Editorial

Locoregionally advanced squamous cell carcinoma of the head and neck: chemoradiation or bioradiation

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Concurrent high-dose cisplatin-based chemoradiation (CCRT) is the preferred standard of care for patients with locoregionally advanced squamous cell carcinoma of the head and neck (LA-HNSCC) (1,2). The addition of cetuximab to irradiation (RT) improves locoregional control and prolongs progression-free survival (PFS) and overall survival (OS) (3,4). The combination of an EGFR-directed monoclonal antibody and cisplatin-based CCRT is not superior to cisplatin-based CCRT alone, but adds toxicity, and is therefore not recommended (5,6). Until recently, there were no direct comparisons between cisplatin-based CCRT and RT + cetuximab. Nevertheless, RT + cetuximab are widely rumored to be less toxic than cisplatin-based CCRT and is commonly advocated in patients unsuitable for cisplatin-based CCRT (7).

Magrini *et al*. (8) conducted a phase II, multicenter, open-label, randomized trial comparing the RT + cetuximab to a modified CCRT approach with weekly cisplatin, 40 mg/m^2. The primary end point of the study was compliance and toxicity of the two treatment regimens. Assuming a compliance rate of 71% with CCRT and 90% with RT + cetuximab, a sample size of 65 patients per treatment arm would provide an 80% power to detect a 20% difference in compliance with a 5% significance level. Unfortunately, due to slow accrual, the trial was closed prematurely after enrollment of 70 patients, reducing the power of the trial. Nevertheless, the topic was considered interesting enough and the attempt to try to execute the study appreciated enough to have it published in a high-ranked journal and to have it accompanied by a well-written editorial in the same issue (9). Hematologic, renal, and gastrointestinal toxicities were observed more frequently in the CCRT arm. Drug dosage reduction occurred in 34% of patients given RT + cetuximab and in 53% of patients given CCRT (ns). Patients in the RT + cetuximab arm were more likely to have a break of more than 10 days, required more nutritional support, and in addition experienced more grade ≥3 skin toxicity. Overall, serious adverse events related to treatment, including four versus one toxic deaths, were higher in the RT + cetuximab arm (19% *vs*. 3%, P=0.044). Patterns of failure and survival were similar between the treatment arms (8). Despite the large difference in local control in favour of CCRT at one (84% *vs*. 64%) and 2 years (80% *vs*. 53%), this difference missed statistical significance marginally (P=0.073), underscoring the lack of power of the trial (8,9). The trial can certainly be criticized (9): compliance is not a hard endpoint and was remarkably low in both arms when compared to compliance in large randomized phase III trials (3,5,9), the cetuximab infusion reaction rate was higher than expected, and the rate of grade 5 toxicities in the cetuximab arm was unexplicable and shocking (9). Nevertheless, the results of the phase II trial by Magrini *et al*. are in line with the outcome of the CONCERT-2 trial (8). In that study accelerated fractionation RT with three cycles of panitumumab at 9 mg/kg every 3 weeks was compared to CCRT with two cycles of high dose cisplatin (100 mg/m^2 every 3 weeks) in a randomized phase II trial. The trial recruited 152 patients, assuming a locoregional control rate (primary endpoint) at 2 years of 41% with CCRT and of 50% with RT + panitumumab, although any

formal hypothesis testing was not planned and P values were descriptive only.

Local-regional control at 2 years was 61% (95% CI, 47–72%) with CCRT and 51% (95% CI, 40–62%) with RT + panitumumab. The most frequent grade 3/4 adverse events were mucosal inflammation (40% with CCRT versus 42% with RT + panitumumab), dysphagia (32% *vs.* 40%), and radiation skin injury (11% *vs.* 24%). Serious adverse events were reported in 40% of patients with CCRT and 34% of patients with RT + panitumumab. Median relative dose intensity was 99% (IQR 93.5–100.6) for cisplatin and 100% (IQR 95.5–102) for panitumumab. In the RT + panitumumab group, 7% of the patients had treatment interruptions that lasted for more than 10 cumulative days compared with none in the CCRT group. At 2 years, PFS events occurred in 39% of the patients in the CCRT group and in 59% of the patients in the RT + panitumumab group (HR =1.73, 95% CI, 1.07–2.81%; P=0.03). Two-year locoregional control rate [67% (95% CI, 28–88%) *vs.* 66% (95% CI, 36–84%); HR =0.95, 95% CI, 0.22–4.01%; P=0.94] and 2-year PFS [76% (95% CI, 33–94%) *vs.* 60% (32–80%)] in the p16-positive patients were very similar between CCRT and RT + panitumumab. However, only 24 patients had p16-positive tumors, therefore precluding firm conclusions regarding this particular population (10).

The outcomes in these two randomized phase II trials are consistent with the results of a meta-analysis on platinum-based CCRT versus RT + cetuximab, published in 2014 (11), which analyzed 1,808 patients enrolled in three prospective and 12 retrospective trials. Overall, CCRT was associated with a significantly better 2-year OS [relative risk (RR) =0.66; 95% CI, 0.46–0.94%; P=0.02), 2-year PFS (RR =0.68; 95% CI, 0.53–0.87%; P=0.002], and 2-year locoregional relapse rate (RR =0.63; 95% CI, 0.45–0.87%; P=0.005) as compared to RT + cetuximab (11).

In a retrospective review of patients treated at Memorial Sloan Kettering Cancer Center (12), RT + cetuximab was associated with an inferior 4-year OS and a higher 4-year local failure rate (LFR) as compared to the combination of radiotherapy with either carboplatin/5FU or high dose cisplatin. Four-year OS rates were 40.9%, 70.2%, and 86.9% (P<0.0001), respectively, and LFR at 4 years were 40.2%, 9.7%, and 6.3% (P<0.0001), respectively. Late toxicity was highest with carboplatin/5-FU and did not differ between RT + cisplatin and RT + cetuximab (12).

In a matched-pair comparison of platinum-based CCRT and RT + cetuximab, RT + cetuximab was associated with a significantly worse cause-specific survival and OS, although this difference was only seen in the patients under 65 (13). In a single institution retrospective comparison, RT + cetuximab induced a significantly higher incidence of grade ≥3 radiation dermatitis than platinum-based CCRT (43% *vs.* 3%, respectively, P<0.01) and patients tended to experience grade ≥3 mucositis/stomatitis more frequently (14).

In contrast, Strom *et al.* found no difference in locoregional control, distant metastasis rate, or OS between RT + cetuximab and CCRT with cisplatin given every 3 weeks (15). The National Cancer Institute of Canada Clinical Trials Group HN.6 study (NCT00820248) is a phase III trial in which patients were randomized between accelerated fractionation radiotherapy (AFX) plus three cycles of panitumumab at 9 mg/kg every 3 weeks or standard fractionation RT plus cisplatin, 100 mg/m^2 every 3 weeks, also for three administrations. As the radiotherapy fractionation was different between arms, this trial is a comparison between two treatment strategies rather than a straightforward comparison between CCRT and RT + panitumumab. With a median follow-up of 46 months, PFS with RT + panitumumab was not superior to RT + cisplatin and therefore the primary endpoint was not met. In fact, the 2-year PFS (primary endpoint) was 73% (95% CI, 65–79%) with RT + cisplatin and 76% (95% CI, 68–82%) with RT + panitumumab (HR =0.95; 95% CI, 0.6–1.5%; P=0.83). Upper bound of HR's 95% CI exceeded the pre-specified non-inferiority margin, which indicated that also non-inferiority of RT + panitumumab versus RT + cisplatin was not proven, making the results of the study inconclusive. The incidence of any grade >3 non-hematologic adverse event was 88% with CCRT and 91% with RT + panitumumab (P=0.25), although grade 3/4 mucositis and dermatitis occurred more frequently with RT + panitumumab (16). There were no lasting differences in Quality of Life although a temporary advantage, which was gone by 8 weeks after treatment, was observed with RT + panitumumab at the end of treatment, for some subscales (FACT-Physical Well-Being, MDADI Physical, and SWAL-Qol Eating Duration, Eating desire, and Mental Health (16,17).

Patients with HPV-positive oropharyngeal carcinoma (OPC) clearly have a better prognosis than patients with HPV-negative OPCs (18). Based on results of several other randomized trials, improvement in outcome seems irrespective of the type of treatment the patient is receiving. In fact, retrospective subanalyses in randomized trials were not conclusive on a specific benefit of one particular treatment over the other in patients with HPV-positive

tumors (19,20). More recently, in a large multicenter retrospective cohort study, a cumulative cisplatin dose <200 mg/m^2 (*vs.* >200 mg/m^2) was detrimental in patients with HPV-negative tumors but had no impact in patients with HPV-positive tumors, suggesting that de-intensification of treatment might be possible without jeopardizing outcome in patients with HPV-positive tumors (21).

Most of the ongoing randomized phase III trials comparing RT + cetuximab to CCRT with cisplatin are in patients with HPV-positive tumors (22-24). Whatever the outcome in these trials, this will not be representative for the large group of patients with HPV-negative tumors. However, the GORTEC 2007-01 trial might shed light on this crucial question because most of the patients in GORTEC 2007-01 had HPV-negative tumors (25). In this trial 406 patients with oral cavity, oro/hypopharynx and larynx cancers with no or limited nodal spread (N0–N2a) were randomized to be treated with RT + cetuximab (arm A) or RT + carboplatin/infusional 5-FU + cetuximab (arm B). The RT + carboplatin/infusional 5-FU (carboplatin 70 mg/m^2/d + 5-FU 600 mg/m^2/d, d1–d4, weeks 1, 4 and 7) during RT is an accepted standard of care platinum-based CCRT approach with level IA evidence (1,26). P16 status (a reliable surrogate marker for HPV in OPC) in this study was available in 89% of the OPC patients and proved to be positive only in 21% of the OPC patients. Accepting that the incidence of p16 positivity is much lower in non-OPC sites, the majority of patients in this study had HPV-negative tumors. With a median follow-up of 4.4 years, the 3-year PFS rate was 52.3% in arm B *vs.* 40.5% in arm A (HR =0.73; 95% CI, 0.57–0.94%; P=0.015). Also the locoregional control was markedly improved (HR =0.54; 95% CI, 0.38–0.76%; P=0.0005), but there was a non-significant gain in OS (HR =0.80; 95% CI 0.61–1.05%; P=0.11). Unless there is a specific interaction between cetuximab and carboplatin/infusional 5-FU that would refute the outcome of RTOG 0522 (no benefit of adding cetuximab to cisplatin-based CCRT), the outcome GORTEC 2007-01 can be seen as a positive trial showing that platinum-based CCRT is superior to RT + cetuximab in the type of patients that included in GORTEC 2007-01.

Patients treated with induction chemotherapy frequently receive up to 300 mg/m^2 of cisplatin prior to definitive CCRT. The administration of cisplatin either weekly or 3-weekly is particularly challenging or sometimes even unfeasible in these patients (27). For such patients an EGFR-directed monoclonal antibody might be an attractive alternative (28).

However, in that setting, RT + cetuximab has not shown to be unequivocally superior to CCRT. In the TREMPLIN larynx preservation trial, a randomized phase II study, patients received first three cycles of TPF (docetaxel and cisplatin 75 mg/m^2 each on day 1 and 5-fluorouracil 750 mg/m^2 per day on days 1 through 5), and then, when responding, were randomized to receive conventional fractionation radiotherapy with concurrent cisplatin 100 mg/m^2 per day on days 1, 22, and 43 or concurrent cetuximab, 400 mg/m^2 loading dose and 250 mg/m^2 per week during RT. There was no difference between arms in grade 3/4 mucositis, but grade 3/4 in-field skin toxicity was observed more frequently in the RT + cetuximab arm. Treatment compliance was better with RT + cetuximab as 43% *vs.* 71% of patients received the full protocol, respectively. However, except for renal toxicity (grade 1) in patients receiving cisplatin, late toxicity, occurring 6 months or later after end of treatment, did not differ significantly between the two arms. There were fewer local failures with CCRT although patients treated with RT + certuximab were more likely to be salvaged by surgery.

In a trial conducted by the Italian Gruppo di Studio Tumori della Testa e del Collo (GSTTC), patients with LA-SCCHN, after an initial randomized phase II part (with two arms) of standard fractionation RT plus two cycles of cisplatin/5-FU with/without prior TPF induction chemotherapy (29), were randomized in the phase III part of the study to two forms of locoregional therapy (CCRT or RT + cetuximab) with or without prior TPF, in a 2×2 factorial design, ultimately at the end resulting in numerically unbalanced treatment arms. Chemoradiation consisted of two cycles of cisplatin/5-FU (20 mg/m^2/day, day 1–4, and 800 mg/m^2/day, day 1–4, respectively).

One of the co-primary endpoints was in-field grade 3/4 toxicity. The trial had an 80 % power to detect a difference of 10% in grade 3/4 in field toxicity in favor of the cetuximab arm. The primary endpoint was not met as there was no statistically significant difference in in-field grade 3/4 toxicity. However, surprisingly the compliance was better in the platinum-based CCRT arms. In fact, more patients required interruptions of radiotherapy of >3 consecutive days, leading to a significantly longer median duration of radiotherapy in the cetuximab containing arms, and less patients received concomitant treatment with cetuximab as planned (30,31). The Spanish Head and Neck Cancer Cooperative Group (TTCC) conducted a randomized phase III non-inferiority trial comparing RT + cetuximab versus standard CCRT with high dose

cisplatin after prior administration of three cycles of TPF induction chemotherapy. Thus far only toxicity data have been presented. Grade 3/4 gastrointestinal and hematologic toxicity was less common with RT + cetuximab and grade 3/4 dermatological toxicity, radiation-induced skin toxicity, and mucosal toxicity occurred less frequently with CCRT (32). INTERCEPTOR is another ongoing randomized phase III trial conducted by the Gruppo Oncologico del Nord-Ovest (Italy), comparing platinum-based CCRT and RT + cetuximab after prior TPF induction chemotherapy. The trial is still recruiting and results are eagerly awaited (33).

RT plus cetuximab has also been compared to CCRT after prior induction chemotherapy in patients with stage III–IVb nasopharyngeal carcinoma. Xu *et al.* (34) reported on a randomized phase II trial, in which patients received two cycles of docetaxel 75 mg/m^2 and cisplatin 80 mg/m^2 and were than randomized to receive intensity modulated RT (IMRT) with either weekly cisplatin, 30 mg/m^2 or cetuximab. The trial was closed prematurely because of unexpectedly high rates of grade 3/4 mucositis in the IMRT + cetuximab arm.

In conclusion, the incomplete prospective randomized phase II trial by Magrini *et al.* (8) further adds to the expanding concern that EGFR-based bioradiation might be inferior to platinum-based CCRT in patients with LA-SCCHN in terms of efficacy but even in terms of toxicity, undermining the idea that bioradiation represents a de-escalation of treatment. Results of the ongoing trials with RT + cetuximab versus cisplatin-based CCRT in patients with HPV-positive OPC are eagerly awaited in that respect. However, additional data suggest that this concern should be even higher in patients with HPV-negative tumors. We therefore question whether such results can be extrapolated to the HPV-negative population, even when the trials in HPV-positive OPC patients would show equivalence of the two approaches. For that reason, today CCRT with 3-weekly high-dose cisplatin should remain the preferred standard of care nonsurgical treatment approach for LA-SCCHN.

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Footnote

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