Cisplatin-based chemoradiation plus cetuximab in locally advanced head and neck cancer: a phase II clinical study

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Background: Intensification of chemoradiation for advanced head and neck squamous cell carcinoma (HNSCC) is unlikely due to toxicity. Cetuximab combined either with radiotherapy or with chemotherapy showed favourable toxic profile with positive results in both combinations. Therefore, cetuximab could intensify chemoradiation without worsening toxicity. We conducted a phase II study of chemoradiation and cetuximab.

Patients and methods: Eligible patients had stage III–IV M0 HNSCC. Treatment consisted of three cycles of cisplatin (20 mg/m2/day × 5 days) and fluorouracil (200 mg/m2/day × 5 days) rapidly alternated to three split courses of radiotherapy up to 70 Gy and concurrent weekly cetuximab. The primary end point of the study was complete response (CR) rate. Secondary end points were toxicity, progression-free survival (PFS) and overall survival (OS).

Results: Forty-five patients were enrolled: median age was 56 years, 38 had stage IV disease and 40 nodal involvement. CR occurred in 32 patients (71%). PFS and OS was 21+ months and 32.6+, respectively. Acute grade 3–4 toxic effects were in the expected range, but grade 3 radiodermatitis occurred in 33 patients.

Conclusions: The combination of cetuximab, cisplatin, fluorouracil and radiotherapy leads to a very high proportion of CR and it is feasible with toxic effects similar to those expected by radiochemotherapy. The only unexpected toxicity was skin toxicity: grade 3 radiodermatitis occurred in 73% of the patients.

Key words: cetuximab, chemoradiation, head and neck cancer

Introduction

Chemoradiation is widely accepted as the standard of care for patients with unresectable, locally advanced head and neck squamous cell carcinoma [1] (HNSCC). However, the 5-year absolute survival rates remain poor [2, 3] and treatment is hampered by major toxicity [4], thus making intensification unlikely to be achieved. Therefore, novel therapies are needed to produce survival gain without worsening toxicity.

Elevated levels of epidermal growth factor receptor (EGFR) are common in HNSCC [5–7] and correlate with resistance to radiation, higher risk of local relapse and poor overall survival (OS) [7–12]. The anti-EGFR antibody cetuximab (Erbitux®), when associated with radiation therapy, significantly improves locoregional control and survival in patients with HNSCC [13], without increasing radiotherapy-related toxicity, compared with radiotherapy alone. Similarly, combining cetuximab with cisplatin and fluorouracil in recurrent or metastatic disease significantly improves clinical outcome without major changes in toxicity (EXTREME study) [14]. These positive results suggest that cetuximab could allow for chemoradiation intensification. Unfortunately, Pfister et al. [15] have shown that cetuximab combined with chemoradiation increases severe toxic effects and have therefore recommended that less toxic chemoradiation schedules should be employed. Alternating chemoradiation might be an acceptable alternative to strictly concurrent chemoradiation [16]. Available clinical data show that both acute and late toxic effects of radiotherapy are not enhanced by alternating chemoradiation [17–19], indicating that this schedule combined with cetuximab could avoid excessive toxicity.
We report a phase II study (Alternating Radiotherapy and Chemotherapy combined with Cetuximab, AlteRCC) designed to investigate the activity and safety profile of this combined approach in patients suitable for chemoradiation but not for surgery.

**patients and methods**

**eligibility criteria**

Enrolled patients were required to have histologically confirmed HNSCC of oral cavity, larynx, oropharynx or hypopharynx; age of 18 years or more; adequate liver (total bilirubin <1.5 × upper normal limit, alkaline phosphatase and aspartate aminotransferase <2.5 × upper normal limit), kidney (creatinine <1.3 mg/dl) and bone marrow (white blood cell ≥3000/μl, granulocytes ≥1500/μl, platelet count ≥100 000/μl and haemoglobin ≥9 g/dl) function; Eastern Cooperative Oncology Group performance status 0 or 1 and stage III or IVa to b with measurable lesions (AJCC staging system, sixth edition [20]). All patients provided a written informed consent for this study, which was approved by the institutional Ethical Committee of S. Croce General Hospital. All patients accrued into the present study were evaluated by a multidisciplinary team and were considered unresectable due to disease extension or poor surgical curability. Exclusion criteria were prior treatment of HNSCC, concurrent active malignancies except in situ skin carcinoma, carcinoma of the nasopharynx and pregnancy or breast-feeding.

**treatment**

Radiotherapy was administered as a single daily fraction (days 1–5 and weeks 2–3, 5–6 and 8–10). A dose of 50 Gy/2 Gy per fraction to the clinical target volume, including the tumour [gross tumor volume on primary (GTVp)], the metastatic lymph nodes [gross tumor volume on node (GTVn)] and the draining clinical negative lymphatic pathways [elective clinical target volume (CTV)] [21, 22], was prescribed with a dose homogeneity of <5% to +7% as recommended by ICRU report no. 50 [23]. The five isocentric photon field techniques, described by Fogliata et al. [24], was adapted to the single real clinical situation. A further booster dose up to 66–70 Gy was prescribed to the clinical target volume including only GTVs and GTVn using a not standardised three-dimensional conformal technique. Organs at risk involved in this treatment and normally considered were spinal cord, salivary glands and apexes of the lungs. A maximum point dose of 45 Gy was set as an overall constraint to the spinal cord. The schedule was alternating with chemotherapy as described by Merlano et al. [17]. Chemotherapy was delivered on days 1–5 and weeks 1, 4 and 7. Cetuximab was delivered weekly on day 1, from weeks 1 to 10.

Chemotherapy consisted of cisplatin 20 mg/m²/day delivered i.v. in 15 min during a 2-h forced hydration with 2 l saline supplemented with KCl 20 mEq and MgSO₄ 1 g. Fluorouracil 200 mg/m²/day was administered as an i.v. bolus at the end of hydration.

Cetuximab was administered at an initial dose of 400 mg/m² followed by a weekly dose of 250 mg/m². Pre-treatment with diphenhydramine 50 mg and dexamethasone 8 mg was standard. No dose modification was allowed. In case of grade 3 radiodermatitis, cetuximab was discontinued until recovery to grade 2.

Patients with N2-3 disease at baseline were allocated to prophylactic neck dissection irrespectively of their response. Patients with residual neck disease were recommended for salvage surgery.

**pre-study procedures and evaluation**

Baseline evaluation included medical history, physical examination, panendoscopy and basic nutritional evaluation. All patients were offered dental prophylaxis and received a Hohn-type central venous device. Computed tomography (CT) scan or magnetic resonance imaging (MRI) of the primary site and neck were used for staging. Complete haematological, coagulation and blood chemistry profiles together with urine analysis, chest X-rays and electrocardiogram were requested to confirm eligibility.

**on-study patient evaluation and results assessment**

During treatment, patients underwent weekly physical and nutritional evaluation and blood cell count. Comprehensive blood chemistry profiles were carried out at 21-day intervals or when clinically required.

Hospitalisation of patients developing grade ≥3 stomatitis or grade 4 haematological toxicity was mandatory. All patients showing a >25% reduction of body weight in 2 months before treatment or during treatment received nutritional support. In case of grades 3–4 stomatitis, nutritional support was considered irrespective of body weight. Nutritional support was administered orally until possible. Patients with severe dysphagia received adequate enteral or parenteral nutrition. Antibiotic prophylaxis with ciprofloxacin 500 mg twice a day was given to patients with <100 neutrophils/μm³. Standard therapy for febrile neutropenia consisted of ceftriaxone and amikacin.

In order to assess response, CT or MRI scans of the head and neck were planned 1 and 3 months after the end of the treatment. Follow-up consisted of physical examinations every second month and CT scan every fourth month until 2 years past diagnosis. From years 3–5 after diagnosis, patients underwent clinical control every fourth month and CT scan every sixth month. Toxicity was graded according to National Cancer Institute–Common Toxicity Criteria for Adverse Events version 3 system [25].

Tumour size was calculated by multiplying the maximal tumour diameters measured on bidimensional imaging studies. Complete response (CR) was a total disappearance of radiographic evidence of tumour. Partial response (PR) was a ≥50% reduction in the product of the maximal bidimensional tumour diameters. Stable disease was any change between ±25% and −50% in tumour size, and progressive disease included any increase >25% from baseline or the appearance of any new lesion.

**statistical methods**

AlteRCC was a single-arm phase II study, conducted according to the optimal two-stage design by Simon [26]. The primary end point was to increase the CR rate. Assuming that the expected CR rate with alternating chemoradiation is 50% [18] (p0) and the level of interest was established as an increase up to 70% (p1). Therefore, accepting α and β errors of 0.10, at least 26 CRs were to be observed out of 45 patients.

Secondary end points included toxicity, progression-free survival (PFS) and OS. Acute toxicity and OS were evaluated in all treated patients. PFS was evaluated in all patients except those lost during follow-up. In this case, patients were withdrawn at the time of the last follow-up from PFS analysis, whereas information about life/death status were obtained from the registry. PFS was computed as the time from the beginning of treatment to disease progression or death for any cause (intent to treat). Living patients without evidence of progression were censored at the last follow-up. OS was considered as the time from the beginning of treatment to death for any cause. Living patients were withdrawn at the last follow-up. Both PFS and OS were estimated using the method of Kaplan and Meier [27].

**results**

**patient characteristics**

Forty-five patients were accrued (October 2005 to December 2007). Table 1 summarises the relevant patients’ features. Median age was 56 years (24–75). Males accounted for 82% of the population and most patients had primary tumours of the

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**original article**

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to make full-dose delivery feasible. Thirty-five patients (78%) required hospitalisation in order on treatment deaths and 1 withdrawn consensus) received Eighteen patients received 68–70 Gy, 23 received 66 Gy and 4 (3 127 courses of chemotherapy instead of 135 were delivered. stage IV disease (84%). usual supportive treatment (hygienic measures and emulsions and infections [28]. The first eight patients were treated with as contact with clothes, favouring the onset of pain, bleeding became dry and inelastic, thus vulnerable to microinjuries, such epidermis and of the superficial dermis. Clinically, the skin subepidermis. Rare areas showed limited necrosis of the underwent skin biopsy, revealing thin epidermis with highly adverse events
activity
Overall, 32 CRs (71.1%) and 9 PRs (20%) were recorded (Table 2). Three patients died during treatment (one acute heart failure and two aspiration pneumonia). The protocol advisory board considered all the deaths unrelated to the use of cetuximab. One patient spontaneously withdrew from the study. Since an intent-to-treat approach was pursued, these patients were classified as treatment failure.

Table 1. Main patient characteristics

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>45</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female</td>
<td>37/8</td>
</tr>
<tr>
<td>Median age (range)</td>
<td>56 (24–75)</td>
</tr>
<tr>
<td>Median Eastern Cooperative Oncology Group</td>
<td>0 (0–1)</td>
</tr>
<tr>
<td>Primary site, n (%)</td>
<td>Oropharynx 15 (34), Hypopharynx 11 (24), Larynx 12 (27), Oral cavity 5 (11), Tx 2 (4)</td>
</tr>
<tr>
<td>Stage, n (%)</td>
<td>III 7 (16), IV 38 (84)</td>
</tr>
<tr>
<td>Node, n (%)</td>
<td>N0 5 (11), N1-2 35 (78), N3 5 (11)</td>
</tr>
</tbody>
</table>

Table 1. Main patient characteristics

oropharynx, advanced neck involvement (>N2 = 78%) and stage IV disease (84%). Overall, 422 cetuximab administrations instead of 450 and 127 courses of chemotherapy instead of 135 were delivered. Eighteen patients received 68–70 Gy, 23 received 66 Gy and 4 (3 on treatment deaths and 1 withdrawn consensus) received <66 Gy. Thirty-five patients (78%) required hospitalisation in order to make full-dose delivery feasible.

adverse events
Major adverse events are listed in Table 2. Stomatitis occurred in all 45 patients (16 grade 4 and median duration 13.7 days). Total parenteral nutrition was required in 22 patients (49%), with median duration 30.5 days (5–90). Four patients (8%) received enteral nutrition. Painful dysphagia (9% grade 2 and 7% grade 3) most likely was responsible for two fatal cases of aspiration pneumonia.

Radiodermatitis occurred in all patients. One patient underwent skin biopsy, revealing thin epidermis with highly atrophic basal stratum and inflammatory infiltration of the subepidermis. Rare areas showed limited necrosis of the epidermis and of the superficial dermis. Clinically, the skin became dry and inelastic, thus vulnerable to microinjuries, such as contact with clothes, favouring the onset of pain, bleeding and infections [28]. The first eight patients were treated with usual supportive treatment (hygienic measures and emulsions containing trolamine), without adequate control of symptoms of uncomfortable dermatitis. Further patients were treated using hydrogel for the painful crusty exudate debridment and covering the injured skin with ultrathin hydrocolloid dressing until recovery as described by Russi et al. [28]. In all cases, the irradiated skin completely recovered a few days after treatment. Adequate prevention of excessive liquid loss from the skin helped to avoid symptoms related to this toxicity, thus allowing for correct treatment delivery [28]. A generalised acne-like rash was observed in eight patients (18%). This type of rash has been clearly correlated with the use of EGFR inhibitors, including cetuximab [29–33]. Other acute adverse events were in line with previous chemoradiation trials [34].

time to progression and OS
Data were analysed according to the intent-to-treat principle. Six patients died without cancer and were considered as relapsed at the time of death (causes of death: pneumonia (two patients), myocardial infarction, bleeding, sepsis and unknown in one case). Therefore, 26 of 45 patients have been considered relapsed at the latest analysis (30 June 2009), yielding an estimated median 21+ months PFS, with a projected 38% of patients alive and progression free at 45 months (Figure 1). At the same time point, 21 of 45 patients have died, giving an estimated median 32.6+ months OS, with a projected 40% of patients alive at 45 months (Figure 2).

toxicity and response in elder patients
Four patients were older than 70 (72–75) years. All had stage IVa oropharyngeal cancer. All developed grade 3 leukopenia and one died of acute ischaemic heart failure during treatment. The remaining patients are currently alive and disease free at 15, 20 and 38 months. Among five patients between 65 and 70 years (four stage IVa and one stage IVb), two died of progressive disease at 19 and 21 months, whereas three are alive and disease free at 12, 28 and 32 months. Responses in nine patients <65 years were six CRs, two PRs and one early death. One partial responder underwent neck surgery, which rendered him disease free, followed by a second neck surgery due to nodal recurrence 6 months later. This patient is alive and disease free at 28 months. Two patients that achieved CR underwent prophylactic neck dissection because of gross neck disease at diagnosis. Nonetheless, one of them relapsed in the neck, lung and liver at 9 months and died of disease at 21 months.

role of prophylactic surgery
Eleven patients (seven were N2 and four N3 at diagnosis, overall 24%) underwent prophylactic neck dissection, none having residual microscopic disease. Three additional patients underwent neck dissection due to positive CT scan at the end of treatment (one was N3 and two N2 at diagnosis). Histology confirmed residual disease and surgery rendered all of them disease free. CR rate after salvage surgery was 77.7%. Among 14 patients that underwent neck dissection, 7 relapsed (5 previous N2 and 2 previous N3). Two of them relapsed in the neck or in neck and primary site, while the remaining developed distant metastases (four patients) or T recurrence.
The AlteRCC trial was designed to evaluate the combination of cetuximab and chemoradiation using a rapidly alternating chemoradiation regimen, which is a minor variation of the strictly concurrent chemoradiation approach [16]. Three randomised trials have compared this rapidly alternating chemoradiation regimen with standard radiotherapy [17], partially accelerated radiotherapy [18], or induction chemotherapy followed by radiation [19], showing similar or even significantly lower acute toxic effects [19]. In contrast, all the trials based on concurrent chemoradiation have reported a significant increase in toxicity as compared with standard radiotherapy [35]. Thus, rapidly alternating chemotherapy and radiotherapy could represent a valuable solution for a less toxic chemoradiation regimen, as suggested by Pfister et al. [15].

In line with our initial aim, AlteRCC succeeded to increase the CR rate from 50% to 70%. We also notice that, despite a case of heart attack, the nine patients >65 years showed a generally good tolerance to treatment and six of them achieved a CR.

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**Table 2. Treatment responses and toxicities**

<table>
<thead>
<tr>
<th>Response</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective response rate, %</td>
<td>91.1%</td>
</tr>
<tr>
<td>CR, n (%)</td>
<td>32 (71.1)</td>
</tr>
<tr>
<td>PR, n (%)</td>
<td>9 (20)</td>
</tr>
<tr>
<td>Failures, n (%)</td>
<td>4 (8.9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>45 evaluable patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Relative frequencies of observed acute toxic effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Leukopenia</td>
<td>12 (27)</td>
<td>1 (2)</td>
<td>14 (31)</td>
<td>17 (38)</td>
<td>1 (2)</td>
</tr>
<tr>
<td></td>
<td>Neutropenia</td>
<td>12 (27)</td>
<td>1 (2)</td>
<td>14 (31)</td>
<td>15 (33)</td>
<td>3 (7)</td>
</tr>
<tr>
<td></td>
<td>Grade 3–4 with fever</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Anaemia</td>
<td>13 (29)</td>
<td>12 (27)</td>
<td>16 (35)</td>
<td>4 (9)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia</td>
<td>26 (58)</td>
<td>5 (11)</td>
<td>7 (16)</td>
<td>6 (13)</td>
<td>1 (2)</td>
</tr>
<tr>
<td></td>
<td>Non-haematological toxic effects, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stomatitis</td>
<td>2 (4)</td>
<td>3 (7)</td>
<td>11 (24)</td>
<td>13 (29)</td>
<td>16 (36)</td>
</tr>
<tr>
<td></td>
<td>Dysphagia</td>
<td>38 (84)</td>
<td>0</td>
<td>4 (9)</td>
<td>3 (7)</td>
<td>0</td>
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<tr>
<td></td>
<td>Radiodermatitis</td>
<td>0</td>
<td>1 (2)</td>
<td>11 (24)</td>
<td>33 (74)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>C225-induced rash</td>
<td>37 (82)</td>
<td>3 (7)</td>
<td>2 (4)</td>
<td>3 (7)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Diarrhoea</td>
<td>34 (76)</td>
<td>4 (9)</td>
<td>3 (7)</td>
<td>4 (9)</td>
<td>0</td>
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<tr>
<td></td>
<td>Alopecia</td>
<td>30 (67)</td>
<td>10 (22)</td>
<td>4 (9)</td>
<td>1 (2)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Peripheral neuropathy</td>
<td>44 (98)</td>
<td>1 (2)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
<td>6 (13)</td>
<td>18 (40)</td>
<td>20 (44)</td>
<td>1 (2)</td>
<td>0</td>
</tr>
</tbody>
</table>

| Worse non-haematological toxicity | Stomatitis |
| Worse overall toxicity | Stomatitis |

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**Figure 1.** Progression-free survival distribution.
Several trials have already improved the CR rate of cisplatin-based rapidly alternated chemoradiation either by adding a third drug or by substituting fluorouracil with more active drugs, yielding CR rates between 68% and 79% [36–39]. Nonetheless, all were hampered by a worrisome increase in life-threatening toxic effects. In contrast, AlteRCC achieved a CR rate >70% without significantly worsening life-threatening toxic effects. Indeed, although three (7%) treatment-related fatal events occurred during AlteRCC, this impressive data are consistent with most regimens that use concurrent chemoradiation [4]. For example, the regimen proposed by Adelstein et al. [40], which is widely accepted as the standard chemoradiation approach, is hampered by a 5% mortality rate.

The incidence of grade 3–4 toxic effects in AlteRCC was also similar to that reported using concurrent or rapidly alternated chemoradiation [4, 40], except for a higher rate of stomatitis (65%) and for cutaneous toxicity in the irradiated area. The high rate of stomatitis in AlteRCC might be due to the addition of cetuximab to chemoradiation. Indeed, Lefebvre et al. [19] reported only 23% grade 3–4 mucosal reaction using the same chemoradiation regimen without cetuximab. Notably, stomatitis was manageable with the use of total parenteral nutrition or enteral nutrition. Incidentally, the high percentage of patients receiving TPN in our study simply reflects the expertise of our centre.

Cutaneous toxicity in the radiation field has been recently described in patients treated with cetuximab and radiotherapy without chemotherapy, but the incidence in our study appears to be even higher [41–44]. Chemotherapy, and particularly fluorouracil, may account for this. However, skin toxicity was fully manageable [28], and rapid healing without scarring was always achieved within a few days after the end of the treatment. Based on the biopsy carried out in one case, we have classified this toxicity as grade 3 radiodermatitis [45]. Notably, all the studies describing similar lesions have also reported complete skin healing without disfiguring scars [42–44]. Overall, we administered 422 of the 450 planned doses of cetuximab, despite skin toxicity. This figure does not correspond with the percentage of patients who developed grade 3 skin reactions and who should have interrupted cetuximab according to the protocol regulations. This was because, having acquired a good expertise with this toxicity and its management, we decided to continue treatment without breaks and manage the skin toxicity during therapy.

Single-arm phase II studies cannot produce reliable information on PFS and OS. Nonetheless, patients treated with AlteRCC show a favourable outcome, with a median 21+ months PFS and a median 32.6+ months OS.

In conclusion, the addition of cetuximab to rapidly alternating chemoradiation allows for treatment intensification, but it is hampered by an unexpected skin toxicity. The incidence of mucositis also seems to be increased. Both these toxic effects are manageable and do not preclude treatment. However, in our opinion, skin toxicity could be reduced by avoiding fluorouracil, which has its own additional skin toxicity. Indeed, radiotherapy for head and neck cancer, different from what observed, for example, in rectal cancer, gives a significant radiation dose to the skin and, therefore, an overlapping effect of radiotherapy, fluorouracil and cetuximab may explain our observations. For this reason, we are now evaluating a new similar phase II study excluding fluorouracil.

disclosure

Merlano and Benasso report serving on paid advisory boards and receiving lecture fees from Merck. The authors declare no conflict of interest.

references


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