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Short Communication: Interim toxicity analysis for patients with limited stage small cell lung cancer (LSCLC) treated on CALGB 30610 (Alliance) / RTOG 0538

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Abstract

Introduction—The CALGB 30610/RTOG 0538 randomized trial was designed to test whether high-dose thoracic radiotherapy (TRT) would improve survival compared with 45 Gy twice-daily (BID) TRT in limited stage small cell lung cancer (LSCLC). Two piloted experimental TRT regimens were of interest to study, 70 Gy daily (QD) and 61.2 Gy concomitant boost (CB). Driven by concerns about adequate patient accrual, a study design was employed that eliminated

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one experimental TRT arm based on early interim toxicity and tolerability, with the study then continuing as a traditional 2-arm phase III study.

Methods—Patients with LSCLC were assigned to receive four cycles of cisplatin and etoposide chemotherapy with one of 3 TRT regimens starting with either the first or second cycle of chemotherapy. The interim endpoint was the cumulative highest toxicity calculated from a scoring system based on treatment-related grade 3 and higher toxicity and the ability to complete therapy in the experimental arms.

Results—The final interim analysis was performed after 70 patients accrued to each experimental cohort, and a difference in treatment related toxicity scoring was not found ($p = 0.739$). Severe esophageal toxicity was comparable in both cohorts. Pulmonary toxicity was low overall, though 4 patients (5.7%) on the 61.2 Gy arm developed grade 4 dyspnea, which was not observed in the 70 Gy arm. A protocol mandated decision was made to discontinue the 61.2 Gy arm following review of toxicity with the Data and Safety Monitoring Board.

Conclusion—A randomized trial design using a planned early interim toxicity analysis to discriminate between experimental treatment arms is feasible in a phase III setting. Refinement of the design could increase the likelihood of detecting clinically meaningful differences in toxicity in future studies.

Keywords

small cell; radiotherapy dose; fractionation

1.0 Introduction

The optimal thoracic radiotherapy (TRT) regimen, concurrent with systemic chemotherapy, is an area of active study in limited stage small cell lung cancer (LSCLC). The current standard, 45 Gy BID in 1.5 Gy fractions, was defined in a prior Intergroup phase 3 trial (INT 0096). Although overall survival (OS) was improved with BID TRT compared with QD TRT to the same dose of 45Gy[1], the BID regimen has not been widely adopted as routine standard practice in the United States, in part because of the increased toxicity associated with BID TRT[2]. Moreover, the benefit of BID TRT has been questioned given the low biologic predicted efficacy of the 45 Gy QD RT regimen used on INT 0096. As such, two alternative regimens with substantially higher predicted biologic efficacy, 70 Gy QD TRT over 7 weeks and 61.2 Gy CB TRT over 5 weeks with BID treatment the final 9 days, were prospectively evaluated in the cooperative group setting with initial encouraging results[3,4].

Both high-dose QD TRT and CB TRT were of interest to study, but it was recognized that conducting a three-arm phase 3 trial would not be feasible given the large number of patients required. Thus, a toxicity-based approach was utilized in designing Cancer and Leukemia Group B (CALGB) 30610/ Radiation Therapy Oncology Group (RTOG) 0538, with early assessment of toxicity and tolerability performed to discontinue one of the experimental arms. The study then continued as traditional randomized trial with a primary OS endpoint. CALGB is now part of the Alliance for Clinical Trials in Oncology.

2.0 Methods

The overall trial design has been previously published[5]. Each participant signed an IRB-approved, protocol-specific informed consent document in accordance with federal and institutional guidelines. In brief, ECOG performance status 0–2 patients with LSCLC and regional lymph node involvement, excluding contralateral hilar and supraclavicular nodes, were randomly assigned 1:1:1 to receive four cycles of cisplatin and etoposide chemotherapy with one of three TRT regimens starting with either the first or second cycle of chemotherapy. Stratification factors included gender, performance status, weight loss of more than 5% prior to study entry, and radiotherapy planning technique (3D conformal vs intensity modulated). TRT was directed to the areas of disease involvement on CT and/or FDG-PET imaging and the ipsilateral hilum was included in the target volume regardless of clinical involvement. Allowance for repeat simulation and adaptation of the radiotherapy plan was included in both regimens.

An interim toxicity scoring system was developed specifically for this protocol assigning 1 point for grade 3 non-hematologic toxicity and/or grade 4 hematologic toxicity, 2 points for grade 4 non-hematologic toxicity or failure to complete 4 cycles of chemotherapy, and 3 points for any grade 5 toxicity. Only the highest single toxicity score (CTCAE v 3) for each patient was included. All treatment related AEs were used in the analysis, regardless of whether the AE was determined to be directly associated with radiotherapy. With the toxicity score of each patient, the p-values for a two-sample t-test and a permutation t-test from comparing the toxicity scores of the two experimental treatment arms were calculated. Data collection and statistical analyses were conducted by the Alliance Statistics and Data Center (SDC). Data quality was ensured by review of data by the SDC and by the study chairperson following Alliance policies.

The trial was designed such that toxicity severity scores were to be compared after accrual of 30, 50 and 70 patients to each experimental arm, and permutation t-test used to compare toxicity severity scores. If a significant difference was not found after analysis of 70 patients in each cohort, then the study mandated for discontinuation of a treatment arm following review by the study team and the Data and Safety Monitoring Board (DSMB).

3.0 Results

The trial was activated March, 2008. Seventy patents had been accrued to each experimental cohort from a total of 75 centers at the time of interim toxicity analysis in May, 2012. The DSMB released this data for presentation in 2019 and a confirmatory analysis was performed April, 2019.

The median age for patients on each treatment arm was 62 years, with a slightly higher percentage of male patients in the 70 Gy arm (51.4%) than the 61.2 Gy arm (47.3%). Flourodeoxyglucose F 18 (^{18}F-FDG) positron emission tomography staging was performed in 36 patients (51%) in the 70 Gy arm and 33 patients (47%) in the 61.2 Gy arm. Additional patient and treatment characteristics are shown in table 1.

Analysis following accrual of 30, 50, and then 70 patients to each experimental regimen failed to demonstrate a significant difference in treatment-related toxicity (p = 0.739, permutation t test). A significant difference in toxicity scores was also not observed when assessed without consideration of attribution of the toxicity to treatment (p-value = 0.630, permutation t test).

Table 2 lists grade 3+ treatment-related adverse events (AEs) occurring in more than 10% of either arm. Grade 3 and grade 4 overall toxicity was 21.4% and 54.3% in the QD arm vs. 20% and 57% in the CB arm, while grade 3 and grade 4 non-hematologic toxicity was 10% and 12.9 % in the QD arm vs. 12.9% and 14.3% in the CB arm. Pulmonary toxicity was relatively uncommon with 2.9 % grade 3 pneumonitis observed in each cohort. Grade 4 dyspnea was not observed in the QD arm, but reported in 4 patients (5.7 %) in the CB arm. Grade 4 pulmonary toxicity developed during active chemotherapy and either during or after TRT in each patient, resulting in discontinuation of protocol therapy. All were planned with 3D conformal radiotherapy. The sole death attributed to treatment was in the CB arm and related to febrile neutropenia. The eventual decision to close the CB arm was based on a qualitative review of the toxicity distribution as the protocol mandated discontinuing one experimental arm.

Variables that may impact toxicity such as stage, tumor volume, and tumor location were not readily available, but a post-hoc analysis was performed to assess radiation dose to normal lung and esophagus. Data was obtained for the majority of patients in each cohort (table 3).

4.0 Discussion

At the time that the CALGB 30610 trial was designed, there was substantial interest in studying high dose thoracic radiotherapy. Advances in radiotherapy planning and treatment techniques were thought to facilitate the safe delivery of higher doses of TRT in both locally advanced non-small cell lung cancer (LANSCLC) and LSCLC. The 70 Gy QD regimen studied by CALGB and the 61.2 Gy CB regimen developed by RTOG both had higher predicted efficacy than standard 45 Gy BID, but it was recognized that completing accrual to a full-fledged three arm trial would be challenging. This led to development of a design where relatively “real-time” assessment of toxicity of the 2 experimental arms could be performed and allow one arm to be dropped relatively early with the trial continuing as a traditional phase III comparison.

Though significant differences in toxicity were not observed between experimental arms, the design facilitated a transition to a 2-arm trial, necessary for successful trial completion. The ultimate decision to discontinue the 61.2 Gy CB arm was based on qualitative toxicity assessment, including reporting of grade 4 pulmonary toxicity with CB but not with QD TRT, as well as consideration of maintaining the most clinically relevant experimental arm. Patterns of care studies show the majority of patients are treated with QD TRT in clinical practice, in part because of logistical considerations, but also due to concerns about heightened toxicity with BID TRT.[2] Given the similar toxicity profile of the 2 experimental arms, retaining the 70 Gy daily regimen seemed to have the largest potential impact on clinical practice. Alternatively, the CB regimen design has the advantage of maintaining an

element of treatment acceleration while also increasing nominal TRT dose, and the reduced treatment time may be important in fast growing tumours such as SCLC. While a past trial assessed the CB regimen, long-term outcomes for this cohort in the current study will be of particular interest[4].

The decision to use measures of toxicity and tolerability, rather than efficacy, to discriminate between experimental treatment arms was made in an effort to reduce the study to 2 arms in timely manner. Even then, it took longer than expected before a final decision to drop the CB TRT arm, in part because initial interim analyses failed to show differences in toxicity between arms.

Enhancements could be considered that might improve the trial design and permit both a speedier and perhaps more valid decision. There has been substantial recent experience defining the value of patient-reported outcomes (PROs), which are now appropriately routinely integrated in many trials[6]. This point is further emphasized by the inconsistency of traditional prospective data collection highlighted in table 2. For example, in the CB TRT arm 11 patients were scored as having Grade 3 + dysphagia with only 3 patients scored as Grade 3+ esophagitis, even though the definition is of both toxicities is the same. In addition, restricting revising the toxicity scoring system to only include AEs more directly related to radiotherapy treatment would also yield a more valid comparison, and the inclusion of AEs such as hypokalemia and hyponatremia (table 2) may have confounded the toxicity analysis. A better-balanced comparison could also be accomplished using a more sophisticated algorithm to stratify patients, which might consider both the extent of tumor and volume of normal tissue, such as lung esophagus and heart, at risk for TRT. In particular, outcomes from the RTOG 0617 trial in non-small cell lung cancer (NSCLC) have highlighted the potential impact of normal tissue dose on subsequent toxicity and ultimate OS[7]. A limited post-hoc analysis performed for the current study shows that dose to lung and esophagus were relatively higher for the QD cohort compared with the CB cohort (table 3). This suggests that the QD cohort may have been at greater risk for treatment-related toxicity, though more in-depth analysis is needed.

Despite initial enthusiasm that increasing TRT dose via standard fractionation would improve outcomes, disappointing results from the CONVERT trial in LSCLC and the phase III RTOG 0617 trial in LANSCLC have called the approach of using high nominal dose once-daily TRT into question.[7,8] A total nominal dose of 66 Gy QD TRT did not improve OS compared with the lower nominal dose of 45 Gy BID TRT in CONVERT, with the hazard ratio favouring the BID arm, and OS was significantly decreased with 74 Gy QD TRT (compared with 60 Gy) on RTOG 0617. The reason high dose QD TRT failed to improve outcomes on these trials is not clear, but may relate in part to the toxic effects of dose escalation, even though modern radiotherapy techniques were used and treatment volumes were limited by omitting elective nodal irradiation.

Given these results, the ultimate outcomes of patients treated with 70 Gy QD TRT on CALGB 30610, which should be available for presentation in mid to late 2021, will be of particular value in helping to determine whether this is indeed a viable approach. Data from the ongoing prospective phase III NRG trial assessing the role of immunotherapy in LSCLC

(LU-005), which allows a choice of either 66 Gy QD or 45 Gy BID TRT, will further contribute to the knowledge base defining the TRT therapeutic ratio in LSCLC.[9]

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HIGHLIGHTS

- CALGB 30610/RTOG 0538 used a novel design in order to select one of two high dose radiotherapy regimens to compare against standard 45 Gy BID in limited stage small cell lung cancer (LSCLC)
- The experimental regimen, either 70 Gy once-daily (QD) and 61.2 Gy concomitant boost (CB), would be chosen based on interim toxicity and tolerability
- Both experimental regimens appeared tolerable and had similar toxicity scores.
- The decision to discontinue the 61.2 Gy CB arm was based on the observation that more patients experience grade 4 pulmonary toxicity with this regimen. It was also believed that studying 70 Gy QD would have the larger potential impact on clinical practice.
- Suggestions for improvement in similar trial designs are discussed.
- Long-term outcomes of the study will provide further data regarding the therapeutic ratio of high dose QD radiotherapy in LSCLC

Table 1.

Select Patient and Treatment Characteristics

	Arm B (N=70)	Arm C (N=70)	Total (N=140)	p value
Weight Loss 6 Months Prior to Study				0.5316
<=5% / 6 months	57 (81.4%)	54 (77.1%)	111 (79.3%)	
>5% / 6 months	13 (18.6%)	16 (22.9%)	29 (20.7%)	
Performance Status				0.7957
0	30 (42.9%)	30 (42.9%)	60 (42.9%)	
1	34 (48.6%)	36 (51.4%)	70 (50.0%)	
2	6 (8.6%)	4 (5.7%)	10 (7.1%)	
Radiotherapy Method				1.0000
IMRT	21 (30.0%)	21 (30.0%)	42 (30.0%)	
3D	49 (70.0%)	49 (70.0%)	98 (70.0%)	
RT Start Time				0.5740
Cycle 1	49 (70.0%)	50 (71.4%)	99 (70.7%)	
Cycle 2	21 (30.0%)	20 (28.5%)	40 (28.6%)	

RT, radiotherapy

Table 2.

Commonly Occurring (> 10% in any arm) Grade 3+ Adverse Events (AE)

	Arm B (N=70)	Arm C (N=70)	Total (N=140)
Evaluable for AE Analyses	64 (91.4%)	66 (94.3%)	130 (92.8%)
Neutropenia	50(71.4%)	47(67.1%)	97(69.3%)
Leukopenia	45(64.3%)	41(58.6%)	86(61.4%)
Anemia	15(21.4%)	16(22.9%)	31(22.1%)
Dehydration	17(24.3%)	11(15.7%)	28(20%)
Esophageal pain	13(18.6%)	15(21.4%)	28(20%)
Dysphagia	14(20%)	11(15.7%)	25(17.9%)
Lymphopenia	9(12.9%)	14(20%)	23(16.4%)
Hypokalaemia	8(11.4%)	13(18.6%)	21(15%)
Thrombocytopenia	10(14.3%)	11(15.7%)	21(15%)
Nausea	10(14.3%)	10(14.3%)	20(14.3%)
Febrile neutropenia	7(10%)	9(12.9%)	16(11.4%)
Fatigue	9(12.9%)	6(8.6%)	15(10.7%)
Hyponatraemia	7(10%)	8(11.4%)	15(10.7%)
Esophagitis	11(15.7%)	3(4.3%)	14(10%)
Emesis	9(12.9%)	5(7.1%)	14(10%)

AE, adverse event

Table 3.

Radiation Dose to Normal Lung and Esophagus

	Arm B	Arm C	All
Esophageal Mean Dose			
N	51	60	111
Mean	2904 Gy	2500 Gy	2686 Gy
Median	2890 Gy	2502Gy	2683 Gy
Q1, Q3	1971, 3713	1739, 3054	1935, 3265
Lung Mean Dose			
N	53	60	113
Mean	1940 Gy	1760 Gy	1844 Gy
Median	1910Gy	1717 Gy	1830 Gy
Q1, Q3	1615, 2341	1406, 2028	1477, 2135
Lung V20			
N	53	61	114
Mean	33.3 %	30.9 %	32.0 %
Median	33.0 %	32.0 %	32.0 %
Q1, Q3	27.0, 39.5	25.7, 38.0	27.0, 38.6

N, number of patients; Q, quartile; V20, volume of lung to receive ≥20 Gy