Critical Reviews in Oncology / Hematology 120 (2017) 98–110

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Review

Incidence of skin toxicity in squamous cell carcinoma of the head and neck treated with radiotherapy and cetuximab: A systematic review

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ARTICLE INFO

Keywords:
Head and neck cancer
Radiotherapy
Cetuximab
Dermatitis
Rash

ABSTRACT

Purpose: Radiotherapy plus cetuximab is an effective combination therapy for locally advanced head and neck squamous cell carcinoma. The aim of our study was to determine the frequency of skin toxicity in patients receiving the combined treatment.

Results: Forty-eight studies were included in our analysis, for a total of 2152 patients. The mean rates of G3/G4 radiation dermatitis and acneiform rash were 32.5% (SD: 20.4; 95% CI: 28.5–36.5) and 13.4% (SD: 11.5; 95% CI: 11.2–15.6), respectively. The majority of studies referred to CTCAE scales for reporting both side effects (85.7% and 92.1%, respectively). Data on the management of skin toxicity were available in only 35.4% of the reviewed literature.

Conclusions: severe radiation dermatitis is a frequent side effect induced by the combination of radiotherapy and cetuximab in head and neck cancer. The lack of predictive biomarkers of toxicity hampers the possibilty to design preventive measures on a personalized basis.

1. Introduction

The incidence of head and neck cancer is increasing: overall, it represents the sixth most common neoplasm (Kamangar et al., 2006), with over 600.000 new cases diagnosed annually worldwide. In over 60% of patients, the disease is discovered at a loco-regionally advanced stage that requires a combined multimodal strategy if a curative intent is pursued. Currently, cisplatin-based concomitant chemo-radiation is the standard non-surgical approach in locally advanced squamous cell carcinoma of the head and neck (SCCHN) (Pignon et al., 2009), although hampered by the occurence of severe side effects and poor compliance. Given the observation that more than 90% of SCCHN overexpress the Epidermal Growth Factor Receptor (EGFR) and that EGFR-mediated pathways play a crucial role in SCCHN proliferation, an alternative strategy to the cisplatin-based regimen was recognized in the inhibition of EGFR signaling. In 2006, Bonner and colleagues published the results of the IMCL 9815 trial (Bonner et al., 2006), showing that the addition to radiation (RT) of Cetuximab (CTX), a chimeric mouse IgG1 monoclonal anti-EGFR antibody, led to better median loco-regional control and overall survival (OS) compared with RT alone without an increased rate of > G3 acute toxicity or a detrimental effect on quality of life (Curran et al., 2007). In light of the evidence provided by this randomized study, the concomitant regimen received FDA approval for the treatment of locally advanced SCCHN. However, the issue of tolerability to the concurrent treatment was raised by case reports, cooperative (Giro et al., 2009) and early institutional (Pryor et al., 2009) experiences reporting a high rate of severe skin side effects. In particular, several authors described the occurrence of an enhanced, rapidly developing dermatitis with distinct clinical features partly different from what usually observed with RT alone, namely due to the presence of worsened xerosis, a generally more intense inflammatory response in the affected tissue, coexistence of desquamation and papulo-pustular ("acneiform") rash and finally a peculiar, painful and sometimes hemorrhagic crusty exudate with potential septic complications. The frequency of this overlapping "in-field" toxicity induced by the combination of RT and CTX has yet to be clearly determined. Overall, the correct recognition, grading and therapeutic management of the ad-hoc defined "bio-radiation" dermatitis (BRD) (Bernier et al., 2011) represent still today potential limitations (Langendijk and Oosting, 2011) towards the use of CTX in locally advanced SCCHN, since in this regard the indications from the literature are heterogeneous and lack prospective validation in controlled clinical

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http://dx.doi.org/10.1016/j.critrevonc.2017.10.011
Received 6 March 2017; Received in revised form 28 September 2017; Accepted 29 October 2017

trials. Moreover, at present no specific patient, disease and treatment related-features allow to predict the onset or the degree of severity of BRD throughout a standard 7-week course of radiation. In order to assess the cumulative incidence of acute skin toxicity in SCCHN patients treated with CTX and RT, we performed a systematic review of the literature focusing on studies published after the IMCL 9815 trial. We also aimed to analyze what grading scales were used to report on treatment side effects and to check whether specific supportive care interventions were adopted, if any.

2. Materials and methods

Following the methodology of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement (Liberati et al., 2009), a systematic review of the literature was conducted, focusing on the development of skin toxicity due to the concomitant use of CTX and RT in locally advanced SCCHN. Relevant articles were identified searching Medline (through PubMed) by use of the appropriate MeSH terms for the following search items: bio-radiation dermatitis, radiation dermatitis, acneiform rash, skin toxicity *AND* head neck cancer *AND* cetuximab AND Radiotherapy (Radiation therapy, Radiation). The review of the literature was restricted to articles published between February 2006 (time of publication of the IMCL 9815 trial) and October 2016 (cutoff, 31/10/16). Only fully published articles in English reporting data on acute skin toxicity were considered eligible. For the purpose of our analysis, case reports, case series with less than 10 patients, reviews and consensus papers were not taken into account. Moreover, articles analyzing anti-EGFR drugs other than cetuximab (such as TKI's), re-irradiation, post-operative setting and palliative radiation schedules were excluded. Papers reporting on therapies incorporating CTX within induction chemotherapy regimens were also not considered due to the potential confounding effect of skin toxicity developed before RT start. Therefore, only articles focused on the concurrent administration of RT and CTX in SCCHN with curative intent and adequate information provided on skin toxicity were selected. The adherence to the prespecified eligibility criteria was independently verified by two authors (PB, ID). In case of disagreement, a consensus choice was taken with a third author (ML), blinded to the selection process. Patients', disease and treatment-related features were collected from every paper, whenever available. The rate of G3/G4 skin toxicity was reported in terms of acneiform rash, radiation dermatitis or ad-hoc definitions. We sought to evaluate the compliance to treatment in terms of elapsed RT days and CTX relative dose intensity (RDI). The toxicity grading scales adopted in the articles were registered. Finally, the management recommendations on how to prevent and treat the occurrence of skin toxicity were reported, whenever described. In order to assess the risk of bias in the examined literature, the Cochrane Review tool for assessment of bias in publications (Higgins and Altman, 2008) was adopted by two authors (ML, ID). For every study, we evaluated the individual risks of selection (biased allocation to interventions), performance (knowledge of the allocated interventions), detection (lack of precise definition and reliable method to detect and report the outcome), attrition (deviations or handling of incomplete outcome data) and reporting (bias due to selective outcome reporting) biases, respectively.

Baseline demographics, patients' characteristics, treatment features and toxicity data were collected by the first author (PB), verified by two reviewers (ML and ID) and summarized using descriptive statistics.

3. Results

3.1. Studies characteristics

Out of 547 references identified by using our predefined search criteria, 253 papers were screened through abstracts assessment (Fig. 1). Overall, 107 articles were evaluated for eligilibity: 48 of them (Giro et al., 2009; Pryor et al., 2009; Pfister et al., 2006; Teoh et al., 2008; Lord et al., 2008; Fountzilas et al., 2009; Chan et al., 2009; Koutcher et al., 2009; Tomková et al., 2010; Buiret et al., 2010; Koukourakis et al., 2010; Kuhnt et al., 2010; Walsh et al., 2011; Kao et al., 2011; Merlano et al., 2011; Studer et al., 2011; Selzer et al., 2011; Pryor et al., 2011; Wieczorek et al., 2011; Argiris et al., 2011; Agarwal et al., 2011; Dattatreya and Goswami, 2011; Ma et al., 2012; Valeriani et al., 2012; Suntharalingam et al., 2012; Acevedo-Henao et al., 2012; Rampino et al., 2012; Jensen et al., 2012; Alongi et al., 2012; Lefebvre et al., 2013; Niu et al., 2013; Ye et al., 2013; He et al., 2013; Okano et al., 2013; Keil et al., 2013; Saigal et al., 2014; Hu et al., 2014; Fury et al., 2014; Ang et al., 2014; Strojan et al., 2014; Feng et al., 2014; Levy et al., 2014; Thomson et al., 2015; Kurokawa et al., 2015; Sakashita et al., 2015; Xu et al., 2015; Magrini et al., 2016; Levy et al., 2016) were deemed to provide adequate information on treatment-related skin side effects and were therefore included in the review. Fifty-nine articles were excluded due to missing or incomplete data on toxicity (Caudell et al., 2008 ; Dequanter et al., 2010; Beijer et al., 2013; Egloff et al., 2014; Montejo et al., 2011; Koutcher et al., 2011; Levy et al., 2011; Tong et al., 2012; Kim et al., 2012; Ley et al., 2013; Riaz et al., 2013; Pajares et al., 2013; Fayette et al., 2013; Huang et al., 2014; Birnbaum et al., 2014; Shapiro et al., 2014; Tang et al., 2015; Ricci et al., 2015; Strom et al., 2015; Riaz et al., 2016; Bibault et al., 2016), adoption of unconventional RT schedules (Jensen et al., 2011; Balermpas et al., 2009; Zwicker et al., 2011; Heron et al., 2011; Balermpas et al., 2012; Matuschek et al., 2013; Mesía et al., 2013; Milanović et al., 2013; Lartigau et al., 2013; Vargo et al., 2014; Harari et al., 2014), inclusion of CTX into induction chemotherapy regimens (Birnbaum et al., 2010; Haddad et al., 2009; Argiris et al., 2010; Adkins et al., 2013; Wanebo et al., 2014; Mesia et al., 2016; Villaflor et al., 2016), for being exclusively management recommendations (Bernier et al., 2011; Russi et al., 2007; Bernier et al., 2008; Pinto et al., 2011; Dean et al., 2011; Cabezón-Gutiérrez et al., 2012; Cante et al., 2013; Revannasiddaiah et al., 2013; Russi et al., 2015; Zhu et al., 2016; Pinto et al., 2016) or case reports. In 41.7% of the included studies, a high − uncertain risk of selection bias was found, mainly due to the explicit allocation to RT − CTX of elderly or fragile patients with contraindication to cisplatin, thus potentially influencing the risk of toxicity onset compared with the general target population. Due to the retrospective nature of a substantial number of trials and the impossibility to perform a blinded analysis of study subjects, the evaluation of performance bias was not applicable in our review. The risk of detection bias was generally low (83,3% of studies) in view of the accurate definition of toxicity through validated scales. The risk of attrition bias was also low (85,4% of studies) due to the limited time span of onset of acute toxicity, resulting in adequate availability of data. Finally, the risk of reporting bias was low in most included studies (81.2%) except the minority (18.8%) with an unclear risk due to incomplete or missing description of one of the prespecified outcomes (acneiform rash). Although the risk of heterogeneity in the studied population couldn't be minimized, we observed an overall low risk of bias in the selected literature, given the chosen outcome (acute toxicity) for whom optimal detection and use of validated scales were possible.

The included works were almost equally balanced in terms of study design (Table 1), being 25/48 (52%) retrospective and 23/48 (48%) prospective. Of the latter group, the majority were single-arm phase 2 studies (15/48, 31.3%), followed by 4 phase 1/phase 1–2 trials (8.3%), 3 phase 2 randomized trials (6.3%) and one phase 3 randomized trial (2.1%).

The overall patients' population consisted of 3429 subjects: 2152 of them were treated with a backbone schedule of concurrent RT and CTX and therefore represent the reference cohort of the analysis (Fig. 2).

3.2. Skin toxicity

As in the IMLC 9815 trial, acute skin toxicity was assessed through