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Clinical Trial

Chemoradiotherapy with FOLFOX plus cetuximab in locally advanced oesophageal cancer: The GERCOR phase II trial ERaFOX☆

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Abstract ***Background:*** To determine efficacy and toxicity of radiation therapy combined with oxaliplatin, 5-fluorouracil, and folinic acid (FOLFOX) and cetuximab in patients with locally advanced oesophageal cancer.

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Patients and methods: Patients with stage III oesophageal or gastro-oesophageal junction cancer were enrolled in a Simon's two-stage phase II study. Patients received FOLFOX and weekly cetuximab on week 1–10 with concurrent radiotherapy (50.4 Gy in 30 fractions) on week 5–10. Primary end-point was clinical overall response rate (ORR). An ORR rate of more than 50% was expected.

Results: Among the 79 included patients, clinical ORR was 77% with 40% complete responses. Median overall survival and progression-free survival were 21.6 and 11.3 months, respectively. The most common grade III–IV toxicities observed during experimental chemoimmunotherapy followed by chemoradiation included neutropenia (28%), oesophagitis (12%), rash (11%), and allergy (9%). There was one treatment-related death due to oesophagitis with gastrointestinal bleeding.

Conclusions: Cetuximab-FOLFOX regimen combined with radiotherapy demonstrated its efficacy and was well tolerated. Unfortunately, these results were not confirmed in two recent phase III studies.

1. Introduction

Oesophageal cancer is the eighth-most common cancer worldwide, with 481,000 new cases estimated in 2008, and the sixth-most common cause of death from cancer [1]. There are two main histological types of oesophageal cancer, squamous cell carcinoma (SCC) and adenocarcinoma (AC). Recently, the incidence of AC of the lower oesophagus and gastro-oesophageal junction (GEJ) has increased whilst the incidence of SCC has fallen slightly in populations of the Western countries.

Surgery is the cornerstone in the treatment of oesophageal cancer and is considered for all patients with potentially resectable tumours. Patients with localised tumours not considered for surgery can be treated with chemoradiation (CRT) with curative intent. The role of neoadjuvant CRT remains highly debated despite numerous clinical trials [2].

In the past few years, optimisation of CRT was addressed by combining different chemotherapy regimens with radiation therapy (RT). The most commonly used regimen in combination with RT is cisplatin and 5-fluorouracil (5FU) [3]. The FOLFOX regimen, a combination of oxaliplatin, 5FU and folinic acid, used with concurrent RT provided a similar outcome when compared to cisplatin-5FU in a phase III trial, with similar tolerance but is more convenient to administer [4].

Epidermal growth factor receptor (EGFR) expression occurs in 30–50% of oesophageal cancer patients and is a bad prognosis factor [5]. Radiation induces an increase in the expression of EGFR in cancer cells and blockade of EGFR by cetuximab sensitises cells to the effects of radiation *in vitro* and *in vivo* [6]. It has been suggested that addition of cetuximab to standard chemotherapy for metastatic oesophageal SCC might increase treatment efficacy [7]. In locally advanced oesophageal cancer, cetuximab in combination with CRT showed promising results in a phase IB/II trial [8].

The ERaFOX phase II study was designed to evaluate the efficacy and tolerance of cetuximab in combination with FOLFOX-based chemotherapy and CRT in locally advanced oesophageal or GEJ carcinomas.

2. Patients and methods

2.1. Patient eligibility criteria

Previously untreated patients with histologically confirmed SCC or AC of the thoracic oesophagus or the GEJ were included in this prospective multicentre trial. Patients with stage III were eligible. Other eligibility criteria included age 18–70 years, Eastern Cooperative Oncology Group performance status of 0–1, and adequate haematological, renal and hepatic function.

All patients provided their written informed consent before registration. The protocol was approved by the Centre Léon Bérard (Lyon Sud-Est IV, France) ethics committee (ClinicalTrials.gov study identifier: NCT00578201).

2.2. Treatment

All included patients were scheduled to receive a two-stage treatment consisting of two cycles of induction chemotherapy followed by CRT with three concurrent cycles of chemotherapy (Fig. 1).

The induction chemotherapy consisted of two cycles of FOLFOX (oxaliplatin 85 mg/m^2 on day 1, folinic acid 400 mg/m^2 on day 1, followed by 5FU 2400 mg/m^2 as 44 h infusion), given every 2 weeks, and cetuximab (first infusion 400 mg/m^2 then 250 mg/m^2), given weekly. Induction chemotherapy was followed by RT combined with three concurrent cycles of chemotherapy (same regimen but 5FU infusion dose reduced to 1800 mg/m^2). Anti-histaminic prophylaxis was given to every patient before administration of cetuximab.