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Original Research

Simvastatin plus capecitabine–cisplatin versus placebo plus capecitabine–cisplatin in patients with previously untreated advanced gastric cancer: A double-blind randomised phase 3 study

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Abstract ***Purpose:*** We aimed to the addition of synthetic 3-hydroxy-3-methyglutaryl coenzyme A (HMG-CoA) reductase inhibitor, simvastatin to capecitabine–cisplatin (XP) in patients with previously untreated advanced gastric cancer (AGC).
Methods: In this double-blind, placebo-controlled, phase III study, we enrolled patients aged 18 years or older with histological or cytological confirmed metastatic adenocarcinoma of the stomach or gastroesophageal junction (GEJ) at nine centres in Korea. Patients, stratified by disease measurability and participating site, were randomly assigned (1:1) to receive capecitabine 1000 mg/m^2 twice daily for 14 days and cisplatin 80 mg/m^2 on day 1 every 3 weeks plus either simvastatin 40 mg or placebo, once daily. Cisplatin was given for 8 cycles; capecitabine and simvastatin were administered until disease progression or unacceptable toxicities. This study is registered with ClinicalTrials.gov, number NCT01099085.

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Results: Between February 2009 and November 2012, 244 patients were enrolled and assigned to treatment groups (120 simvastatin, 124 placebo). Median progression free survival (PFS) for 120 patients allocated XP plus simvastatin was 5.2 months (95% confidence interval (CI) 4.3–6.1) compared with 4.63 months (95% CI 3.5–5.7) for 124 patients who were allocated to XP plus placebo (hazard ratio 0.930, 95% CI 0.684–1.264; $p = 0.642$). 63 (52.5%) of 120 patients in simvastatin group and 70 (56.4%) of 124 had grade 3 or higher adverse events.
Conclusions: Addition of 40 mg simvastatin to XP does not increase PFS in our trial, although it does not increase toxicity. Low dose of simvastatin (40 mg) to chemotherapy is not recommended in untargeted population with AGC.

1. Introduction

Gastric cancer (GC) is the second most common cause of cancer-related death world-wide and the most frequently occurring malignancy in Korea [1,2]. Although most patients with the early stage disease receive surgical resection with curative intent, more than 60% of these patients have a high rate of locoregional as well as distant recurrence [3–5]. For patients with unresectable, recurrent or advanced gastric cancer (AGC), systemic chemotherapy can improve survival and symptom control. Combination chemotherapy improves treatment outcomes compared with mono-chemotherapy or best supportive care (BSC) in patients with advanced gastric cancer [6]. Although there is no internationally accepted standard of first line chemotherapy regimen, either infusional or oral fluoropyrimidine plus platinum compound is now regarded as a standard regimen. However, more than half of patients with AGC who receive standard chemotherapy did not achieve response, and even in responders, the duration of response was as short as a few months [7].

Statins are synthetic 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors which are commonly used drugs for treatment of hypercholesterolemia. Statins inhibit the rate limiting step of the mevalonate pathway in which mevalonic acid is the precursor in the biosynthesis of isoprenoid molecules such as cholesterol, dolichol and ubiquinone. Mevalonate-derived prenyl groups, farnesyl pyrophosphate (FPP) and geranylgeranyl pyrophosphate (GGPP), facilitate essential intracellular functions of various proteins [8–10]. FFP and GGPP are essential substrates for posttranslational modifications of rat sarcoma viral oncogene homologue (RAS) and ras homologue gene family, member A (RHOA), which play an important role in cellular proliferation. Based on the effect of statin on posttranscriptional modifications of RAS and RHOA, the antitumour effect of statins has been suggested in various cancer cell lines [11–13]. However, most studies used high concentrations of statin which was not feasible for human use to demonstrate an antitumour effect [14–16]. Recently, we demonstrated antitumour effect of simvastatin using a dose level that is equivalent to cardiovascular therapeutic dose level in humans [17,18]. In addition, other studies reported that low concentrations of statins induced apoptosis of microvascular endothelial cells and lowered vascular endothelial growth factor (VEGF) serum levels implicating a possible antiangiogenic role in cancer treatment [19,20]. Hence, our group conducted clinical trials for chemotherapy plus low-dose simvastatin in various cancer types and demonstrated that there were no additive side-effects [18,21].

In the placebo-controlled, double-blinded, simvastatin in combination with capecitabine–cisplatin (XP) in advanced gastric cancer study, we aimed to assess efficacy and safety of the addition of simvastatin to first line capecitabine–cisplatin (XP) chemotherapy in patients with unresectable advanced or metastatic gastric adenocarcinoma.

2. Patients and methods

2.1. Study design

This study was a prospective, random-assignment, double-blinded, placebo-controlled phase III clinical trial. The protocol was approved at each participating site by an institutional review board. This study was registered with ClinicalTrials.gov, identifier: NCT01099085 and conducted according to the Declaration of Helsinki and all of its amendments. All patients provided written informed consent before study enrolment.

Patients were assigned (1:1 ratio) to each treatment group by using randomisation with participating sites and disease measurability (measurable disease/un-measurable disease) as stratification factors.

2.2. Eligibility criteria

Patients were enrolled to this study based on the following eligibility criteria: histologically or cytologically confirmed adenocarcinoma of the stomach and gastroesophageal junction (GEJ); stage IV disease (based on American Joint Committee on Cancer 2002 staging system) not amenable to surgery, radiation or combined modality therapy with curative intent; measurable or evaluable disease based on Response Evaluation Criteria