Severe lung and skin toxicity during treatment with gemcitabine and erlotinib for metastatic pancreatic cancer

Stefan Boeck, Andreas Hausmann, Roland Reibke, Christoph Schulz and Volker Heinemann

Gemcitabine in combination with the oral epidermal growth factor receptor tyrosine kinase inhibitor erlotinib is a new treatment option for patients with advanced pancreatic cancer. The nonhematological side effects of this regimen mainly include diarrhea and skin rash. For each of these drugs, gemcitabine and erlotinib, lung toxicties have been described previously. In this report, we present the first case of a nonlung cancer patient experiencing not only acne-like skin toxicity, but subsequently also severe interstitial lung disease during therapy with gemcitabine and erlotinib. Both therapeutic agents were suspected as a possible cause of this adverse event. An interaction between gemcitabine and erlotinib might have also contributed to the pathogenesis of this pulmonary toxicity. Treatment with high-dose steroids was, however, very effective in our patient and a complete recovery appeared within a few days. Thus, pulmonary side effects should be regarded carefully in pancreatic cancer patients receiving palliative therapy with gemcitabine and erlotinib.
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Department of Internal Medicine III, Klinikum Grosshadern, Ludwig-Maximilians-University of Munich, Germany

Correspondence to Dr Stefan Boeck, Department of Internal Medicine III, Klinikum Grosshadern, Ludwig-Maximilians-University of Munich, Marchioninistr, 15, 81377 Munich, Germany
Tel: +49 89 7095 2208; fax: +49 89 7095 5256;
e-mail: stefan.boeck@med.uni-muenchen.de

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Introduction

During the last decade, chemotherapy with single-agent gemcitabine has evolved as a standard of care for patients with advanced pancreatic cancer [1]. A recently presented phase III trial comparing gemcitabine in combination with erlotinib to gemcitabine plus placebo showed a statistically significant survival benefit for the combination regimen (hazard ratio 0.81, 95% confidence interval 0.67–0.97; $P = 0.025$) [2]. The toxicity profile of tyrosine kinase inhibitors (TKI) targeting the epidermal growth factor receptor (EGFR) – like gefitinib or erlotinib – mainly includes skin toxicity (acne-like rash) and diarrhea [3]. Few reports also indicate the occurrence of life-threatening pulmonary toxicities like pneumonitis or interstitial lung disease (ILD) during EGFR-targeted treatment in nonsmall cell lung cancer (NSCLC) patients [3,4]. The prevalence of ILD in patients with NSCLC treated with EGFR TKI is thought to range between 1 and 3% [4,5]. The exact mechanisms of EGFR TKI-associated ILD have not, however, been fully elucidated yet. Furthermore, gemcitabine (as single agent or within combination chemotherapy regimens) is known to induce low rates of pulmonary toxicity [6].

Case report

This case report presents a 59-year-old male patient (a former smoker without a history of pulmonary disease) with metastatic pancreatic adenocarcinoma, who was admitted to the hospital in August 2006 for initiation of palliative treatment. Chemotherapy with gemcitabine (applied according to the Burris regimen [1]) plus erlotinib (150 mg daily) was started within an ongoing phase III trial. After 2 weeks on study treatment, our patient developed a severe skin rash (National Cancer Institute Common Toxicity Criteria grades 2–3), mainly affecting the face and chest (Fig. 1), which could not be controlled by oral treatment with minocyclin, a tetracycline analog. Erlotinib was temporarily discontinued for 1 week and treatment was started with isotretinoin. After a first objective improvement of the rash, erlotinib was reintroduced at a reduced dose of 100 mg daily. Seven weeks after the start of combination therapy with gemcitabine and erlotinib (and 7 days after the last gemcitabine application in treatment cycle one of the Burris regimen [1]) the patient presented with fever up to 39.5°C. No clinical focus of infection was found, vital signs were stable, the C-reactive protein (CRP) level was slightly elevated (2.8 mg/dl; reference range < 0.5 mg/dl) and the chest radiograph showed a possible infiltration in the right middle lobe. Oral antibiotic treatment with moxifloxacin was started and isotretinoin treatment was stopped due to a further improvement of skin rash. Two days later the patient reported with persistent high fever without cough or dyspnea. Laboratory testing showed a rising CRP level (9.6 mg/dl) and the patient was admitted to the hospital for intravenous antibiotic therapy. Despite treatment with piperacillin/tazobactam, fever persisted and the CRP level increased up to a maximum of

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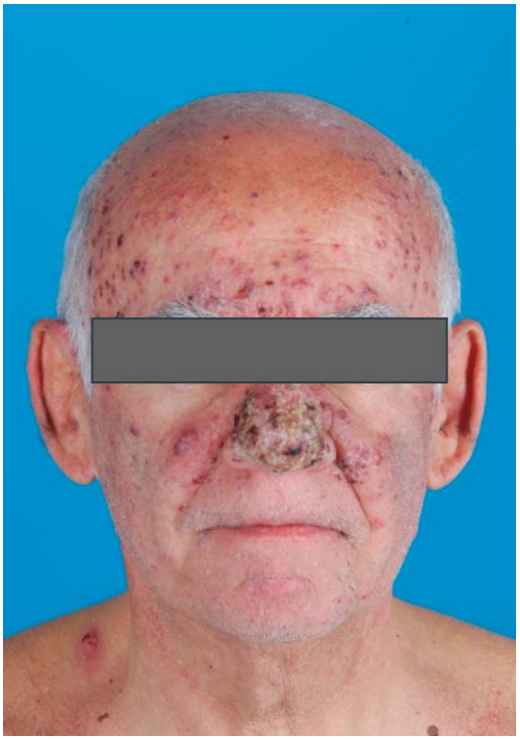
26.6 mg/dl. The interleukin-6 level (11 pg/ml) and also the procalcitonin level (0.2 ng/ml; reference range below 0.5 ng/ml), however, remained low. Two days after the initiation of treatment with intravenous antibiotics, the patient developed rapidly severe dyspnea with a partial respiratory insufficiency (at a nasal oxygen flow rate of 10 l/min: $pO_2 = 64$ mmHg, $pCO_2 = 36$ mmHg, $S_aO_2 = 90\%$). A promptly performed computed tomography (CT) scan of the chest in high resolution showed a diffuse atypical infiltration of both lungs with no signs of pulmonary edema or pleural effusions (Fig. 2a). On that day, erlotinib was discontinued (4 days after the first symptoms of ILD). Subsequently, the antibiotic treatment was escalated with the addition of clarithromycin; empiric antiviral therapy with aciclovir and antifungal treatment with voriconazol was also added. As there were no signs of cardiac insufficiency (e.g. pulmonary edema or pleural effusions), no diuretic treatment was applied. Despite intensive surveillance tests including repeated blood cultures and a bronchoalveolar lavage, no indication was obtained for bacterial, fungal or viral infections. In addition, the microbiological tests remained negative for *Pneumocystis jiroveci*, *Toxoplasma gondii* and *Mycobacterium tuberculosis* complex.

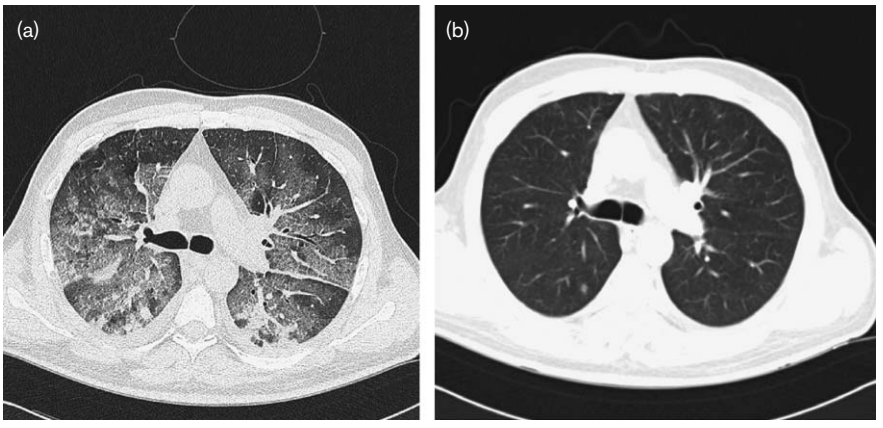
Fig. 1



Skin rash after 2 weeks of treatment with gemcitabine and erlotinib.

When the respiratory insufficiency had persisted for 2 more days despite broad-spectrum antibiotic therapy, the decision was taken to evaluate the effect of high-dose steroid therapy. Prednisolone was applied at an initial dose of 900 mg/day for 3 days and caused a rapid improvement of the patient's condition. Parallel to the clinical improvement, the highly elevated CRP levels dropped quickly (e.g. from 26.6 to 3.1 mg/dl after 3 days of steroid treatment). A CT scan with intravenous contrast performed 7 days after initiation of steroid treatment (and 9 days after the initial high-resolution CT scan, see Fig. 2a) showed a complete recovery of ILD (Fig. 2b). Prednisolone was subsequently reduced and stopped after 16 days of treatment. Stable disease was determined by imaging criteria (according to Response

Fig. 2



(a) High-resolution CT scan of the chest shows diffuse atypical infiltration of both lungs. (b) Complete recovery of ILD confirmed in a staging CT scan with intravenous contrast performed after 7 days of prednisolone treatment. CT, computed tomography; ILD, interstitial lung disease.

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Evaluation Criteria in Solid Tumors) and the serum tumor marker carbohydrate antigen 19-9 (CA 19-9) decreased from 106 to 42.5 U/ml. Despite disease stabilization under treatment with gemcitabine and erlotinib, therapy was classified as treatment failure (due to unacceptable toxicity) and the patient continued chemotherapy – according to the study protocol – with oral capecitabine.

Discussion

This is the first complete case report of a severe ILD syndrome under the combination of gemcitabine and erlotinib [2,7]. A recently published phase IB trial included one NSCLC patient (previously treated with chemoradiation) who developed a lethal adult respiratory distress syndrome occurring 7 days after initiation of treatment with gemcitabine and erlotinib (100 mg daily). This event was interpreted by investigators as an erlotinib- and/or gemcitabine-induced pneumonitis; however, no statement regarding the clinical course and treatment of this fatal pneumonitis was given by the authors [7]. To our knowledge, this case furthermore represents the first suspected EGFR TKI-related severe ILD, which appeared in a nonlung cancer patient. With regard to the etiology and pathogenesis of the observed ILD, three hypotheses may be formulated:

(1) The potential role of gemcitabine in the development of ILD is supported by a previous study reporting 178 patients with gemcitabine-associated lung injury. In this report, the first recognition of a pulmonary toxicity occurred after a median duration of 48 days after initiation of gemcitabine treatment. Clinical features in this patient population mainly included dyspnea, fever and pulmonary infiltrates [6].
(2) Comparable clinical symptoms were described for NSCLC patients experiencing EGFR TKI-associated ILD. The median time from start of treatment with EGFR TKI to the first clinical signs of ILD was approximately 30 days [4]. In our patient, the association of a severe skin reaction and the delayed lung toxicity (appearing approximately 5 weeks after the first symptoms of rash) also supports an important role of erlotinib in the pathogenesis of this ILD.
(3) It cannot be ruled out that both agents – gemcitabine and erlotinib – or an interaction between the two drugs contributed to the development of severe ILD.

In conclusion, in patients with pancreatic cancer treated with gemcitabine and erlotinib, pulmonary side effects should be regarded carefully. A quick diagnosis and treatment of such severe adverse events is strongly recommended. According to this case report, high-dose steroids appear to be an effective treatment for patients developing ILD under the combined therapy with gemcitabine and erlotinib.

Acknowledgements

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