Lung Cancer 102 (2016) 9–14

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Tumour size reduction after the first chemotherapy-course and outcomes of chemoradiotherapy in limited disease small-cell lung cancer

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ARTICLE INFO

Article history:
Received 14 July 2016
Received in revised form
23 September 2016
Accepted 11 October 2016

Keywords:
Early response
Predictive
Survival
Concurrent
Chemotherapy
Radiotherapy

ABSTRACT

Objectives: Concurrent chemotherapy and thoracic radiotherapy (TRT) is recommended for limited disease small-cell lung cancer (LD SCLC). TRT should start as early as possible, often meaning with the second course due to patient referral time and the fact that TRT planning takes time. Early assessment of response to the first course of chemotherapy may be a useful way to individualise treatment. The aims of this study were to assess tumour size reduction after the first chemotherapy-course, and whether this reduction was associated with outcomes in LD SCLC.

Material and methods: A randomised trial comparing twice-daily (45 Gy/30 fractions) with once-daily (42 Gy/15 fractions) TRT, given concurrently with four courses of cisplatin/etoposide (n = 157) was the basis for this study. Tumour size was assessed on CT scans at baseline and planning scans for TRT according to RECIST 1.0.

Results: CT scans were available for 135 patients (86%). Ninety-four percent had a reduction in tumour size after the first chemotherapy-course. The median reduction in sum of diameters (SOD) of measurable lesions was ÷16 mm (÷84 to +10 mm), corresponding to ÷18% (÷51 to +12%). Eighty-two percent had stable disease, 18% partial response. Reduction in SOD was significantly associated with complete response at first follow-up (OR: 1.05, 95% CI 1.01–1.09; p=0.013), PFS (HR: 0.97, 95% CI 0.96-0.99; p=0.001), and overall survival (HR: 0.98, 95% CI 0.96–1.00; p=0.010).

Conclusion: Response from the first course of chemotherapy had a significant positive association with outcomes from chemoradiotherapy, and might be used to stratify and randomise patients in future studies.

1. Introduction

Concurrent chemotherapy and thoracic radiotherapy (TRT) is the recommended treatment for LD SCLC [1–7]. Cisplatin plus etoposide constitutes the standard chemotherapy regimen [2,8], and should commence as soon as possible due to the potentially rapid progress of SCLC [9]. Guidelines recommend that radiotherapy should be administered along with the first or second course of chemotherapy [1–4], since meta-analyses have shown improved

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http://dx.doi.org/10.1016/j.lungcan.2016.10.003
0169-5002/

survival when TRT starts within 30 days after start of chemotherapy, and when the time from start of any treatment until the end of radiotherapy (SER) is short [6,7]. Although starting TRT concomitant with the first course results in the lowest SER, TRT is often administered concomitant with the second chemotherapy course due to time-delay in the referral and TRT planning process [10–13].

There is often a tumour response between the first and second chemotherapy-course, allowing for smaller radiotherapy fields and less toxicity than when TRT starts along with the first course. But little is known about the extent of the response. Most patients (80–90%) with LD SCLC respond to chemoradiotherapy, but the 5-year survival is only 25% [14]. Studies indicate that early response to treatment is associated with better outcomes [15–17], and might be a method for identifying patients who do not benefit from TRT.

We analysed LD SCLC patients enrolled in a randomised trial comparing two three-week schedules of TRT, administered concurrently with cisplatin plus etoposide. The aim was to assess the reduction in tumour size after the first chemotherapy course, and to investigate whether this tumour size reduction was associated with outcomes of therapy.

2. Material and methods

2.1. Design and approvals

The trial was approved by the Regional Committee for Medical Research Ethics in Central Norway, the Norwegian Social Science Data Services and the Norwegian Directorate for Health and Social Affairs.

2.2. Patients

Eligible patients had SCLC confined to one hemithorax, the mediastinum, the contralateral hilus and the supraclavicular regions; WHO performance status (PS) 0–2; and adequate kidney and bone marrow function. Pleural effusion was allowed if cytological negative. Four courses of cisplatin plus etoposide (PE1-4) were planned for all patients, and they were randomly allocated to receive TRT of 45 Gy in 30 fractions (twice daily; BID) or 42 Gy in 15 fractions (once daily; OD). Good responders were offered prophylactic cranial irradiation (PCI) of 30 Gy in 15 fractions.

Patients who completed at least two PE-courses and TRT were eligible for the present study, provided that the baseline CT scan and CT planning scan for TRT were available. Patients with a baseline scan more than two months prior to, or a planning scan more than one month later than start of treatment were excluded. Since there were no significant differences in toxicity, response-rates, progression free survival (PFS), or overall survival (OS) between the treatment arms in the main trial [18], we analysed all patients as one cohort in the present study.

2.3. Response evaluations

Timing of treatment and response evaluation are presented in Fig. 1. A baseline CT scan for staging (CT1) was obtained before PE1. Response to the first course (RE1) was assessed by comparing CT1 with the CT planning scan for TRT (CT2) obtained 2–3 weeks after PE1. A CT scan for response evaluation after completion of study treatment (RE2) was conducted 2–3 weeks after PE4 (CT3).

Response to overall therapy (RE2) was evaluated according to the RECIST 1.0 criteria [19]. Measurable lesions were defined as lesions ≥10 mm. Up to 10 target lesions (maximum 5 per organ) were measured. Sum of largest diameter (SOD) of target lesions at CT1 was compared with SOD of these lesions at CT2. Complete response (CR): Disappearance of all measurable lesions. Partial response (PR): A reduction in SOD of ≥30%. Progressive disease (PD): An increase in SOD of ≥20%. Stable disease (SD): A change in SOD between +20% and −30% [19].

A central review of RE1 was conducted by a radiologist (MH) and an oncologist (TH). Since staging of disease was based on CT alone, using the RECIST 1.0 criteria for response evaluation, we additionally performed all analyses evaluating only the change in size of the primary tumours. Not all lymph nodes considered pathological according to RECIST 1.0 are defined as pathological according to RECIST 1.1.

2.4. Other assessments

Stage of disease was assessed according to TNM v6 [20]. PFS was defined as time from randomisation until progression or death; OS as time from randomisation until death of any cause. Median follow-up for PFS was 58 months (range: 30–97); 31 patients were progression free when this follow-up ended (July, 2013). Median follow-up time for survival was 89 months (range: 61–128); 30 patients were alive when survival follow-up ended (February, 2016).

2.5. Statistical considerations

Survival was estimated using the Kaplan-Meier method and compared using the log-rank test. Pearson's Chi-square and Fisher's exact tests were used for group comparisons. The Cox proportional hazard method was used for multivariate survival analyses, and binomial logistic regression for the other multivariate analyses. Multivariate models were adjusted for baseline characteristics and TRT schedule. Associations between reduction in tumour size and outcomes of therapy were analysed using percent reduction of SOD as a continuous variable and according to RECIST categories. The significance level was defined as $p < 0.05$.

3. Results

3.1. Patients and treatment completion

Complete descriptive and clinical data are presented in Table 1. We enrolled 157 patients at 18 hospitals in Norway between May 2005 and January 2011 [18]. Twenty-two patients were excluded from these analyses due to missing baseline (n = 5) or planning (n = 11) CT scan; baseline CT scan more than two months prior (n = 1) or planning CT scan one month later (n = 2) than start of chemotherapy; and TRT not completed (n = 3). Thus, 135/157 patients (86%) were eligible for the present study. Median age was 64 years; 53% were men; 15% had PS 2 and 74% stage III disease. Mean number of PE-courses was 3.86, 118 patients (87%) completed four courses. Sixty patients (44%) received TRT as 45 Gy in 30 fractions. One hundred and fifteen patients (85%) received PCI, and 64 (47%) received second-line chemotherapy.

3.2. Time between CT scans

Median time from CT1 until start of PE1 was 17 days (range: 0–60). Median time from start of PE1 until CT2 was 18 days (range: 6–30). Median time from CT1 until CT2 was 35 days (range: 14–85).

3.3. Tumour size reduction after the first chemotherapy-course

Median SOD on CT1 was 96 mm (range: 14 to 260 mm); on CT2 76 mm (range: 14 to 196 mm). One-hundred and twenty-seven patients (94%) had a reduction in tumour size. Median change in SOD from CT1 until CT2 was ÷16 mm (range: ÷84 to +10 mm), corresponding to a median change of ÷18% (range ÷51 to +12%) in