Radiation Therapy Oncology Group (RTOG) 0241: Phase I study of irinotecan and cisplatin in combination with twice daily thoracic radiotherapy (45Gy) or once daily thoracic radiotherapy (70Gy) in patients with limited stage small cell carcinoma of the lung (LD-SCLC).

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ABSTRACT

PURPOSE: Determine the feasibility and safety of adding irinotecan to cisplatin and radiotherapy (RT) in patients (pts) with limited-stage small cell lung cancer (LS-SCLC).

MATERIAL AND METHODS: Eligibility stipulated Zubrod PS 0-1, adequate physiologic function, and pretreatment FEV1 ≥ 1 liter. Irinotecan was escalated in sequential cohorts from 40 mg/m^2 (level 1), to 50 mg/m^2 (level 2), up to 60 mg/m^2 (level 3) days 1 and 8 in combination with cisplatin 60 mg/m2 every 3 weeks for 4 cycles. RT was administered either twice (45 Gy) or once daily (70 Gy), sequences A and B respectively. Dose-limiting toxicities (DLTs) were defined as grade (Gr) 4 esophagitis, pneumonitis, diarrhea or neutropenic fever; thrombocytopenia requiring transfusion; any toxicity precipitating RT interruption > 1 week; or any Gr 5 toxicity.

RESULTS: Of 34 analyzable patients (20 on sequence A, 14 on sequence B) accrued, median age was 64 (range, 49-79), 18 (53%) were female, 24 (71%) had PS 0. One attributable DLT was observed in sequence A; 2 in sequence B at dose level 2 including 1 pt each with Gr 4 diarrhea and esophagitis. No Gr 5 toxicities were observed during RT. Five pts (15%) experienced Gr 3 esophageal toxicity; 3 late Gr 3/4 lung toxicities. Two-year survival rates in sequences A and B were 50% and 43%, respectively.

CONCLUSION: In LS-SCLC, in combination with cisplatin and either BID RT (45 Gy) or daily RT (70 Gy), irinotecan is safe and feasible with recommended doses of 60 mg/m^2 and 40 mg/m^2 days 1 and 8, respectively.

Introduction:

Small cell carcinoma of the lung (SCLC) accounts for 15% of newly diagnosed pulmonary cancers each year in the United States [1-6], constituting 25,000 cases. Although the percentage of cases diagnosed as SCLC has dropped over the past three decades, it is unlikely we will witness a further decline in incidence.[1,5] Limited stage (LS) disease confined to a manageable radiation portal is potentially curable, but includes less than one third of newly diagnosed patients.

Unfortunately, we have made little headway in the therapy of LS SCLC over the past 25 years.[4] Checkpoint inhibitors have had a modest, but signficant impact on outcome in extensive stage disease over the past five years,[5, 6] but are only beginning to be tested in LS SCLC in phase II or phase III studies.[7] Within the cooperative groups in North America, in the decade ending in 2007, there were no phase III studies evaluating new systemic approaches in limited disease.

The best outcomes in LS-SCLC have been observed with concurrent chemotherapy and radiation. The Japanese Clinical Oncology Group (JCOG) compared concurrent radiation (RT) with etoposide and cisplatin (EP) upfront to sequential chemotherapy followed by definitive local RT. The concurrent approach yielded a doubling in long-term survival (30% versus 15%, p=0.057).[8] The National Cancer Institute of Canada (NCIC) evaluated early versus delayed concurrent chemotherapy with RT, in the context of alternating cyclophosphamide, doxorubicin and vincristine (CAV) chemotherapy and EP. RT was given over three weeks at a dose of 1.5 Gy BID M-F to 45 Gy. Concurrent early chemoradiation led to a statistically significant survival advantage with 5-year survival rate of 20% compared to 10% for delayed concurrent chemoradiation[9]. The North American Intergroup compared twice daily RT over 3 weeks (wks) (45 Gy/1.5 Gy BID/3 wks) to once daily radiation over a 5-week period to the same total dose (45 Gy/1.8 Gy QD M-F 5 wks). Chemotherapy consisted of 4 cycles of etoposide and cisplatin starting day 1 with RT. The twice daily approach yielded a clinically meaningful improvement in five-year survival: 26%

compared to 16% for the control (once daily) arm[10]. This benefit was statistically significant, although arguably, the RT doses administered were not biologically equivalent. At the time our study evaluating irinotecan was initiated, the intergroup trial was the last phase III cooperative group trial in LS-SCLC conducted in North America. More recently, the Cancer and Leukemia Group B (CALGB) in a phase II effort showed that RT doses up to 70 Gy could be administered safely in combination with standard etoposide and platinum.[11] Long-term survival rates rivaled, if not exceeded, the results of the intergroup trial. This dose was subsequently compared to 45 Gy BID in a prospective, randomized phase III, nationwide study (CALGB 30610 and yielded *de facto* therapeutic equivalence[12] Currently, in North America, once daily RT is more commonly instituted in LS SCLC than BID RT even though it has never been shown to be superior.

n extensive-stage SCLC, the JCOG showed a survival advantage for combination cisplatin and irinotecan compared to conventional etoposide and cisplatin[13]. The trial reported by Noda et al, in the New England Journal of Medicine demonstrated a 3 month improvement in median survival and a fourfold improvement in 2 year survival rates (19.5% versus 5.2%). These results proved statistically significant at the time of interim analysis, and led to early stoppage of the trial. It also kindled further interest in using irinotecan in both the extensive and limited disease setting.

In addition, irinotecan has demonstrated synergy with cisplatin and is a known radiosensitizer[14], arguably more potent than etoposide in combination with RT. Hence, based on the promising results observed in the JCOG trial and the putatively beneficial interaction between irinotecan and both cisplatin and RT, we mounted a randomized phase I trial to determine the maximum tolerated dose (MTD) of irinotecan in combination with cisplatin at a dose of 60 mg/m^2 every 3 weeks, and either standard RT (45 Gy 1.5 Gy/fx BID over 3 wks) or full dose daily single fractionated RT (70 Gy, 2 Gy/fx QD over7 wks).

Material and Methods

Patient Population

Eligibility for this trial stipulated histologic or unequivocal cytologic proof of SCLC and clinical stage I-IIIB confined to a single hemithorax (limited stage disease). Patients with malignant pleural or pericardial effusion or N3 disease on the basis of contralateral hilar or contralateral supraclavicular involvement were excluded. Those with pleural effusions too small to extract under CT guidance and not evident on chest x-ray were eligible. Additional entry criteria included measurable disease; age ≥18 years; Zubrod performance status (PS) 0-1; and adequate end organ indices including ANC ≥1500/mL; platelets ≥120,000/mL; bilirubin ≤1.5 ml/dL; creatinine ≤1.5 ml/dL. FEV1 of ≥1L/second was also required. Patients were required to be chemotherapy-and radiation-naïve. Patients of child bearing potential were obligated to practice adequate contraception. Pregnant or lactating women were deemed ineligible. All participating sites were required to have Institutional Review Board approval, and all patients signed a study-specific informed consent.

Objectives

The primary objective of this study was to determine the MTD of irinotecan in combination with cisplatin and either twice-daily RT (45 Gy/3 weeks) or single daily RT (70 Gy/7 weeks). Secondary objectives included evaluation of qualitative and quantitative toxicities.

Study Schema

Sequence A patients received RT 1.5 Gy bid Monday through Friday in 30 fractions over 3 weeks to a total dose of 45 Gy. The cisplatin dose was fixed at 60 mg/m^2 every 3 weeks. Irinotecan was escalated in sequential cohorts from 40mg/m^2 to

50mg/m^2 and ultimately to 60 mg/m^2 days 1 and 8. The first cycle of chemotherapy coincided with RT; the second, third and fourth cycle were given after RT concluded.

Sequence B featured full dose RT 2Gy daily Monday through Friday in 35 fractions over 7 elapsed weeks to a total dose of 70Gy. Cisplatin, as in arm 1, was fixed at 60 mg/m^2 every three weeks; irinotecan was escalated in sequential cohorts from 40 to 50 to 60 mg/m^2 days 1 and 8. For enrollees on Sequence B, the first two cycles of chemotherapy coincided with RT. The subsequent two cycles were given post completion of chemoradiation.

In both sequences, the RT target volume included the primary tumor and the involved lymph nodes plus a margin of 2 cm. Elective nodal irradiation was not used. Simulation was mandatory, preferably with a CT simulator. Three-dimensional RT was encouraged, but was not mandated; intensity-modulated RT (IMRT) was not allowed. Beam energies of 6-10 MV only were allowed. Prophylactic Cranial Irradiation (PCI) was encouraged for those patients who achieved a complete response in the chest after chemoradiotherapy and PCI doses between 25-36 Gy (the latter fractionated either once or twice daily) were allowed.

Chemotherapy Administration

Irinotecan and cisplatin were each administered over 60 minutes. Standard anti-emetics, including HT3 antagonists were employed. In addition, patients were recommended to receive dexamethasone, and, if necessary, low doses of anxiolytics like lorazepam. A minimum of 3 liters of fluid were given before, during and after each dose of cisplatin.

Statistical Design and Methods

This phase I study was launched to establish the MTD of irinotecan, given during each of the two sequences of chemoradiation. Three to six eligible and evaluable patients were needed for each dose level. The maximum projected accrual was 36

patients. Dose escalation took place in an alternating stepwise fashion, such that only one dose level within a sequence was escalated at any time. A new dose level was not opened until the acceptability and tolerability of the preceding dose level in that particular sequence had been determined. In addition, only one sequence (A or B) was open to accrual at any time.

Dose-limiting toxicities (DLTs) within 90 days from the start of RT included the following toxicities:

- Acute grade 3 or 4 neutropenic fever (later revised to grade 4 only)
- Acute thrombocytopenia requiring transfusion
- Acute grade 4 esophagitis
- Acute grade 3 or 4 diarrhea (later revised to grade 4 only)
- Acute grade 4 pneumonitis
- Treatment-related grade 5 toxicity
- Any other clearly attributable treatment-related toxicity, grade 3 or higher, requiring interruption of radiation for more than one week.

If. after 90 days of evaluation, the current dose level was deemed acceptable, accrual to the next sequence and dosing level was permitted. Six patients were to be accrued to each dose level. A dose level within a sequence was considered acceptable if there were no DLTs in the first 3 patients (0/3), or if one of the first 3 patients (1/3) and none of the next 3 patients (0/3) experienced a DLT. At a given dose level, the probability of halting dose escalation when the true toxicity was $\geq$ 50% was 83%. If the true DLT rate was 20%, then there was a 29% likelihood of halting dose escalation prematurely at a given dose level.

Summary statistics (e.g., percentages, means, standard errors, and ranges) were calculated for pre-treatment demographics, treatment-related toxicities, and treatment compliance for each level within each sequence. Acute radiation and chemotherapy toxicities were graded using CTC version 2.0 criteria. [15] Late toxicities were reported using the RTOG/EORTC Late Toxicity Criteria. [16] Overall survival (OS) and progression-free survival (PFS) were evaluated and estimated using the Kaplan-Meier

method.[17] Events for PFS included progression (local-regional or distant failure) or death due to any cause. Both OS and PFS were measured from the date of study entry to the date of death, date of last follow-up, or date of progression (for PFS). The study was not designed, nor powered to make statistical comparisons between sequences or dose levels for efficacy endpoints.

Results

Radiation Therapy Oncology Group (RTOG) 0241 opened March 17, 2003 and closed for accrual November 29, 2005. Accrual averaged 1.2 patients per month. Thirty-six patients were accrued: 26 from RTOG members or their affiliates; 8 from the RTOG CCOP; and 2 from the CALBG. Of 36 patients, 2 were deemed ineligible: one had metastatic disease at entry; the other received no protocol therapy. Consequently, 34 patients were eligible and evaluable.

Demographics

Pretreatment characteristics for each sequence are listed in Tables 1A and 1B. The median age was 63 (range, 49-79) on sequence A and 65 (range, 42-77) on sequence B. Twenty percent had a Zubrod performance status (PS) of 1 on sequence A compared to 43% on sequence B. Sixty-eight percent had < 5% weight loss in the 3 months preceding trial entry. Ninety-seven percent were Caucasian; two patients were Hispanic. Five (15%) patients had stage I-II SCLC; 16 (47%) patients had stage IIIA SCLC; 4 (12%) had IIIB disease; the actual stage was unclear in 9 (26%). Twenty-four of 34 (71%) had N1-N3 nodal disease at study entry. Eight (24%) patients had N0 disease. Nodal status in two (6%) was unknown.

Establishing DLT in sequence A

One patient on dose level 1 of sequence A was initially found to have a DLT, characterized as grade 3 diarrhea (part of the DLT definition when the trial opened). No

additional cases of grade 3 diarrhea were reported during chemoradiation on that arm after escalation to dose levels 2 and 3. However, 2 other patients on level 1 of sequence A experienced grade 3 diarrhea during their post radiation chemotherapy. Following a conference call involving the study chairs and RTOG staff, as well as treating physicians, it was decided that grade 3 diarrhea and/or grade 3 febrile neutropenia would no longer be considered a DLT. Accordingly, since these toxicities were considered part of the standard profile of irinotecan, a June 2004 protocol revision redefined DLTs and was approved by CTEP. Therefore, using this revised definition, no DLTs were observed in sequence A dose level 1.

In sequence A, dose level 2, one patient experienced grade 3 thrombocytopenia. A second patient at this level succumbed in November 2004 to late pneumonitis. Review of hospital records revealed multifocal, multiorgan failure, in the setting of possible, opportunistic pulmonary supra-infection, but no significant drop in blood counts. After a conference call, including staff not directly involved with this study, a final determination indicated that the death was no more than possibly attributable to treatment and would not be considered a DLT. The final dose level (sequence A, level 3) opened to accrual on 4/8/2005, and closed on 11/29/2005. Amongst 6 eligible and evaluable patients at that level, there were no reported DLTs. Hence, the MTD for sequence A was determined to be dose level 3: cisplatin 60 mg/m^2 day 1 and irinotecan 60 mg days 1 and 8 for 1 cycle in conjunction with thoracic RT (1.5 Gy, BID, M-F over 3 weeks to a dose of 45 Gy). .

Establishing DLT in sequence B

At dose level 1, seven eligible and evaluable patients were accrued from 10/21/2003 through 2/19/2004. No DLTs were reported. At dose level 2, seven patients were accrued, in whom 2 DLTs were observed; one was a grade 4 gastrointestinal illness, including diarrhea; the other was characterized by esophageal inflammation and spasm. Each DLT was confirmed by physician review. Consequently, the MTD on sequence B was determined to be dose level 1: cisplatin 60

mg/m^2 day 1 and irinotecan 40 mg/m^2 days 1 and 8, in conjunction with thoracic RT (2.0 Gy, once daily, M-F over 7 weeks to a dose of 70 Gy).

Toxicities

For both sequences, grade $\geq$ 3 toxicities reported as definitely, probably, or possibly related to treatment are listed in Table 2. Myelosuppression was the most common toxicity in both sequences. In the course of the entire study, there were two episodes of febrile neutropenia. The overall incidence of grade $\geq$ 2 pulmonary toxicity was 38%, and grade $\geq$ 3 pulmonary toxicity was 12%. Fifteen patients (44%) experienced grade 3 or 4 GI toxicity, predominantly diarrhea.

Late RT toxicity is summarized in Table 3. One instance of grade 4 pneumonitis was reported in the sequence A, level 2. In sequence B, level 2, one additional patient each experienced late grade 3 pneumonitis or grade 3 pleural effusion, and 3 patients developed grade 3 esophageal toxicities, including radiation-induced esophageal ulceration or dysphagia.

Treatment Compliance

RT compliance is summarized in Table 4 and chemotherapy compliance is shown in Table 5. The vast majority of pts (94%) were treated per protocol, or with acceptable variations. Eighty-five percent (29/34) of pts received chemotherapy per protocol. Dose intensity for irinotecan rose on average on sequence A from 27 mg/m^2 per week (level 1) to 29.7 mg/m^2 per week (level 2), up to 34 mg/m^2 per week (level 3). Commensurate figures for irinotecan on sequence B were 31.4 mg/m^2 per week (level 1), rising slightly to 33.8 mg/m^2 per week (level 2).

Response and Survival Data

In sequence A, using BID RT, the overall response rate was 90% with a complete response (CR) rate of 60%. Median progression-free survival (PFS) time was 13.5 months (95%CI: 0.7, 3.1 years), with median survival time (MST) of 22.6 month (95% CI: 0.8, 3.7 years), and a 2-year overall survival (OS) rate of 50% (95% CI, 27-69%). In sequence B, featuring a cumulative RT dose of 70 Gy, the overall response rate was 93% with a 57% CR rate; median PFS time was 12.8 months (95% CI: 0.5, 4.3 years), with MST of 16.1 months (95% CI: 0.9, 4.3 years), and a 2-year OS rate of 43% (95% CI, 18 -66%). These data are summarized in Tables 6 to 8 and Figures 1 and 2.

Discussion

Irinotecan has emerged as a critical agent in the treatment of advanced SCLC. Japanese trials showed a survival advantage for irinotecan in combination with cisplatin compared to standard etoposide and cisplatin, and helped established a new treatment paradigm in Japan.[18] More recently, a study from Scandinavia comparing carboplatin and oral etoposide to irinotecan and carboplatin using a Eurocentric every 3 week irinotecan schedule showed a survival advantage for the irinotecan combination in a cohort of extensive stage patients with unrestricted performance status.[19]

However, the success of this agent observed in Japan and Scandinavia was not consistently replicated in the rest of the world, particularly in the United States.[20, 21] A largely North American effort, more than twice the size of the Japanese trial, compared etoposide and cisplatin to a *weekly* schedule of irinotecan and cisplatin in an attempt to capitalize on the putative synergy of these two agents and to mitigate toxicity, but this study failed to show a survival advantage for the irinotecan arm.[20] The largest trial to date, orchestrated by the Southwest Oncology Group (SWOG) replicated the dosing and schedule employed in the Japanese trial. Preliminary results demonstrated no advantage for irinotecan compared to etoposide in this setting.[21] MSTs were 9.9 and 9.1 months for the irinotecan and etoposide arms, with respective one-year OS rates of 41% and 34%. Surveys of Network For Oncology Communication and Research (NOCR) suggest that fewer 10-15% of oncologists in the US at most have implemented

irinotecan as part of first line treatment, and that this percentage has since declined. A somewhat higher percentage use it in the second line setting.[22] One suspects that the negative results of the SWOG trial further dimmed enthusiasm for this agent in North America. As to the disparities in toxicity and efficacy observed between Japan and North America, it has been speculated that ethnic differences in Uridine Diphosphate-Glucuronosyltransferase (UGT) 1A1*28 polymorphisms may have been be responsible.23need reference

Although pre-clinical models clearly show a radiosensitizing effect for irinotecan,[12] with the exception of RTOG 0241 reported in this manuscript, there have been no other studies, to date, evaluating the role of irinotecan in combination with standard cisplatin and radiation in treatment-naïve, limited-stage SCLC. Based on a phase II protocol that showed both feasibility and efficacy, a Japanese trial compared IP to EP in patients who had already completed combination EP and radiation, and failed to show a survival advantage for IP.[24] However, this study did not assess the potential radiosensitizing role of irinotecan in the limited disease setting. In locally advanced NSCLC, investigators at Fox Chase Cancer Center established an MTD for cisplatin of 25 mg/m^2 weekly, in combination with irinotecan 30 mg/m^2 weekly without break during concurrent radical thoracic RT.[25] Choy et al have shown that irinotecan at a dose of 20 to 30 mg/m^2 weekly was safe in combination with carboplatin (AUC 2 weekly) and full dose RT.[26, 27]

Because the SWOG trial replicating the Japanese effort failed to show a survival advantage in extensive SCLC, it is doubtful if irinotecan will replace etoposide in the limited SCLC setting, at least in North America. Of course, one could readily argue that irinotecan is a much more potent radiosensitizer compared to etoposide and would, therefore, deserve separate assessment regardless of the outcome of the SWOG trial. However, in the absence of clear-cut, positive phase III data, it would be difficult to convince most thoracic oncologic investigators to implement this sort of trial. Moreover, the survival results to date in our effort, albeit a small sample, do not distinguish themselves from the results observed in larger, phase III efforts[7, 8, 9].

Nevertheless, although the incidence of esophagitis was a bit higher than one might otherwise expect in this setting, our trial demonstrated the feasibility of integrating irinotecan into the LS-SCLC treatment paradigm, with acceptable levels of toxicity. In addition, we showed that "full dose" irinotecan at 60 mg/m2 IV days 1 and 8 could be combined successfully with full dose cisplatin and twice daily XRT to 45 Gy. Whether the second cohort featuring 70 Gy could have continued accrual to the third dose level remains open to speculation. In retrospect, one of the dose limiting toxicities was clearly related to diarrhea, rather than pneumonitis or esophagitis, suggesting perhaps that the feasibility of true dose-limiting toxicity in combined modality therapy was not necessarily identified. However, this issue is likely moot if irinotecan is not developed further in the first line setting in SCLC. On the other hand, this regimen would certainly be attractive for further testing in Japan and other nations where irinotecan has emerged as part of standard frontline treatment in SCLC. In addition, this study provides an alternative strategy for definitive, combined modality therapy during times of drug shortages. In the US, periodic shortages of intravenous etoposide have occurred. There are also situations where the use of irinotecan in LS-SCLC might be relevant. As an example, we have treated patients whose disease relapsed within 6-12 months in locoregional nodes after surgical resection of very early stage SCLC, followed by adjuvant etoposide and cisplatin; the use of local RT with cisplatin and irinotecan, in lieu of etoposide, would be "attractive" in such a scenario. Under these circumstances, the optimal dose of irinotecan and cisplatin in the context of full dose single daily fractionated RT in limited SCLC could be explored further. Only one other trial to date has combined irinotecan with cisplatin and RT in LS-SCLC: irinotecan was dosed at 40 mg/m2 days 1, 8 and 15 monthly in combination with cisplatin 60 mg/m2 day 1 and RT (50.4 Gy) given daily and yielded a median PFS of 12 mos, median OS of 20 mos and 1 and 2 year survival rates of 85% and 35% respectively.[24]

Finally, this study was a pioneering, cooperative group effort, attempting to integrate a novel cytotoxic combination in SCLC with two distinct radiation schedules, alternating accrual between each sequence. The execution of this study demonstrated that this sort of strategy is feasible within the cooperative group structure in the United States and Canada. The RT doses in this trial ultimately cohere with the RT doses

used in the much larger phase III trial comparing twice daily RT (45 Gy) to once daily RT (70 Gy) in combination with standard EP;

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Table 1A: Pretreatment Characteristics for Sequence A

	Level 1 (n=7)		Level 2 (n=7)		Level 3 (n=6)		Total (n=20)	
Age								
Median	59		63		63		63	
Range	49 – 79		57 – 70		61 – 68		49 – 79	
	n	%	n	%	n	%	n	%
Gender								
Male	2	29	4	57	5	83	11	55
Female	5	71	3	43	1	17	9	45
Race								
White	7	100	7	100	5	83	19	95
Black or African American	0	0	0	0	1	17	1	5
Ethnicity								
Hispanic or Latino	0	0	1	14	0	0	1	5
Not Hispanic or Latino	7	100	5	71	6	100	18	90
Unknown	0	0	1	14	0	0	1	5
Zubrod Performance Status								
0	5	71	6	86	5	83	16	80
1	2	29	1	14	1	17	4	20
Estimated % weight loss in last 3 months								
<5%	4	57	5	71	3	50	12	60
5%-<10%	1	14	1	14	2	33	4	20
Unknown	2	29	1	14	1	17	4	20
Stage group								
II	1	14	1	14	1	17	3	15
IIIA	3	43	5	71	2	33	10	50
IIIB	0	0	0	0	1	17	1	5

	Level 1		Level 2		Level 3		Total	
Unknown	3	43	1	14	2	33	6	30
Primary tumor location								
Right upper lobe	0	0	1	14	1	17	2	10
Right mainstem bronchus/Right hilum	1	14	2	29	0	0	3	15
Right lower lobe	2	29	1	14	2	33	5	25
Left upper lobe	1	14	3	43	1	17	5	25
Left mainstem bronchus/Right hilum	2	29	0	0	1	17	3	15
Left lower lobe	0	0	0	0	1	17	1	5
Unknown	1	14	0	0	0	0	1	5
N classification								
N0	1	14	2	29	1	17	4	20
N1	1	14	1	14	1	17	3	15
N2	3	43	4	57	3	50	10	50
N3	0	0	0	0	1	17	1	5
Unknown	2	29	0	0	0	0	2	10

Table 1B: Pretreatment Characteristics for Sequence B

	Level 1 (n=7)		Level 2 (n=7)		Total (n=14)	
Age						
Median	69		61		65	
Range	59 – 74		42 – 77		42 – 77	
	n	%	n	%	n	%
Gender						
Male	3	43	2	29	5	36
Female	4	57	5	71	9	64
Race						
White	7	100	7	100	14	100
Black or African American	0	0	0	0	0	0
Ethnicity						
Hispanic or Latino	1	14	0	0	1	7
Not Hispanic or Latino	5	71	7	100	12	86
Unknown	1	14	0	0	1	7
Zubrod Performance Status						
0	5	71	3	43	8	57
1	2	29	4	57	6	43
Estimated % weight loss in last 3 months						
<5%	5	71	6	86	11	79
5%-<10%	1	14	1	14	2	14
Unknown	1	14	0	0	1	7
Stage group						
I	1	14	1	14	2	14
II	0	0	0	0	0	0
IIIA	3	43	3	43	6	43
IIIB	2	29	1	14	3	21

	Level 1		Level 2		Total	
Unknown	1	14	2	29	3	21
Primary tumor location						
Right upper lobe	0	0	3	43	3	21
Right mainstem bronchus/Right hilum	1	14	0	0	1	7
Right middle lobe	0	0	1	14	1	7
Right lower lobe	2	29	0	0	2	14
Multiple right lobes	0	0	1	14	1	7
Left upper lobe	2	29	1	14	3	21
Left mainstem bronchus/Right hilum	0	0	1	14	1	7
Left lower lobe	2	29	0	0	2	14
N classification						
N0	1	14	3	43	4	29
N1	0	0	1	14	1	7
N2	3	43	3	43	6	43
N3	3	43	0	0	3	21

Table 2: Chemotherapy and Acute Radiotherapy Toxicity – Grade 3+ *Reported as Definitely, Probably or Possibly Related to Treatment*

	Sequence A, Level 1 (n=7) Grade		Sequence B, Level 1 (n=7) Grade		Sequence A, Level 2 (n=7) Grade			Sequence B, Level 2 (n=7) Grade		Sequence A, Level 3 (n=6) Grade	
Category	3	4	3	4	3	4	5	3	4	3	4
Auditory/hearing	0	0	0	0	0	0	0	1	0	0	0
Blood/bone marrow	4	3	2	1	3	1	0	1	1	1	0
Cardiovascular (arrhythmia)	0	0	0	0	0	0	0	1	0	0	0
Cardiovascular (general)	1	0	0	0	0	0	0	0	1	0	0
Constitutional symptoms	1	0	1	0	1	0	0	0	1	0	0
Gastrointestinal	4	0	3	0	3	1	0	1	2	1	0
Infection/febrile neutropenia	1	0	0	0	0	0	1	2	0	0	0
Metabolic/laboratory	3	0	1	0	1	1	0	1	0	0	0
Neurology	1	0	0	0	0	0	0	1	0	0	0
Pain	0	0	1	0	0	0	0	0	0	1	0
Pulmonary	1	0	0	0	1	1	0	0	1	0	0
Worst non-hematologic	5 (71%)	0 (0%)	3 (43%)	0 (0%)	4 (57%)	1 (14%)	1 (14%)	0 (0%)	3 (43%)	1 (17%)	0 (0%)
Worst overall	4 (57%)	3 (43%)	3 (43%)	1 (14%)	5 (71%)	1 (14%)	1 (14%)	0 (0%)	3 (43%)	2 (33%)	0 (0%)

Table 3: Late Radiotherapy Toxicity

	Sequence A, Level 1 (n=7) Grade		Sequence B, Level 1 (n=7) Grade		Sequence A, Level 2 (n=7) Grade				Sequence B, Level 2 (n=7) Grade			Sequence A, Level 3 (n=6) Grade	
	1	2	1	2	1	2	3	4	1	2	3	1	2
Esophagus	0	0	2	0	0	1	0	0	0	0	3	0	0
Skin (within the irradiated field)	1	0	0	0	0	0	0	0	0	0	0	1	0
Lung	3	1	2	2	1	2	0	1	1	2	2	0	1
Heart	0	1	0	1	0	0	0	0	1	0	0	0	0
Bone	0	0	1	0	0	0	0	0	0	0	0	0	0
Other	0	0	0	0	1	1	0	0	1	2	0	0	1
Worst overall	3 (43%)	2 (29%)	2 (29%)	2 (29%)	1 (14%)	3 (43%)	0 (0%)	1 (14%)	0 (0%)	1 (14%)	4 (57%)	1 17%	1 (17%)

Table 4: Radiotherapy Treatment Compliance

	Sequence A, Level 1 (n=7)		Sequence B, Level 1 (n=7)		Sequence A, Level 2 (n=7)		Sequence B, Level 2 (n=7)		Sequence A, Level 3 (n=6)		Total (n=34)	
	n	%	n	%	n	%	n	%	n	%	n	%
Per Protocol	7	100	6	86	5	71	6	86	6	100	30	88
Acceptable Variation	0	0	1	14	1	14	0	0	0	0	2	6
Unacceptable Deviation	0	0	0	0	1	14	0	0	0	0	1	3
Incomplete RT/Refusal	0	0	0	0	0	0	1	14	0	0	1	3

Table 5: Chemotherapy Treatment Compliance and Irinotecan Dose Intensity

	Sequence A, Level 1 (n=7)		Sequence B, Level 1 (n=7)		Sequence A, Level 2 (n=7)		Sequence B, Level 2 (n=7)		Sequence A, Level 3 (n=6)		Total (n=34)	
	n	%	n	%	n	n	%	%	N	%	n	%
Per Protocol	**5**	**71**	**6**	**86**	**7**	**100**	**7**	**100**	**4**	**67**	**29**	**85**
Not specified by reviewer	0	0	0	0	1	14	0	0	0	0	1	3
No modifications and/or delays	2	40	2	33	3	43	3	43	0	0	10	34
Modifications and/or delays	3	60	4	67	3	43	4	57	4	100	18	62
Not Per Protocol	**2**	**29**	**1**	**14**	**0**	**0**	**0**	**0**	**2**	**33**	**5**	**15**
Not specified by reviewer	0	0	0	0	0	0	0	0	1	50	1	20
Modifications and/or delays exceed protocol parameters, dose < 80%	2	100	1	100	0	0	0	0	1	50	4	80
Overall Dose Intensity (mg/m^2/wk)	(n=7)		(n=7)		(n=7)		(n=7)		(n=4*)		(n=32*)	
Median	27.0		31.4		29.7		33.8		34.0		31.4	
Range	17.6 – 36.2		14.1 – 33.5		25.3 – 39.4		4.1 – 36.7		26.5 – 34.6		4.1 – 39.4	

*1 patient had incomplete irinotecan delivery information, 1 patient had conflicting dosage data.

Table 6: Overall Survival

Time (years)	Sequence A % Alive (95% CI)	Sequence A # at Risk	Sequence B % Alive (95% CI)	Sequence B # at Risk
0	100% (N/A)	20	100% (N/A)	14
1	70.0% (45.1, 85.3)	14	78.6% (47.2, 92.5)	11
2	50.0% (27.1, 69.2)	10	42.9% (17.7, 66.0)	6
3	35.0% (15.7, 55.2)	7	28.6% (8.8, 52.4)	4
4	25.0% (9.1, 44.9)	3	28.6% (8.8, 52.4)	3
5	N/A*	0	19.0% (3.6, 43.7)	1
Dead/Total	15/20		12/14	
MST (95% CI)	1.9 (0.8, 3.7)		1.3 (0.9, 4.3)	
Median follow-up for all patients (Min-Max)	1.9 (0.6 – 5.0)		1.3 (0.7 – 5.7)	
Median follow-up for alive patients (Min-Max)	4.1 (3.7 – 5.0)		4.4 (3.9 – 5.0)	

Abbreviations: MST, median survival time, CI, confidence interval
*Last patient censored at 4.99 years.

Figure 1 - SEE CORRESPONDING PDF

Table 7: Progression-Free Survival

Time (years)	**Sequence A** % Alive Without Failure (95% CI)	# at Risk	**Sequence B** % Alive Without Failure (95% CI)	# at Risk
0	100% (N/A)	20	100% (N/A)	14
1	50.0% (27.1, 69.2)	10	50.0% (22.9, 72.2)	7
2	30.0% (12.3, 50.1)	6	28.6% (8.8, 52.4)	4
3	30.0% (12.3, 50.1)	6	28.6% (8.8, 52.4)	4
4	18.8% (5.2, 38.6)	2	28.6% (8.8, 52.4)	3
5	N/A*	0	19.0% (3.6, 43.7)	1
Failed /Total	16/20		12/14	
MST (95% CI)	1.1 (0.7, 3.1)		1.1 (0.5, 4.3)	

Abbreviations: MST, median survival time, CI, confidence interval
*Last patient censored at 4.99 years.

Figure 2 - SEE CORRESPONDING PDF

Table 8: Response

	Sequence A Best Observed Response		**Sequence B** Best Observed Response	
	n	%	n	%
Complete Response	12	60	8	57
Partial Response	6	30	5	36
Stable Disease	2	10	0	0
Progressive Disease	0	0	1	7

References:

1. American Cancer Society. Cancer Facts and Figures 2005. Atlanta, GA: American Cancer Society, 2005. Available online at http://www.cancer.org/docroot/STT/stt_0.asp. 5 Last accessed June 15, 2005.
2. Simon GR, Turrisi A: Management of small cell lung cancer: ACCP evidence-based clinical practice guidelines, 2nd edition. Chest 132:324S-339S, 2007 (suppl 3)
3. Ettinger DS. Overview and state of the art in the management of lung cancer. Oncology (Huntingt), 2004; 18(7 Suppl 4):3-9.
4. Stupp R, Monnerat C, Turrisi AT 3rd, et al. Small cell lung cancer: state of the art and future perspectives. Lung Cancer 2004; 45(1):105-17.
5. Murren JR, Turrisi AT, Pass HI. Small cell lung cancer. In: DeVita VT, Jr, Hellman S, Rosenberg SA, editors. Cancer: principles and practice of oncology. 7th edition. Philadelphia: Lippincott, Williams & Wilkins; 2005. p. 810-843.
6. Osterlind K. Chemotherapy in small cell lung cancer. Eur Respir J 2001 Dec; 18(6):1026-43.
7. Takada, M., Fukuoka, M., Kawahara, M., Sugiura, T., Yokoyama, A., Yokota, S., Nishiwaki, Y., Watanabe, K., Noda, K., Tamura, T., Fukuda, H., Saijo, N. (2002). Phase III Study of Concurrent Versus Sequential Thoracic Radiotherapy in Combination With Cisplatin and Etoposide for Limited-Stage Small-Cell Lung Cancer: Results of the Japan Clinical Oncology Group Study 9104. *J. Clin. Oncol.* 20: 3054-3060
8. Murray N, Coy P, Pater JL et al. The importance of time for thoracic radiation in the combined modality treatment of limited stage small-cell lung cancer. J Clin Oncol 11: 336-344, 1993.
9. Turissi AT, Kim K, Blum R, Sause WT, Livingston RB, Komacki R, Wagner H, Eisner S, Johnson DH. Twice daily compared with once daily thoracic radiotherapy in limited small cell lung cancer treated concurrently with cisplatin and etoposide. N Eng J Med 340: 265-271, 1999.

10. Choi NC, Herndon JE 2nd, Rosenman J, Carey RW, Chung CT, Bernard S, Leone L, Seagren S, Green M. Phase I study to determine the maximum-tolerated dose of radiation in standard daily and hyperfractionated-accelerated twice-daily radiation schedules with concurrent chemotherapy for limited-stage small-cell lung cancer. J Clin Oncol. 1998 Nov;16(11):3528-36
11. Noda K, Nishiwaki Y, Kawahara M, et al: Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small cell lung cancer. N Engl J Med 346:85-91, 2002
12. Tamura K, Takada M, Kawase I, et al. Enhancement of tumor radio-response by irinotecan in human lung cancer xenografts. Jpn J Cancer Research 1997;88:218-223
13. Hermes A, Bergman B, Bremnes R, et al: Irinotecan plus carboplatin versus oral etoposide plus carboplatin in extensive small-cell lung cancer: A randomized phase III trial. J Clin Oncol 26:4261-4267, 2008
14. Hanna N, Bunn PA, Jr., Langer C, et al. Randomized phase III trial comparing irinotecan/cisplatin with etoposide/cisplatin in patients with previously untreated extensive-stage disease small-cell lung cancer. J Clin Oncol 2006; 24:2038-2043
15. Natale RB, Lara PN, Chansky K, et al S0124: A randomized phase III trial comparing irinotecan/cisplatin (IP) with etoposide/cisplatin (EP) in patients with previously untreated extensive stage small cell lung cancer (E-SCLC) Proc Am Soc Clin Oncol 2008, A-7512, p400s
16. Green MR, Dowlati A, Yellamraju L, Daniels L, Willey J, Andrews M, Leff R. Irinotecan-cisplatin therapy for patients with extensive-stage small cell lung cancer: use patterns among American medical oncologists 2000-2006J Thorac Oncol. 2007 Oct;2(10):953-6
17. Saijo, H., Takada, Y., Ichinose, Y., Eguchi, K., Kudoh, S., Matsui, K., Nakagawa, K., Takada, M., Negoro, S., Tamura, K., Ando, M., Tada, T., Fukuoka, M. (2006). Phase II Study of Etoposide and Cisplatin With Concurrent Twice-Daily Thoracic Radiotherapy Followed by Irinotecan and Cisplatin in Patients With Limited-Disease Small-Cell Lung Cancer: West Japan Thoracic Oncology Group 9902.. *J. Clin. Oncol.* 24: 5247-5252 [Abstract]

18. Langer CJ, Somer R, Litwin S, Feigenberg S, Movsas B, Maiale C, Sherman E, Millenson M, Nicoloau N, Huang C, Treat J Phase I study of radical thoracic radiation, weekly irinotecan, and cisplatin in locally advanced non-small cell lung carcinoma. J Thorac Oncol. 2007 Mar;2(3):203-9
19. Chakravarthy A, Choy H, DeVore RD, Roberts J, Yunus F, Gagasia M et al. A phase I trial of outpatient weekly irinotecan and carboplatin with concurrent radiation therapy for stage III unresectable non-small cell lung cancer: A Vanderbilt Cancer Center Affiliate Network trial. Proc Am Soc Clin Oncol 2000, 19: A-2040.
20. Chakravarthy A, Choy H A phase I trial of outpatient weekly irinotecan/carboplatin and concurrent radiation for stage III unresectable non small-cell lung cancer: a Vanderbilt-Ingram Cancer Center Affiliate Network Trial. Clin Lung Cancer. 2000 May;1(4):310-1
21. Arbuck SG, Ivy SP, Setser A; et al. The Revised Common Toxicity Criteria: Version 2.0. CTEP Website. http://ctep.info.nih.gov.
22. Cox JD, Stetz J, Pajak TF et al: Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC) Int J Radiat Oncol Biol Phys. 31(5):1341-6, 1995
23. Kaplan EL and Meier P: Nonparameteric estimation from incomplete observations. J. Amer. Statist. Assoc. 1958, 53:457-481
24. Shin, C, Shim JJ, In KH, Kang KH, Yoo SH, Phase II study of irinotecan plus cisplatin with concurrent radiotherapy for the patients with limited-disease small-cell lung cancer_Lung Cancer (2006) 53, 361—366