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Monoclonal antibody-induced papulopustular rash: Clinical course, communication to health-care professionals and reactive measures as reported by patients

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ABSTRACT

Purpose: The primary end-point was to describe the clinical course of monoclonal antibody-induced papulopustular rash (mAB-induced PPR), when patients alert health-care providers and the subsequent reactive measures employed. Exploring the predictors affecting PPR grading was the secondary end-point.
Methods: A multicentre retrospective study involving six Italian oncology outpatient departments was conducted. Thirty-nine patients with cancer undergoing cetuximab or panitumumab treatment were included. Information was collected through medical records and face-to-face interviews. mAB-induced PPR was scored by patients' self-reported Common Terminology Criteria for Adverse Eventsv4.02 and was defined as severe when the grade $\geq$3.
Results: Thirty-five (89.7%) patients developed a rash, which was severe in nine cases. The rash usually appeared within the first week after starting the drug (22, 62.8%), peaked in severity during the first month (26, 74.3%) and resolved 4–8 weeks after the end of mABs therapy (15, 45.7%). At the time of the interviews, the rash was not still resolved in almost half (n = 16) of the patients. Twenty-six (74.3%) patients reported sequelae and the mostly common were erythema (21, 81%) and dry skin (14, 54%). Only half of the patients informed health-care professionals as soon as the rash appeared. All the patients treated the rash topically and mAB therapy was modified in 16 (45.7%) cases (reduction, n = 10; discontinuation, n = 9; withdrawal, n = 2). No association between male gender, age, fair skin, current smokers during therapy and PPR grading escalation was found.
Conclusions: The clinical course of the rash was pathognomonic. Patients should be further encouraged to communicate the onset of a rash to health-care professionals as soon as it appears to avoid grading escalation and sequelae. The adoption of CTCAE as a patient-reported outcome may become an instrument to help health-care providers in tailoring treatment measures.

1. Introduction

The Epidermal Growth Factor Receptor (EGFR) is a transmembrane glycoprotein that modulates cell proliferation and survival. The EGFRis produced in excessive quantities in human tumours of epithelial origin and this excess boosts tumour growth and progression (Myskowski and Halpern, 2009; Segaert and Van Cutsem, 2005). Two strategies can be adopted to target the EGFR pathway: monoclonal antibodies (mABs) and small molecule tyrosine kinase inhibitors (TKIs). The former (cetuximab, panitumumab) bind to the extracellular domain of the EGFR, blocking its activation and signal transduction, whereas TKIs (erlotinib, lapatinib, gefitinib) selectively inhibit the tyrosine kinase activity of the intracellular domain of the EGFR arresting receptor phosphorylation (Myskowski and Halpern, 2009; Segaert and Van Cutsem, 2005).

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EGFR inhibitors (EGFRIs) are generally well tolerated by patients and do not have the systemic side effects characterizing other cytotoxic medications. However, EGFRIs and particularly mABs are associated with dermatological side effects described as a unique class-specific semiology; within these, the acneiform or papulopustular rash (PPR) is the most common although xerosis, eczema, pruritus, fissures on hands and heels, telangiectasia, hyperpigmentation, hair changes and paronychia have been also described (Segaert et al., 2009; Segaert and Van Cutsem, 2005).

Many studies on PPR have been conducted as a secondary analysis of clinical trials (Herbst et al., 2010; Lynch et al., 2010; Bokemeyer et al., 2009; Wilke et al., 2008; Cunningham et al., 2004), while few studies have been conducted from a nursing perspective (Dunsford, 2008; Oishi, 2008). Moreover, the latter were all secondary studies focusing on nursing management of mAB-induced skin toxicities. In addition, to our knowledge, no studies have been reported examining the experience of patients regarding the evolution of the phenomenon over time, when patients contact health-care professionals and reactive measures are adopted.

A recent systematic review of 50 studies (Bachet et al., 2012) showed EGFR-induced folliculitis tended to be greater in frequency and severity with mABs than with TKIs. The frequency of all-grade folliculitis was 70% higher in 11 out of 15 (73%) mAB-based studies compared with eight out of 24 (33%) TKI-based studies. Moreover, severe (grade 3–4) folliculitis was 10% higher in 13 out of 24 (54%) mAB studies and in only three out of 26 (12%) TKI studies.

The incidence of mAB-induced severe rash may range between 3% and 26% (Tol et al., 2008; Hecht et al., 2007; Baselga et al., 2005) and this wide range may be partially due to differences in recording modalities (single event, i.e. rash, orcomposite categories, i.e. skin reactions) or due to the adoption of multiple versions of the severity scale of the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE). The CTCAE Version 2 gave great importance to the involved body surface (BS) which may be misleading since rashes associated with EGFRIs are generally confined to the face and upper trunk. The CTCAE Version 3 added a new item concerning acneiform eruption. The current 4.03 version is based on the involved BS and two subjective measures, pain and the intervention(s) needed according to physician assessment (National Cancer Institute , 2009). In Table 1, an example of the scale is reported.

This PPR usually develops as a sensory disturbance with erythema and oedema within the first week of EGFRI therapy, followed by itchy and tender erythematous papules and pustules in the sebaceous areas (scalp, face, upper chest and back) overthe following 1–3 weeks. The peak is reached 4–6 weeks after the start of EGFRI and its severity decreases after 6–8 weeks, but long-term sequelae such as erythema, xerosis and hyperpigmentation can last for months or years (Lacouture et al., 2011; Eaby et al., 2008; Segaert& Van Cutsem, 2005).

The severity of folliculitis is dose-dependent (Segaert et al., 2009; Perez-Soler and Saltz, 2005) and the concomitant radiotherapy (Tejwani et al., 2009) or chemotherapy (Balagula et al., 2011) may function as an exacerbating risk factor. Balagula and colleagues (2011), in their meta-analysis including 9 trials regarding 2664 cetuximab-treated patients, found that cetuximab significantly increased the risk of high-grade rash when combined with chemotherapy (Relative Risk [RR] = 37.7, 95% Confidence Interval [CI] = 17.8–80.0, $p < 0.001$). However, some evidence showed that a rash might be a clinical marker for response since positive correlations between PPR and outcome have been reported with mABs as well as with TKIs (Segaert et al., 2009; Lièvre et al., 2008; Jackman et al., 2007; Wacker et al., 2007). Patients with a rash were found to survive longer than those without (Ocvirk et al., 2010; Lièvre et al., 2008; Jackman et al., 2007). In addition, documented data even suggests a positive correlation between increasing rash severity and increasing response and survival (Peeters et al., 2009; Pérez-Soler and Saltz, 2005; Pérez-Soler et al., 2004). However, the meta-analysis developed by Balagula and colleagues (2011) documented no significant correlation between the RR of high-grade PPR and the hazard ratio of progression-freesurvival ($p = 0.73$) or overall survival ($p = 0.73$).

Dermatological toxicity may have a negative impact on psychosocial well-being and quality of life (QoL), leading people to worry, experience depression and avoid social activities (Wagner and Lacouture, 2007). Joshi et al. (2010), in their retrospective study on 67 patients assessing QoL through the Skindex-16 questionnaire, found that the greater the rash severity, the greater the reduction in QoL, most affecting negatively emotions. Moreover, several patients complained of EGFRI-induced sequelae such as xerosis and hyperpigmentation when PPR was not promptly treated (Segaert and Van Cutsem, 2005). In addition, a survey of oncology practitioners documented that 32% of providers discontinued therapy and 76% modified doses due to severe rash (Hassel et al., 2010). Therefore, patients should be recommended to contact health-care professionals as soon as they develop any symptom of skin toxicity aiming at avoiding dose modifications that may reduce treatment efficacy (Eaby et al., 2008).

To date, few management guidelines for EGFRI-induced rash have been published (Baas et al., 2012; Lacouture et al., 2011; Potthoff et al., 2011; Ouwerkerk and Boers-Doets, 2010; Melosky et al., 2009), and most of them are based on uncontrolled trials or case series studies. However, the efficacy of preventive management strategies may be maximized (Lacouture et al., 2010; Jatoi et al., 2008; Scope et al., 2007), minimizing the need for dose reduction and delays that may compromise the benefits of EGFRIs. In accordance with the rash severity, available treatment measures range from topical agents (mild reactions), systemic treatment with tetracycline (moderate reactions) or therapy discontinuation (severe or life-threatening reactions) (Potthoff et al., 2011; Ouwerkerk and Boers-Doets, 2010; Melosky et al., 2009). An example of

Table 1
CTCAE v4.0 Tool for papulopustular rash and recommended treatments: an example.

GRADE	3	Treatment
Definition: A disorder characterized by an eruption consisting of papules (a small, raised pimple) and pustules (a small pus filled blister), typically appearing in face, scalp, and upper chest and back Unlike acne, this rash does not present with whiteheads or blackheads, and can be symptomatic, with itchy or tender lesions.	Papules and/or pustules covering >30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self-care ADL; associated with local super-infection with oral antibiotics indicated	Skin type-adjusted moisturizer Topical and systemic treatment (see grade 2) Consider oral isotretinoin or systemic steroids Refer to dermatologist Reduce EGFRI dose as per label and monitor for change in severity

Abbreviations: ADL, Activity of Daily Living; BSA, Body Surface Area; EGFRI, Epidermal Growth Factor Receptor Inhibitor.
Treatments based on information from Potthoff et al. (2011).
Sources: CTCAE v 4.0 available from http://ctep.cancer.gov, 20 November 2014.