Novel treatment (new drug/intervention; established drug/procedure in new situation)

Dramatic response to inhaled dobesilate in a patient with lung squamous cell cancer

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Summary

The effectiveness of local application, by inhalation, of dobesilate, an inhibitor of fibroblast growth factor signalling, in a patient with squamous cell lung carcinoma is reported. To our knowledge, these are the first published data on the efficacy of dobesilate in the treatment of this disease. The antimitotic, antiangiogenic, proapoptotic and anti-inflammatory activities of dobesilate can be important factors to consider, in explaining the efficacy of the treatment. Dobesilate administration can be a therapeutic option in patients with lung cancer having poor performance status or severe complications.

CASE PRESENTATION

A 78-year-old male diabetic patient, with a medical history of extirpated vesicle cancer, was referred to the department of oncology, with a grade III chronic obstructive pulmonary disease, arterial hypertension and myocardial ischaemia with unstable angina. He suddenly presented with productive purulent cough, haemoptysis, dyspnoea, stridor, tachypnoea and tachycardia, and haemoglobin saturation of 94% in 2.5 litres of O₂, then being referred to the emergency department. The patient was hospitalised at the pneumology department for clinical stabilisation with inhaled oxygen, corticoids, antibiotics and bronchodilators. Once the patient's physiological constants were stabilised, the treatment was stopped. Bronchoscopy revealed a protuberant carinal tumour that extended and almost completely occluded both principal bronchia but more severely the right one, and clearly explains the severe dyspnoea of the patient when he was admitted to the emergency department (figure 2A).

H&E stained sections from biopsied mass at the carina led to a diagnosis of squamous cell carcinoma with mucosal invasion. Sections immunostained with anti-CD34 and anti-Ki67 antibodies, that label endothelium and proliferative cells, respectively, revealed a prominent neovascularisation and cell proliferation (figure 1). In addition, staining with antibodies recognising basic fibroblast growth factor (bFGF or FGF2) detected this protein in many tumour cells (figure 1). The accumulation of FGF is directly correlated with the proliferation of tumour cells and to altered homeostasis of the tissues surrounding the tumour, which is as much a feature as a facilitator of aggressive tumour growth.

After 5 days, a treatment with dobesilate was started. The drug (500 mg twice a day), was administered as a diethylammonium 2,5-dihydroxybenzenesulfonate (etamsylate; Dicynone; Sanofi-Aventis, Paris, France) vaporised solution, mixed with the aspirated air, using an electronic apparatus to dispense medication in aerosol form (eFlow

rapid PARI GmbH, Starnberg, Germany). After 5 days of dobesilate treatment, bronchoscopy showed a drastic reduction of the tumour mass. Figure 2C shows an enlarged picture for easier visualisation of the anatomical details of the right bronchus, the most affected one (for illustrative purposes, figure 2B shows an enlargement of the same bronchus before the treatment, extracted from the picture of figure 2A –frame–). As figure 2C shows, although remaining tumoral mass is still appreciated in carina, the lumen of the right principal bronchus is completely clear. No adverse effects were observed during treatment and patient did not show any significant change in ventilatory pattern, haemoglobin saturation, cardiac rate and respiratory frequency. After treatment, the patient was subsequently discharged, and resumed his habitual life at home, waiting for a future appointment at the department of oncology for follow-up.

DISCUSSION

Here we report that local inhibition of the FGF signalling system, in a patient who had been diagnosed with lung squamous cell carcinoma (L-SCC), causes a dramatic retraction of the tumour. Prior to the treatment, the patient had been stabilised with inhaled oxygen, corticoids, antibiotics and bronchodilators. Never a retraction of the tumour had been observed when the plain stabilisation protocol is applied.

Lung cancer remains as one of the leading causes of cancer-related death in developing countries. Approximately 85% of lung cancer cases are classified as non-small-cell lung cancer (NSCLC) that includes two predominant subtypes, adenocarcinoma and squamous cell carcinoma, which comprise 40% and 25% of NSCLC, respectively.^{1 2} Novel treatment that target the epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF) have emerged for NSCLC management. Both anti-EGFR and anti-VEGF therapies have provided certain amelioration in some patients with lung adenocarcinoma.

Figure 1 Sections of invasive lung cell carcinoma stained with Ki67, CD34 and basic fibroblast growth factor (bFGF) antibodies. Nuclear Ki67 staining showed high-proliferative activity in tumour cells (A). CD34 staining depicted evident tumour neovascularisation (B). Several tumour cells showed cytoplasmic bFGF immunostaining (C), stained sections with Ki67 and bFGF were counterstained with haematoxylin.

Figure 2 Bronchoscopic findings of the effect of inhaled dobesilate in lung squamous cell carcinoma. (A) Shows a bronchoscopy at baseline. (B) A magnification of the rectangular area of the right principal bronchus of (A). (C) Shows a similar bronchoscopic area of the right principal bronchus as (B), but taken after 5 days of dobesilate treatment.

However, long-term results have not fulfilled the initial expectations.^{3–4} Furthermore, anti-EGFR and anti-VEGF therapies were associated with important side effects.^{5–9} In the case of L-SCC, targeted-therapies have not yet been fully developed, and the outcomes are rather poor, despite the recent improvements in traditional treatment modalities such as surgery and radiotherapy.^{10–11} Therefore, exploring new pathways able to lead to the development of new therapeutic options to treat L-SCC is obviously of utmost importance,¹² and urgently needed. FGFs have been implicated in a wide variety of human pathological conditions including cancer.^{13–17} Upregulated FGF signalling contributes to the development of cancer by acting on cancer or stromal cells, sometimes in both of them, causing inflammation, angiogenesis and contributing to the proliferation, survival, invasion and metastasis of the cancerous cells. FGFs have been implicated in autocrine signalling loops that lead to tumour proliferation and angiogenesis in NSCLC, and have been strongly associated with poor survival.^{18–22} Furthermore, FGF is potentially at the basis of the mechanism of resistance developed by tumours to both anti-EGFR and anti-VEGF therapies.^{23–25} On the basis of these data it has been proposed that FGF represents a promising therapeutic target in NSCLC.^{25–26} As a milestone in developing rational and safe therapies against FGF activities in neoplasms, we have spent important efforts in the development of synthetic inhibitors of FGF.²⁷ Among them, dobesilate is one of the most powerful inhibitor of FGF-driven activities.²⁸ We have shown that dobesilate recognises both FGF and its receptors, displacing heparin from its binding site, modifying the three-dimensional structure of the growth factor, at its receptor recognising site, and, consequently, dissociating the receptor-growth factor signalling complex.²⁸

On the basis of our positive experience in patients with skin neoplasms treated with dobesilate,^{29–31} and on recent animal studies that have shown the clinical efficacy of inhaled antineoplastic drugs,^{32–33} we decided to treat patients with L-SCC with inhaled dobesilate. Results obtained with the first patient to whom this treatment was applied are presented in this case report. In this patient a dramatic positive response was observed, as early as 5 days after the administration of the drug. Inhibition of inflammation, cell survival, cell proliferation and neovascularisation induced by FGF are processes inhibited by dobesilate that may account for the effectiveness of the treatment.^{28–34–35} Finally, it seems rather obvious that, according to the results presented in this case report, targeting FGF with selective inhibitors may allow for the development of novel therapeutic strategies to improve the survival of L-SCC patients.

Learning points

- ▶ Lung squamous cell carcinoma (L-SCC) comprises 25% of non-small cell lung cancer.
- ▶ L-SCC overexpresses fibroblast growth factor (FGF) and its receptors.
- ▶ Inhibition of FGF with dobesilate elicits a dramatic positive response in a patient with L-SCC.

Competing interests None.

Patient consent Obtained.

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