Preventing or treating anti-EGFR related skin rash with antibiotics?

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Cutaneous folliculitis (a papulopustular acne-like skin rash), which is a common skin rash, is a dermatological phenomenon that is universally observed in the treatment of anti-epidermal growth factor receptor inhibitors in solid tumours (either tyrosine kinase inhibitors or monoclonal antibodies). Its appearance is quite common (about 60–80% of patients treated), is usually of a low or moderate grade (G1–2) and is typically associated with facial disfigurement and cutaneous adnexa changes (hair and eyelash alterations, ungueal infections, skin pruritus, xerosis, skin pigmentation, and bacterial suprainfection in rare cases). Severe cutaneous adverse events lead to psychological distress, and quality of life is probably impaired in these patients. The rash is generally mild to moderate, but of a high grade (G3/4) in 5% to 20% of patients. The typical papulopustular rash occurs within 1 to 3 weeks of starting treatment, and is fully developed at weeks 3 to 5. Usually, these skin toxicities are treated with both topical (moisturizers, emollients, topical antibiotics/steroids) and/or systemic measures (oral antibiotics, steroids and antihistaminic drugs). General recommendations suggest the use of topical agents for G1 events, with both topical and systemic treatment proposed for more severe grades. Appropriate preemptive measures are strongly recommended before and during treatment with anti-EGFR agents in the cancer setting.

An impressive overview of 59 studies published on the issue from 2005 to 2011 has recently been released. This presents the current position on the condition, which is mainly obtained from prospective observational or retrospective case studies, as well as low quality randomized research (1). In particular, 45 studies on oral antibiotics were extracted, 25 of which suggested the use of systemic antimicrobials for G2–3 skin rashes. A further 11 did not specify any treatment, and four advised the use of antimicrobials for all and G1 grades, respectively.

EGFR inhibitor drugs induce the expression of specific chemokines (CCL2, CCL5, CCL27, and CXCL14) in epidermal keratinocytes, and impair the production of antimicrobial peptides and skin barrier proteins. Furthermore, treated keratinocytes facilitate lymphocyte recruitment, but show remarkably reduced cytotoxic activity against Staphylococcus aureus (2,3). In this scenario, there is a rationale for a therapeutic (preventive) role of antibiotic prophylaxis. In particular, doxycycline and minocycline, which are tetracyclines commonly used for acne vulgaris, are candidates for this. Their anti-inflammatory properties could also be useful in this setting.

On 10 March, Melosky and colleagues published a Canadian phase III trial (4) in the *Journal of Clinical Oncology*. This compared upfront *vs.* the reactive (at G2b-3 rash appearance) use of minocycline for 1 month *vs.* no treatment unless the rash is severe (at least G3) in patients with lung cancer treated with erlotinib after first line treatment failed. The co-primary objectives of this study were to determine and compare the overall incidence of any grade of an erlotinib-induced rash among the three treatment arms, and to determine whether the rash course is self-limiting. Secondary endpoints included the time it took to reduce the severity of the erlotinib-induced rash by 1 grade, the maximum severity of the erlotinib-induced rash, the time to the first presentation of the rash, the relationship between the incidence and maximum severity of the rash, the tumour response to erlotinib for those patients with measurable disease, and survival. Quality of life was also evaluated. The primary endpoint was not satisfied with a prophylactic antibiotic; that is, the grade of rash was similar, irrespective of the timing of the minocycline (84%, 84% and 82% for all three treatment arms). The

incidence of the G3 rash was, however, significantly reduced in arm 1 (prophylactic) *vs*. arm 3 (control; 12% and 28%, respectively; P=0.0455), and in arm 2 (reactive) *vs*. 3 (control; 8% and 28%, respectively; P=0.0092). Rash onset was also delayed by five days in the preemptive arm. This means that oral tetracyclines could only prevent severe toxicity, but not a mild rash. This suggests that the rash is probably an immunological (positive) event that occurs in almost all immunocompetent subjects with cancer treated with anti-EGFR agents, while antibiotics may perhaps only prevent a complicated rash (with bacterial suprainfection?). The rash was also not self-limiting and persisted for all the treatment durations, irrespective of the arms. Paradoxically, however, the time to resolution was 1 month longer for the preemptive arm. Overall survival did not change (and was as expected), and quality of life was also not altered by the rash (contrary to our expectations).

A major limitation of this study is that it did not include preemptive measures in the three arms. In the STEPP trial by Lacouture *et al*. (5), the preemptive arm involved a skin treatment (beginning 1 day before the administration of the first panitumumab dose and continued through weeks 1 to 6) that consisted of a skin moisturizer, sunscreen applied to exposed skin areas, a topical steroid applied at bedtime, and 100 mg of doxycycline twice per day. In this study, G2–3 events were reduced by 62% to 29% (70% less risk), and quality of life improved compared to the reactive arm.

In oncology, prevention is better than treating any side effects, for example the avoidance of the classical side effects of chemotherapy such as nausea/vomiting and stomatitis, as this can improve compliance, avoid dose reduction and delays, and may enhance quality of life. A skin rash also leads to body alterations in severe skin domains, with hard to treat signs and symptoms (facial disfigurements, xerosis with fissuration, pruritus, eye adnexa infections with potentially severe ocular involvement, and mucositis). Probably, not all these events are prevented with antibiotics, but some may have a major impact on the quality and outcome of the cure. For example, in a therapeutic setting as first-line therapy for advanced colorectal cancer with potentially resectable liver metastases, a short and intensive conversion therapy with a chemotherapy doublet + cetuximab or panitumumab (in RAS wt patients) may cause liver lesions to become resectable and so curable by surgeons. Similarly, a definitive treatment of locally advanced head and neck cancer with radiotherapy + cetuximab may be potentially curative in most patients. In these two examples, preventing dose reduction or interruption could be crucial for the outcome of patients, leading to the completion of the definitive cure as quickly as possible.

When the level of evidence is weak and derived from small randomized trials or retrospective observations, a meta-analysis is an instrument for aggregating all these data. We recently conducted a systematic review and meta-analysis of all the studies published on the issue of skin rash prevention with antibiotics (6). We calculated that prophylactic, instead of reactive, minocycline or doxycycline can prevent all grade (G1–4) and severe grade (G2–4) events by 50% and 70%, respectively. This translated into a 10% and 25% absolute risk reduction of these events, respectively. The results were similar with both antibiotics. We also did not find any difference in other skin events that typically occurred, except for paronychia. In terms of the choice of agent (Melosky *et al*. used minocycline for 4 weeks), the literature data and our findings suggest that, for patients with an acneiform skin rash, minocycline, which is more lipophilic and may therefore achieve higher concentrations in the pilosebaceous unit, should be preferred over doxycycline, even if the former has a slightly worse profile with respect to adverse events. In a metastatic setting, the possible interaction of these drugs with cytotoxics should be considered, and the less toxic antibiotic (doxycycline) may be preferred. The authors of the pan Canadian rash trial also argued that the overall survival of patients is similar with early or deferred antibiotics. This should be the case, because it is the occurrence of the rash that has a positive effect on survival, and not its treatment. Conversely, they observed that a prophylactic antibiotic arm with erlotinib is associated with a double survival duration (3.6 *vs*. 1.8 months in arm 1 *vs*. arms 2 and 3). This means that reducing the burden of toxicity probably improves adherence to and compliance with treatment and prevents futile treatment breaks. Safety was also not a concern, with similar rates of adverse events across all arms.

Overall, controversial data have been published, with some positive studies and other negative ones, leading to contentious findings. Our recent aggregated analysis of 13 studies nevertheless shows that tetracyclines can reduce the incidence of the severe skin rash risk associated with anti-EGFR agents by a clinically significant magnitude. Skin care is essential both pre- and during treatment, and reactive measures should be immediately offered for a therapeutic purpose when the rash appears. Melosky *et al*.'s findings add some data to the overall literature burden and confirm that prophylactic tetracyclines are moderately effective and safe in cancer patients, even if they do not change the natural history of the acneiform rash. We agree with a recently published Italian expert recommendation (7): "*The main conclusion drawn*

was that the use of preemptive antibiotics cannot be recommended routinely; however, as some patients can benefit clinically from treatment with tetracyclines, these can be offered on an individual basis in an attempt to reduce the severity of the rash and improve QoL".

In summary, the management strategy for skin toxicities should be universal, with accurate patient instructions and education about skin care. New topical agents are currently under development as potential therapies for the rash. These include vitamin K and, in particular, vitamin K1 (fillochinone) and K3-based creams (menadione). Emollient agents, sunlight exposure protection, and a reduction in the use of cosmetics are also suggested. The aggressive management of the skin rash, once developed, is crucial for avoiding treatment interruptions or delays. Psychological support for patients is also potentially beneficial, and they should be informed that the appearance of the rash is a positive and not a negative event. Indeed, G2–3 rashes have been associated with an improved prognosis in both colorectal and lung cancer studies (8,9).

In conclusion, we believe that an oral course of at least 4 weeks of tetracyclines, plus nurse counselling and preventive (skin care) measures, could be offered to all patients starting (potentially curative) treatment with commonly approved anti-EGFR drugs, unless they are contraindicated (for medical reasons or drug interactions) or not tolerated due to side effects.

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Footnote

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Comment on: Melosky B, Anderson H, Burkes RL, *et al.* Pan Canadian Rash Trial: A Randomized Phase III Trial Evaluating the Impact of a Prophylactic Skin Treatment Regimen on Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitor-Induced Skin Toxicities in Patients With Metastatic Lung Cancer. J Clin Oncol 2016;34:810-5.

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