Previously irradiated areas spared from skin toxicity induced by cetuximab in six patients: implications for the administration of EGFR inhibitors in previously irradiated patients

Skin toxicity induced by epidermal growth factor receptor (EGFR) inhibitors is well known, and indeed it is even debated whether it may mirror antitumor activity. In this report, we evaluate six patients, in whom the acneiform skin rash induced by cetuximab sharply spared previously irradiated areas.

Patient characteristics and treatment details are reported in Table 1. The interval between radiotherapy and cetuximab-based therapy varied from 3 to 68 months (median 15.5 months), while radiation doses ranged from 36 to 70 Gy. In all patients, cetuximab was administered weekly, with a loading dose of 400 mg/sqm, and then maintained by 250 mg/sqm. As expected, acneiform rash developed early after cetuximab administration. It, however, selectively spared previously irradiated fields.

Previous dose of radiation therapy as well as the interval elapsing from it were most varied. This indicates that, whatever the mechanism behind, this must be early and specific.

In head and neck cancer, the concomitant administration of an anti-EGFR treatment and radiation did result in improved efficacy; it was associated with the typical acneiform eruption, but without enhancement of local mucositis and dermatitis [1]. The antitumor activity, however, was clearly not precluded. Therefore, we can conclude that, if a problem does exist with anti-EGFR agents and radiation therapy, it would affect only patients receiving radiation therapy before, not concurrently with, anti-EGFR treatment.

EGFR is primarily expressed and activated in the basal layer of epidermal and follicular keratinocytes, contributing to their biology and homeostasis [2]. EGFR homodimerization leads to activation of human epidermal receptor (HER)-signaling network in normal keratinocytes [3]. The blockade of this pathway through EGFR-targeting drugs seems to cause the typical folliculitis, however, the mechanism is not yet completely known [4].

In regard to the effects of radiation on skin, in the first 3 weeks during irradiation there is a seesaw of degeneration and regeneration of the basal layer, with an increase in mitotic index, typically not associated with changes in microvasculature [5]. On the contrary, in the period following radiation therapy, epidermis scars over time, undergoing changes marked by keratinocyte hyperproliferation and altered differentiation, as well as progressive endothelial loss without replacement. This results in decreased skin vasculature. Late changes of the basal layer are associated with hyperexpression of EGFR and abnormality in transforming growth factor-β1 [6], which may

<table>
<thead>
<tr>
<th>Patient</th>
<th>Disease</th>
<th>Site of previous irradiation</th>
<th>Maximum radiotherapy dosage (Gy)</th>
<th>Interval between end of radiotherapy and start of cetuximab (months)</th>
<th>Skin toxicity (CTCAE v3.0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Recurrent salivary gland tumor</td>
<td>Right parotid region omolateral neck</td>
<td>70</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>Recurrent salivary gland tumor</td>
<td>Oropharynx right neck</td>
<td>70</td>
<td>19</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>Metastatic head and neck squamous cell cancer</td>
<td>Left parotid region level 1–II neck nodes</td>
<td>68</td>
<td>36</td>
<td>2</td>
</tr>
<tr>
<td>4 (Figure 1)</td>
<td>Metastatic salivary gland tumor</td>
<td>Oral cavity bilateral upper and middle neck</td>
<td>54</td>
<td>68</td>
<td>2</td>
</tr>
<tr>
<td>5 (Figure 2)</td>
<td>Metastatic salivary gland tumor</td>
<td>Right breast axillary region</td>
<td>50</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>6</td>
<td>Metastatic skin annexial cancer</td>
<td>Spine tract D12-L2</td>
<td>36</td>
<td>5</td>
<td>1</td>
</tr>
</tbody>
</table>

CTCAE v3.0, Common toxicity criteria adverse events version 3.0.
well modify the epidermal sensitivity to EGFR inhibitors, possibly by altering the normal HER pathway activation system. Therefore, one can make at least two hypotheses, whose implications would be different. Under the first hypothesis, the simple mechanism by which the action of anti-EGFR agents is prevented at the skin level might be the trivial fact that the drug does not reach this compartment because of poor microvasculature. Interestingly, this skin-sparing effect was observed also by other authors with small molecules [7]. The damage to microvasculature should be therefore of such an extent as to prevent small molecules also from reaching the target; furthermore, this effect was clinically sharp and independent of the previous radiation dose. In any case, if the drug supply to the skin were the actual problem, it would be very unlikely, of course, that sparing in skin toxicity is paralleled by sparing in antitumor effect.

The other hypothesis has obviously to do with the effect on the target, following skin changes, which, as said above, might affect the skin sensitivity to EGFR inhibitors. Under this hypothesis, it would be more difficult, in principle, to exclude that these agents might be less active against previously irradiated tumors. Interestingly, a positive correlation between the antitumor effect of these agents and the degree of skin toxicity has been suggested by many [8].

A clear-cut correlation with the biomolecular effects on skin cells, however, has been much less demonstrated. Moreover, the pathway of EGFR activation in cancers targeted by these agents mainly involves heterodimerization of ErbB2 and ErbB3 [9]. This does not apply to the skin, in which homodimerization is prevalent [4]. Therefore, the biomolecular mechanisms of skin toxicity and antitumor activity are inherently different, thus making it not so inevitable that toxicity sparing is paralleled by lower clinical efficacy. A final conclusion, however, cannot be made, and the possibility of an adverse impact of prior radiation therapy on anti-EGFR agents cannot be ruled out under this hypothesis.

In brief, we believe that the clinical observation of such a clear-cut sparing of skin toxicity from anti-EGFR agents in previously irradiated areas should lead (i) to properly study the underlying mechanisms and (ii) more importantly, to assess in clinical studies the efficacy of these drugs against lesions irradiated before their administration.

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