European Journal of Cancer 75 (2017) 73–82

Available online at www.sciencedirect.com

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journal homepage: www.ejcancer.com

Original Research

Gemcitabine–erlotinib versus gemcitabine–erlotinib–capecitabine in the first-line treatment of patients with metastatic pancreatic cancer: Efficacy and safety results of a phase IIb randomised study from the Spanish TTD Collaborative Group

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http://dx.doi.org/10.1016/j.ejca.2016.12.032

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Received 18 July 2016; received in revised form 30 November 2016; accepted 26 December 2016
Available online 7 March 2017

KEYWORDS
Gemcitabine;
Erlotinib;
Capecitabine;
First-line;
Metastatic pancreatic cancer

Abstract ***Background:*** Gemcitabine and erlotinib have shown a survival benefit in the first-line setting in metastatic pancreatic cancer (mPC). The aim of this study was to assess whether combining capecitabine (C) with gemcitabine + erlotinib (GE) was safe and effective versus GE in patients with mPC.
Patients and methods: Previously untreated mPC patients were randomised to receive G (1000 mg/m^2, days 1, 8, 15) + E (100 mg/day, days 1–28) + C (1660 mg/m^2, days 1–21) or GE, q4 weeks, until progression or unacceptable toxicity. Primary end-point: progression-free survival (PFS); secondary end-points: overall survival (OS), response rate, relationship of rash with PFS/OS and safety.
Results: 120 patients were randomised, median age 63 years, ECOG status 0/1/2 33%/58%/8%; median follow-up 16.5 months. Median PFS in the gemcitabine–erlotinib–capecitabine (GEC) and GE arms was 4.3 and 3.8 months, respectively (hazard ratio [HR]: 0.88, 95% confidence interval [CI]: 0.58–1.31; p = 0.52). Median OS in the GEC and GE arms was 6.8 and 7.7 months, respectively (HR: 1.09, 95% CI: 0.72–1.63; p = 0.69). Grade 3/4 neutropenia (GEC 43% versus GE 15%; p = 0.0008) and mucositis (GEC 9% versus GE 0%; p = 0.03) were the only statistically significant differences in grade 3/4 adverse events. PFS and OS were significantly longer in patients with rash (grade ≥1) versus no rash (grade = 0): PFS 5.5 versus 2.0 months (HR = 0.39, 95% CI: 0.26–0.6; p < 0.0001) and OS: 9.5 versus 4.0 months (HR = 0.51, 95% CI: 0.33–0.77; p = 0.0014).
Conclusion: PFS with GEC was not significantly different to that with GE in patients with mPC. Skin rash strongly predicted erlotinib efficacy.
The study was registered with ClinicalTrials.gov: NCT01303029.

1. Introduction

Pancreatic cancer is the eighth most common cancer in Europe, accounting for 3% of cancers in 2012 [1]. Survival is poor; 1-year survival has been estimated at 21% and less than 10% of pancreatic cancer patients survive for more than 5 years [2].

Since 1997, gemcitabine therapy has been the standard first-line treatment for patients with unresectable locally advanced or metastatic pancreatic cancer (mPC) [3]. Whereas many phase II studies evaluating combination chemotherapies in patients with advanced pancreatic cancer have shown promising results, most subsequent phase III studies have not shown significantly improved survival [for review see 4]. However, in 2007, the combination of gemcitabine plus erlotinib (GE) was shown to modestly, but statistically significantly, improve survival compared with gemcitabine alone, which was the primary objective of the study [5]. A phase III trial conducted by a French consortium study group in patients with metastatic pancreatic adenocarcinoma and an Eastern Cooperative Oncology Group (ECOG) score of 0–1 found that the combination of 5-FU, folinic acid, oxaliplatin and irinotecan (FOLFIRINOX) was associated with a median increase in overall survival (OS) of 4.3 months compared with gemcitabine [6]. The MPACT study randomised 842 patients with mPC and a Karnofsky Index above 70% to either gemcitabine or gemcitabine plus nab-paclitaxel and reported significantly increased OS (8.5 versus 6.7 months) and progression-free survival (PFS) (5.5 versus 3.7 months) with the combination [7].