Efficacy of Pregabalin in the Management of Cetuximab-Related Itch

To the Editor:

Cetuximab is a drug with an expanding role in the treatment of solid tumors, in particular epidermal growth-factor receptor or EGFR-expressing metastatic colorectal cancer. Like other EGFR inhibitors (panitumumab, matuzumab) and EGFR-specific tyrosine kinase inhibitors (gefitinib, erlotinib), cetuximab is characterized by significant incidence of skin reactions (80%–86% of patients), such as acneiform eruption, xerosis, eczema, and hair and nail changes.[1] These skin reactions can be complicated by itch. Treatment of itch is based on oral antihistamines and topical creams. No standard treatment is suggested in case of failure of these drugs.[2–4]

New anti-epileptic drugs, particularly gabapentin, have proven to be safe and effective in the treatment of itch of various origins.[5–7] Pregabalin has similar structure and action to gabapentin and it is indicated for the management of neuropathic pain. It has never been tested for the treatment of itch.

Case

A 62-year-old man, affected by a primary intestinal-type adenocarcinoma of the nasal cavity, locally advanced, was observed at the Medical Oncology Department of the University of L'Aquila in February, 2006. Clinicopathological and immunohistochemical findings were according to criteria to diagnose this tumor. The patient was previously treated with surgery and chemotherapy. A total body computed tomography (CT) scan, performed in January, 2006, revealed progressive disease. Histologic tissues were evaluated and the tumor proved to be strongly EGFR-positive; therefore, a cetuximab-based chemotherapy was scheduled. Fifteen days after the first course, the patient was admitted to the Medical Oncology Department for a Grade 3 skin toxicity, classified according to the National Cancer Institute Common Toxicity Criteria version 2.0. Skin was dry with acneiform eruptions distributed in scalp, face, and thorax; there were bloody scratch lesions. Intense itch was scored 9–10 by the patient on a Numerical Rate Scale (NRS). He had distressing sleep deprivation for one week. Evaluation with the Edmonton Symptom Assessment System (ESAS) revealed depression (ESAS 9), anxiety (ESAS 8), and asthenia (ESAS 7). Others common causes of itch (cholestatic jaundice, iron deficiency, renal failure, diabetes, pain treatment with opioids) were excluded.

Oral antihistamines (promethazine 50 mg twice daily) and topical anti-inflammatory cream were started. After two days of treatment, itch was not improved. Sleep deprivation, asthenia, anxiety, and depression remained severe (ESAS >7).

The patient was very distressed and disposed to stop chemotherapy. Oral antihistamines were interrupted and pregabalin (Lyrica®, Pfizer Italia) was started at 75 mg twice daily. After 2 days, itch was slightly improved (NRS 5–6) and the dose of pregabalin was titrated to 100 mg twice daily. Itch ameliorated significantly (NRS ≤ 3), as well as depression (ESAS 4), anxiety (ESAS 3), and asthenia (ESAS 3). Transient drowsiness (ESAS 7 scored by patient; Epworth Sleepiness Scale Grade 2, scored by the physicians) was evidenced for three days. Scheduled chemotherapy was restarted and second and third courses administered.

Twelve days after the third course, the patient was admitted to the Pneumology Unit of our hospital for a pulmonary microembolism. Without consultation with medical oncology physicians, and although adverse effects were not evidenced, pregabalin was withdrawn. Severe itch recurred promptly; our unit was involved in the therapeutic plan and pregabalin was restarted (100 mg twice daily), with a rapid resolution of itch. The patient is still in treatment, without evidence of itch and/or adverse effect from pregabalin.

Comment

Gabapentin recently was proven to be safe and effective in the treatment of itch. The mechanism of action is unclear and it has been hypothesized to be both central and peripheral. Gabapentin, as well as pregabalin, inhibits release of calcitonin gene-related peptide, which is a mediator of itching, from primary afferent neurons through an increase of γ-aminobutyric

acid in the spinal cord.[8] Moreover, gabapentin may modify central perception of itch by a modulation of μ-opioid receptors.[9]

Pregabalin is very similar to gabapentin regarding structure and mechanism of action. Compared to gabapentin, pregabalin is characterized by a more rapid time of response. Based on this characteristic, pregabalin has been preferred to gabapentin to obtain the most rapid response for a very distressing symptom. Pregabalin does not bind to plasma proteins and it is not subject to hepatic metabolism; these characteristics make it particularly attractive for patients with advanced cancer, who often present with low levels of plasma proteins and/or hepatic failure.[10]

In our patient, pregabalin seemed to be effective in the treatment of cetuximab-related itch. Drowsiness was the only adverse effect registered; it was transient and did not require specific treatment. We observed a dose-response effect. Therefore, we suggest a careful titration of doses to obtain the best response and minimize the adverse effects. Compliance with cetuximab-based chemotherapy was maintained and scheduled chemotherapy was not modified.

To our knowledge, this is the first report on the treatment of itch with pregabalin. Considering the expanding role of cetuximab in the management of solid tumors, and the significant incidence of itchy skin reactions, pregabalin should be considered a promising drug to treat this distressing adverse effect. Further evaluations are warranted to confirm or refute our observation.

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References

1. Segaert S, Can Cutsem E. Clinical signs, pathophysiology and management of skin toxicity during therapy with epidermal growth factor receptor inhibitors. Ann Oncol 2005;16: 1425–1433.

2. Segaert S, Tabernero J, Chosidow O, et al. The management of skin reactions in cancer patients receiving epidermal growth factor receptor targeted therapies. J Dtsch Dermatol Ges 2005;3: 599–606.

3. Lacouture ME, Basti S, Patel J, Benson A 3rd. The SERIES clinic: an interdisciplinary approach to the management of toxicities of EGFR inhibitors. J Support Oncol 2006;4(5):236–238.

4. Perez-Soler R, Delord JP, Halpern A, et al. HER1/EGFR inhibitor-associated rash: future directions for management and investigation outcomes from the HER1/EGFR inhibitor rash management forum. Oncologist 2005;10:345–356.

5. Scheinfeld N. The role of gabapentin in treating disease with cutaneous manifestations. Int J Dermatol 2003;42:491–495.

6. Winhoven SM, Coulson IH, Bottomley WW. Brachioradial pruritus: response to treatment with gabapentin. Br J Dermatol 2004;150:786–787.

7. Yesudian PD, Wilson NJE. Efficacy of gabapentin in the management of pruritus of unknown origin. Arch Dermatol 2005;141:1507–1509.

8. Fehrenbacher JC, Taylor CP, Vasko MR. Pregabalin and gabapentin reduce release of substance P and CGRP from rat spinal tissues only after inflammation or activation of protein kinase C. Pain 2003;105:133–141.

9. Yoon MH, Choi J, Jeong SW. Spinal gabapentin and antinociception: mechanisms of action. J Korean Med Sci 2003;18:255–261.

10. Shneker BF, McAuley JW. Pregabalin: a new neuromodulator with broad therapeutic indications. Ann Pharmacother 2005;39:2029–2037.

A Case of Visceral Post-Stroke Pain

To the Editor:

I report a patient who was a right-handed, married, male, noninsulin-dependent diabetic (treated with metformin 500 mg b.d.) former crane driver who, in 1991, at the age of 52, had a stroke, which caused left-sided ataxia and nystagmus. This resolved after a short (but unknown) time. Six months later, he experienced a burning sensation in his right