cm margin. Two Gy daily fractions were delivered initially to PTV-1 until a dose of 44 Gy. Subsequently, an additional 26 Gy was delivered to PTV-2. The cumulative dose to gross disease was 70 Gy.

Initially 2 dimensional as well as 3 dimensional conformal techniques were allowed. Intensity-modulated radiation therapy was not allowed. In either case, beam configurations were chosen to minimize dose to the heart and lungs. No corrections were made for tissue heterogeneity. The maximum dose to the spinal cord was limited to 50 Gy. Initial normal tissue sparing guidelines were to limit 50% of the total lung volume < 25 Gy. The entire heart volume was recommended to be < 25 Gy. Treatment was delayed only for grade 4 esophagitis or grade 4 neutropenia with fever. Prophylactic cranial irradiation was offered to patients with a complete response (CR) or a very good partial response (PR) as determined by restaging studies following the completion of all therapy.

Radiation planning information was collected retrospectively from prospectively collected radiation quality control documents stored at the Quality Assurance Review Center (Providence, RI, USA). For each patient, total radiation dose delivered, total lung volume, mean lung dose, volume of lung receiving 5, 10, 20 Gy, maximum lung dose, pre-induction GTV, PTV-1 volume, radiation energy(ies), number of radiation beams used, and radiation field size were collected. Lung volume was abstracted from data provided to QARC, and as reporting method was not specified in the protocols included primarily total lung volume but also less commonly, total lung volume-GTV/CTV/PTV. These data were augmented with tumor and demographic data collected per protocol.

Pulmonary toxicity was scored using the NCI common terminology criteria for adverse events that evolved over the time of these protocols. CALGB 39808 and 30002 used CTC version 2.0, while CALGB 30206 used CTCAE version 3.0. The grading of pulmonary toxicity between these two scales is similar, but not identical.

Statistical Analysis Method

Univariate analyses were performed using Fisher’s exact 2-sided test for categorical variables and Wilcoxon rank-sum test on continuous variables to examine the relationship between maximum pulmonary toxicity (grade 0–2 vs. 3–5) and patient and treatment related factors. Pulmonary function data was not routinely collected and could not be included in this analysis. A p-value <0.05 was considered statistically significant.

Results

Of the 211 patients enrolled on these studies, 100 patients completed all therapy including full dose radiation therapy and had appropriate radiation dose volume information available for review. Patient and tumor characteristics are listed in Table 1. Included patients were compared to those receiving 4–6 cycles of chemotherapy but without radiation therapy information available to determine if the study sample was representative of the entire cohort. There were no significant demographic, progression free survival, or overall survival differences between included and excluded patients who received 4–6 cycles of chemotherapy as shown in Table 1b. The majority (59%) of the patients were male and predominantly white. Characteristics were well balanced between the studies except for performance status, which was significantly better in 30206, and disease free survival were similar in all three studies, with the median overall and disease free survival for all patients in this analysis being 22.6 months and 13.9 months, respectively shown in Table 2.

Post treatment pulmonary toxicity

Three patients experienced grade 3 post-treatment pulmonary toxicity likely related to the treatment; two with grade 3 pneumonitis/pulmonary infiltrates and one with grade 3 singletus. There was no difference in outcome when patients with any attribution of toxicity were included or if the analysis was restricted to patients with toxicity likely related to treatment. No patient experienced grade 4–5 post-treatment pulmonary toxicity. Factors associated with grade 3 or greater post-treatment pulmonary toxicity are listed in Table 3. Patients who experienced post-treatment pulmonary toxicity were more likely to be older (median age 69 vs 60, p=0.09) and have smaller total lung volumes 2565 cc vs 3530 cc, p=0.05). The volume of lung irradiated to lower, intermediate, and higher doses of radiation, either trended toward, or was significantly associated with higher chance of grade 3 toxicity. Specifically, patients experiencing grade 3 toxicity the volume of lung receiving 5 Gy (V5) median 70% vs 50%, p=0.09, V10 63% vs 42%, p=0.07, V20 50% vs 35%, p=0.04, V40 38% vs 24% p=0.01 and V60 25% vs 13%, p=0.01. Additionally, the mean lung dose in patients experiencing grade 3 toxicity was 31.1 Gy vs 19.7 Gy in those with grade 0–2 toxicity, p=0.02. Of note, 30 patients had a V20 >40%, with 9 >50%. When patients with grade 2 or greater toxicity were compared to those with grade 0–1 toxicity, there were no statistically significant differences in dose volume parameters.

Discussion

In this retrospective analysis of 3 completed clinical trials using dose escalated once daily concurrent chemoradiotherapy, we found that traditional dose-volume metrics for non-small cell lung cancer predicted for post-treatment pulmonary toxicity. In particular, patients with larger volumes of lung exposed to 20 Gy and higher mean lung doses were more likely to experience pulmonary toxicity. These data confirm the standard practice of using these dose-volume metrics developed for non-small cell lung cancer, in patients treated with concurrent chemotherapy and high dose daily-fractionated radiotherapy for LS-SCLC.

Perhaps the most interesting finding from this analysis was the limited high grade post-treatment pulmonary toxicity reported on the three prospective phase II cooperative group studies, despite high radiation doses to large lung volumes. Possible explanations could include patient selection, as only patients who initiated radiotherapy and were treated to 70 Gy and had radiation dose-volume data were included. Furthermore, radiotherapy planning in these studies required treatment of post-chemotherapy volumes based on randomized data[9], limiting treatment fields and lung exposure. Additionally, this could be explained by the difficulty of collecting accurate cardiopulmonary adverse events data in LS-SCLC patients with extensive tobacco abuse histories and high likelihood for COPD or CHF exacerbations. Perhaps the natural history of LS-SCLC with high distant progression rates could have influenced the detection of treatment related pulmonary toxicity. Furthermore, it could be possible that high-grade treatment related toxicity is less in this population of LS-SCLC than in similar NSCLC patient populations.

Data on pulmonary function testing results, and current smoking status, were not available for this analysis and could have influenced the presence or intensity of radiation related pulmonary toxicity. Although, we can reasonably assume that there was a high prevalence of patients with a heavy smoking history given the etiology of SCLC. Additionally, concurrent medication usage was not available in this analysis. We acknowledge that concurrent use of non-steroidal anti-inflammatory medications, HMG-coA reductase inhibitors, angiotensin converting enzyme inhibitors, and glucocorticoids have all been associated with decreased radiation related lung injury in clinical and pre-clinical models.

Two other intriguing possibilities could explain the lack of high-grade post-treatment pulmonary toxicity. The first is that increasing use of 3D conformal radiotherapy could have reduced the incidence of high-grade toxicity. Additionally, all of these studies included central QA with rapid review. Correction of radiotherapy protocol violations early in the course of treatment could have had a significant impact, as central review of radiotherapy plans has been associated with improved outcomes in prospective clinical trials[10].

Conclusion

In conclusion, a low incidence of grade 3 or higher post-CRT pulmonary toxicity was seen in this population of patients treated with induction chemotherapy followed by concurrent carboplatin, etopside, and 2 Gy daily radiotherapy to 70 Gy. Standard radiation dose-volume metrics including mean lung dose and V20 can predict for higher risk of pulmonary toxicity. Whether the therapeutic index of high dose QD TRT compares favorably with BID TRT is currently under investigation in two phase III intergroup studies, including CALGB/RTOG/ECOG/NCI/SWOG (NCT00632853) and the other including Cancer Research UK, EORTC, NCIC, Spanich Lung Cancer Group, Groupe Francais De Pneumo-Cancerologie, Intergroupe Francophone de Cancerologie Thoracique (NCT00433563).

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Summary

LS-SCLC is treated with concurrent chemoradiotherapy. Exact dose/volume metrics for post-treatment toxicity are unknown. We nalyzed dose/volume data from three phase II cooperative-group studies evaluating predictors for high-grade post-treatment cardiopulmonary toxicity. We found that mean lung dose, age, volume lung receiving 20 Gy (V20) among others associated with high-grade pulmonary toxicity.

Table 1

Summaries of patient's characteristics for CALGB 30002, 30206, and 39808

		30002 (N = 34)	30206 (N = 57)	39808 (N = 9)	Overall (N =100)	Fisher's exact p-value for balance among 3 studies
Gender						
	Male	16 (47%)	34 (60%)	6 (67%)	56	0.4683
	Female	18 (53%)	23 (40%)	3 (33%)	44	
Age						
	Median(min, max)	62 (45, 78)	60 (41, 77)	54 (49, 79)	61 (41, 79)	0.8712
	<=59	14 (41%)	25 (44%)	5(56%)	44	
	60–69	14 (41%)	22 (39%)	2(22%)	38	
	>=70	6 (18%)	10 (18%)	2(22%)	18	
Race						
	White	32 (94%)	55 (96%)	9(100%)	96	0.7468
	Black	2 (6%)	2 (4%)	0(0%)	4	
Performance						
Status						
	0	15 (44%)	40 (70%)	3(33%)	58	0.0147
	1	18 (53%)	17 (30%)	6(67%)	41	
	2	1 (3%)	0 (0%)	0(0%)	1	
Weight loss						
	<5%	21 (62%)	48 (84%)	8 (89%)	77	0.1758
	5% - <10%	7 (21%)	4 (7%)	1(11%)	12	
	10%- <20%	1 (3%)	3 (5%)	0 (0%)	4	
	>=20%	2 (6%)	2 (4%)	0 (0%)	4	
	Missing	3 (9%)	0 (0%)	0(0%)	3	
Pleural Effusion						
	No	33 (97%)	51 (89%)	9(100%)	93	0.3178
	Yes	1 (3%)	6 (11%)	0(0%)	7	

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b Comparisons between included patients and excluded patients who had completed 4, 5 or 6 cycles of treatment					
		Excluded & completed 4+ cycles N=78	**Included N=100**	**Overall N =178**	**Fisher's exact p-value for comparison between included and excluded**
Gender					
	Male	33(42%)	56(56%)	89	0.0963
	Female	45(58%)	44(44%)	89	
Age					
	Median(min, max)			62(38,79)	0.4667
	<=59	35(45%)	44(44%)	79	
	60–69	34(44%)	38(38%)	72	
	>=70	9(12%)	18(18%)	27	
Race					
	White	70(90%)	96(96%)	166	0.2162
	Black	6(8%)	4(4%)	10	
	Other	2(2%)	0(0%)	2	
Performance Status					
	0	38(49%)	58(58%)	96	0.3997
	1	38(49%)	41(41%)	79	
	2	2(2%)	1(1%)	3	
Weight loss					
	<5%	53(68%)	76(76%)	129	0.1492
	5% - <10%	13(17%)	12(12%)	25	
	10%- <20%	10(13%)	4(4%)	14	
	>=20%	2(2%)	4(4%)	6	
	Missing	0(0%)	4(4%)	4	
Pleural Effusion					
	No	76(97%)	93(93%)	169	0.3022
	Yes	2(3%)	7(7%)	9	

Table 2

Overall and Progression-Free Survival Status (N=100) by Protocol

	# Death /#Failure				Median (months) (95%CI)			
	CALGB 30002 (N=34)	**CALGB 30206 (N=57)**	**CALGB 39808 (N=9)**	**All 3 Studies (N=100)**	**CALGB 30002**	**CALGB 30206**	**CALGB 39808**	**All 3 Studies**
Overall Survival	26	42	8	76	21.2 (16.2, 47.5)	21.2 (16.8, 29.4)	35.1 (10.3,56.5)	22.6 (18.5,29.4)
Progression-free Survival	26	45	8	79	13.6 (10.6, 23.6)	13.3 (11.6,16.7)	19.0 (3.5,53.2)	13.9 (12.6,16.7)

Table 3

Association of radiation dose-volume parameters and post-treatment grade 3 or greater pulmonary toxicity *

Variables	Grade 0 – 2 Median (n)	Grade 3 Median (n)	Wilcoxon rank-sum test (0–2) vs (3–5) p-value (n, #s Grade(0–2)/ #s Grade (3–5)
Age	60 (n=97)	69 (n=3)	p=0.0906 (n=100,97/3)
TLV	3530 (n= 91)	2565 (n=3)	p=0.0520 (n=94, 91/3)
PTV1	469 (n=69)	707 (n=2)	p=0.6653 n=(71, 69/2)
GTV	31 (n=78)	49 (n=3)	p=0.1407 (n=81, 78/3)
PTV1/TLV * 100	13 (n=68)	29 (n=2)	P=0.3718 (n=70, 68/2)
Lung V5	50 (n=97)	70 (n=3)	P=0.0944 (n=100, 97/3)
Lung V10	42 (n=97)	63 (n=3)	P=0.0718 (n=100, 97/3)
Lung V20	35 (n=97)	50 (n=3)	P=0.0379 (n=100,97/3)
Lung V40	24 (n=97)	38 (n=3)	P=0.0135 (n=100,97/3)
Lung V60	13 (n=97)	25 (n=3)	P=0.0093 (n=100,97/3)
Mean Dose (Lung)	1971 (n=87)	3110 (n=3)	P=0.0193 (n=90, 87/3)
Mean Dose (Heart)	1715 (n=79)	3622 (n=3)	P=0.1207 (n=82, 79/3)

* No patient experienced grade 4–5 toxicity