Adjuvant chemotherapy following chemoradiotherapy as primary treatment for locally advanced cervical cancer versus chemoradiotherapy alone (OUTBACK): an international, open-label, randomised, phase 3 trial

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Clinical Trial

BACKGROUND

Standard treatment for locally advanced cervical cancer is chemoradiotherapy, but many patients relapse and die of metastatic disease. We aimed to determine the effects on survival of adjuvant chemotherapy after chemoradiotherapy.

METHODS

The OUTBACK trial was a multicentre, open-label, randomised, phase 3 trial done in 157 hospitals in Australia, China, Canada, New Zealand, Saudi Arabia, Singapore, and the USA. Eligible participants were aged 18 year or older with histologically confirmed squamous cell carcinoma, adenosquamous cell carcinoma, or adenocarcinoma of the cervix (FIGO 2008 stage IB1 disease with nodal involvement, or stage IB2, II, IIIB, or IVA disease), Eastern Cooperative Oncology Group performance status 0-2, and adequate bone marrow and organ function. Participants were randomly assigned centrally (1:1) using a minimisation approach and stratified by pelvic or common iliac nodal involvement, requirement for extended-field radiotherapy, FIGO 2008 stage, age, and site to receive standard cisplatin-based chemoradiotherapy (40 mg/m2 cisplatin intravenously once-a-week for 5 weeks, during radiotherapy with 45·0-50·4 Gy external beam radiotherapy delivered in fractions of 1·8 Gy to the whole pelvis plus brachytherapy; chemoradiotherapy only group) or standard cisplatin-based chemoradiotherapy followed by adjuvant chemotherapy with four cycles of carboplatin (area under the receiver operator curve 5) and paclitaxel (155 mg/m2) given intravenously on day 1 of a 21 day cycle (adjuvant chemotherapy group). The primary endpoint was overall survival at 5 years, analysed in the intention-to-treat population (ie, all eligible patients who were randomly assigned). Safety was assessed in all patients in the chemoradiotherapy only group who started chemoradiotherapy and all patients in the adjuvant chemotherapy group who received at least one dose of adjuvant chemotherapy. The OUTBACK trial is registered with ClinicalTrials.gov, NCT01414608, and the Australia New Zealand Clinical Trial Registry, ACTRN12610000732088.

FINDINGS

Between April 15, 2011, and June 26, 2017, 926 patients were enrolled and randomly assigned to the chemoradiotherapy only group (n=461) or the adjuvant chemotherapy group (n=465), of whom 919 were eligible (456 in the chemoradiotherapy only group and 463 in the adjuvant chemotherapy group; median age 46 years [IQR 37 to 55]; 663 [72%] were White, 121 [13%] were Black or African American, 53 [6%] were Asian, 24 [3%] were Aboriginal or Pacific islander, and 57 [6%] were other races) and included in the analysis. As of data cutoff (April 12, 2021), median follow-up was 60 months (IQR 45 to 65). 5-year overall survival was 72% (95% CI 67 to 76) in the adjuvant chemotherapy group (105 deaths) and 71% (66 to 75) in the chemoradiotherapy only group (116 deaths;

difference 1% [95% CI -6 to 7]; hazard ratio 0·90 [95% CI 0·70 to 1·17]; p=0·81). In the safety population, the most common clinically significant grade 3-4 adverse events were decreased neutrophils (71 [20%] in the adjuvant chemotherapy group vs 34 [8%] in the chemoradiotherapy only group), and anaemia (66 [18%] vs 34 [8%]). Serious adverse events occurred in 107 (30%) in the adjuvant chemotherapy group versus 98 (22%) in the chemoradiotherapy only group, most commonly due to infectious complications. There were no treatment-related deaths.

INTERPRETATION

Adjuvant carboplatin and paclitaxel chemotherapy given after standard cisplatin-based chemoradiotherapy for unselected locally advanced cervical cancer increased short-term toxicity and did not improve overall survival; therefore, it should not be given in this setting.