Editorial

Postoperative treatment for head and neck cancer: the emerging role of EGFR-targeted therapy

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Squamous cell carcinoma of the head and neck (SCCHN) commonly invades local structures and spreads to regional lymph nodes. Treatment with surgery alone is usually inadequate to achieve optimal locoregional control in locally advanced SCCHN, which has led to the use of postoperative radiotherapy in selected high-risk patients (1). Pivotal randomized trials reported in the early 90s showed that postoperative radiotherapy results in better locoregional control than preoperative radiotherapy and that the optimal dose is reached at about 63 Gy (2,3).

The addition of chemotherapy to radiotherapy was a further attempt to improve efficacy results in locally advanced SCCHN. Two phase III trials examined the added benefit of high-dose cisplatin at 100 mg/m^2 given every 3 weeks for 3 cycles in combination with radiotherapy as adjuvant treatment for completely resected high-risk SCCHN. The Radiation Therapy Oncology Group (RTOG) 9501 trial enrolled patients with 2 or more lymph nodes, extracapsular spread, or positive margins (4). This trial demonstrated an improvement in locoregional control and disease-free survival (DFS) but not overall survival (OS) with the addition of cisplatin to postoperative radiotherapy. An unplanned long-term analysis with a minimum follow-up of 10 years, perhaps due to the dwindling number of patients at late time points, failed to show a statistically significant benefit in any of the efficacy parameters (5). A second trial with a similar design that conducted by the EORTC (European Organisation for Research and Treatment of Cancer) had overlapping but distinct eligibility criteria. This study enrolled patients with stage III/IV disease, except T3N0 larynx; pT1-2N0-1 were required to have either perineural spread, extranodal spread, positive margins, or vascular tumor embolism; also, patients with oral cavity or oropharyngeal tumors with spread to level IV or V lymph nodes were eligible (6). The EORTC trial showed not only an advantage in locoregional control and progression-free survival with cisplatin but also a statistically significant survival benefit. Widely accepted high-risk features assessed at pathology review that necessitate postoperative radiotherapy are positive margins and extracapsular nodal spread, as shown in a combined analysis of the RTOG and EORTC trials (7). However, minor risk factors, such as perineural invasion, depth of invasion for tongue cancer, and number of lymph nodes, may be relevant for therapeutic decisions. Human papillomavirus (HPV) tumor positivity is a favorable prognostic factor in the postoperative setting; whether treatment strategies should be modified for patients with good prognosis HPV positive tumors remains to be determined (8).

Other non-platinum systemic agents have been investigated in combination with radiotherapy for locally advanced SCCHN. The taxanes, such as paclitaxel or docetaxel, are potent radiosensitizers, with antitumor activity in SCCHN. Nevertheless, no phase III trial with a taxane and radiotherapy in patients with locally advanced SCCHN has been reported yet. The advent of targeted agents has broadened the horizons in SCCHN therapeutics. Cetuximab, a chimeric monoclonal antibody against epidermal growth factor receptor (EGFR), significantly improved locoregional control, progression-free survival

(PFS) and OS when combined with radiotherapy compared to radiation therapy alone as primary therapy in patients with locally advanced SCCHN. Notably, the addition of cetuximab to cisplatin and radiotherapy was investigated in RTOG 0522. This adequately powered phase III trial showed that cetuximab did not improve any efficacy endpoint in the primary treatment of locally advanced SCCHN, in either HPV-positive or -negative disease (9). However, the role of cetuximab as component of postoperative treatment is a subject of ongoing research. Moreover, it remains unclear which chemotherapy agent is the best to combine with cetuximab and radiotherapy in postoperative treatment.

Harari *et al.* reported the results of RTOG 0234, a phase II randomized trial that evaluated two cetuximab-containing doublets, cisplatin/cetuximab or docetaxel/cetuximab given concurrently with postoperative radiotherapy (10). Eligibility required completely resected pathologic stage III/IV SCCHN with positive margins, extracapsular nodal extension, or 2 or more positive lymph nodes. Patients were randomly assigned to 60 Gy radiation with cetuximab plus either cisplatin 30 mg/m^2 or docetaxel 15 mg/m^2 once per week. A total of 238 patients were enrolled in RTOG 0234. With an adequate follow-up of 4.4 years, 2-year OS was 69% for the cisplatin arm and 79% for the docetaxel arm; 2-year DFS was 57% and 66%, respectively. Similarly to analysis of other trials, patients with p16-positive oropharyngeal cancer tumors showed markedly improved survival outcome relative to patients with p16-negative oropharyngeal cancers. Toxicities in the two arms were within what expected; there was no difference in grade 3 to 4 mucositis between the two arms. The investigators compared the DFS reported in RTOG 0234 to that in the chemoradiotherapy arm of the RTOG 9501 trial. The comparison to this historical control yielded a hazard ratio of 0.76 for the cisplatin arm versus control (P=0.05) and 0.69 for the docetaxel arm versus control (P=0.01), corresponding to an absolute improvement in 2-year DFS of 2.5% and 11.1%, respectively. Therefore, DFS in both arms compared favorably to a historical control. However, the non-platinum regimen of cetuximab/docetaxel had numerically superior survival results to cetuximab/cisplatin. It is puzzling why the combination of cetuximab, cisplatin, and radiotherapy does not lead to optimal results in either the postoperative or the primary therapy setting. A plausible explanation for the lack of an added benefit with this combination may be that cetuximab and cisplatin have overlapping mechanisms of radiation sensitization, since they both inhibit the repair of DNA double strand breaks (11). It can be hypothesized that non-platinum cytotoxics may be optimal in combination with cetuximab and radiotherapy (12,13).

The NRG Oncology cooperative group is currently conducting a three-arm randomized phase II/III trial (RTOG 1216) in patients with high-risk resected SCCHN defined as extracapsular nodal spread or positive margins that compares adjuvant radiotherapy with docetaxel and cetuximab, to radiotherapy with either weekly cisplatin or docetaxel monotherapy (NCT01810913). Finally, for intermediate risk patients an ongoing phase III trial compares postoperative radiotherapy with or without cetuximab (NCT00956007).

Other EGFR-targeted agents, including the oral tyrosine kinase inhibitors lapatinib and afatinib are investigational in SCCHN. Lapatinib was evaluated in a phase III trial but did not demonstrate added benefit to standard radiotherapy and cisplatin (14). Afatinib is also being investigated as adjuvant therapy starting after completion of primary chemoradiotherapy (NCT01345669).

Postoperative treatment of SCCHN is evolving. Whether EGFR inhibitors have a role as components of combined modality approaches after curative surgery remains to be determined by ongoing trials. Other targeted agents, including immunotherapy, are worthwhile exploring as adjuvant therapy.

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Footnote

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References

1. Argiris A, Karamouzis MV, Raben D, et al. Head and neck cancer. Lancet 2008;371:1695-709.
2. Peters LJ, Goepfert H, Ang KK, et al. Evaluation of the dose for postoperative radiation therapy of head and neck cancer: first report of a prospective randomized trial. Int J Radiat Oncol Biol Phys 1993;26:3-11.
3. Tupchong L, Scott CB, Blitzer PH, et al. Randomized study of preoperative versus postoperative radiation therapy in advanced head and neck carcinoma: long-term follow-up of RTOG study 73-03. Int J Radiat Oncol Biol Phys 1991;20:21-8.
4. Cooper JS, Pajak TF, Forastiere AA, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. N Engl J Med 2004;350:1937-44.
5. Cooper JS, Zhang Q, Pajak TF, et al. Long-term follow-up of the RTOG 9501/intergroup phase III trial: postoperative concurrent radiation therapy and chemotherapy in high-risk squamous cell carcinoma of the head and neck. Int J Radiat Oncol Biol Phys 2012;84:1198-205.
6. Bernier J, Domenge C, Ozsahin M, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. N Engl J Med 2004;350:1945-52.
7. Bernier J, Cooper JS, Pajak TF, et al. Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (#9501). Head Neck 2005;27:843-50.
8. Samuels SE, Eisbruch A, Beitler JJ, et al. Management of locally advanced HPV-related oropharyngeal squamous cell carcinoma: where are we? Eur Arch Otorhinolaryngol 2015. [Epub ahead of print].
9. Ang KK, Zhang Q, Rosenthal DI, et al. Randomized phase III trial of concurrent accelerated radiation plus cisplatin with or without cetuximab for stage III to IV head and neck carcinoma: RTOG 0522. J Clin Oncol 2014;32:2940-50.
10. Harari PM, Harris J, Kies MS, et al. Postoperative chemoradiotherapy and cetuximab for high-risk squamous cell carcinoma of the head and neck: Radiation Therapy Oncology Group RTOG-0234. J Clin Oncol 2014;32:2486-95.
11. Dittmann K, Mayer C, Rodemann HP. Inhibition of radiation-induced EGFR nuclear import by C225 (Cetuximab) suppresses DNA-PK activity. Radiother Oncol 2005;76:157-61.
12. Nakata E, Hunter N, Mason K, et al. C225 antiepidermal growth factor receptor antibody enhances the efficacy of docetaxel chemoradiotherapy. Int J Radiat Oncol Biol Phys 2004;59:1163-73.
13. Rosenthal DI, Harari PM, Giralt J, et al. Impact of p16 status on the results of the phase III cetuximab (cet)/radiotherapy (RT). J Clin Oncol 2014;32:abstr 6001.
14. Harrington K, Temam S, Mehanna H, et al. Postoperative adjuvant lapatinib and concurrent chemoradiotherapy followed by maintenance lapatinib monotherapy in high-risk patients with resected squamous cell carcinoma of the head and neck: A phase III, randomized, double-blind, placebo-controlled study. J Clin Oncol 2015;33:4202-9.

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