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Letter to the Editor

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ABSTRACT

With the increased use of tyrosine kinase inhibitors as successful therapy in selected malignancies, their adverse effects will grow, especially when combination therapy is used.

We present a relatively young patient who was successfully treated with erlotinib and sunitinib for her metastatic non-small-cell lung cancer (NSCLC), but died because of the serious event of a necrotizing pancreatitis with severe hypocalcaemia, which we suppose to be an adverse event of the therapy used.

Fatal necrotizing pancreatitis during combined treatment with erlotinib and sunitinib

To the Editor,

Targeted anticancer therapy with tyrosine kinase inhibitors (TKIs) has shown remarkable efficacy in selected malignancies. With increased use of these new agents, the knowledge about their adverse effects will grow, even more when combinations of TKIs are used. Erlotinib (Tarceva®, Roche) has been approved for the treatment of advanced or metastatic non-small-cell lung cancer (NSCLC) after the failure of prior chemotherapy [1]. Sunitinib (Sutent®, Pfizer) has been approved for the treatment of metastatic renal cell carcinoma [2], and has been investigated in a single arm phase II trial in NSCLC [3]. Often reported side effects are for erlotinib rash and diarrhea en for sunitinib diarrhea, nausea, mucositis and rash. We report a patient who developed necrotizing pancreatitis during combination treatment with erlotinib and sunitinib.

The patient is a 46-year-old female with NSCLC (adenocarcinoma). One year before she had received sequential chemo-radiation for locally advanced disease. By now, she presented with clear distant metastases (not histologically or cytologically proven) and participated in a phase 3 multicenter clinical trial on the efficacy and safety of sunitinib in patients with NSCLC treated with erlotinib (Pfizer, Protocol A6181087), and received oral erlotinib 150 mg once daily and oral sunitinib 37.5 mg once daily, both continuously. She experienced mild diarrhea but no other side effects. After 12 weeks on this treatment she presented at the emergency department because of abdominal pain, nausea and vomiting. Her medical history revealed myocardial infarction and hypercholesterolemia and she used aspirin, metoprolol and atorvastatin as medication. She used no alcohol. Physical examination revealed an acutely ill, dehydrated woman with clinical symptoms of pancreatitis. She had no fever. Laboratory examination is shown in Table 1. Most remarkable were the extreme low serum calcium and increased serum amylase. At ultrasonography there were neither gallstones nor biliary duct dilatation. An abdominal CT scan showed an enlarged pancreas and ascites. We concluded that the patient was suffering from acute pancreatitis, with secondary extreme low serum calcium. Since she had no other risk factors for pancreatitis, it was most probably related to the medication she used.

Table 1
Laboratory examination.

Variables (blood/serum)	Results Day 1	Normal values
Hemoglobin	8.0	7.4–9.9 mmol/L
Leucocytes	12.2	3.5–11.0 × 10^9/L
Creatinine	273	50–80 μmol/L
Calcium (ionised)	0.62	1.10–1.32 mmol/L
Calcium (total)	1.00	2.10–2.55 mmol/L
Magnesium	0.41	0.65–1.05 mmol/L
Bilirubin	22	0–17 μmol/L
Alkaline phosphatase	119	0–120 U/L
Aspartate aminotransferase (ASAT)	84	1–40 U/L
Alanine aminotransferase (ALAT)	35	0–45 U/L
Lactate dehydrogenase	1781	1–450 U/L
Amylase	1011	1–220 U/L
C-reactive protein	265	0–9 mg/L
Albumin	24.8	35–50 g/L
Triglycerides	1.8	0.8–1.7 mmol/L
Lactic acid	1.9	0.5–1.8 mmol/L

At admission, all medication was stopped. The patient was rehydrated, received intravenous calcium and magnesium suppletion, and parenteral nutrition. The clinical situation however deteriorated. She developed high fever, and a second CT scan was suitable to necrotizing pancreatitis. Despite maximal supportive care, the patient died 4 weeks after admission. Obduction confirmed the diagnosis of necrotizing pancreatitis with extended peripancreatic fat necrosis (Fig. 1). Vital tumour was not found anywhere in the body, suggesting that the therapy revealed a good tumour response after 12 weeks of treatment.

Asymptomatic elevations in serum amylase and serum lipase have been reported in about 5% of patients being treated with sunitinib [2,4]. Lareb, the Dutch registration centre for adverse events, has confirmed that other cases of pancreatitis and hypocalcaemia in patients treated with erlotinib or sunitinib have been reported, but so far there have been no publications on fatal pancreatitis during this therapy.

In conclusion: we report a patient with fatal necrotizing pancreatitis, with at presentation an extreme low serum calcium, occurring after 12 weeks of combined treatment with erlotinib and sunitinib. Since there were no classic risk factors for pancreatitis, and since elevated serum amylase and pancreatitis is being observed during treatment with sunitinib or erlotinib, it is probable

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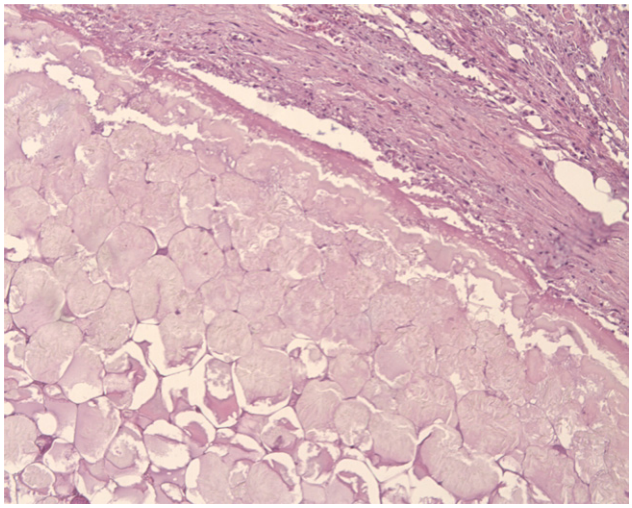

Fig. 1. Necrotizing pancreatitis with peripancreatic fat necrosis.

that this combination therapy is responsible for this fatal pancreatitis.

Conflicts of interest

The authors indicate no potential conflicts of interest.

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