Management of severe infusion reactions after cetuximab

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To the Editor

The rare instances of severe infusion reactions accompanying the initial stages of treatment with cetuximab are considered to be an absolute contraindication of further treatment with this drug [1]. Anecdotal evidence suggests that treatment with another antibody against the epidermal growth factor receptor, panitumumab, may be safe following a severe infusion reaction to cetuximab [2]. However, specific information on manifestations and management of severe infusion reactions associated with the administration of cetuximab is lacking, as reflected in the recent review by Patel and Goldberg [1]. Although in most clinical trials, severe infusion reactions were rare, a high incidence of severe infusion reactions after the administration of cetuximab has been reported in Tennessee and North Carolina [3]. Similarly, we have observed an unusual incidence of severe infusion reactions in patients treated with cetuximab at our institution (4 of 43 cases; 9%). We have reported that treatment could be resumed under careful monitoring in an intensive care unit (ICU) in two patients who experienced severe infusion reactions after cetuximab [4]. We describe here a similar experience in two additional cases.

A 68-year-old man with liver metastases of rectal carcinoma progressive after two lines of chemotherapy was indicated for intravenous therapy with cetuximab (loading dose 400 mg/m^2, subsequently 250 mg/m^2 weekly) followed by irinotecan (180 mg/m^2), leucovorin (200 mg/m^2), and 5-fluorouracil (400 mg/m^2 bolus and 1200 mg/m^2 for 46 hours) every 2 weeks. The first dose of cetuximab is administered in our center according a standard protocol in a 2-hour infusion after pre-medication with the H_1-antihistaminic agent bisulepin (1 mg intravenously). Immediately after beginning the first infusion on September 6, 2006, the patient had a feeling of dyspnea, followed by loss of consciousness, apnea and non-palpable carotid pulse activity. The infusion was stopped and cardiopulmonary resuscitation was started (at 08 45 a.m.). After a few chest compressions, the pulse was palpable, spontaneous breathing resumed, and the patient subsequently regained consciousness. The patient's blood pressure was 90/60 mm Hg, his heart rate 112/min, the arterial oxygen saturation (measured by pulse oximetry) was 91%. After transferring him to the ICU, his blood pressure was 113/47 mmHg, his heart rate 95/min, the arterial oxygen saturation 95%, and the respiratory rate 30/min. Saline (3 000 ml, with potassium and magnesium) was infused. As the condition of the patient improved, the situation was explained to him, and therapeutic options were discussed. It was explained that the probability of response to a combination of irinotecan and 5-fluorouracil without cetuximab was low, and alternative options of cancer treatment were limited. The patient was willing to continue chemotherapy with surveillance in the ICU. The infusion of cetuximab was re-started 4 hours after the first infusion attempt. After 30 minutes the infusion was stopped because of abdominal pain. Thirty minutes later the pain spontaneously subsided, and the rest of the infusion was administered without any adverse reaction. Under careful monitoring in the ICU, the infusion of cetuximab could be continued. An increase of urinary neopterin, an indicator of systemic immune activation, [5], was observed (Figure 1). Subsequent infusions of cetux-

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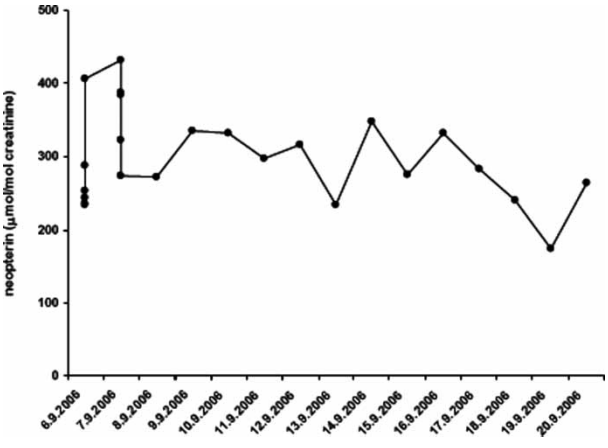

Figure 1. Urinary neopterin before and after the infusion reaction. Urine samples were obtained before the start of therapy, after the infusion reaction with every voiding in the ICU, and then daily. Neopterin, an indicator of systemic immune activation, was determined as described earlier [5]. Urinary neopterin concentrations are usually stable in cancer patients. Increased concentrations reflect immune activation or infections, while decreased urinary neopterin has been associated with tumor control [5].

imab were administered in an outpatient setting without any complications.

After this event, we started to administer the initial infusion of cetuximab in the ICU. In the ICU, another severe infusion reaction was observed after the initial infusion of cetuximab in the same combination in a 60-year-old female with liver metastases of colon carcinoma. After one minute the patient was anxious, had severe dyspnea with bronchoconstriction, hypotension, chest pain, sweating, tachypnea, generalized wheezing. Her blood pressure had dropped to 55/35 mm Hg, and sinus tachycardia of 120/min was observed. Infusion was stopped. Epinephrine (1 mg) and hydrocortisone (200 mg) were administered intravenously. The patient's condition improved rapidly, and she expressed a willingness to continue chemotherapy. After administering 16 mg of dexamethasone, re-infusion of cetuximab was started four hours after the severe infusion reaction. With the exception of facial erythema, the re-infusion of cetuximab was uneventful, and the patient tolerated subsequent outpatient infusions of cetuximab.

Most cases of severe infusion reactions have been described after the administration of chimeric mouse-human antibodies (rituximab, infliximab, or cetuximab), usually immediately after the start of the first infusion. Although the terms "hypersensitivity," "allergic," or "anaphylactoid" were used to describe these reactions, the evidence so far seems to point to non-allergic mechanisms, possibly involving a massive inflammatory response [6]. An increase of urinary neopterin in one of the patients presented here also suggests the activation of systemic inflammatory response. Because severe infusion reactions are rare and unexpected events, few details may be recorded by the staff immediately after the onset of the reaction. Although severe infusion reactions are commonly listed in the reports of clinical trials, relatively little has been published on the clinical manifestations and management of these events. A marked variation in the incidence of severe infusion reactions is evident from the literature. While in large clinical trials, severe infusion reactions have been reported in 2–3% of patients [7], a 22% incidence of severe infusion reactions has been recently reported in North Carolina and Tennessee [3]. A 9% rate of severe infusion reactions in our center is between these two extremes. The reason for this geographical variation concerning severe infusion reactions to cetuximab remains speculative. In the reports from North Carolina and Tennessee, an association was observed between a history of atopy and severe infusion reaction, but even in patients without a history of atopy the incidence of severe infusion reactions was 8% [3]. The administration of corticoid as part of the premedication was not protective [3].

Even less is known about the management of severe infusion reactions with cetuximab. Twenty-four cases of severe infusion reactions to cetuximab, resulting in two deaths, were described in a retrospective analysis of severe infusion reactions to monoclonal antibodies [8]. All 24 severe infusion reactions occurred during the first administration of the drug. Because cetuximab was discontinued in the great majority of these cases, it was not possible to assess the incidence of repetitive severe infusion reactions.

To the best of our knowledge, the present cases represent the most detailed descriptions of severe infusion reaction after administering cetuximab. In contrast to the standard recommendations, two cases reported earlier by us [4] as well as the two present cases, indicate that the cetuximab may be safely readministered within an ICU setting in patients after their initial severe infusion reaction. Moreover, these events do not seem to be repetitive. In fact, our current policy is to administer the first dose of cetuximab in the ICU. This policy may be warranted in places with high incidences of severe infusion reactions. At some institutions, the high rate of severe infusion reactions with cetuximab resulted even in suspension of all clinical trials with this drug [3]. Currently, we can only speculate about the cause of the high incidence of severe infusion reaction after initial dose of cetuximab at our center. As the anecdotal evidence in our cases does not seem to support an allergic etiology, we speculate that the high incidence of severe infusion reaction could be associated with the fact that the drug is administered through central catheters. All but one patient in our center, and all the patients with severe infusion

reactions, had the drug administered via catheter with a subcutaneous port system, introduced through the subclavian vein. We speculate that administering the drug through the catheter into the right atrium could result in uneven concentrations in the pulmonary vascular bed, and the transiently increased concentrations in lung capillaries could trigger an overwhelming inflammatory response resulting in severe infusion reaction.

In conclusion, although the pathogenesis of infusion reactions after cetuximab remains elusive, re-administration of the drug may be safe in an ICU setting.

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Pituitary Adenoma Neuronal CHoristoma – The PANCH syndrome

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To the Editor

Pituitary Adenoma Neuronal CHoristoma (PANCH syndrome) is a rare pathological entity of pituitary with unknown clinical impact.

Case history

Pituitary adenomas are common benign brain tumours that are easily diagnosed on biopsy specimens by typical morphological features. However, rarely, they may have divergent differentiation, necessitating the use of immunohistochemistry (IHC) for better characterization.

A 43-year-old lady presented with progressive weight gain, enlargement of extremities and hirsutism of 2 years duration. MRI scan showed focal enlargement of the pituitary gland suggestive of a macroadenoma (Figure 1). There was no mass effect on the optic pathway and her endocrine profile was normal (T3-2.5 nmol/l, T4-129.1 nmol/l, TSH-0.24 mIU/ml, Prolactin-4.48 ng/ml, GH-2.15 ng/ml, and Cortisol-5.45 ug/dl). She underwent trans-sphenoidal excision of the lesion via a sublabial, rhinoseptal approach with uneventful post-operative recovery. Conventional light microscopy suggested pituitary adenoma with extensive neuronal metaplasia (Figure

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