Lung

Neoadjuvant durvalumab with or without stereotactic body radiotherapy in patients with early-stage non-small-cell lung cancer: a single-centre, randomised phase 2 trial.

Altorki NK, McGraw TE, Borczuk AC, Saxena A, Port JL, Stiles BM, Lee BE, Sanfilippo NJ, Scheff RJ, Pua BB, Gruden JF, Christos PJ, Spinelli C, Gakuria J, Uppal M, Binder B, Elemento O, Ballman KV, Formenti SC.

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BACKGROUND

Previous phase II trials of neoadjuvant anti-PD-1 or anti-PD-L1 monotherapy in patients with early-stage non-small-cell lung cancer have reported major pathological response rates in the range of 15-45%. Evidence suggests that stereotactic body radiotherapy might be a potent immunomodulator in advanced non-small-cell lung cancer (NSCLC). In this trial, we aimed to evaluate the use of stereotactic body radiotherapy in patients with early-stage NSCLC as an immunomodulator to enhance the anti-tumour immune response associated with the anti-PD-L1 antibody durvalumab.

METHODS

We did a single-centre, open-label, randomised, controlled, phase II trial, comparing neoadjuvant durvalumab alone with neoadjuvant durvalumab plus stereotactic radiotherapy in patients with early-stage NSCLC, at NewYork-Presbyterian and Weill Cornell Medical Center (New York, NY, USA). We enrolled patients with potentially resectable early-stage NSCLC (clinical stages I-IIIA as per the seventh edition of the American Joint Committee on Cancer) who were aged 18 years or older with an Eastern Cooperative Oncology Group performance status of 0.0 or 1.0. Eligible patients were randomly assigned (1:1) to either neoadjuvant durvalumab monotherapy or neoadjuvant durvalumab plus stereotactic body radiotherapy (8.0 Gy × 3.0 fractions), using permuted blocks with varied sizes and no stratification for clinical or molecular variables. Patients, treating physicians, and all study personnel were unmasked to treatment assignment after all patients were randomly assigned. All patients received two cycles of durvalumab three weeks apart at a dose of 1·12 g by intravenous infusion over 60 min. Those in the durvalumab plus radiotherapy group also received three consecutive daily fractions of 8.0 Gy stereotactic body radiotherapy delivered to the primary tumour immediately before the first cycle of durvalumab. Patients without systemic disease progression proceeded to surgical resection. The primary endpoint was major pathological response in the primary tumour. All analyses were done on an intention-to-treat basis. This trial is registered with ClinicalTrial.gov, NCT02904954, and is ongoing but closed to accrual.

FINDINGS

Between 25 Jan 2017, and 15 Sept 2020, 96 patients were screened and 60 were enrolled and randomly assigned to either the durvalumab monotherapy group (n=30) or the durvalumab plus radiotherapy group (n=30). 26 (87%) of 30 patients in each group had their tumours surgically resected. Major pathological response was observed in two (6·7% [95% CI 0·8-22·1]) of 30 patients in the durvalumab monotherapy group and 16 (53·3% [34·3-71·7]) of 30 patients in the durvalumab plus radiotherapy group. The difference in the major pathological response rates between both groups was significant (crude odds ratio 16·0 [95% CI 3·2-79·6]; p<0·0001). In the 16 patients in the dual therapy group with a major pathological response, eight (50%) had a complete pathological response. The second cycle of durvalumab was withheld in three (10%) of 30 patients in the dual therapy group due to immune-related adverse events (grade 3.0 hepatitis, grade 2.0 pancreatitis, and grade 3.0 fatigue and thrombocytopaenia). Grade 3.0-4.0 adverse events occurred in five (17%) of 30 patients in the durvalumab monotherapy group and six (20%) of 30 patients in the durvalumab plus radiotherapy group. The most frequent grade 3.0-4.0 events were hyponatraemia (three [10%] patients in the durvalumab monotherapy group) and hyperlipasaemia (three [10%] patients in the durvalumab plus radiotherapy group). Two

patients in each group had serious adverse events (pulmonary embolism [n=1] and stroke [n=1] in the durvalumab monotherapy group, and pancreatitis [n=1] and fatigue [n=1] in the durvalumab plus radiotherapy group). No treatment-related deaths or deaths within 30 days of surgery were reported.

INTERPRETATION

Neoadjuvant durvalumab combined with stereotactic body radiotherapy is well tolerated, safe, and associated with a high major pathological response rate. This neoadjuvant strategy should be validated in a larger trial.