Non-surgical treatment for locally advanced head and neck squamous cell carcinoma: beyond the upper limit

Hiroto Ishiki, Satoru Iwase

Department of Palliative Medicine, The Institute of Medical Science, The University of Tokyo, Shirokanedai, Minatoku, Tokyo 108-8639, Japan
Correspondence to: Hiroto Ishiki. Department of Palliative Medicine, The Institute of Medical Science, The University of Tokyo, 4-6-1, Shirokanedai, Minatoku, Tokyo 108-8639, Japan. Email: ishiki-tky@umin.ac.jp.
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Introduction

The treatment for locally advanced head and neck squamous cell carcinoma (LA-HNSCC) has become dramatically more developed over the past decade. Since LA-HNSCC treatment requires a multidisciplinary approach, this success has been made possible by the efforts and collaboration of various treatment specialists.

In this editorial, we will comment on RTOG0522 (1), a large randomized controlled trial of non-surgical treatment for patients with LA-HNSCC. Although the results of this trial were negative, RTOG0522 was one of the newest challenges in developing a novel treatment paradigm. We discuss the reason with a short review of the history of the development of non-surgical treatment for LA-HNSCC over the past several decades.

Head and neck cancer (HNC)

There are approximately 600,000 new cases of head and neck cancer (HNC) in the world each year. It is the 6th most common cancer throughout the world (2). Approximately 60% of patients have stage III or IV disease at diagnosis (3), and their prognosis remains poor despite the emergence of new therapeutic options over the last few decades. Since the head and neck region contains many organs essential for vital activities such as eating, breathing, speaking and surgical resection cannot avoid jeopardizing such functions to some extent, non-surgical treatment has been developed in addition to surgical procedures. Nowadays, concurrent chemoradiotherapy (CRT) is the non-surgical treatment standard for stage III/IV HNSCC (4).

Development of treatment over the past several decades

In the 1990s, many treatment regimens that combined radiotherapy (RT) and chemotherapy (CT) have been tested. Which treatment combination and sequence is the best? That was the question at that time. In 2000 and 2001, two meta-analyses (5,6) revealed that treatment efficacy is significantly better when platinum-based CT was concurrently delivered with RT, rather than before or after RT. Subsequently, concurrent cisplatin (CDDP) and RT (CDDP-RT) has been the standard for LA-HNSCC.

However, CDDP-RT is so intensive that it was said to be at "the upper limit of human tolerance" (7). Only half to two-thirds of patients could complete concurrent administration of high-dose CDDP at that time (8-10). For this reason, several clinical trials were conducted in 2000s to look for more feasible and effective treatment options. Recently, the benefit of adding the molecular targeting agent cetuximab to RT (bioradiation; BRT) had been reported (11). In addition, the efficacy of docetaxel-containing triplet regimen induction chemotherapy (IC) followed by RT has also been reported (12,13). Although these results had an impact on clinical practice, they were criticized because these treatments were not compared with the standard treatment, CDDP-RT, in phase III trials. However, there are three treatment choices available for LA-HNSCC in clinical practice without a head-to-head comparison: CRT, BRT, and IC followed by RT.

BRT

Cancer treatments using agents that target tumor-specific signal pathways have been developed for many cancers during the 2000s. In HNSCC, epidermal growth factor receptor (EGFR) is abnormally activated, and almost all HNSCC tumors express high levels of EGFR. There is a relationship between higher EGFR expression and poorer survival (14). Therefore, whether inhibition of the EGFR signal pathway is associated with better clinical outcomes was investigated during this period.

Cetuximab is a monoclonal antibody that targets the human EGFR. Its clinical efficacy with CT has been reported in colorectal cancer (15) and HNC (16). Since it also has radiosensitizing effects in animal models, Bonner *et al.* conducted a randomized controlled trial (11) investigating the additional benefit of cetuximab with RT. In this trial, patients with stage III or IV squamous cell carcinoma of the oropharynx, hypopharynx, or larynx were recruited. Eligible patients received either therapeutic RT plus cetuximab or RT alone. The primary endpoint, median duration of locoregional control, was significantly longer among patients treated with cetuximab and RT than those treated with RT alone [24.4 *vs.* 14.9 months; hazard ratio (HR), 0.68; P=0.005]. This was the first trial that showed that molecular-targeting agents add a benefit to RT. On the other hand, this trial has been criticized because the treatment for the control arm was not the standard for stage III/IV LA-HNSCC. Thus, the treatment of choice for LA-HNSCC is CDDP-RT, and BRT should be considered for patients who cannot receive CDDP for some reason (e.g., renal impairment). Whether BRT is superior to CDDP-RT remains unanswered so far. Recently, results from a randomized phase II trial comparing BRT to CDDP-RT have been reported (17). In addition, head-to-head phase III trials are ongoing; the De-ESCALaTE trial (NCT01874171) compares CRT to BRT in stage III/IVa, human papillomavirus (HPV)-positive oropharyngeal cancer and RTOG1016 (NCT01302834) compares CRT to BRT in a similar population. These trials are ongoing and we have to wait for the results.

RTOG0522 study

The RTOG0522 study (1) was planned based on the results of the two studies mentioned above, namely that (I) cetuximab is beneficial in patients with locally advanced HNSCC when concurrently delivered with RT (11); and (II) cetuximab is beneficial for patients with recurrent or metastatic HNSCC when added to platinum-based CT (16). Since the treatment of choice for LA-HNSCC is CDDP-RT, RTOG 0522 was planned to compare the efficacy of cetuximab plus CDDP-RT and CDDP-RT. Patients with stage III or IV HNSCC were randomly allocated to receive either accelerated fractionation (AFx), RT (70 Gy over 6 weeks), two cycles of high-dose CDDP (100 mg/m^2, on days 1 and 22) without (Arm A) or with (Arm B) cetuximab (loading dose 400 and 250 mg/m^2 weekly during RT). The primary endpoint was progression-free survival (PFS); other survival endpoints and adverse events were investigated as secondary endpoints. There were 940 patients enrolled in this trial. However, the results were disappointing. Arm B, the experimental group, did not have a better 3-year PFS rate [61.2% *vs.* 58.9%; HR, 1.08; 95% confidence interval (CI), 0.88–1.32; P=0.76], 3-year overall survival rate (72.9% *vs.* 75.8%; HR, 0.95; 95% CI, 0.74–1.21 P=0.32), 3-year locoregional failure rate (19.9% *vs.* 25.9%; HR, 1.30; 95% CI, 0.99–1.70; P=0.97), or distant metastasis rate (13.0% *vs.* 9.7%; HR, 0.76; 95% CI, 0.51–1.13, P=0.08). Furthermore, the frequency of grade 3 to 4 radiation mucositis, rash, fatigue, anorexia, and hypokalemia were higher in the experimental arm. p16 positivity might be prognostic, but EGFR expression and p16 were not predictive of experimental treatment efficacy.

Negative trial: why?

Although the treatment for the experimental arm was one of the most intensive treatments available for LA-HNSCC at the time, only negative results were obtained. Two reasons for these negative results were explained by the authors (1): "*the toxicity burden of radiation-cisplatin is at the maximum-tolerated level*" and "*platinum derivatives and cetuximab have similar mechanisms of radiation sensitization (i.e., inhibition of repair of radiation-induced DNA damage)*".

In addition, we think there might have been several explanations for these results. First, the cumulative CDDP dose during CRT might have affected the results. Based on a recent report, at least 200 mg/m^2 of CDDP should be administered to obtain an additive effect with RT (18). In RTOG0522, the cumulative dose of CDDP in both arms was less than 200 mg/m^2 (191.9 mg/m^2 in Arm A and 185.7 mg/m^2 in Arm B). In particular, more Arm B patients received less than 160 mg/m^2 of CDDP (9.8% *vs.* 11.5%). Secondly, unplanned RT interruption might have had an effect as

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Table 1 Randomized trials of CRT plus molecular targeting agents

Authors	Year	N	Phase	Setting	CT	RT	Target agent	Result
Mesía et al. (23)	2015	153	rP2	LA	CDDP: 75 mg/m^2, 3 courses	CFx	Panitumumab	Negative
Martins et al. (24)	2013	204	rP2	LA	CDDP: 100 mg/m^2, 3 courses	CFx	Erlotinib	Negative
Harrington et al. (26)	2015	688	P3	PO	CDDP: 100 mg/m^2, 3 courses	CFx	Lapatinib	Negative
Ang et al. (1)	2014	940	P3	LA	CDDP: 100 mg/m^2, 3 courses	AFx	Cetuximab	Negative

CRT, chemoradiotherapy; CT, chemotherapy; RT, radiotherapy; rP2, randomized phase 2; LA, locally advanced; CDDP, cisplatin; CFx, conventional fractionation; P3, phase 3; PO, postoperative; AFx, accelerated fractionation.

well. More than half of the patients in Arm B experienced interruptions in radiation (50.8%), compared to 42.0% in Arm A. Unplanned RT interruption worsens survival by 1.4% per day and 10–12% per week (19). This 8.8% difference in the proportion of patients with interruption could have negatively affected survival in Arm B. Third, 70% (625 patients) of enrolled patients had oropharyngeal cancer, and tumor specimens for a p16 assay were obtained from half (321 patients) of them. Approximately 50% of tested patients were p16 positive. Patients with p16-positive oropharyngeal cancer have a good prognosis and may undergo de-escalation of treatment intensity (20). For such patients, CDDP-RT is intensive enough to achieve a treatment effect. Thus, the protocol treatments of this study could have been too intensive to demonstrate a survival benefit for p16-positive oropharyngeal cancer patients, who accounted for one-third of all patients. These points might be possible reasons for the negative results, in addition to the reasons proposed by the authors.

Future perspective

Improving treatment efficacy for LA-HNSCC by intensifying treatment through (I) adding IC to CRT and (II) adding molecular targeting agents other than cetuximab to CRT has been challenging. The former strategy has been reported in two randomized controlled trials (21,22). Although both trials were underpowered due to a low accrual rate, the benefit of additional IC on CRT was not observed. The latter strategy has also been tried. Although the benefit of adding molecular targeting agents other than cetuximab to CRT has been investigated in phase II and phase III studies (23-26), positive results have not been observed so far (Table 1).

The following alternative strategies seem possible: (I) patient selection; (II) optimizing treatment delivery; and (III) new paradigm.

Patient selection

HPV-positive oropharyngeal cancer is a distinct entity, which has been confirmed genetically (27), with better survival compared to other types of HNC (20). For HPV-positive oropharyngeal cancers, de-escalation of treatment intensity or maintenance of treatment intensity and improving QOL are the objectives. Intensifying treatment might be beneficial for patients with HPV-negative HNSCC.

Optimizing treatment delivery

As already stated, compliance with CDDP-RT is not good, so optimizing treatment delivery is one possible way to improve survival. New cytotoxic agents had been developed after 2000, and whether they improve upon CDDP-RT has been studied, for example, in the RTOG0234 trial (28). This randomized phase II trial of postoperative (PO) treatment reported docetaxel and cetuximab had better efficacy than CDDP and cetuximab as well as compared to historical controls with high-risk HNSCC that received CDDP-RT and underwent resection. Based on this trial, a phase II/III trial for this population is ongoing (RTOG1216; NCT01810913). Development of RT techniques or particle beam therapy might play some role in improving treatment efficacy as well.

Immunotherapy

Immunotherapy has changed existing treatment paradigms in other cancers. This treatment has also been attempted in HNC, both in the locally advanced and recurrent or metastatic setting. The feasibility of adding the anti-cytotoxic T lymphocyte-associated protein 4 (CTLA4) antibody ipilimumab (NCT01860430, NCT01935921), anti-programmed death-1 (PD-1) antibody nivolumab (RTOG3504), or anti-programmed death-ligand 1 (PD-L1)

antibody pembrolizumab (NCT02641093) to RT in the locally advanced setting is currently being investigated in phase I and II trials.

In conclusion, the challenge to overcome "the upper limit of human tolerance" failed in RTOTG0522. While treating patients with LA-HNSCC, patient selection and optimizing treatment delivery could be the keys to obtaining a sufficient treatment effect in current clinical practice. The role of molecular targeting agents remains unclear and should be further investigated.

Footnote

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