Lung

High-dose versus standard-dose twice-daily thoracic radiotherapy for patients with limited stage small-cell lung cancer: an open-label, randomised, phase II trial

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BACKGROUND

Concurrent chemoradiotherapy is standard treatment for limited stage small-cell lung cancer (SCLC). Twice-daily thoracic radiotherapy of 45 Gy in 30 fractions is considered to be the most effective schedule. The aim of this study was to investigate whether high-dose, twice-daily thoracic radiotherapy of 60 Gy in 40 fractions improves survival.

METHODS

This open-label, randomised, phase II trial was done at 22 public hospitals in Norway, Denmark, and Sweden. Patients aged 18 years and older with treatment-naive confirmed limited stage SCLC, Eastern Cooperative Oncology Group (ECOG) performance status 0.0-2.0, and measurable disease according to the Response Evaluation Criteria in Solid Tumours version 1.1 were eligible. All participants received four courses of intravenous cisplatin 75 mg/m² or carboplatin (area under the curve 5.0-6.0 mg/mL × min, Calvert's formula) on day one and intravenous etoposide 100 mg/m² on days one-three every three weeks. Participants were randomly assigned (1:1) in permuted blocks (sized between four and 10) stratifying for ECOG performance status, disease stage, and presence of pleural effusion to receive thoracic radiotherapy of 45 Gy in 30 fractions or 60 Gy in 40 fractions to the primary lung tumour and PET-CT positive lymph node metastases starting 20-28 days after the first chemotherapy course. Patients in both groups received two fractions per day, ten fractions per week. Responders were offered prophylactic cranial irradiation of 25-30 Gy. The primary endpoint, two-year overall survival, was assessed after all patients had been followed up for a minimum of two years. All randomly assigned patients were included in the efficacy analyses, patients commencing thoracic radiotherapy were included in the safety analyses. Follow-up is ongoing. This trial is registered at ClinicalTrials.gov, NCT02041845.

FINDINGS

Between 8 July 2014, and 6 June, 2018, 176 patients were enrolled, 170 of whom were randomly assigned to 60 Gy (n=89) or 45 Gy (n=81). Median follow-up for the primary analysis was 49 months (IQR 38-56). At two years, 66 (74·2% [95% CI 63·8-82·9]) patients in the 60 Gy group were alive, compared with 39 (48·1% [36·9-59·5]) patients in the 45 Gy group (odds ratio 3·09 [95% CI 1·62-5·89]; p=0·0005). The most common grade 3.0-4.0 adverse events were neutropenia (72 [81%] of 89 patients in the 60 Gy group vs 62 [81%] of 77 patients in the 45 Gy group), neutropenic infections (24 [27%] vs 30 [39%]), thrombocytopenia (21 [24%] vs 19 [25%]), anaemia (14 [16%] vs 15 [20%]), and oesophagitis (19 [21%] vs 14 [18%]). There were 55 serious adverse events in 38 patients in the 60 Gy group and 56 serious adverse events in 44 patients in the 45 Gy group. There were three treatment-related deaths in each group (one neutropenic fever, one aortic dissection, and one pneumonitis in the 60 Gy group; one thrombocytic bleeding, one cerebral infarction, and one myocardial infarction in the 45 Gy group).

INTERPRETATION

The higher radiotherapy dose of 60 Gy resulted in a substantial survival improvement compared with 45 Gy, without increased toxicity, suggesting that twice-daily thoracic radiotherapy of 60 Gy is an alternative to existing schedules.