Grading system and management guidelines for dermatitis induced by head and neck radiotherapy plus cetuximab: clinical validation required

Head and neck squamous cell carcinoma (HNSCC) represents a rather heterogeneous group of neoplasms originating from the oral cavity, oropharynx, hypopharynx and larynx. In the last decades, prognosis significantly increased as a result of the introduction of new treatment strategies, such as the addition of concomitant chemotherapy to radiation [1], the use of altered fractionation schedules [2] and, more recently, the use of taxane-based induction chemotherapy [3, 4]. Although outcome in terms of locoregional control and overall survival (OS) are improved, most of these regimens have come to the expense of severe acute and late radiation-induced side-effects, such as mucositis and subsequent swallowing dysfunction. Despite the fact that there is still ample room for improvement, further intensification of concurrent chemoradiation regimens is expected to result in unacceptable acute toxicity rates. In this regard, there has been and will be a growing need for new combined modality strategies that improve treatment efficacy without enhancing radiation-induced side-effects.

In 2006, Bonner et al. reported on the results of a prospective study in which patients with locally advanced (stage III and IV) HNSCC originating from the oropharynx, hypopharynx and larynx were randomly assigned to receive radiotherapy alone or radiotherapy plus cetuximab, a monoclonal antibody against the extracellular domain of the epidermal growth factor receptor [5]. The addition of cetuximab to radiotherapy significantly improved 5-year OS rate for patients treated with radiotherapy alone versus 23% for those treated with radiotherapy plus cetuximab (not significant). Concurrent chemoradiation is considered the standard in locally advanced HNSCC but has not been compared directly to radiotherapy with cetuximab. The latter regimen is increasingly used but mainly for patients with locally advanced HNSCC who are considered ineligible for chemoradiation.

Since the introduction of concurrent radiotherapy and cetuximab in routine clinical practice, several authors published the results of their first experiences and reported much higher incidences of severe radiation dermatitis than were observed in the Bonner trial [5]. Giro et al. [7] described the results of a retrospective study, including 71 assessable patients from 28 European Organisation for Research and Treatment of Cancer (EORTC) institutions in 11 countries. They found 21% grade III and 28% grade IV radiation dermatitis, respectively, which is twofold higher than in the Bonner trial. In addition, Pryor et al. [8] reported a 77% incidence of grade III to IV radiation dermatitis among the first 13 consecutive patients with locally advanced mainly oropharyngeal and hypopharyngeal cancers treated with the same regimen, of whom 46% required hospital admission and 31% treatment breaks. In reply to this paper, Chan et al. [9] reported that they observed a 61% rate of grade III to IV radiation dermatitis among HNSCC patients treated with concurrent hypofractionated radiotherapy and cetuximab. In a prospective non-randomised comparative clinical study, concurrent cetuximab and radiotherapy resulted in a 31% increase in the rate of grade III to IV radiation dermatitis compared with patients treated in the same time period with concurrent chemoradiation [10].

These reports demonstrate that severe radiation-induced skin toxicity is an important and clinically relevant problem in HNSCC patients treated with radiotherapy and cetuximab outside the setting of a clinical trial. Dermatitis is not only burdensome to patients; it sometimes necessitates interruption of radiation treatment, which has a significant adverse impact on locoregional tumour control.

In a phase II study combining chemoradiotherapy with cetuximab, 18 out of 20 patients (90%) developed grade III to IV radiation dermatitis, suggesting that chemotherapy further aggravates radiation-induced skin toxicity when combined with radiotherapy and chemotherapy [11]. These findings launched further investigations on the pathogenesis, risk factors, grading and management of radiation dermatitis.

how to explain differences in severe radiation dermatitis?

It is clear that, with regard to the incidence and severity of radiation dermatitis during concurrent radiotherapy with cetuximab, there is a striking difference between the results observed in the Bonner trial and the reports on the first experience in routine clinical practice.

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A possible explanation for these differences is the use of different toxicity grading systems. In the Bonner trial, acute radiation toxicity was determined using the Radiation Therapy Oncology Group Acute Radiation Morbidity Scoring Criteria [5], while others used different versions of the National Cancer Institute—Common Toxicity Criteria and Adverse Events (NCI–CTCAE) grading system [7]. In some reports, it even remained unclear which toxicity scoring system was used. However, as the definitions of grade II, III and IV only slightly differ between these scoring systems, it is unlikely that the use of different scoring systems is sufficient to explain the discrepancies in the incidences reported.

Another explanation may be publication bias. Out of the 111 EORTC institutions asked to participate in the retrospective study by Giro et al. [7], only 28 institutions responded. It is not unlikely that those institutions that experienced high rates of acute skin reactions were more inclined to respond than others. This may have biased the results and may have lead to an overestimation of the incidence of grade III and IV radiation dermatitis in that study. On the other hand, as acute toxicity was not scored prospectively, the results could have been biased in the opposite direction as well.

Finally, radiation dose and technique may influence the incidence and severity of dermatitis. Giro et al. [7] found a gradual increase in the rate of grade III to IV radiation dermatitis during the radiation course. This observation suggests a dose–response relationship for either radiotherapy or cetuximab or both. However, Studer et al. [10] did not find an obvious correlation between the number of cetuximab cycles and the incidence of grade III to IV radiation dermatitis. In that study, a significant association was found between the dose to the skin and grade III to IV radiation dermatitis. Although not specified in the initial paper of the Bonner trial, given the time period in which patients were included, they were most likely treated with three-dimensional conformal radiotherapy and not with intensity-modulated radiotherapy (IMRT). On the contrary, most patients included in the studies that reported higher rates of radiation dermatitis were treated with IMRT. In some studies, IMRT with frequent use of bolus [build-up material on the skin to ascertain adequate radiation dose to the superficial planning target volume (PTV) in case of PTV’s extending to just under the skin] was given [10], which increases the dose to the skin considerably. Dosimetric studies using IMRT in the head and neck region showed that the skin dose may vary widely depending on the margins taken for PTV shrinkage related to the clinical target volume in the proximity of the skin [12]. As the policies in radiation departments may differ with regard to the radiotherapy treatment planning objectives, the definition of the PTV immediately under the skin surface, and the use of bolus or not, may all interfere with the actual skin dose delivered during radiation and thus with the probability on severe skin reactions.

Although the landmark study [5] did not show an increased incidence of grade III to IV radiation dermatitis, there are abundant data that indicate that patients who are currently selected for concurrent cetuximab with IMRT-based radiation have a high risk on severe acute skin reactions during the course of treatment. Therefore, there is a need for well-defined and concise management guidelines.

### Classification of Radiation Dermatitis

In the current issue of *Annals of Oncology*, Bernier et al. [13] present consensus guidelines for the management of grade III to IV radiation dermatitis in patients receiving concurrent radiotherapy and cetuximab. They also propose a modification of the NCI–CTCAE grading system of radiation dermatitis as they felt that the current system was not adequately designed for this specific type of radiation dermatitis and thus may lead to misclassification and subsequent inappropriate management [13].

Without any doubt, physicians perform not so very well in scoring radiation-induced toxicity when treating patients in clinical trials and in routine clinical practice. A number of studies have shown that physicians tend to underestimate the incidence and severity of treatment-related toxicity [14]. Moreover, interobserver agreement in scoring skin reactions ranges from 65% to 97% depending on the toxicity item [15]. A prerequisite for proper and unambiguous scoring of toxicity with high interobserver agreement is a scoring system that is easy to perform and interpret in a busy clinical environment. The NCI–CTCAE toxicity scoring system has been widely adopted by the oncology community and is used nowadays in most clinical trials. This has resulted in more homogeneous scoring and reporting of treatment-related side-effects. The NCI–CTCAE scoring system has been updated and modified several times based on advancing clinical experience and knowledge of the pathophysiology of side-effects. Bernier et al. identified some shortcomings in the latest version of the NCI–CTCAE scoring system for radiation dermatitis, for which they propose modifications. For example, as radiation dermatitis resulting from the concurrent use of radiotherapy and cetuximab is clinically characterised by the presence of crusts, it is generally impossible to determine the presence of skin necrosis or ulceration of the full thickness of the dermis, as defined in the CTCAE v4.03 (classified under Injury, Poisoning and Procedural Complications). In this regard, it is important to mention that in the retrospective multicenter study on radiation dermatitis during radiotherapy and cetuximab [7], major differences were noted in the reported incidences of grade IV radiation dermatitis between different institutions. Indeed, this may reflect the difficulty in the distinction between grade III and IV as defined by the CTCAE. Although the modifications proposed appear sound, the question arises whether these modifications will really result in more appropriate and accurate scoring and eventually in improved interobserver agreement. One of the shortcomings of toxicity scoring systems is that they are mainly based on common sense and general consensus but lack clinical validation. This is surprising, especially when considering the extensive validation procedures that are required for quality of life questionnaires before introduction into clinical trials (http://groups.eortc.be/qol/documentation_manuals.htm). Validation is of major importance not only for enabling inter-institutional and inter-trial comparisons but also to ensure a safe translation of the proposed management guidelines into routine clinical practice. Shifting the paradigm from expert-based to evidence-based scoring of major toxicity should be the scope of future research, focussing on feasibility, interobserver variability and comparison with the golden standard, being the latest version of the CTCAE. These types of studies could run in parallel with intervention trials as secondary end points.
clinical introduction of guidelines

One of the strengths of the paper of Bernier et al. is that they provide detailed management guidelines based on of the grade of radiation dermatitis. These guidelines are mainly based on expertise and clinical experience of the authors and are generally in line with the guidelines as proposed in 2008 [16]. The clinical benefit of these guidelines has not been validated yet in randomised controlled trials. However, this ‘lack of evidence’ should not be a reason to withhold patients’ supportive care and preventive measures. Many clinicians dealing with head and neck cancer patients have gained experience with the sometimes devastating consequences of radiation dermatitis during concomitant treatment with cetuximab and know how to manage these acute reactions properly. Most of the measures proposed by Bernier et al. are widely accepted and used in daily practice. Therefore, the proposed guidelines could serve as the new standard to be tested against in order to further improve prevention and treatment of radiation dermatitis. It is noteworthy to mention the recently published paper of Selzer et al. [17] who reported on a retrospective evaluation of 112 consecutive patients treated with radiotherapy plus cetuximab. They provide a detailed description of management of skin reactions using topical antibiotic/antifungal agents with or without oral antihistamine and tetracycline. The incidence of grade III and IV radiation dermatitis was 29% and 1%, respectively, which was comparable to a retrospective control group treated with radiotherapy alone or with chemoradiation. These results suggest that with proper management of skin reactions, concurrent radiotherapy with cetuximab can be given without enhancing incidence and severity of skin reactions beyond the rates as are usually seen with the more conventional approaches.

However, prospective validation of the proposed guidelines is mandatory as there are several questions that remain to be answered, such as the value of corticosteroids and the prophylactic administration of antibiotics. Recently, Scope et al. [18] demonstrated in a randomised controlled trial that upfront administration of minocycline reduces the incidence and severity of acneiform rash during cetuximab treatment in colorectal cancer patients treated with cetuximab. It is tempting to hypothesize that upfront treatment with minocycline or doxycycline, which has antibiotic as well as immunomodulatory effects, also reduces radiation dermatitis during cetuximab treatment. This study by Scope et al. [18] clearly illustrates that it is possible to further test aspects of the proposed guidelines in properly conducted clinical studies. Therefore, the expert-based guidelines presented in the current proposed guidelines in properly conducted clinical studies. Therefore, the expert-based guidelines presented in properly conducted clinical studies. Therefore, the expert-based guidelines presented in properly conducted clinical studies.

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disclosure

The authors declare no conflicts of interest.

references