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Original Research

Association of human papillomavirus and p16 status with mucositis and dysphagia for head and neck cancer patients treated with radiotherapy with or without cetuximab: Assessment from a phase 3 registration trial

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Abstract ***Background:*** Mucositis and dysphagia are common adverse effects of radiotherapy (RT) treatment of locally advanced squamous cell cancer of the head and neck (LA-SCCHN). Chemotherapy added to RT increases survival rates but causes worse mucositis and dysphagia. The aim of this analysis was to assess the impact of p16 status on mucositis, dysphagia, and feeding tube use in LA-SCCHN among patients treated with RT ± cetuximab in the phase 3 IMCL-9815 trial.
Methods: Patients received RT plus weekly cetuximab or RT alone. Subgroup analyses were conducted on patients with p16-positive (n = 75) or p16-negative (n = 106) oropharyngeal cancer (OPC), as determined by immunohistochemical analysis. The onset and duration of

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mucositis and dysphagia by treatment arm and p16 status were displayed using Kaplan–Meier curves and the log-rank test. *P* values for the incidence of mucositis and dysphagia were calculated using the Fisher exact test. Feeding tube use was assessed as the percent of patients reporting use.

Results: The baseline characteristics of patients treated with RT ± cetuximab were similar in both the p16-positive and p16-negative OPC subgroups. Patients within the p16-positive OPC subgroup had higher Karnofsky scores and were more likely to have stage T1–T3 cancer and be from the United States. Regardless of p16 status, there was no difference in the onset or duration of grade 3/4 mucositis or dysphagia in patients receiving RT plus cetuximab compared with those receiving RT alone. In the overall population, and the p16-positive and p16-negative OPC subpopulations, feeding tube use was not different for patients receiving RT plus cetuximab compared with RT alone.

Conclusion: Regardless of p16 status, the addition of cetuximab to RT did not alter the incidence, time to onset, severity, or duration of mucositis and dysphagia and did not impact the frequency of feeding tube use.

1. Introduction

Radiotherapy (RT) for locally advanced head and neck squamous cell carcinoma (LA-SCCHN) can induce mucositis, pain, dysphagia, and diminished quality of life [1,2]. Severe mucositis contributes to the need for narcotic analgesics, intravenous fluids, and gastrostomy feeding and may lead to unplanned RT interruptions, thereby compromising outcomes [3,4]. Concurrent chemotherapy improves survival rates for patients with SCCHN compared with RT alone, but often at the expense of increased mucositis and dysphagia. In contrast, the phase 3 IMCL-9815 trial, which investigated addition of the anti–epidermal growth factor receptor (EGFR) monoclonal antibody cetuximab to RT, showed that cetuximab did not appear to worsen these toxicities when added to RT.

These findings and the recent availability of p16 analyses of the IMCL-9815 study prompted us to re-evaluate these toxicities by characterizing onset, duration, and incidence in both p16-positive and p16-negative oropharyngeal cancer (OPC). Analysis of the IMCL-9815 trial recently showed that patients with either p16-positive or p16-negative OPC benefitted from the addition of cetuximab to RT [5]. An interaction analysis did not indicate that there was an association between p16 status and the efficacy of cetuximab [5]. We believe that it is important to further examine the toxicity profiles of the p16-positive and p16-negative groups. Our rationale for this belief is further underscored by the vast differences in prognosis between p16-positive and p16-negative OPC: for patients with p16-positive disease, their long life expectancy highlights the need for efficacious therapies that incur fewer long-term adverse effects (e.g. feeding tube use); in contrast, for patients with poorer-prognosis p16-negative disease, their increased fragility necessitates the avoidance of potentially severe adverse effects (e.g. mucositis).

This study is the first to examine the rate of onset and duration of radiation-induced mucositis and dysphagia for patients receiving RT alone or RT and cetuximab. In addition, the role of p16 status was evaluated in the incidence, onset, and duration of mucositis and dysphagia, as well as feeding tube use, in patients with OPC receiving RT plus cetuximab compared with those receiving RT alone in the IMCL-9815 trial.

2. Methods

2.1. Study design

The design of the phase 3, randomized IMCL-9815 cetuximab registration trial has previously been reported in detail [6,7]. Patients with LA-SCCHN were randomized to receive cetuximab plus RT once daily (2.0 Gy/fraction; 5 fractions/week for 7 weeks), twice daily (1.2 Gy/fraction; 10 fractions/week for 6.0–6.5 weeks), or concomitant boost (72 Gy in 6 weeks, using twice-daily fractionation for the final 2.4 weeks) or RT alone. The trial protocol was approved by the ethics committees of all participating centres. The primary end-point of the study was the duration of locoregional control. Secondary end-points included overall survival, progression-free survival, and response rate. Quality of life and incidence of adverse events were also evaluated. In this retrospective subgroup analysis, feeding tube use and the incidence of mucositis and dysphagia were evaluated in the overall safety population (n = 181), as well as subpopulations of patients with p16-positive and