Squamous head & neck

Debio 1143 and high-dose cisplatin chemoradiotherapy in high-risk locoregionally advanced squamous cell carcinoma of the head and neck: a double-blind, multicentre, randomised, phase 2 study

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BACKGROUND

Debio 1143 is an orally available antagonist of inhibitor of apoptosis proteins with the potential to enhance the antitumour activity of cisplatin and radiotherapy. The radiosensitising effect of Debio 1143 is mediated through caspase activation and tumour necrosis factor (TNF), interferon-γ (IFNγ), cluster of differentiation 8 (CD8) T cell-dependent pathways. We aimed to investigate the efficacy and safety of Debio 1143 in combination with standard chemoradiotherapy in patients with high-risk locally advanced squamous cell carcinoma of the head and neck.

METHODS

This double-blind, multicentre, randomised, phase 2 study by the French Head and Neck Radiotherapy Oncology Group (GORTEC) was run at 19 hospitals in France and Switzerland. Eligible patients were aged 18–75 years with locoregionally advanced, squamous cell carcinoma of the head and neck (characterised as non-metastatic, measurable stage III, IVa, or IVb [limited to T ≥2, N0–3, and M0] disease), Eastern Cooperative Oncology Group performance status of 0 or 1, a history of heavy tobacco smoking (>10 pack-years) with no previous or current treatment for invasive head and neck cancer, and no previous treatment with inhibitor of apoptosis protein antagonists. Patients were randomly assigned (1:1) to receive oral Debio 1143 (200 mg per day on days 1–14 of 21-day cycles, for three cycles) or oral placebo (20 mg/ml, administered at the same dosing schedule) using a stochastic minimisation technique according to node involvement and primary tumour site, and human papilloma virus-16 (HPV-16) status in patients with an oropharyngeal primary tumour site. All patients received standard high-dose cisplatin chemoradiotherapy. The primary endpoint was the proportion of patients with locoregional control 18 months after chemoradiotherapy, analysed in the intention-to-treat population (primary analysis), and repeated in the per-protocol population. Responses were assessed according to response evaluation criteria in solid tumours (version 1.1). This trial is registered with ClinicalTrials.gov, NCT02022098, and is still active but not recruiting.

FINDINGS

Between 25 January, 2016, and 24 April, 2017, 48 patients were randomly assigned to the Debio 1143 group and 48 to the placebo group (one patient in the placebo group did not receive the study drug and was not included in the safety analysis). Median duration of follow-up was 25·0 months (IQR 19·6–29·4) in the Debio 1143 group and 24·2 months (6·6–26·8) in the placebo group. Locoregional control 18 months after chemoradiotherapy was achieved in 26 (54%; 95% CI 39–69) of 48 patients in the Debio 1143 group versus 16 (33%; 20–48) of 48 patients in the placebo group (odds ratio 2·69 [95% CI 1·13–6·42], p=0·026). Grade 3 or worse

adverse events were reported in 41 (85%) of 48 patients in the Debio 1143 group and in 41 (87%) of 47 patients in the placebo group. The most common grade 3–4 adverse events were dysphagia (in 24 [50%] patients in the Debio 1143 group vs. ten [21%] in the placebo group), mucositis (in 15 [31%] vs. ten [21%]), and anaemia (in 17 [35%] vs. 11 [23%]). Serious treatment-emergent adverse events were recorded in 30 (63%) of 48 patients in the Debio 1143 group and 28 (60%) of 47 in the placebo group. In the placebo group, two (4%) deaths were due to adverse events (one multiple organ failure and one asphyxia; neither was considered to be related to treatment). No deaths due to adverse events occurred in the Debio 1143 group.

INTERPRETATION

To our knowledge, this is the first treatment regimen to achieve superior efficacy in this disease setting against a high-dose cisplatin chemoradiotherapy comparator in a randomised trial. These findings suggest that inhibition of inhibitor of apoptosis proteins is a novel and promising approach in this poor prognostic population and warrants confirmation in a phase 3 study with the aim of expanding the therapeutic options for these patients.