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ORIGINAL ARTICLE

Comparison of once daily radiotherapy to 60 Gy and twice daily radiotherapy to 45 Gy for limited stage small-cell lung cancer

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Abstract

Background: This study was designed to compare toxicities, disease control, and survival outcomes for limited disease small-cell lung cancer (LD-SCLC) treated with once daily (QD) versus twice daily (BID) radiotherapy.

Methods: All of the patients received four to six cycles of platinum plus etoposide. In the QD group, irradiation was given via conventional radiotherapy with a dose of 60 Gy at 2 Gy per once-daily fraction. In the BID group, the dose was 45 Gy at 1.5 Gy per twice-daily fraction.

Results: Data from a total of 143 LD-SCLC patients treated at the Shandong Cancer Hospital & Institute were retrospectively analyzed. Statistically significant differences were found in the rates of both grade 2 or higher esophagitis ($P = 0.036$) and pneumonitis ($P = 0.043$) between QD and BID groups, respectively. Grade 3 esophagitis occurred in 6% of patients receiving QD and 19% of those receiving BID therapy. The median overall survival (OS) of all patients was 30.4 months: 29.5 months for QD therapy, and 31.4 months for BID therapy. The two-year OS rate was 43.3% for QD therapy, and 48.8% for BID therapy. The two-year locoregional recurrence-free survival (LRFS) rate was 45% versus 63.4% for the QD group versus the BID group, respectively.

Conclusions: Pneumonitis was more common in the QD group, and esophagitis was more common in the BID group. Although there were no significant differences in OS and LRFS between the QD and BID groups, there was a trend toward improved local control in the BID group.

Introduction

Small cell lung cancer (SCLC) accounts for 10–15% of all lung cancer cases.[1] At the time of diagnosis, 30–40% of SCLC patients present with limited disease (LD) that may be contained in a tolerable radiotherapy (RT) volume.[2]

Concurrent chemoradiotherapy represents the standard treatment for patients with LD-SCLC based on two meta-analyses in the 1990s.[3,4] Nonetheless, despite the combination of thoracic radiotherapy (TRT) and chemotherapy, SCLC is still characterized by inevitable local failure and distant metastasis as a result of its aggressive nature. Standard combination chemotherapy regimens are four to six cycles of etoposide and cisplatin according patients' tolerance to chemotherapy.[5] However, the optimal RT approach remains controversial with respect to timing, dose-fractionation, and target definition. As far as dose-fractionation is concerned, accelerated hyper-fractionated RT (45 Gy with 1.5 Gy twice daily in 3 weeks) and dose-escalated conventional RT (60–70 Gy with 2 Gy once daily in 6–7 weeks) have been documented as reliable schedules, and an international randomized trial (CALGB 30610) is currently underway to compare these two schedules concurrent with chemotherapy in the treatment of LD-SCLC.[6] However, the results will not be available for several years. In the present study we compared toxicities, disease control, and survival in patients treated with either once daily (QD) or twice-daily (BID) RT with platinum-based chemotherapy at our institution.

Methods

Patient selection

Inclusion criteria were: Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; life expectancy > 3 months; age less than 75 years; no serious complications, such as hypertension, coronary heart disease, and psychiatric history; a detailed pretreatment assessment including a bone scan and computed tomography (CT) scan of the head, neck, chest, and abdomen, physical examination, electrocardiogram, complete blood count, urinalysis and chemistry tests (including liver and kidney function tests). The study was under protocols approved by the institutional review boards of the Shandong Cancer Prevention and Treatment Research ethics committee.

Chemotherapy

The most common chemotherapy regimen consisted of etoposide (100 mg/m^2 intravenously on days 1–5) and cisplatin (25 mg/m^2 intravenously on days 1–3) (EP) and was administered every three weeks.

Radiotherapy

Thoracic radiotherapy was performed using a Varian linear accelerator (Varian Medical Systems, Palo Alto, CA, USA). Patients were immobilized in the supine position using a plastic mesh mask and then consecutively underwent CT scanning with 3 mm slice thickness scans. Both of the target volumes for TRT were similar. The gross tumor volume (GTV) referred to the restaging chest CT obtained after induction chemotherapy, including the residual primary tumor and all clinically involved lymphatic regions. When enlarged lymph nodes (greater than 1.0 cm in short axis measurement on CT, or demonstrated positive on the fludeoxyglucose-positron emission tomography [FDG-PET]/CT scan) resolved after induction chemotherapy, the previously involved lymph node regions were still included in the radiation target by reviewing the prechemotherapy CT scan. Elective treatment of clinically uninvolved lymphatic regions was not carried out. The planning target volume (PTV) was defined by the expanding GTV with a 0.8 to 1.5 cm margin.

In the QD group, the prescribed dose was 60 Gy in 30 fractions at 2 Gy QD to the PTV. In the BID group, the prescribed dose was 45 Gy in 30 fractions at 1.5 Gy BID to the PTV. All fractional doses were given five days each week and the BID dose was given at least six hours between fractions.

For each plan, according to different situations, the gantry angles were set to reduce the radiation volume to normal tissues as much as possible. All plans were designed and optimized for Varian Trilogy equipped with a Millennium multileaf collimator (MLC) with 120 leaves for 6- or 15-MV photon beams. All dose distributions were computed with the analytical anisotropic algorithm (AAA) implemented in the Eclipse 8.6.15 treatment planning system with a maximum calculation grid resolution of 2.5 mm. The dose volume histogram (DVH) constraints of the organs at risk (OARs) were as follows: mean lung dose < 20 Gy and lung V20 < 33%; mean heart dose < 30 Gy and heart V40 < 46%; mean esophagus dose < 34 Gy; esophagus V35 < 50%; in the QD group spinal cord Dmax ≦50 Gy; and in the BID group spinal cord Dmax ≦41 Gy.[7,8]

The biological equivalent dose (BED) was calculated using the linear quadratic formula: $BED = (nd)[1 + d/(\alpha/\beta)] - (0.693t/\alpha Tpot)$, where n = the total number of fractions delivered; d = the dose per fraction (Gy); $\alpha/\beta = 10$ for acute effects and tumor control and three for chronic effects; $\alpha = 0.3\ Gy^{-1}$; t = total days in which RT was delivered; and Tpot = potential doubling time (5.6 days).[9,10] The BED using an α/β ratio of 10 was 54.7 and 43.1 Gy for the QD and BID regimens, respectively.

Prophylactic cranial irradiation

After completion of chemotherapy and TRT, patients who achieved a complete response (CR) or near complete response (nCR) were offered the option of prophylactic cranial irradiation (PCI).

Adverse effect assessment

Side effect assessment was graded using the National Cancer Institute Common Toxicity Criteria (version 3.0) during the RT and chemotherapy periods. Three months after treatment, late toxicities were evaluated according to the Radiation Therapy Oncology Group (RTOG)/European Organization for Research and Treatment of Cancer late radiation morbidity scoring schema.

Follow-up

Treatment response was estimated using CT or PET-CT after treatment, according to Response Evaluation Criteria in Solid Tumors (version 1.0). Follow-up after treatment completion was every three months over the first two years and every six months thereafter. Each visit included medical history, physical examination, complete blood count, chest and abdomen CT, brain magnetic resonance imaging/CT, and bone scan (if necessary).

Study endpoints and statistics

Overall survival (OS) was observed from the first day of treatment until death or last follow-up; progression-free survival

(PFS) was observed from the first day of treatment until progress, death or last follow-up; and locoregional recurrence-free survival (LRFS) was observed from the first day of treatment until recurrence, death or last follow-up. OS, PFS, and LRFS were estimated using the Kaplan–Meier method. Differences between the two groups in patient characteristics, toxicity or treatment response were assessed using the *t*-test for numerical data and the Fisher exact test or Chi-square test for categorical data. A value of $P < 0.05$ was considered significant. Statistical calculations were performed using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA).

Results

Patients data

Between June 2008 and December 2013, 143 patients confirmed by pathology or cytology with stage I–III SCLC at the Shandong Cancer Hospital & Institute were retrospectively analyzed. Table 1 shows the main characteristics of the 143 patients; 80 received QD therapy, and 63 BID therapy. The median age was 55 (range, 35–74) and 58 years (range, 45 to 71) for patients receiving QD and BID therapy, respectively. There were no statistically significant differences in patient characteristics between the two groups. The differences in chemotherapy cycle numbers at the time of RT (P = 0.244) were not statistically significant between the two groups. One hundred and twenty-one (85%) patients received etoposide and cisplatin; of the remainder, 12 (8%) received etoposide and carboplatin, and 10 (7%) each received irinotecan and cisplatin or irinotecan and carboplatin. One hundred and twenty-seven patients (89%) received chemotherapy and RT concurrently, and 16 (11%) received sequential chemotherapy followed by RT.

Table 1 Patient characteristics

Characteristic	Value	QD	BID	Total	*P**
Number of patients		80	63	143	
Age (years)	Median	55	58	55	0.573
	Range	35–74	45–71	35–74	
ECOG PS (n)	0–1	74	59	133	0.529
	2	6	4	10	
Gender	Male	57	45	102	0.981
	Female	23	18	41	
Weight loss	0	61	50		0.777
	I	16	10		
	II	3	2		
	III	0	1		
T stage (n)	T1	9	7	16	0.997
	T2	22	20	42	
	T3	26	20	46	
	T4	23	16	39	
N stage (n)	N0	7	6	13	0.851
	N1	12	10	22	
	N2	52	40	92	
	N3	9	7	16	
AJCC 7 stage (n)	I	4	4	8	0.979
	II	14	12	26	
	IIIA	32	24	56	
	IIIB	30	23	53	
Chemotherapy cycle at start of radiation	1–2	46	42	88	0.391
	3–6	24	15	39	
	Sequential	10	6	16	

**P* values were calculated using the *t*-test for numerical data and the Fisher exact or Chi-square test for categorical data. AJCC, American Joint Committee on Cancer; BID, twice-daily; ECOG, Eastern Cooperative Oncology Group; PS, Performance Status; QD, once-daily.

Radiotherapy plan evaluation

The evaluation of the DVH-based parameters of the OARs is shown in Table 2. No significant differences were observed in the comparisons between the parameters of the total lung, ipsilateral lung, contralateral lung, the maximum irradiation dose to the spinal cord, V30 and mean dose to the heart, or V45 and mean esophagus dose (all $P > 0.05$).

Treatment response

Table 3 shows the response rates of the 143 patients. Nearly 90% had objective responses. There were no significant differences in the response rates between the groups. Seventy-seven patients (40 receiving QD and 37 receiving BID radiation) were administered PCI within four weeks of completion of all chemotherapy. There was no difference in PCI between the QD and BID groups. Of these, 62 (80%) received a regimen of 25 Gy in 10 fractions to the entire brain; the remainder received a regimen of 30 Gy in 10 fractions.

Toxicity

The toxicities of the 143 patients are presented in detail in Table 4. There were no significant differences between the groups in the incidence of grade 2 or higher hematologic toxicity. Necessary treatment measures, such as recombinant human interleukin and granulocyte colony stimulating factor, were provided and blood transfusions were given to patients with grade 4 hemoglobin toxicity (all patients fully recovered from hematologic toxicity). Statistically significant differences were found in the rates of both grade 2 or higher esophagitis ($P = 0.036$) and pneumonitis ($P = 0.043$) between the QD and BID groups, respectively. Grade 3 esophagitis occurred in 6% of patients receiving QD and 19% of those receiving BID therapy. The patients with grade 3 esophagitis required intravenous nutrition. None of the patients died of treatment-related causes.

Table 2 Comparisons of the DVH-based parameters of the OARs in the study

	QD mean ± SD Range	BID mean ± SD Range	*P**
GTV (cm^3)	70.4 19.4–102.3	101.2 34.6–134.8	0.236
CTV (cm^3)	160.8 38.4–240.6	201.5 80.9–320.1	0.307
PTV (cm^3)	216.5 97.3–350.7	291.4 154.4–406.9	0.143
Total lungs			
MLD (Gy)†	20.8 ± 1.5	17.3 ± 9.8	0.097
V5 (%)‡	68.3 ± 9.5	65.4 ± 9.3	0.652
V20 (%)‡	27.8 ± 5.2	23.4 ± 4.2	0.302
Ipsilateral lungs			
MLD (Gy)	23.1 ± 3.8	21.1 ± 2.5	0.504
V5 (%)	79.1 ± 9.8	78.3 ± 11.7	0.832
V20 (%)	47.2 ± 8.3	45.3 ± 10.1	0.526
Contralateral lungs			
MLD (Gy)	9.8 ± 3.2	9.1 ± 2.9	0.740
V5 (%)	52.7 ± 12.7	54.8 ± 13.1	0.762
V20 (%)	12.0 ± 7.8	8.1 ± 7.3	0.497
Spinal cord			
Dmax (Gy)††	43.2 ± 2.7	41.5 ± 2.0	0.105
Heart			
Dmean (Gy)†	15.9 ± 6.9	14.8 ± 7.0	0.604
V30 (%)§	23.1 ± 10.3	17.9 ± 11.2	0.452
Esophagus			
MED (Gy)†	28.4 ± 5.7	26.7 ± 4.7	0.567
V45 (%)¶	32.9 ± 5.3	33.0 ± 4.6	0.792

†The mean irradiation dose that the lung, heart and esophagus received, respectively; ‡The volume of the lung that received the 5 Gy and 20 Gy irradiation doses, respectively; §The volume of the heart that received the 30 Gy irradiation dose; ¶The volume of the esophagus that received the 45 Gy irradiation dose; ††The maximum irradiation dose that the spinal cord received.

**P* values were calculated using the *t*-test. BID, twice-daily; CTV, clinical target volume; DVH, dose volume histogram; GTV, gross tumor volume; MLD, median lung dose; OARs, organs at risk; PTV, planning target volume; QD, once-daily; SD, standard deviation.

Table 3 Results of treatment response

Results	QD N = 80	BID N = 63	*P**
			0.948
Response			
Complete response	36 (46%)	33 (52%)	
Partial response	30 (37%)	21 (33%)	
Near complete response	5 (6%)	3 (5%)	
Total	71 (89%)	57 (90%)	
Stable disease	5 (6%)	3 (5%)	
Progressive disease	4 (5%)	3 (5%)	

**P* values were calculated using the Fisher exact test. BID, twice-daily; QD, once-daily.

Survival

The median follow-up was 27.14 months, with a range of six–62 months until the last follow-up date (30 August 2014). Of the 143 patients, 107 had died: 62 (77%) patients who had received QD therapy and 45 (71%) who had received BID therapy. The median OS of all patients was 30.4 months: 29.5 months for QD, and 31.4 months for BID therapy (Figure 1). The two-year OS rate was 43.3% and 48.8% for QD and BID therapy, respectively. The five-year OS rate was 13.3% for QD, and 19.6% for BID therapy. The difference in OS between the two groups was not statistically significant ($P = 0.558$ by the log-rank test). The rate of two-year PFS was 33.2% for patients who had received QD therapy and 33.5% for those who had received BID therapy ($P = 0.515$ by the log-rank test; Figure 2). Although there was no statistically significant difference ($P = 0.068$ by the log-rank test) in LRFS between the QD and BID groups, there was a trend toward improved local control for the BID group, with an estimated two-year LRFS at 45% versus 63.4% for the QD group.

Discussion

There are conflicting reports as to the best method of integrating thoracic radiation with chemotherapy; multi-

Table 4 Treatment-related toxicity

Toxicity	Grade	QD	BID	Total	*P**
Hematologic toxicity (WBC)	≥2	54 (67%)	33 (52%)	87 (61%)	0.214
	≥3	36 (45%)	26 (41%)	62 (43%)	
Hematologic toxicity (PLT)	≥2	16 (20%)	10 (16%)	26 (19%)	0.112
	≥3	9 (11%)	5 (8%)	14 (10%)	
Hematologic toxicity (HB)	≥2	9 (11%)	9 (14%)	18 (13%)	0.634
	≥3	2 (3%)	3 (5%)	5 (3%)	
Stomach/intestine	≥2	42 (53%)	37 (59%)	79 (55%)	0.112
	≥3	16 (20%)	13 (21%)	29 (20%)	
Esophagitis	≥2	34 (43%)	42 (67%)	76 (53%)	0.036
	≥3	5 (6%)	12 (19%)	17 (12%)	
Pneumonitis	≥2	32 (40%)	9 (14%)	41 (29%)	0.043
	≥3	13 (16%)	4 (6%)	17 (12%)	

**P* values were calculated using the Fisher exact test. BID, twice-daily; HB, hemoglobin; PLT, platelet; QD, once-daily; WBC, white blood cell.

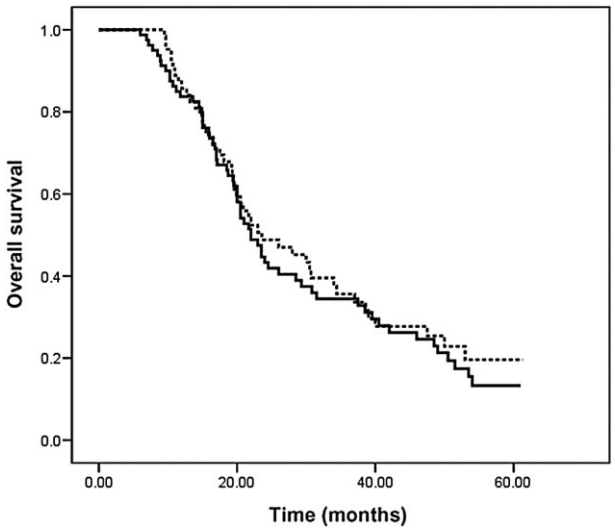

Figure 1 Incidence of overall survival by radiotherapy fractionation pattern. ⌐, once daily (QD); ⌒, twice daily (BID).

institutional cooperative groups have reported results of dose-escalation studies. CALGB 8837 reported the maximum tolerated doses for QD and BID TRT as 70 Gy in 35 fractions and 45 Gy in 30 fractions, respectively.[10] Turrisi *et al.* conducted a randomized trial that demonstrated a BID regimen of 45 Gy in 30 fractions over three weeks that was superior to 45 Gy in 25 daily fractions; as a result of their study, clinical use of accelerated hyper-fractionated RT in LD-SCLC has become more prevalent.[11] The NCCTG 95-20-53 trial, which included six cycles of EP, with cycles four and five including concurrent chemotherapy and TRT (30 Gy/20 BID fractions, a 2-week break, and further 30 Gy/20 BID fractions), resulted in a favorable five-year survival rate of 24%; however, the locoregional failure remained a problem and grade 3 or grade 3+ toxicity were as high as 97%.[10] In the RTOG 0239 study, patients with LD-SCLC were given thoracic radiation to 61.2 Gy over five weeks (daily 1.8 Gy fractions on days 1–22, then BID 1.8 Gy fractions on days 23–33), and the rates of grade 3 esophagitis and local regional failure were 18% and 20%, respectively; the two-year OS rate of 36.6% did not reach the projected goal.[12] The 2014 National Comprehensive Cancer Network (NCCN) recommended the standard doses for QD and BID TRT as 60–70 Gy in 30–35 fractions and 45 Gy in 30 fractions, respectively. In the present study we retrospectively analyzed the outcomes of LD-SCLC patients treated at our hospital with QD (60 Gy/30 fractions) or BID (45 Gy/30 fractions) TRT to obtain insights while awaiting results from CALGB 30610.[6]

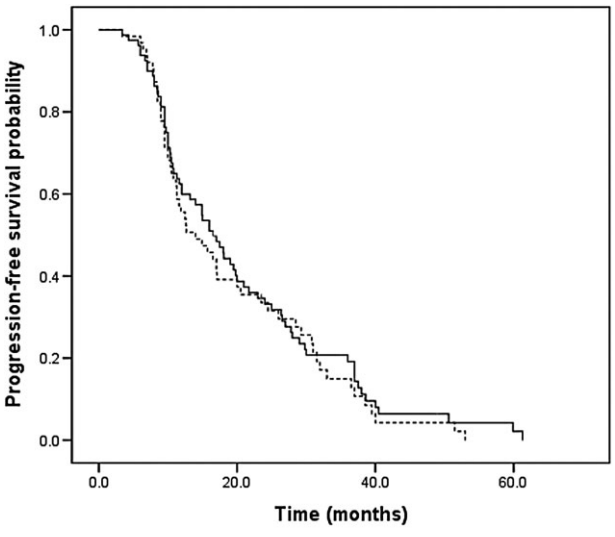

Figure 2 Incidence of progression-free survival by radiotherapy fractionation pattern. ⌐, once daily (QD); ⌒, twice daily (BID).

Mauguen *et al.* found that the rates of acute esophagitis increased in SCLC patients treated with BID TRT and our results also supported this view.[13] The main toxicity problem of the present study was grade 3 esophagitis, affecting 6% versus 19% (QD vs. BID). Esophagitis after RT did not lead to any limitation, and all of the affected patients recovered their ability to swallow. The grade 3 esophagitis rate was lower than 27%, which occurred in the BID arm of INT 0096.[11] INT 0096 protocol called for starting thoracic radiation on day one of chemotherapy on the basis of other studies showing that local control and survival were better when the radiation was started early relative to the chemotherapy.[14,15]

Our data also showed a statistically significant difference in grade 2 or higher pneumonitis, which occurred at higher rates in the QD subgroup. This is in keeping with a study by Gazula *et al.*, which showed higher rates of pneumonitis among LD-SCLC patients treated with a median dose of 61.2 Gy (range 50–66.6) in 1.8–2.0 Gy QD fractions, compared with patients treated with 45 Gy in 1.5 Gy BID fractions.[16] However, Watkins *et al.* did not detect a statistically significant difference in acute toxicities in LD-SCLC patients treated with concurrent chemotherapy and QD versus BID RT.[17]

Thoracic radiation affects patient outcome by decreasing the tumor burden within the chest, resulting in enhanced local control and survival. The BED can be used to compare the efficacy of various dose-fractionation regimens in providing tumor control and survival.[9] Compared with the BID group, QD RT resulted in a higher BED of 54.7 Gy to the tumor. However, in our study, there was no statistically significant difference between the QD and BID groups in terms of OS, PFS or LRFS. The RTOG 0617 study, which concluded that 74 Gy radiation given in 2 Gy fractions with concurrent chemotherapy was not superior to 60 Gy plus concurrent chemotherapy for patients with stage III non-small-cell lung cancer, supported these findings.[18]

Despite the addition of TRT to chemotherapy, local treatment failures occur in approximately one third of LD-SCLC patients treated with the currently accepted optimal therapy.[19] As a dose-response relationship exists in treating LD-SCLC, local control and subsequent survival are associated with dose-fractionation parameters.[8] The INT 0096 protocol supported this view and reported that BID TRT reduced the rate of local failure, with rates of 52% and 36% in the QD and BID groups, respectively ($P = 0.06$). Although no statistically significant difference was observed in LRFS between the QD and BID groups, there was a trend toward improved local control for the BID group in the present study.

Our study was based on a small sample size and potential confounding factors existed, such as patient, tumor, and radiation treatment characteristics.

Conclusion

In conclusion, the present comparative analysis observed that pneumonitis was more common in QD RT to 60 Gy, and esophagitis was more common in BID RT to 45 Gy. Although there were no significant differences in OS and LRFS between the QD and BID groups, there was a trend toward improved local control in the BID group.

Disclosure

No authors report any conflict of interest.

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