REVIEW ARTICLE

Multidisciplinary, Multi-Institutional Consensus on Cetuximab Usefulness in the Treatment of Patients with Head and Neck Squamous Cell Carcinoma

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Abstract Epidermal growth factor receptor is preferably expressed in head and neck squamous cell carcinomas and is a promising therapeutic target. Cetuximab is the only epidermal growth factor receptor-targeted agent that has been approved for the treatment of squamous cell carcinoma. The 2006 FDA-approved indication refers to the use of cetuximab in combination with radiotherapy for the treatment of locoregional, advanced, unresectable head and neck squamous cell carcinoma, except for nasopharyngeal carcinoma. In 2011, the use of cetuximab in combination with platinum and 5-fluorouracil was approved as first-line treatment for recurrent and/or metastatic head and neck squamous cell carcinoma. In order to homogenize and arrive at a multidisciplinary, multi-institutional consensus based on scientific evidence, a meeting was held where the existing literature was reviewed and the role of cetuximab in the treatment of patients with head and neck squamous cell carcinoma was discussed. This work reviews current evidence-based indications for the use of cetuximab in the treatment of patients with head and neck squamous cell carcinoma. (creativecommons.org/licenses/by-nc-nd/4.0/).

KEYWORDS
Cetuximab; Head and neck cancer; Head and neck squamous cell carcinoma

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INTRODUCTION

Cetuximab (CTX) is a chimeric anti-epidermal growth factor receptor (EGFR) IgG1 monoclonal antibody. Binding of the antibody to the receptor blocks endogenous ligands (epiregulin, amphiregulin, betacellulin, transforming growth factor, epidermal growth factor) binding and promotes internalization of the receptor, which leads to EGFR signaling cascade deregulation. The blockade inhibits cell proliferation, angiogenesis, and metastasis and restores apoptosis. At the extracellular level, it promotes immune system cytotoxic cells attack against EGFR-expressing tumor cells, due to the recognition of the IgG1 Fc region by natural killer cells. In combination with radiotherapy (RT), CTX inhibits DNA repair and tumor angiogenesis, while facilitating apoptosis, radio-sensitizing cells at G1 phase, and reducing radio-resistance of cells at S phase.

Head and neck squamous cell carcinoma (HNSCC) treatment of choice has been surgery followed by radiotherapy; however, at locoregionally advanced or inoperable stages, the association of chemotherapy (CT) with RT (CTRT) emerged in the 1990s as an alternative that offered better control than RT alone. Subsequent studies demonstrated that concomitant CTRT had superior outcomes when compared with RT alone, with overall survival (OS) improvement in patients with unresectable tumors, in patients at high risk or relapse after surgery, and as a non-surgical-conservative option of choice for advanced laryngeal and pharyngeal tumors candidate for laryngectomy. However, toxicity emerged as a limitation for systematic administration in patients who are often fragile and with serious comorbidities. Knowledge of the receptors and signaling pathways involved in the genesis and progression of HNSCC led to the development of anti-EGFR monoclonal antibodies and tyrosine kinase-inhibiting molecules. Cetuximab, a monoclonal antibody, has been tested in associations with CT and RT, and has demonstrated activity with a favorable toxicity profile. The indication approved by the FDA in 2006 refers to the use of CTX in combination with RT for the treatment of locoregionally advanced, unresectable HNSCC, except for nasopharyngeal carcinoma, in disease persisting to other treatments, in unresectable tumors, in patients at high risk for progression (p = 0.006) and death by 26%. The study demonstrated activity with a favorable toxicity profile. The indication approved by the FDA in 2006 refers to the use of CTX in combination with RT for the treatment of locoregionally advanced, unresectable HNSCC, except for nasopharyngeal carcinoma, in disease persisting to other treatments, in organ-preservation attempts (larynx), and concomitantly with RT in locoregionally advanced disease. In 2011, the use of CTX was approved in combination with platinum and 5-fluorouracil (5-FU) as first-line treatment for recurrent and/or metastatic HNSCC. This work reviews current indications, based on existing evidence, for the use of CTX in the treatment of patients with HNSCC.

MATERIALS AND METHODS

A panel comprised of 11 specialists experienced in the treatment of head and neck cancer from different disciplines and who represented health institutions that treat the largest numbers of HNSCC patients in Mexico was integrated with three medical oncologists, four radio-oncologists, and four surgical oncologists, who gathered in Mexico City on May 2, 2016. The meeting was moderated by a medical oncologist. The purpose of the meeting was to generate a diagnosis on current perception on the use of CTX in HNSCC and to arrive to a consensus based on current scientific evidence about possible applications of the drug in adherence to the country’s characteristics.

Prior to the meeting, the participants answered a 13-questions questionnaire (Table 1). The questions were formulated based on a previous literature review. The participants quantified their answers according to a level of agreement/disagreement scale from 1-5 (where 1 is total disagreement and 5 is total agreement).

RESULTS

The results are presented in figure 1 according to Table 1 questions.

DISCUSSION

Question 1: In locally advanced disease, do you consider that cetuximab addition to radiotherapy represents a clinical benefit for the patient?

Bonner, et al. conducted a phase III trial to assess CTX associated with RT in patients with locally advanced oropharyngeal, hypopharyngeal, and laryngeal squamous cell carcinoma (SCC), non-candidates for surgery. Patients were randomized to RT and concomitant CTX at weekly standard doses (n = 211) vs. RT without CTX (n = 213) for 6-7 weeks. Loco-regional control was 24.4 months in patients with CTX and 14.9 months without CTX (p = 0.005). After a 54-month mean follow-up, overall survival (OS) was 49.0 and 29.3 months with and without CTX, respectively (p = 0.03), progression-free survival (PFS) was 17.1 and 12.4 months with and without CTX, and, finally, CTX addition decreased the risk for progression (p = 0.006) and death by 26%. The study concluded that concomitant treatment with RT and CTX improves loco-regional control and reduces mortality without increasing the most common RT-associated adverse events. Five-year OS was 45.6 and 36.4% in the groups with and without CTX, respectively. The OS was higher in patients who developed acneiform rash (at least grade 2) compared...
to those who developed grade 1 rash or did not experience it at all (p = 0.002). This was the first study to demonstrate the additive effects of CTX and RT by improving survival in advanced SCC versus RT alone. By the time the study was published, concomitant CTRT had become the standard of care for unresectable HNSCC. Dattatreya, et al.\textsuperscript{6} recorded 19 unresectable patients treated with CTX/RT, with Bonner’s scheme, and observed overall responses (OR) of 68.42% and two-year OS of 84%. Two years after the protocol was concluded, 13 patients remained free of progression. These results corroborated Bonner’s findings. Okano, et al.\textsuperscript{7} assessed CTX with concomitant RT boost in 22 patients with standard-dose CTX for seven weeks and RT at 1.8 Gy once daily for 3.6 weeks, followed by 1.8 Gy in the morning and 1.5 Gy at noon for 2.4 weeks. All patients completed at least 70% of the scheme. At eight weeks, OR was 82%. Table 2 compiles different results of studies with CTX in locally advanced disease. In summary, CTX addition to RT improves OS and locoregional control when compared with RT alone.

Question 2: In locally advanced disease, do you consider the efficacy of cetuximab concomitantly with radiotherapy equivalent to chemo-radiotherapy efficacy?

There are no comparative studies between CTX/RT and high-dose CTRT. Lefebvre, et al.\textsuperscript{13} compared two groups post-induction QT, with 116 cases being analyzed. No significant differences were observed between both groups with regard to larynx preservation (95 vs. 93%), laryngeal function preservation (87 vs. 82%) and OS (92 vs. 89%). Levy, et al.\textsuperscript{23} made an indirect comparison in a meta-analysis that included studies of cisplatin plus RT vs. RT alone, and CTX plus RT vs. RT alone. The study failed to find evidence of superiority between CTRT and CTX/RT when locoregional control and OS outcomes were analyzed. Both treatments can be considered equally efficacious when administered together with RT. Treatment selection can be made based on the toxicity profile. In summary, CTX/RT offers the same possibility of organ preservation as CTRT; however, there are no studies comparing both treatments in locoregionally advanced disease.

Question 3: In locally advanced disease, do you consider there is a benefit when using cetuximab concomitantly with radiotherapy after induction chemotherapy?

Lefebvre, et al.\textsuperscript{13} compared the efficacy and safety of induction CT followed by CTRT or CTX/RT with the purpose of preserving the larynx. Previously untreated patients with stage III or IV larynx/hypolarynx cancer received three induction CT cycles with docetaxel 75 mg/m\textsuperscript{2} and cisplatin (CDDP), each on day 1, and 5-FU 750 mg/m\textsuperscript{2} on days 1-5. Patients with responses < 50% underwent laryngectomy. Patients with higher responses were randomized to standard RT (70 Gy) and CDDP (100 mg/m\textsuperscript{2}/day) on days 1, 22, and 43 of RT (group A) or to standard RT and CTX at standard...
doses during RT (group B). Three months later, organ preservation was assessed, with pharyngeal function and OS being evaluated 18 months later. Out of 153 initial cases, 116 were analyzed. No significant differences were observed between group A and B with regard to larynx preservation (95 vs. 93%), laryngeal function preservation (87 vs. 82%) and OS (92 vs. 89%), respectively. However, treatment tolerance was superior with CTX/RT, and rescue surgery was feasible only in patients treated with CTX/RT. CTRT acute toxicity generated more protocol changes in comparison with CTX/RT. In the CTRT group, 22.4% of patients developed chronic renal toxicity. With regard to treatment compliance, 42% of patients received all three CDDP planned cycles in group A, and 71% of patients received all seven CTX planned cycles in group B. The study corroborated the favorable toxicity profile of the CTX-scheme, as well as higher rates of compliance, and failed to demonstrate clinical superiority of CTRT over CTX/RT. Two additional studies explored the efficacy of induction CT followed by CTX/RT with CTX. Keil, et al. assessed 49 patients who received three induction cycles: docetaxel (75 mg/m²), CDDP (75 mg/m²) on day 1, and 5-FU (750 mg/m²/day) on days 1 through 5, followed by CTX/RT with CTX at standard weekly doses. At three months, complete response (CR) was observed in 33 patients. Two years later, 25 patients remained with CR. Two-year PFS was 59% and two-year OS was 63%. The most common adverse effects were radiodermatitis (30%), mucositis (27%), and non-febrile neutropenia (17%). Rampino, et al. also assessed two cycles of docetaxel, CDDP, and 5-FU followed by CTX/RT. In 36 stage III and IV patients, CR was 60.6% and partial response (PR) was 33.3%. Toxicity included febrile neutropenia (6%), during induction, and dermatitis (48%), mucositis (33%), and dysphagia (12%) during the CTX/RT phase. In summary, CTX/RT after induction CT in responders with organ-preservation attempt offers the same results as CTRT, with a better safety profile and higher treatment adherence. In addition, rescue surgery in patients failing after CTX/RT has higher rates of success and lower rates of complications than that in patients treated with concomitant CT and RT.

### Table 2. Cetuximab in locoregionally advanced head and neck squamous cell carcinoma

<table>
<thead>
<tr>
<th>(n)</th>
<th>Neoadjuvance</th>
<th>Treatment</th>
<th>Clinical indicators</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>47</td>
<td>CTX+P+Ca</td>
<td>RT or CTRT or SX</td>
<td>OR: 19%</td>
<td>Kies, et al. 2010^6</td>
</tr>
<tr>
<td>30</td>
<td>CTX+P+C+5-FU</td>
<td>RT+C</td>
<td>CR: 77%</td>
<td>Adkins, et al. 2013^9</td>
</tr>
<tr>
<td>22</td>
<td>CTX+D+C+5-FU</td>
<td>RT+CTX</td>
<td>PR: 91% y</td>
<td>Charalambakis et al. 2013^10</td>
</tr>
<tr>
<td>74</td>
<td>CTX+P+C+Ca</td>
<td>RT+CTX+P+Ca</td>
<td>87% y</td>
<td>Wanebo, et al. 2014^14</td>
</tr>
<tr>
<td>39</td>
<td>CTX+D+C</td>
<td>RT+CTX+C</td>
<td>CR: 78% y</td>
<td>Argiris, et al. 2010^12</td>
</tr>
<tr>
<td>211</td>
<td>CTX+D+C</td>
<td>CTX</td>
<td>PR: 68.4%</td>
<td>Bonner, et al. 2006^4</td>
</tr>
<tr>
<td>19</td>
<td>RT+CTX</td>
<td></td>
<td>OS: 84% y</td>
<td>Dattatreya, et al. 2011^11</td>
</tr>
<tr>
<td>22</td>
<td>RT+CTX</td>
<td></td>
<td>LRC: 3/18</td>
<td>Okano, et al. 2013^7</td>
</tr>
<tr>
<td>116</td>
<td>TPF</td>
<td>RT+CTX</td>
<td>82%</td>
<td>Lefebvre, et al. 2013^13</td>
</tr>
<tr>
<td>49</td>
<td>TPF</td>
<td>RT+CTX</td>
<td>33/44</td>
<td>Keil, et al. 2013^14</td>
</tr>
<tr>
<td>36</td>
<td>TPF</td>
<td>RT+CTX</td>
<td>60.6%</td>
<td>Rampino, et al. 2012^12</td>
</tr>
<tr>
<td>91</td>
<td>RT+CTX</td>
<td>CTX</td>
<td>100%</td>
<td>Mesia, et al. 2013^6</td>
</tr>
<tr>
<td>20</td>
<td>RT+CTX+G</td>
<td></td>
<td>61.5%</td>
<td>Granados, et al. 2011^17</td>
</tr>
<tr>
<td>60</td>
<td>RT+CTX+C</td>
<td>CTX</td>
<td>66.7%</td>
<td>Egloff, et al. 2014^8</td>
</tr>
<tr>
<td>238</td>
<td>RT+CTX+C</td>
<td></td>
<td>69%</td>
<td>Harari, et al. 2014^19</td>
</tr>
<tr>
<td>45</td>
<td>RT+CTX+D</td>
<td></td>
<td>79%</td>
<td>Merlano, et al. 2011^11</td>
</tr>
<tr>
<td>43</td>
<td>RT+CTX+C+5-FU</td>
<td></td>
<td>71%</td>
<td>Suntharalinga, et al. 2012^21</td>
</tr>
<tr>
<td>33</td>
<td>RT+CTX+P+Ca</td>
<td></td>
<td>84%</td>
<td>Kao, et al. 2011^22</td>
</tr>
</tbody>
</table>

5-FU: 5-Fluorouracil; C: cisplatin; Ca: carboplatin; CR: complete response; CTRT: chemo-radiotherapy; CTX: cetuximab; D: docetaxel; G: gemcitabine; H: hydroxyurea; LRC: locoregional control; mo: months; n: patient number; OR: overall response; OS: overall survival; P: paclitaxel; PFS: progression-free survival; PR: partial response; RT: radiotherapy; SX: surgery; y: years; TPF: taxane, platinum and fluorouracil.
Question 4: In recurrent/metastatic disease, do you consider the efficacy of cetuximab concomitant with chemotherapy to be equivalent to the efficacy of chemotherapy alone?

The European Society for Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN) international guidelines support the use of CTX as first-line treatment in patients with persistent, recurrent/metastatic disease. The pivotal study was coordinated by Vermorken, et al. As a previous exercise in 2007,24 his group assessed the feasibility and safety of CTX monotherapy at usual doses for six weeks in patients progressing on platinum-based therapy (2-6 cycles). Out of 103 patients whose disease progressed, 53 received CTX with or without platinum. With monotherapy, response rate was 13%, disease control 46%, and time to progression was 70 days. With combined therapy, OR was zero, disease control occurred in 26%, and time to progression was 50 days; OS reached 178 days. This study showed that single-drug CTX is active and well tolerated. One year later, the same author25 published the phase III EXTREME trial. The study enrolled 422 patients with untreated recurrent/metastatic SCC; half of them received CDDP (100 mg/m²) on day 1, or carboplatin (AUC = 5) plus 5-FU (1000 mg/m²/day) during four days every three weeks for a maximum of six cycles. The remaining patients received the same CT plus CTX at standard doses for a maximum of six cycles. Patients with stable disease (SD) on treatment with CT plus CTX continued with CTX until progression or unacceptable toxicity. The study demonstrated that CTX addition to CDDP or carboplatin and 5-FU significantly improves response with regard to CT alone. Addition of CTX prolonged OS from 7.4 to 10.1 months (p = 0.04), PFS from 3.3 to 5.6 months (p < 0.001) and increased the response rate from 20 to 36% (p < 0.001). Finally, the addition of CTX decreased the risk of death by 20%. Treatment duration with CTX was 18 weeks. The CTX relative dose intensity (RDI) was higher than 80% in 84 and 82% of patients at first phase of therapy and at follow-up, respectively. This was the first randomized trial to demonstrate benefit when adding a new drug to CDDP-based therapy over CT alone, thus concluding that the addition of CTX to platinum and 5-FU-based CT increases OS as first-line in patients with recurrent/metastatic HNSCC. The triple combination of CTX, CDDP, and 5-FU has been repeatedly assessed. Yoshino, et al.26 assessed the CTX, CDDP, and 5-FU combination as first-line therapy in metastatic recurrent SCC, using CTX at standard weekly doses, CDDP at 100 mg/m² on day 1, and 5-FU at 1000 mg/m²/day on days 1 through 4, for a maximum of six cycles. The OR rate was 36%, disease control rate was 88%, and PFS and OS were 4.1 and 14.1 months, respectively. With the same protocol, Guo, et al.27 explored the addition of CTX to cisplatin and 5-FU-based CT in 68 Asian patients. The OR rate was 55.9%, including two complete responses. The OS was 12.6 months.

<table>
<thead>
<tr>
<th>(n)</th>
<th>Treatment</th>
<th>OR</th>
<th>CR</th>
<th>PR</th>
<th>OS</th>
<th>PFS</th>
<th>LRC</th>
</tr>
</thead>
<tbody>
<tr>
<td>117</td>
<td>C+CTX</td>
<td>26</td>
<td></td>
<td></td>
<td>9.2 mo</td>
<td>4.2 mo</td>
<td>Burtness, et al. 2005</td>
</tr>
<tr>
<td>96</td>
<td>C+CTX</td>
<td>10</td>
<td></td>
<td>6.1 mo</td>
<td>2.8 mo</td>
<td>53%</td>
<td>Baselga, et al. 2005</td>
</tr>
<tr>
<td>222</td>
<td>C or Ca+5-FU+CTX</td>
<td>36</td>
<td>10.1 mo</td>
<td>5.6 mo</td>
<td></td>
<td>Vermorken, et al. 2008</td>
<td></td>
</tr>
<tr>
<td>121</td>
<td>C+5-FU+CTX</td>
<td>24</td>
<td>11.0 mo</td>
<td>8.0 m</td>
<td>48.9%</td>
<td>De Mello, et al. 2014</td>
<td></td>
</tr>
<tr>
<td>33</td>
<td>C+5-FU+CTX</td>
<td>36</td>
<td>14.1 mo</td>
<td>4.1 mo</td>
<td>88%</td>
<td>Yoshino, et al. 2013</td>
<td></td>
</tr>
<tr>
<td>68</td>
<td>C+5-FU+CTX</td>
<td>56</td>
<td>12.6 mo</td>
<td>6.6 mo</td>
<td></td>
<td>Guo, et al. 2014</td>
<td></td>
</tr>
<tr>
<td>46</td>
<td>P+CTX</td>
<td>54</td>
<td>8.1 mo</td>
<td>4.2 mo</td>
<td>80%</td>
<td>Hitt, et al. 2012</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>P+CTX</td>
<td>55</td>
<td>9.1 mo</td>
<td>5.4 mo</td>
<td></td>
<td>Jimenez, et al. 2013</td>
<td></td>
</tr>
<tr>
<td>42</td>
<td>P+CTX</td>
<td>38</td>
<td>7.6 mo</td>
<td>3.9 mo</td>
<td>74%</td>
<td>Perón, et al. 2012</td>
<td></td>
</tr>
<tr>
<td>84</td>
<td>CTX+D</td>
<td>11</td>
<td>6.7 mo</td>
<td>3.1 mo</td>
<td>51%</td>
<td>Cnedler, et al. 2013</td>
<td></td>
</tr>
<tr>
<td>54</td>
<td>C+D+CTX</td>
<td>44</td>
<td>14 mo</td>
<td>6.2 mo</td>
<td></td>
<td>Guigay, et al. 2015</td>
<td></td>
</tr>
<tr>
<td>73</td>
<td>RT+CTX</td>
<td>59.4</td>
<td>18 mo</td>
<td>15 mo</td>
<td></td>
<td>Jensen, et al. 2010</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>RT+CTX</td>
<td>47</td>
<td>8.3 mo</td>
<td>7.3 mo</td>
<td>33% 1 y</td>
<td>Balempas, et al. 2012</td>
<td></td>
</tr>
<tr>
<td>70</td>
<td>RT+CTX</td>
<td></td>
<td>24.5 mo</td>
<td></td>
<td></td>
<td>Heron, et al. 2011</td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>RT+CTX</td>
<td>58.4</td>
<td>47.5% 1 y</td>
<td></td>
<td>91.7%</td>
<td>Lartigau, et al. 2013</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>RT+CTX</td>
<td>10 mo</td>
<td>33% 1 y</td>
<td></td>
<td></td>
<td>Vargo, et al. 2015</td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>RT+CTX</td>
<td>64 1 y</td>
<td>49 1 y</td>
<td>51 1 y</td>
<td></td>
<td>Vargo, et al. 2014</td>
<td></td>
</tr>
</tbody>
</table>

5-FU: 5-Fluorouracil; C: cisplatin; Ca: carboplatin; CR: complete response; CTRT: chemo-radiotherapy; CTX: cetuximab; D: docetaxel; G: gemcitabine; H: hydroxyurea; LRC: locoregional control; mo: months; n: patient number; OR: overall response; OS: overall survival; P: paclitaxel; PFS: progression-free survival; PR: partial response; RT: radiotherapy; SX: surgery; y: years; TPF: taxane, platinum and fluorouracil.
and PFS was 6.6 months. De Mello, et al. \(^{28}\) retrospectively assessed 121 patients who received CDDP plus 5-FU and CTX every three weeks for a maximum of six cycles. Patients with stable disease continued to receive CTX until progression or unacceptable toxicity. The addition of CTX led to an OS of 11 months and PFS of eight months. The disease control rate was 48.9% and OR rate was 23.91%. Table 3 compiles different results of trials with CTX in recurrent/metastatic disease. In summary, the highest response rate and the best control are obtained in patients receiving the

Table 4. Management strategies for patients developing radiodermatitis while on treatment with cetuximab plus radiotherapy

<table>
<thead>
<tr>
<th>Management</th>
<th>Grade II</th>
<th>Grade III</th>
<th>Grade IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up/Continuity*</td>
<td>Twice-weekly. Continue treatment.</td>
<td>Assess the need for daily follow-up. Frequent monitoring looking for signs of local or systemic infection. In case of reaction occurring with doses (\geq 50) Gy, consider brief interruption.</td>
<td>Continuous follow-up. Cetuximab should be interrupted until skin reactions resolve to at least grade II. In case of severe infection, consider the use of IV antibiotics in the absence of response to oral therapy. Hospitalize the patient.</td>
</tr>
<tr>
<td>1. Dry desquamation without scales:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Corticosteroid-based creams or ointments for a limited period (1-2 weeks). In the presence of signs of infection, topical antiseptics and antibiotics. Consider them for prevention of more severe reactions.</td>
<td>1. Confluent moist desquamation without scales: Topical antiseptic. Consider topical corticosteroids daily application to reduce inflammation for a limited period (1-2 weeks). Topical antibiotics against <em>Staphylococcus aureus</em> if there are signs of infection. Consider systemic antibiotics in case of more severe infection. Eosin or zinc preparations on folds.</td>
<td>2. Confluent moist desquamation with scales: Topical antiseptic. If the infection increases in intensity, consider the use of IV antibiotics in the absence of response to oral therapy. Consider debridement with hydrogels. Avoid trauma to prevent infections. Consider hydrofiber dressings can be used after RT completion.</td>
</tr>
<tr>
<td>Management</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Moist desquamation in folds:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Topical antiseptic. Consider topical corticosteroids daily application to reduce inflammation for a limited period (1-2 weeks). Topical antibiotics against <em>Staphylococcus aureus</em> if there are signs of infection. Consider systemic antibiotics in case of more severe infection. Eosin or zinc preparations on folds.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Dry desquamation with isolated, non-hemorrhagic scales:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Topical antiseptics. Consider topical corticosteroids daily application to reduce inflammation for a limited period (1-2 weeks). Topical antibiotics against <em>Staphylococcus aureus</em> if there are signs of infection. Consider systemic antibiotics in case of more severe infection.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*In grade I, follow-up frequency is weekly, unless there is rapid progression.
Adapted from Bernier, et al. 2011\(^{44}\).
CT/CTX association, with this association therefore being the treatment of choice in recurrent/metastatic disease.

**Question 5: In locally advanced and recurrent/metastatic disease, do you consider the cetuximab toxicity profile to be predictable and manageable?**

Although in CTX/RT-treated patients dermatitis intensity is higher and appears earlier in comparison to RT alone, resolution times are shorter, treatment compliance rates are higher, and skin sequelae such as scars generally do not persist. In summary, currently available information allows concluding that bio-radiotherapy-associated dermatitis is a predictable, manageable, and reversible event, the correct management of which does not affect treatment continuity or clinical outcome. Tables 4 and 5 summarize considerations on management and patient education exposed by Russi, et al.43 and Bernier, et al.44.

**Question 6: In locally advanced disease, do you consider there are differences in chemo-radiotherapy vs. bio-radiotherapy toxicity profiles?**

Lefebvre, et al.13 compared the efficacy and safety of induction CT followed by CTRT or CTX/RT for larynx preservation. There were no differences in grade 3 or 4 mucositis between groups, and the CTRT group had more grade 3 and 4 skin reactions. The CTRT group showed more renal and hematologic toxicity and decreased functional activity leading to more protocol modifications owing to acute toxicity (57 vs. 34%). With regard to late toxicity (at least six months after treatment completion), CTRT led to more renal dysfunction (22.4 vs. 0%). Taberna, et al.45 identified CTRT as a risk factor for moderate (odds-ratio [OR]: 0.292; 95% confidence interval [CI]: 0.125-0.680; p = 0.004) and severe late toxicity (OR: 0.299; 95% CI: 0.0909-0.999; p = 0.05) in comparison with CTX/RT. In summary, patients treated with CTRT with CDDP show higher rates of chronic, severe and irreversible toxicity in comparison with patients treated with CTX/RT.

**Question 7: In recurrent/metastatic disease, do you consider that the cetuximab toxicity profile permits its use as long-term maintenance therapy?**

With the EXTREME scheme, the incidence of grade 3 or 4 adverse events was similar between the compared groups (CTX/CT and CT alone), except for skin reactions (9 vs. 1%), hypomagnesemia (5 vs. 1%) and sepsis (4 vs. 1%), with greater effects associated with CTX. In summary, in recurrent and/or metastatic disease, CTX-produced toxicity is not maintenance-treatment limiting.
Question 8: In locally advanced disease, does cetuximab addition to radiotherapy negatively affect patients’ quality of life?

Curran, et al. assessed Bonner’s study patients’ quality of life using the European Organization for Research and Treatment of Cancer (EORTC) quality of life QLQ-C30 and head and neck QLQ-35 questionnaires at treatment initiation and at 1, 4, 8, and 12 months. Out of 424 patients, 213 received RT alone and 211 RT plus CTX. The CTX/RT improved locoregional control (p = 0.005) and OS (p = 0.03) vs. RT alone, with no significant differences in quality of life. In summary, CTX addition does not affect quality of life.

Question 9: In recurrent/metastatic disease, does cetuximab addition to chemotherapy negatively affect patient quality of life?

Mesia, et al. examined treatment impact on quality of life in patients participating in Vermorken’s study, according to EORTC criteria (QLQ-30 quality of life and QLQ-35 head and neck questionnaires). Out of 442 randomized patients, 291 completed the questionnaires. The study concluded that the addition of CTX to platinum and 5-FU-based CT does not worsen quality of life; in fact, better quality of life/health global status was demonstrated (p = 0.041), with no difference in the social functioning scale, and better control of pain and swallowing problems. In summary, cetuximab addition to chemotherapy not only does not decrease quality of life, but improves it by decreasing neoplasm-associated symptom intensity.

Question 10: In locally advanced disease, do you consider the rates of adherence to cetuximab concomitant with radiotherapy more favorable with regard to chemotherapy?

In the study of Bonner, et al., 90% of patients received all eight planned doses. Similarly, an important aspect to be highlighted in the study of Lefebvre, et al. is the compliance rates, where the percentage of patients who completed the initially planned dose was 43% in the group of patients with CTRT and 71% in the CTX/RT group. The protocol was modified due to acute toxicity in 57% of patients with CTRT and in 34% with CTX/RT. Another study with larynx-preservation purposes using neoadjuvant CT with docetaxel, CDDP and 5-FU followed by CTX/RT or CTRT, revealed higher rates of compliance with the use of CTX/RT (79.5%) vs. CTRT with CDDP (51.7%). In contrast, the number of patients receiving therapy with CDP has been observed to decrease with increasing treatment duration: using a CTRT scheme (CDDP 100 mg/m² q3wk), compliance rates of 88, 66 and 49% were obtained at first, second, and third cycle of treatment, respectively. In summary, treatment adherence rates are higher with CTX than with chemotherapy.

Question 11: In recurrent/metastatic disease, do you consider that cetuximab addition to chemotherapy negatively affects treatment adherence rates?

In the EXTREME trial, 84% of patients receiving CTX after initial loading dose recorded a relative dose intensity (RDI) of 80% or higher, and 82% of patients reported an equal RDI in the maintenance phase. Patients in the CTX group received a mean of five CT cycles, and patients in the CT alone group, four cycles. For 89% of patients in the CTX group and 86% in the CT alone group, RDI was 80% or higher. Similarly, the GORTEC study reported a RDI of 80% or higher in 84% of patients, and 79% of patients initiated the maintenance phase. During that phase, RDI for CTX was close to 100%; mean duration of the maintenance phase was 4.6 ± 4.5 months. One patient was treated with CTX during maintenance for a period longer than 22 months. In summary, adherence rates were similar to those for CT in both groups, suggesting that CTX addition did not affect standard treatment tolerance.

Question 12: Do you consider that patients treated with bio-radiotherapy have better chances for surgical rescue and less postoperative complications?

Lefebvre, et al. showed that rescue surgery was possible only in patients undergoing CTX/RT after induction CT. Leon, et al. recorded the clinical response and surgical complications after rescue surgery due to relapse after CTRT (n = 154) or CTX/RT (n = 33). The CTX/RT-treated patients had higher mean age and ECOG with regard to CTRT-treated patients; 37.2% of patients with CTRT and 61.5% with CTX/RT underwent rescue surgery. A multivariate analysis demonstrated that the surgical rescue-associated variable with more weight was initial treatment. The frequency of postoperative complications was higher among those who received CTRT (62.5%) in comparison with CTX/RT (12.5%). Five-year OS after rescue surgery was 26.0% for patients who received CTRT and 70.0% for those with CTX/RT. In summary, patients with recurrence after CTX/RT were better candidates for rescue surgery than those who had been treated with CT/RT, with a lower rate of postoperative complications and better OS.

Question 13: In locally advanced disease, do you consider concomitant use of cetuximab with radiotherapy to be cost-beneficial?

In locoregionally advanced carcinomas, the CTX/RT scheme is cost effective. Brown, et al. estimated CTX/RT cost-effectiveness in comparison with RT alone. Independent economic analyses were carried out in Belgium, France, Italy, Switzerland, and the UK, with the economic model being based on patient data extracted from Bonner’s study. Each country’s specific costs of care came from official sources. Panels of clinical experts estimated the resources and validated the assumptions employed to extrapolate costs and health outcomes. In the analysis, incremental cost per quality-adjusted life year (QALY) for patients receiving CTX/RT...
vs. RT alone among all countries was € 7,538 to 10,836. This cost-effectiveness analysis indicated that CTX addition offers a good value/price alternative compared to RT alone. Another pharmaco-economic study supports the concomitant use of CTX with RT. To estimate the real-world incremental cost per QALY with the CTX/RT scheme vs. RT alone as first-line treatment, a Markov model was constructed with the following classifications: “alive without progression”, “alive with progression”, and “deceased”. One-month transition probabilities were estimated based on clinical trial data and retrospective real-world data from two Dutch head and neck cancer centers (2007-2010, n = 141). Incremental costs per gained QALY range from € 14,624 to 38,543, and acceptability curves for different scenarios show probabilities ranging from 0.76 to 0.87, with CTX/RT being cost-effective in comparison with RT alone. In summary, current results show that CTX/RT combination treatment is a cost-effective treatment option for patients with locally advanced HNSCC.

Note: In different institutions of Mexico’s health sector, the heterogeneous availability of different therapies complicates both first-line and second-line treatment of patients with head and neck cancer. The largest experience has been obtained from patients with locally advanced, unresectable disease that are not amenable for CTRT, and from the rescue attempt of patients with persistent or metastatic disease, not candidates for other treatments. This is why inter-institutional opinion differs with regard to availability of therapies and optimal timing for their use. The present consensus was based on worldwide recommendations based on updated scientific evidence.

CONCLUSIONS

Cetuximab is an alternative in the therapeutic agents for cancer originating in the mucous membranes of the head and neck area. In locoregionally advanced disease, CTX associated with RT is superior to RT alone, without an important increase in toxicity and less morbidity than the CTRT association. The CTX/RT treatment offers similar OS and locoregional control to the CTRT association, with less toxicity and higher treatment adherence, and in case rescue surgery is required, it can be accomplished more often and with lower morbidity than in CTRT-treated patients.

In patients treated with organ-preservation attempts, especially those with laryngeal cancer in whom total laryngectomy is indicated owing to the extension of the neoplasm, CTX/RT in those showing complete response to induction CT offers similar results as CTRT, with less toxicity, higher treatment adherence, and higher possibility of surgical rescue if required. Bio-radiotherapy is an option as initial treatment in patients in whom tumor recurrence can be expected (organ preservation, mainly oral cavity and hypopharynx), with the purpose to facilitate surgical rescue if required and reduce morbidity. In recurrent/metastatic disease, CTX addition to platinum-based therapy is the option that offers the largest number of responses, without therapy tolerance and patient quality of life being affected, which is why it is considered the treatment of choice.

DECLARATION OF INTEREST

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REFERENCES

Consensus on the use of cetuximab in head and neck cancer


