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The addition of pravastatin to chemotherapy in advanced gastric carcinoma: A randomised phase II trial

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ABSTRACT

Purpose: Statins have for long been considered to play a potential role in anticancer treatment based upon their ability to inhibit the mevalonate synthesis pathway. This randomised phase II trial compared the efficacy and safety of pravastatin added to epirubicin, cisplatin and capecitabine (ECC versus ECC + P) in patients with advanced gastric carcinoma.

Methods: Patients were randomised to receive up to six cycles of 3-weekly ECC with or without pravastatin (40 mg, once daily from day 1 of the first cycle until day 21 of the last cycle). Primary end-point was progression-free rate at 6 months ($PFR_{6months}$). Secondary end-points were response rate (RR), progression-free survival (PFS), overall survival (OS) and safety. For early termination in case of futility, a two-stage design was applied ($P_0 = 50\%$; $P_1 = 70\%$; $\alpha = 0.05$; $\beta = 0.10$).

Results: Thirty patients were enrolled. $PFR_{6months}$ was 6/14 patients (42.8%) in the ECC + P arm, and 7/15 patients (46.7%) in the control arm, and therefore the study was terminated after the first stage. In the ECC and ECC + P arm, RR was 7/15 (46.7%) and 5/15 (33.3%), median PFS was 5 and 6 months and median OS was 6 and 8 months, respectively. Toxicity data showed no significant differences, although there was a trend towards more gastrointestinal side-effects such as diarrhoea and stomatitis in the ECC + P arm.

Conclusion: In this randomised phase II trial the addition of pravastatin to ECC did not improve outcome in patients with advanced gastric cancer. Therefore, further testing of this combination in a randomised phase III trial cannot be recommended.

1. Introduction

Worldwide, gastric adenocarcinoma is the fourth most common cancer type.[1] Patients with advanced, non-resectable disease have a dismal prognosis with a median overall survival of 3–5 months. In advanced gastric carcinoma 5-fluorouracil-containing chemotherapy has shown to increase overall survival when compared to best supportive care, making chemotherapy a viable treatment option for these patients.[2–4] In addition, several randomised phase III trials have established the combination of epirubicin, cisplatin and capecitabine (ECC) as a potential standard of care.[5] Still, prognosis

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of patients with advanced gastric carcinoma remains poor with a median progression-free survival and overall survival of 6–7 and 9–11 months, respectively.[6]

HMG-CoA-reductase inhibitors, frequently referred to as statins, are commonly prescribed drugs to lower serum cholesterol. Statins act by decreasing synthesis of mevalonate, the precursor of cholesterol. Mevalonate is also a precursor for isoprenoids, which play an important role in the membrane attachment of several GTP-binding proteins. These are pivotal in down-stream signalling of many plasma membrane receptors involved in cellular processes such as proliferation, differentiation and apoptosis. By decreasing synthesis of isoprenoids and other yet unknown mechanisms, statins exert antiproliferative effects, attenuate metastatic potential, inhibit angiogenesis and enhance antitumour immunity in tumour cells.[7] By these mechanisms, statins exhibit antitumour activity against a wide range of tumour types including gastric carcinoma.[8,9] Moreover, in patients with advanced gastric carcinoma, high-dose statins induced disease stabilisation for 16 weeks in some patients.[9]

Statins have shown *in vitro* and in animal models to interact synergistically with several chemotherapeutic agents including cisplatin,[10] 5-fluorouracil[11] and doxorubicin,[12] the latter being structurally almost identical to epirubicin. The exact mechanism underlying this synergism is not fully elucidated, but might involve a statin-induced decrease in Bcl-2.[11]

Pravastatin is one of the most commonly prescribed statins and is known for its mild toxicity profile. It is more hydrophilic than other statins resulting in higher concentrations in peripheral tissues such as the stomach.[13] Clinically pravastatin demonstrated preliminary hints of efficacy in patients with hepatocellular carcinoma, where patients treated with pravastatin 40 mg once daily (OD) after chemotherapy showed increased survival compared to patients without pravastatin.[14]

Based upon its mechanism of action, non-overlapping toxicity profile and the synergistic interaction in particular, the combination of ECC with pravastatin was chosen in this randomised phase II study to assess its role in patients with advanced gastric carcinoma.

2. Patients and methods

2.1. Eligibility criteria

Patients with a histologically proven gastric adenocarcinoma not amenable for curative resection and with evaluable disease according to Response Evaluation Criteria in Solid Tumours (RECIST) were eligible.[15] No prior chemotherapy, radiotherapy or the use of HMG-CoA-reductase inhibitors was allowed. Other eligibility criteria included: age $\geqslant$18 years; Eastern Cooperative Oncology Group (ECOG) performance $\leqslant$2; adequate bone marrow function (white blood cell count (WBC) $>3.0\times10^9$/L, absolute neutrophil count (ANC) $>1.5\times10^9$/L, platelet count $>100\times10^9$/L, haemoglobin >6.0 mmol/L), hepatic function (total bilirubin level $\leqslant$1.5 times upper limit of normal (ULN), serum alanine transferase (ALT) and aspartate aminotransferase (AST) $\leqslant$3 times ULN or $\leqslant$5 times ULN in case of liver metastases) and renal function (creatinine clearance $\geqslant$60 mL/min). The study was approved by the local Ethics Committee and was conducted according to the Declaration of Helsinki and Good Clinical Practice guidelines. All patients gave written informed consent prior to any study related procedures.

2.2. Treatment

Patients were randomised to receive ECC with pravastatin (ECC + P; experimental arm) or ECC alone (control arm). ECC was given every 3 weeks for a maximum of six cycles. On day 1 of every cycle epirubicin was administered as intravenous (i.v.) bolus injection of 50 mg/m^2, followed by i.v. cisplatin at a dose of 60 mg/m^2 over 3 h followed by hydration. Capecitabine 1000 mg/m^2 was taken orally twice daily on days 1–14. In the experimental arm, patients received pravastatin 40 mg OD from day 1 of the first cycle to day 21 of the last ECC cycle. Patients were not allowed to receive growth factors for myelosuppression. Dose reductions (up to 50% of starting dose of either epirubicin or capecitabine, but not cisplatin or pravastatin) and/or treatment delays (up to a maximum of 3 weeks) were allowed in case of haematological and non-haematological toxicities (e.g. renal, hepatic or skin toxicity, or hand–foot syndrome, diarrhoea or mucositis).

2.3. Evaluation and outcomes

Pre-treatment evaluation included a full medical history, physical examination, full blood cell count with differential, serum biochemistry including lipid profile and coagulation tests and computed tomography of chest and abdomen within 28 d before the start of therapy. During treatment, history taking, physical examination including toxicity assessment, haematology and serum biochemistry tests were performed before and 10–14 d after every ECC cycle. Tumour measurements were performed at baseline, every other cycle and every 3 months after completion of study treatment until progressive disease, as was assessed according to RECIST.[15]

2.4. Statistical methods

Primary end-point was progression-free rate at 6 months after randomisation ($PFR_{6months}$). The expected $PFR_{6months}$ of ECC was set at 50% and it was aimed that the experimental arm would yield a $PFR_{6months}$ of 70%. Two hypotheses were tested: (1) $PFR_{6months}$ in the ECC + P arm is <50%, which means no further testing is warranted, and (2) $PFR_{6months}$ in the ECC + P arm is >70%, which allows for further testing. Both hypotheses were tested with type I and II errors of 0.05 (α) and 0.10 (β), respectively. According to a Simon's two-stage phase II optimal design,[16] a sample size of 15 in each arm was required for the first stage. If fewer than 8 patients out of the first 15 patients in the experimental arm achieved $PFR_{6months}$, the study was to be terminated. Otherwise, another 56 patients were accrued accounting for a total of 43 patients in both arms.

Secondary end-points included response rate (RR), progression-free survival (PFS) and overall survival (OS) according to the intention-to-treat analysis. Descriptive statistics were reported as estimates with accompanying 95% confidence intervals (CI) for PFS, OS and occurrence of toxicity. PFS and

OS were calculated using Kaplan–Meier methodology. PFS was calculated from the start of treatment until the date of progression or death of any cause. Comparison of adverse events was performed using the Chi-square test. Calculations were performed using SPSS v.15.

3. Results

3.1. Patient characteristics

From February 2005 to May 2009, 30 patients were enrolled. Baseline characteristics are summarised in Table 1. The study groups were well balanced in terms of their baseline characteristics, with a median age of 58 years (range 36–74 years) and a male–female ratio of approximately 4:1. Most patients had ECOG-performance score 1 and the most frequent sites of metastatic spread were to lymph nodes (90%) and peritoneum (30%). Forty-three percent of patients had two or more sites of metastases.

3.2. Treatment

A total of 68 cycles in the ECC arm and 54 cycles in the ECC + P arm were administered with a mean of 4.5 and 3.6 cycles per patient (range: 1–6), respectively. The mean relative dose intensities of epirubicin, cisplatin and capecitabine were comparable in both groups as well as with the mean number of days of a delay in treatment per patient (7.3 and 6.4 d, respectively). Pravastatin was taken according to predefined plan by all patients in the ECC + P arm, except for 2 patients who by mistake stopped pravastatin from days 15–21 during two and four cycles, respectively.

Table 1 – Patient characteristics.

Characteristics	ECC	ECC + P
Total number of patients	15	15
Sex		
Male	13	11
Female	2	4
Age (years)		
Median	57	59
Range	42–74	36–73
ECOG performance status[a]		
0	4	4
1	11	9
2	–	2
Prior surgery		
Yes	5	4
No	10	11
Metastatic sites[b]		
Lymph nodes	14	13
Liver	2	1
Peritoneum	4	5
Bone	–	2
Lung	2	1
Other	4	1
Number of metastatic sites		
1	8	9
2	4	4
>2	3	2

[a] Eastern Cooperative Oncology Group.
[b] Some patients had lesions at multiple sites.

3.3. Study end-points

One patient in the ECC + P arm was not evaluable for $PFR_{6months}$ due to stereotactic radiotherapy given after 5 months. $PFR_{6months}$ therefore was 6/14 patients (42.8%) in the ECC + P arm, and as this did not meet the predefined criteria to proceed to the second stage, the study was terminated. $PFR_{6months}$ was 7/15 patients (46.7%) in the control arm.

Responses were observed in 7/15 (46.7%) of patients in the control arm and in 5/15 (33.3%) of patients in the ECC + P arm ($p = 0.473$). Six patients underwent surgery or radiotherapy during follow-up. Eventually all patients progressed, except 1 patient who had surgery and is still alive. Median PFS was 6 (95% CI, 3.39–8.61) and 5 (95% CI, 3.83–6.17) months in the experimental and the control arm, respectively (Fig. 1). Median OS was 8 (95% CI, 3.02–12.98) and 6 (95% CI, 4.93–7.08) months in the experimental and the control arm, respectively (Fig. 1).

3.4. Safety

Table 2 presents the incidence of adverse events according to the study group. As compared to ECC, haematologic toxicity and the occurrence of febrile neutropenia were similar, with the suggestion of more severe (grade 3) thrombocytopenia in the ECC + P arm. Haematological toxicity led to early termination of chemotherapy treatment in 6 patients ($n = 3$, both arms). The occurrence of lethargy and peripheral neuropathy was similar in both arms. Diarrhoea and stomatitis occurred more frequently in the ECC + P arm (26.7% versus 66.7%, $p = 0.065$ and 46.7% versus 80%, $p = 0.058$, respectively). At 60 d from randomisation, rate of death from any cause did not differ significantly between the two arms. No patients experienced recognisable adverse events (myopathy or increased serum creatine phosphokinase concentrations) attributable to pravastin.

4. Discussion

In recent years, the possible beneficial effect of statins in cancer prevention and treatment has repeatedly been suggested. In particular, the role of statins in cancer prevention has been extensively investigated, but recently published large meta-analyses did not reveal such a protective effect.[17,18] The potential role of statins to potentiate antitumour activity of conventional chemotherapeutic drugs has also been explored in clinical studies; one study assessed the combination of simvastatin with first-line chemotherapy in metastatic colorectal cancer patients, while another study explored the role of fluvastatin with multi-agent chemotherapy in paediatric brain stem tumours. Both studies showed feasibility of the combinations and interesting antitumour activity when compared to historic data.[19,20] However, as both studies were not randomised, their results are somewhat difficult to interpret.

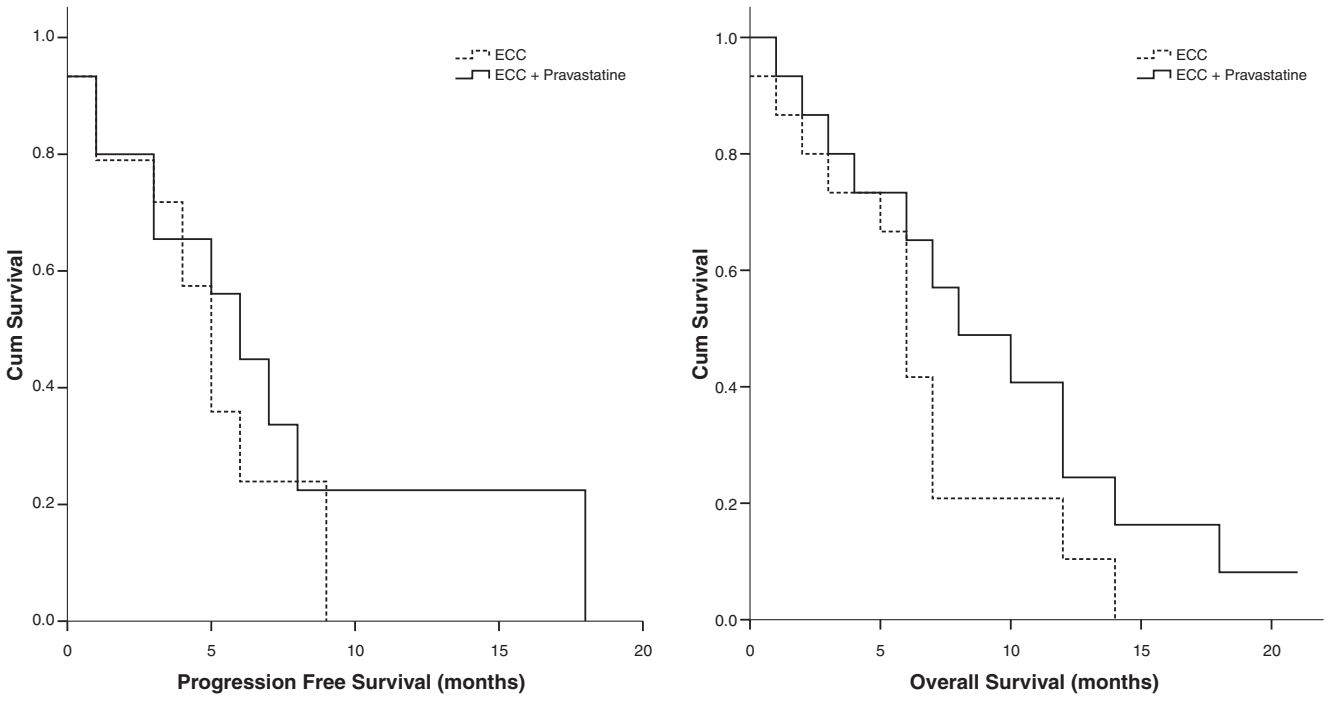

Fig. 1 – Kaplan–Meier estimates of PFS and OS.

Table 2 – Toxicity profile.

Adverse event	NCI-CTC[a] grade (%)			
	ECC (N = 15)		ECC + P (N = 15)	
	All grades	Grade 3 or 4	All grades	Grade 3 or 4
Anemia	14 (93.3)	3 (20.0)	13 (86.7)	2 (13.3)
Thrombopenia	6 (40.0)	–	8 (53.3)	2 (13.3)
Neutropenia	10 (66.7)	7 (46.7)	9 (60.0)	8 (53.3)
Febrile neutropenia	–	2 (13.3)	–	3 (20.0)
Diarrhea	4 (26.7)	–	10 (66.7)	3 (20.0)
Stomatitis	7 (46.7)	–	12 (80.0)	–
Hand–foot syndrome	1 (6.7)	–	2 (13.3)	–
Nausea and vomiting	12 (80.0)	1 (6.7)	15 (100.0)	1 (6.7)
Peripheral neuropathy	8 (53.3)	1 (6.7)	9 (60.0)	1 (6.7)
Alopecia	15 (100.0)	NA	15 (100.0)	NA
Lethargy	15 (100.0)	4 (26.7)	15 (100.0)	4 (26.7)
Thromboembolism	2 (13.3)	NA	4 (26.7)	NA
Skin rash	2 (13.3)	–	3 (20.0)	–
Myalgia	1 (6.7)	–	1 (6.7)	–
Death within 60 d after randomization	1 (6.7)	NA	1 (6.7)	NA

NA, not applicable.
a NCI-CTC: National Cancer Institute Common Toxicity Criteria.

To the best of our knowledge, this study of ECC with or without pravastatin in patients with advanced gastric carcinoma is the first randomised trial assessing the effect of a statin added to standard chemotherapy in patients with a solid tumour. Consistent with observations from a large randomised trial in patients with advanced gastric carcinoma, a $PFR_{6months}$ of approximately 50% in the ECC arm was observed in our study.[6] Unfortunately enough, the addition of pravastatin to this regimen failed to increase $PFR_{6months}$ in this study, which according to predefined design was terminated after the first 30 patients were analysed. In addition to the observed lack of effect in the primary end-point, RR, PFS and OS also did not differ between both treatment groups, further underlining a lack of benefit of pravastatin in this study. Of note here is that due to the small number of patients studied and the chosen phase II design, this study is underpowered to assess significant differences for these parameters between the two treatment arms.

With regard to safety and tolerability, the addition of pravastatin to ECC induced only mild additional toxicity, in partic-

ular diarrhoea and stomatitis. Diarrhoea is a well-known side-effect of pravastatin occurring in 0.1–1% of patients. We consider the combination of capecitabine with pravastatin to be accountable for this side-effect, which could also be the case for the observed stomatitis. Perhaps the immunomodulatory effects of pravastatin potentiate the mucocutaneous toxicity action of capecitabine given in this ECC chemotherapy.[21] The frequency of other frequently occurring side-effects of ECC, such as fatigue and peripheral neuropathy, was not affected by pravastatin.

Based upon the results of this first randomised study in patients with advanced gastric cancer, we conclude that the addition of pravastatin to ECC does not improve efficacy. As advocated by the Clinical Trial Design Task Force of the National Cancer Institute Investigational Drug Steering Committee, this phase II study had a randomised comparative design, used PFR at a given time point (i.e. 6 months) as primary endpoint and had sufficient power to make a well-balanced outcome-based decision with a sample size of 30 patients.[22] Therefore we conclude that the addition of pravastatin to ECC does not increase activity of this regimen. The conclusion from this randomised phase II trial provides strong and scientific evidence to discourage the initiation of a large and costly phase III trial to further explore the role of pravastatin in combination with ECC in patients with advanced gastric cancer.

Conflict of interest statement

The authors declare no conflicts of interest.

REFERENCES

1. Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. *J Clin Oncol* 2006;**24**:2137–50.
2. Murad A, Santiago F, Petroianu A, et al. Modified therapy with 5-fluorouracil, doxorubicin, and methotrexate in advanced gastric cancer. *Cancer* 1993;**273**:10618–23.
3. Glimelius B, Ekström K, Hoffman K, et al. Randomized comparison between chemotherapy plus best supportive care with best supportive care in advanced gastric cancer. *Ann Oncol* 1997;**8**:1–6.
4. Pyrhönen S, Kuitunen T, Nyandoto P, et al. Randomized comparison of fluorouracil, epidoxorubicin and methotrexate (FEMTX) plus supportive care with supportive care alone in patients with non-resectable gastric cancer. *Br J Cancer* 1995;**71**:587–91.
5. Wagner AD, Unverzagt S, Grothe W, et al. Chemotherapy for advanced gastric cancer. *Cochrane Database Syst Rev* 2010;**17**(3):CD004064.
6. Cunningham D, Starling N, Rao S, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. *N Engl J Med* 2008;**358**:36–46.
7. Sleijfer S, van der Gaast A, Planting AST, Stoter G, Verweij J. The potential of statins as part of anti-cancer treatment. *Eur J Cancer* 2005;**41**:516–22.
8. Chan KKW, Oza AM, Siu LL. The statins as cancer agents. *Clin Cancer Res* 2003;**9**:10–9.
9. Kim WS, Kim MM, Choi HJ, et al. Phase II study of high-dose lovastatin in patients with advanced gastric adenocarcinoma. *Investig New Drugs* 2001;**19**:81–3.
10. Feleszko W, Zagozdzon R, Golab J, Jakobisiak M. Potentiated antitumour effects of cisplatin and lovastatin against MmB16 melanoma in mice. *Eur J Cancer* 1998;**34**:406–11.
11. Agarwal B, Bhendwal S, Halmos B, et al. Lovastatin augments apoptosis induced by chemotherapeutic agents in colon cells. *Clin Cancer Res* 1999;**5**:2223–9.
12. Feleszko W, Mlynarczuk I, Balkiwiec-Iskra EZ, et al. Lovastatin potentiates antitumor activity and attenuates cardiotoxicity of doxorubicin in three tumor models in mice. *Clin Cancer Res* 2000;**6**:2044–52.
13. Germershausen JI, Hunt VM, Bostedor RG, et al. Tissue selectivity of the cholesterol-lowering agents lovastatin, simvastatin and pravastatin in rats in vivo. *Biochem Biophys Res Commun* 1997;**8**:1–6.
14. Kusama T, Yamasaki E, Nagase T, et al. Effect of pravastatin on survival in patients with advanced hepatocellular carcinoma. A randomized controlled trial. *Br J Cancer* 2001;**84**:886–91.
15. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumours. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000;**92**:205–16.
16. Simon R. Optimal two-stage design for phase II clinical trials. *Control Clin Trials* 1989;**10**:1–10.
17. Haukka J, Sankila R, Klaukka T, et al. Incidence of cancer and statin-usage linkage study. *Int J Cancer* 2010;**126**:279–84.
18. Kuoppala J, Laminpaa A, Pukkala E. Statins and cancer: a systematic review and meta-analysis. *Eur J Cancer* 2008;**44**:2122–32.
19. Lee J, Jung KH, Park YS, et al. Simvastatin plus irinotecan, 5-fluorouracil, and leucovorin (FOLFIRI) as fist-line chemotherapy in metastatic colorectal patients: a multicenter phase II study. *Cancer Chemother Pharmacol* 2009;**64**:657–63.
20. López-Aguilar E, Sepúlveda-Vildósola AC, Betanzos-Cabrera Y, et al. Phase II study of metronomic chemotherapy with thalidomide, carboplatin-vincristine-fluvastatin in the treatment of brain stem tumors in children. *Arch Med Res* 2008;**39**:655–62.
21. Shaw SM, Fildes JE, Yonan N, Williams SG. Pleiotropic effects and cholesterol-lowering therapy. *Cardiology* 2009;**112**:4–12.
22. Seymour L, Percy Ivy S, Sargent D, et al. The design of phase II clinical trials testing cancer therapeutics: consensus recommendations from the Clinical Trial Design Task Force of the National Cancer Institute Investigational Drug Steering Committee. *Clin Cancer Res* 2010;**16**:1764–9.