関わらず，必ずしもそれにこだわることなく国によってさまざまなレジメンでCRTの臨床試験が行われていることは興味深いことである[6]。

術後化学放射線療法

術後に再発や転移の可能性が高い症例を対象にして術後に化学放射線療法を行うことが検討されるようになりさまざまな第Ⅲ相臨床試験が行われている[7~9]。2004年には口腔・中咽頭・下咽頭・喉頭を原発巣とする頭頸部扁平上皮癌に対する術後化学放射線療法の有用性がヨーロッパとアメリカから報告された。いずれも，術後再発に対してリスクが高いと考えられる症例を定義して化学放射線療法を行う臨床試験である。

Bernierらヨーロッパのグループは EORTC22931試験[10]を報告したが，第Ⅲ・Ⅳ期の症例に対して根治的手術を施行した後に断端陽性や転移リンパ節の節外浸潤などがある症例に対して，CDDPと放射線治療併用療法を施行した。EORTC22931試験では334例を対象に5年無増悪生存割合が化学放射線療法で47%に対して放射線単独療法で36%（p=0.04），5年生存割合が化学放射線療法で53%に対して放射線単独療法で40%（p=0.02）といずれもCDDPによる化学放射線療法が放射線単独療法より優れていることが示された。

一方，Cooperらアメリカのグループは RTOG9501試験[11]の結果を報告した。ここでも，放射線治療と共に併用化学療法としてCDDP(100 mg/m^2，q3w）を使用しており，RTOG95-01試験では416例を対象に3.8年無増悪生存割合が化学放射線療法で40%に対して放射線単独療法で30%（p=0.04）と有意に良好であったが，全体生存割合では化学放射線療法で50%に対して放射線単独療法で41%とCDDPによる化学放射線療法が良好な傾向を示したが有意差は認めなかった(p=0.19)。

以上の結果から欧米では，局所進行頭頸部扁平上皮癌の手術後再発ハイリスク群に対する術後補助療法は化学放射線療法が標準と考えられ，併用化学療法としてはCDDP 100 mg/m^2，の3週ごと投与が欧米における最も標準的なレジメンと考えられている。

導入化学療法

CDDPが頭頸部癌に適応となった頃からすべての治療に先立って化学療法を行う試みが行われてきた。これは1983年にFreiらによってneoadjuvant chemotherapyとして提唱され[12]，現在は導入化学療法（induction chemotherapy：ICT）とよばれることが多い。以後，さまざまな臨床試験が行われたがほとんどの試験で生存期間に対する上乗せ効果を証明した結果は得られなかった[13]。

しかし一方で，ICTによる機能温存治療が注目されている。すなわちICTの効果を認めた場合はCRTによって喉頭温存を目指す第Ⅲ相試験が行われている。その代表的な報告としてVA studyがある[14]。進行喉頭癌症例に対してFPを2コース施行し効果を認めた場合はさらに1コース追加してその後放射線療法を施行する場合と，喉頭全摘術を施行する場合の2アームでランダム化比較試験をおこなった結果，ICT群と手術群では2年生存率は68%と差がなく，ICT群では2年で66%の喉頭温存率が得られたと報告されている。下咽頭癌における喉頭温存治療に関しては，Lefebvreらが EORTCで行った臨床試験を報告しており，FPを3コース施行するICT群と手術群では3年および5年生存率に差がなく喉頭温存率は3年で42%であったと報告している[15]。これらの第Ⅲ相試験から，ICTによる生存への上乗せ効果は期待しにくいが，ICTの効果によって機能温存治療の可能性が示唆されてきた。

一方，FPにDOCを加えた3剤併用のTPFは強力な併用化学療法として注目されるようになった。TPFによるICTの有用性に関して2つの第Ⅲ相試験がヨーロッパとアメリカから相次いで発表された。それらは2007年に報告されたTAX323試験とTAX324試験である[16,17]。まず，TAX323試験はヨーロッパの共同研究グループEORTCから報告されたものであり，358例の初回治療例で切除不能な局所進行頭頸部癌症例が登録された。これらは，導入化学療法としてFPとTPFに無作為割り付けが行われた。FPとしてCDDPは100 mg/m^{2}で第1日目に投与し5-FUは1000 mg/m^2

で第1日目から第5日目まで5日間の持続投与とした。TPF療法ではCDDPは75 mg/m^2，DOCは75 mg/m^{2}でともに第1日目に投与し，5-FUは750 mg/m^{2}で第1日目から5日間の持続投与とした。その後に続く放射線療法は化学療法を併用しなかった。その結果，奏効率はTPFがFPに対して有意に良好であり，無増悪生存期間と全生存期間でも有意に勝っていた。

TAX324試験は，アメリカのPosnerらのグループから発表されたものであり，やはりTPF療法またはFP療法を導入化学療法としてその後にCRTを施行する第Ⅲ相比較試験である。対象は未治療で切除不能症例と機能温存を目指した症例も含まれた。501例の症例が登録されTPFまたはFPに割り付けられ21日ごとに3コースの化学療法が施行された。レジメンはTAX323とほぼ同様であるが放射線療法はICの後，カルボプラチン併用で70～74 Gyの放射線療法を施行した。

本試験は2011年に中央値で6年の観察期間による長期成績が報告されている[18]。経過観察の中間値は72.2カ月で5年生存率はTPFで52%，FP療法で42%であり，生存期間は中間値で各々，70.6カ月，34.8カ月とTPFで有意に勝っていた。部位別やステージ別に長期成績が解析されており，TPFは機能温存治療例やstage Ⅳで有意に生存期間が長い結果となっている。このようにTPFは優れた効果を示すが毒性も強いことが問題となる。一方，長期経過では，胃瘻に依存する割合や気管切開を行った割合では両者ともに差がなかったとしており，TPFの副作用は長期的なQOLの低下には結びつかないと述べている。

分子標的薬と抗がん薬の併用

頭頸部癌に対する代表的な分子標的薬であるセツキシマブと化学療法の併用は，再発・転移癌に対するVermorkenらが行ったextreme studyが重要である[19]。これは，再発・転移頭頸部癌症例に対してCDDPまたはカルボプラチンと5-FUとの併用療法にセツキシマブの同時併用を行う群（A群）と行わない群（B群）との比較試験であり，ヨーロッパ17カ国が参加し420例が登録された大規模比較試験である。その結果，全体生存期間に関しては平均生存期間がセツキシマブ併用で10.1カ月，非併用群で7.4カ月と有意に延長した。再発・転移癌に対する治療で生存期間の延長が証明された画期的な報告である。

完全ヒト型IgG2抗体であるパニツムマブは，遠隔転移再発頭頸部扁平上皮癌を対象としたシスプラチン+5-FU療法（FP）とFP+パニツムマブとのランダム化比較試験（SPECTRUM試験）として日本も参加した世界共同試験を試行し，その結果が2010年のヨーロッパ腫瘍会議で報告された。その結果，無増悪生存期間はパニツムマブ併用で優れていたが全生存期間では，パニツムマブ併用群，FP療法群で有意差を認めなかった[20]。この原因として，ヒト乳頭腫ウイルス（HPV）陽性中咽頭癌の存在が注目されている。

近年，欧米で中咽頭癌におけるHPVの感染率は60%以上と報告され，HPV陽性中咽頭癌は増加傾向があると報告されている。HPV陽性中咽頭癌は化学療法に対する感受性が高いと考えられている。先に述べたSPECTRUM試験では無再発生存と全生存期間ともにHPV陽性患者では両群に差が認められなかったが，HPV陰性患者ではパニツムマブ併用群において有意に優れていた。HPV陰性頭頸部癌においてもEGFR阻害薬の効果が優れていることが示唆される結果であり，今後はHPV感染の有無が分子標的薬剤の治療開発に影響してくるものと考えられる。

まとめ

海外では頭頸部癌に対するさまざまな臨床試験が行われ，化学放射線療法はレベルの高いエビデンスが証明されている。現在進行中の大規模な比較試験が多数あるがアメリカをはじめ，ほとんどのプロトコールがICT施行後にCRTを行うsequential CRTが比較対象となっている。アメリカでは術後の高リスク例に対する術後RTとの併用を検討する目標症例数700例規模の試験や，HPV陽性例を対象とした試験も計画されている。Lefebvreらは EORTC-24891試験の10年後の結果を報告している。これは，下咽頭癌を対象として喉頭摘出を含む根治手術と術後照射に対して，PFによるICTを行ってCRの場合には放射線療

法を施行し喉頭を温存するランダム化比較試験である[21]。評価可能症例194例のうち，手術群（94例）およびCT（ICT）群（100例）の10年生存率は13.8%および13.1%，10年PFSは8.5%および10.8%であり，CT群の10年喉頭機能維持率は8.7%であった。すなわち，どちらの治療法によっても生命予後は同等であり，CT施行後生存例の半数以上で喉頭機能が維持されることが明らかとなった。このように海外，特にヨーロッパでは機能温存を目指してICTを積極的に取り入れた臨床試験を行っている。今後，海外から多くのデータが提示されると思われるが，わが国でもJCOG頭頸部がんグループなどから，標準治療に結びつくデータを発信することが望まれる。

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Randomized Phase II/III Trial of Post-operative Chemoradiotherapy Comparing 3-Weekly Cisplatin with Weekly Cisplatin in High-risk Patients with Squamous Cell Carcinoma of Head and Neck: Japan Clinical Oncology Group Study (JCOG1008)

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A randomized Phase II/III study was launched in Japan to evaluate the non-inferiority of concurrent chemoradiotherapy with weekly cisplatin (40 mg/m^2) compared with concurrent chemoradiotherapy with 3-weekly cisplatin (100 mg/m^2) for post-operative high-risk patients with locally advanced squamous cell carcinoma of head and neck. This study began in October 2012, and a total of 260 patients will be accrued from 18 institutions within 5 years. The primary endpoint of the Phase II part is proportion of treatment completion and that of the Phase III part is overall survival. The secondary endpoints are relapse-free survival, local relapse-free survival, nutrition-support-free survival, non-hospitalized treatment period during permissible treatment period and adverse events. This trial was registered at the UMIN Clinical Trials Registry as UMIN 000009125 [http://www.umin.ac.jp/ctr/].

Key words: head and neck cancer – post-operative chemoradiotherapy – high-risk patients – clinical trials – Phase II/III

INTRODUCTION

Head and neck cancer is relatively rare but increasing steadily in Japan. Squamous cell carcinoma is the most common histological type and comprises ~90% of head and neck cancer.

The prognosis of post-operative Stage III/IV locally advanced squamous cell carcinoma of head and neck (SCCHN) is still poor. Integrated analysis of RTOG95-01 (1) (Radiation Therapy Oncology Group) and EORTC22931 (2) (European Organisation for Research and Treatment of Cancer) demonstrated that microscopically positive resection margin and extracapsular nodal extension are high-risk factors for recurrence in post-operative locally advanced SCCHN. Moreover, these two trials revealed that the standard therapy for post-operative locally advanced SCCHN with high-risk factors for recurrence is surgery followed by chemoradiotherapy (CRT) with 3-weekly cisplatin (CDDP) at 100 mg/m^2 (3-weekly CDDP + RT); this adjuvant 3-weekly CDDP + RT showed 5-year survival of ~50% (1–4).

Meanwhile, concurrent CRT with weekly CDDP at 40 mg/m^2 (weekly CDDP + RT) is a promising regimen for post-operative locally advanced SCCHN with high-risk factors for recurrence. CDDP is expected to have a radiosensitizing effect when it is administered every week during radiation therapy and the dose intensity of weekly CDDP (40 mg/m^2/week) is higher than that of 3-weekly CDDP (33 mg/m^2/week). In fact, promising results of post-operative weekly CDDP + RT were reported in two prospective trials (5,6). In addition, weekly CDDP + RT has several advantages over 3-weekly CDDP + RT in terms of safety and toxicity. First, hematological toxicity tends to be milder in weekly CDDP + RT than in 3-weekly CDDP + RT. In particular, most published reports described that the incidence of Grade 3/4 neutropenia was ~30% in 3-weekly CDDP + RT compared with ~10–15% in weekly CDDP + RT (1,7–14). Second, auditory disorders are a problem associated with 3-weekly CDDP + RT, and weekly CDDP + RT is superior to the former due to the lower likelihood of neurotoxicity. In particular, CDDP-related auditory disorder is a dose-limiting toxicity; it occurs dose-dependently and is irreversible in most cases (15–18). In fact, in the RTOG95-01 study, the incidence of neurotoxicity including Grade 3 or more auditory disorders was 10% after 3-weekly CDDP + RT for head and neck cancer (1). In addition, in a feasibility study led by the National Cancer Center Hospital East, Grade 2 or more auditory disorder was observed in 8% of patients (7). On the other hand, there have been no reports on Grade 3 or more auditory disorders with weekly CDDP + RT. Hokkaido University and National Cancer Center Hospital East also reported that the incidence of Grade 2 or more auditory disorders was 0% in a retrospective study of weekly CDDP + RT in Japanese (8). Third, renal disorders rarely occur with weekly CDDP + RT, which is a major additional merit. In a retrospective overseas study reported by Uygun et al. (14), the incidence of Grade 3/4 renal disorder was lower with weekly CDDP + RT than with 3-weekly CDDP + RT. CDDP-related renal disorder is also dose-dependent and weekly CDDP + RT is superior in this regard. In fact, a Japanese study reported that, although no difference was observed in the incidence of Grade 3/4, the incidence of Grade 2 or more, for which dose reduction or discontinuation of CDDP must be considered, was 30–32% in 3-weekly CDDP + RT compared with 2–15% in weekly CDDP + RT, showing a significantly lower incidence with the latter (7–9). Finally, these potential merits of safety and toxicity for weekly CDDP + RT may lead to a shorter hospitalization period than for 3-weekly CDDP + RT. Therefore, we planned to test the non-inferiority of weekly CDDP + RT compared with 3-weekly CDDP + RT.

In this randomized controlled study, we set 3-weekly CDDP + RT as the standard treatment arm and weekly CDDP + RT as the experimental treatment arm. For safety and feasibility data in Japanese post-operative high-risk patients with locally advanced SCCHN, only one feasibility study ($N = 25$) led by the National Cancer Center Hospital East is available for 3-weekly CDDP + RT. In addition, for weekly CDDP + RT, few safety and feasibility data have been accumulated in Japan, Europe and the USA Considering the above circumstances together, we evaluate the feasibility and safety of both treatment arms in the Phase II part at first and then proceed to the Phase III part to test the non-inferiority of weekly CDDP + RT compared with 3-weekly CDDP + RT as a standard treatment.

The Protocol Review Committee of the Japan Clinical Oncology Group (JCOG) approved the protocol in August 2012 and the study was activated in October 2012. This trial was registered at the UMIN Clinical Trials Registry as UMIN 000009125 [http://www.umin.ac.jp/ctr/index.htm].

PROTOCOL DIGEST OF THE JCOG 1008

Purpose

The aim of this study is to evaluate the non-inferiority of weekly CDDP + RT compared with 3-weekly CDDP + RT for post-operative high-risk patients with locally advanced SCCHN.

Study Setting

A multi-institutional randomized Phase II/III study.

Resources

This study is supported by National Cancer Center Research and Development Funds (23-A-16 and 23-A-21).

Endpoints

The primary endpoint of the Phase II part is the proportion of treatment completion in all eligible patients. The definition of complete treatment is as follows: 3-weekly CDDP + RT arm, completion of radiation therapy within 66 days and administration of two out of three courses of 3-weekly CDDP during the radiation treatment period or within 14 days from the last day of completion of radiation; weekly CDDP + RT arm, completion of radiation therapy within 66 days and administration of five out of seven courses of weekly CDDP during the radiation treatment period.

The primary endpoint of the Phase III part is overall survival, which is defined as days from randomization to death from any cause and censored at the latest day without an event. The secondary endpoints are relapse-free survival, local relapse-free survival, nutrition-support-free survival, non-hospitalized treatment period during the permissible treatment period and adverse events. Relapse-free survival is defined as days from randomization to any disease relapse or death from any cause and censored at the latest date when the patient is alive. Local relapse-free survival is defined as days from randomization to local and regional disease relapse or death from any cause and censored at the latest date when the patient is

evaluated as event-free. Nutrition-support-free survival denotes the percentage of surviving patients not requiring any nutrition support at the time of treatment start and then 2, 6, 12, 24, 36, 48 and 60 months after registration. The non-hospitalized treatment period during the permissible treatment period is defined as the difference between the duration of actual hospital stays and the permissible treatment period (66 days).

Eligibility Criteria

Inclusion Criteria

For inclusion in the study, the patient must fulfill all of the following criteria:

(1) Histologically proven squamous cell carcinoma in resected specimen.
(2) Primary lesion located in the oral cavity, oropharynx, hypopharynx or larynx.
(3) Pathological Stages III, IVA or IVB (UICC seventh edition).
(4) High risk of locoregional recurrence, defined as fulfilling (i) and/or (ii):
  (i) microscopically positive resection margin;
  (ii) extracapsular nodal extension.
(5) Within 56 days of surgery.
(6) No distant metastasis in head and neck contrast CT or MRI, chest contrast CT or upper abdominal contrast CT within 28 days before registration.
(7) Aged 20–75 years old.
(8) ECOG performance status of 0 or 1.
(9) No prior radiation therapy, chemotherapy or hormonal therapy for target or non-target cancers.
(10) Adequate organ function.
(11) Normal electrocardiogram.
(12) Written informed consent.

Exclusion Criteria

Patients are excluded if they meet any of the following criteria:

(1) Active multiple primary cancers; synchronous or metachronous (within 5 years) double cancers except carcinoma *in situ* or intramucosal tumor.
(2) Infection requiring systemic treatment.
(3) Fever exceeding 38°C at registration.
(4) Women who are or may be pregnant, or who are nursing.
(5) Psychosis or psychiatric symptoms/signs that are judged to make participation in the study difficult.
(6) Long-term use of systemic steroidal treatment (oral/intravenous).
(7) Uncontrolled diabetes mellitus.
(8) Complication with unstable angina, or history of myocardial infarction within the last 6 months.
(9) Uncontrolled hypertension.

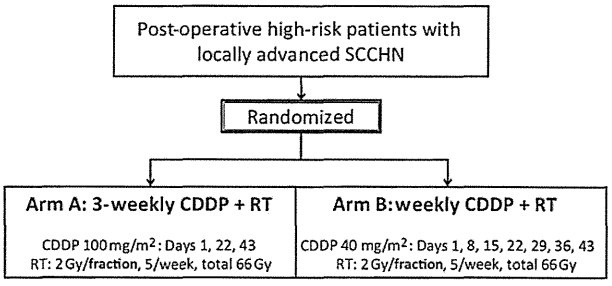

Figure 1. Schema of the study.

(10) Pleural effusion, pericardial effusion or ascites that requires drainage.
(11) Hepatitis B antigen-positive.
(12) Judged to have difficulty in abstaining from smoking or alcohol during the protocol treatment.

Treatment Methods

The protocol treatment consists of 3-weekly CDDP + RT and weekly CDDP + RT (Fig. 1).

Chemotherapy

Patients in the 3-weekly CDDP + RT arm receive concurrent CRT with CDDP at 100 mg/m^2. CDDP is administered on Days 1, 22 and 43, repeated every 3 weeks for three cycles. Patients in the weekly CDDP + RT arm receive concurrent CRT with CDDP at 40 mg/m^2. CDDP is administered on Days 1, 8, 15, 22, 29, 36 and 43, repeated every week for seven cycles.

Radiation Therapy

Radiation therapy is administered with high-energy photons of 4–10 MV X-rays to a total dose of 66 Gy in 33 fractions over 6.5 weeks. The gross tumor volume is not defined in this trial because macroscopic sites of the disease were resected before registration. The clinical target volume (CTV) initial includes locally resected lesion and potential lymph node metastasis area, and CTV boost is defined as a high-risk area with a positive node with extracapsular extension and/or a positive surgical margin with a 1–1.5 cm margin. The planning target volumes (PTV) for CTV initial and CTV boost (PTV initial and PTV boost) are defined as 0.5–1 cm margins around CTV initial and CTV boost to compensate for setup variations and internal organ motion. A total of 46 Gy is delivered to PTV initial, and then an additional 20 Gy is provided to PTV boost.

Follow-up

All enrolled patients are followed up for at least 5 years. The efficacy and the safety are to be evaluated at least every 3 months during the first year, at least every 4 months during

the second year, every 6 months during the third year, and every 12 months during the fourth and fifth years. Data on the use and methods of nutrition support are reported at 2, 6, 12 and then every 12 months until 60 months after registration.

Study Design and Statistical Analysis

This trial is designed to evaluate the non-inferiority of weekly CDDP + RT compared with 3-weekly CDDP + RT for post-operative high-risk patients with locally advanced SCCHN. The planned accrual period is 5 years, and the follow-up period is 5 years after completion of accrual.

In the Phase II part, the planned sample size is 66 patients, which was calculated based on an expected proportion of complete treatment of 80% and a threshold of 50%, with a one-sided alpha of 0.025 and a beta of 0.1.

In the Phase III part, the primary analysis is carried out at 5 years after accrual completion. The hazard ratio between the treatment arms and its confidence interval, estimated by the Cox proportional hazard model stratified by the high-risk factors for recurrence (microscopically positive resection margin and extracapsular nodal extension), is used to test the non-inferiority of the weekly CDDP + RT arm in terms of overall survival. The significance level is set at 0.05 in a one-sided test because of the non-inferiority design of the study. One hundred and sixty-one events would be required to demonstrate, with a statistical power of 75%, that the weekly CDDP + RT arm is not inferior to the 3-weekly CDDP arm in terms of overall survival, with a non-inferiority margin of 10% at 5-year overall survival. Non-inferiority will be concluded if the upper limit of the confidence interval of the hazard ratio does not exceed the limit of 1.32, which is in accord with the non-inferiority margin. According to Schoenfeld and Richter's method (19), a sample size of 260 patients is necessary to observe 161 events, considering the accrual and follow-up periods and that the estimated 5-year overall survival rates of the 3-weekly CDDP + RT arm and the weekly CDDP + RT arm are 49 and 52%, respectively.

Interim Analysis and Monitoring

In this Phase II/III trial, three interim analyses are planned. The first interim analysis is planned at the time of protocol treatment completion of all registered patients in the Phase II part to evaluate the feasibility and safety of both treatment arms and to determine the progression to the Phase III part. The second interim analysis is planned when half of the planned sample size is registered to determine whether the registration of the Phase III part should be continued. The third interim analysis is planned after the registration completion to determine the continuation to the follow-up. The trial will be terminated when the primary objective is accomplished at each interim analysis.

The Data and Safety Monitoring Committee of the JCOG will independently review the interim analysis reports and recommend that the trial either be continued or terminated early. Central monitoring will be performed every 6 months by the JCOG Data Center to evaluate study progress and improve study quality.

Participating Institutions (from North to South)

Hokkaido University Hospital, Miyagi Cancer Center, Tohoku University Hospital, Jichi Medical University Hospital, National Cancer Center Hospital East, Tokyo Jikei Medical University Hospital, National Hospital Organization Tokyo Medical Center, Cancer Institute Hospital, Tokai University, Shizuoka Cancer Center, Aichi Cancer Center, Nagoya University Hospital, Kinki University Hospital, Osaka Prefectural Hospital Organization, Osaka Medical Center for Cancer and Cardiovascular Diseases, Kobe University Hospital, Hyogo Cancer Center, Nara Medical University, Shikoku Cancer Center.

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Conflict of interest statement

None declared.

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REVIEW ARTICLE

Recent multidisciplinary approach with molecular targeted drugs for advanced head and neck cancer

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Abstract The multidisciplinary approach is becoming the standard for treatment of advanced head and neck cancer. Combined modality treatment preserves quality of life as well as improving the length of survival time. Molecular targeted drugs have become very important in the multidisciplinary approach for the treatment of advanced head and neck cancer. Cetuximab has been shown to have locoregional control and additional survival benefits in locally advanced squamous cell carcinoma of the head and neck as well as additional survival benefits in distant metastatic/recurrent squamous cell carcinoma of the head and neck. Recently, many clinical studies of the multidisciplinary approach including cetuximab have been carried out in Europe and the US. It has been shown that cetuximab in combination with radiotherapy (RT) is significantly superior to the RT alone in median locoregional control duration and median overall survival (OS). For recurrent or metastatic disease, the results of a phase III randomized control study of CDDP + 5-fluorouracil combination therapy with or without cetuximab reported that OS was significantly longer with than without cetuximab, demonstrating an additional survival benefit of cetuximab. Many trials including induction chemotherapy are being conducted. Clinical trials with cetuximab have also been conducted in Japan. Though combination with cetuximab shows some benefit, further studies are necessary to obtain the standard treatments for a multidisciplinary approach for advanced head and neck cancer.

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Keywords Head and neck cancer · Chemoradiation · Cetuximab · Clinical trials

Introduction

For the treatment of early-stage head and neck cancer, surgery and radiotherapy are standard treatments. However, for advanced head and neck cancer, combined modality treatment with surgery, radiotherapy, and chemotherapy (CT) together is required. Combined modality treatment preserves quality of life as well as improving the survival rate. Chemoradiotherapy (CRT), which is a simultaneous combination of radiotherapy (RT) and CT, improves the prognosis and locoregional control of locally advanced squamous cell carcinoma of the head and neck (LA-SCCHN) and also improves functional preservation, such as laryngeal preservation compared with RT alone. However, because recurrence is reported to be observed in about half of patients, CRT is still not a satisfactory method. It has been reported that overexpression of epidermal growth factor receptor (EGFR) is observed in 80–90 % of SCCHN and that its expression frequency is increased as precancerous lesions progress to invasive cancers [1]. In addition, overexpression of EGFR is associated with an increase in tumor size, progression of stage, increase in the risk of recurrence, low sensitivity to RT, and poor prognosis, etc. [2–4]. For this reason, EGFR has become an important target molecule for drug therapy for head and neck cancers; therefore, various EGFR-related drugs (molecular targeted drugs) have been developed, and their clinical studies are ongoing.

Cetuximab, an IgG1 chimeric antibody that binds specifically to EGFR, was launched as a treatment for EGFR-positive, unresectable advanced/recurrent colorectal cancer

in Japan in 2008. The usefulness of the combination of cetuximab with RT as treatment for LA-SCCHN has also been confirmed, and this treatment method has been approved in 88 countries, including approvals by the European Medicines Agency and the Food and Drug Administration in 2006. In addition, in 19 countries including the US, cetuximab was approved as a monotherapy for recurrent/distant metastatic squamous cell carcinoma of the head and neck (R/M-SCCHN) that has become resistant to platinum-based chemotherapy. Furthermore, additional survival benefits were observed with the combination of cetuximab with CT for R/M-SCCHN, and therapy with a combination of cetuximab and platinum-based CT for R/M-SCCHN has been approved in 82 countries, including the EU and the US. Cetuximab is described in the National Comprehensive Cancer Network (NCCN) Guidelines [5] as one of the alternatives for the treatment of both LA-SCCHN and R/M-SCCHN.

Phase II studies in LA-SCCHN and R/M-SCCHN have been completed in Japan as well. In this review, I will discuss the world's current status (efficacy and safety) and future perspectives of treatment of SCCHN with anti-EGFR monoclonal antibodies.

Clinical studies that provided a rationale for the NCCN guidelines

The use of cetuximab in the US has been increasing since the drug was described in the NCCN Guidelines of the US as a treatment for LA-SCCHN and R/M-SCCHN. According to the results of the Longitudinal Oncology Registry of Head and Neck Carcinoma (LORHAN) study (data of 4,243 patients in 100 facilities in the US obtained from 2005 to 2010) [6], the regimen most frequently used in combination with RT for the treatment of LA-SCCHN was cisplatin (CDDP) alone, followed by cetuximab. The use of cetuximab has been increasing yearly, and there have been many studies regarding the method of its administration.

Chemoradiotherapy for LA-SCCHN

In the NCCN guidelines [5], CDDP and cetuximab are described as CTs (monotherapies) used in combination with RT for LA-SCCHN. Bonner et al. [7] compared the RT + cetuximab combination group and the RT-alone group in 424 patients with LA-SCCHN in their UAB-9901 study (phase III study) and showed that the combination group was significantly superior to the RT-alone group in median locoregional control duration [24.4 vs. 14.9 months; hazard ratio (HR) 0.68, $p = 0.005$] and median overall survival (OS) (49 vs. 29.3 months; HR 0.74, $p = 0.03$), demonstrating that the combination of cetuximab with RT confers an additional survival benefit compared with RT-alone. Based on this result, cetuximab + RT therapy can be considered as a standard alternative in patients in whom CRT (CDDP + RT) is not appropriate. This therapy is also described in the Clinical Practice Guidelines [8] of the European Society of Medical Oncology (ESMO) as an alternative for the aged because cetuximab + RT therapy has been confirmed to possess similar or better efficacy and lower toxicity than CRT. Accordingly, cetuximab + RT therapy is positioned as a therapy that can replace CRT.

In sequential CRT, cetuximab is described as a drug to be used concomitantly with RT after induction chemotherapy (ICT) has been performed. In the TREMPLIN study by Lefebvre et al. [9], TPF [docetaxel (DTX) + CDDP + 5-fluorouracil (5-FU)] therapy was first performed in 153 patients with LA-SCCHN as an ICT, then cetuximab + RT therapy or RT + CDDP therapies were performed in 116 patients who showed partial response (PR) or better responses. The results of the 2 therapies were comparable for laryngeal function preservation rate, survival rate, and locoregional control effect, while the incidences of acute toxicity and late effects were observed more frequently in the RT + CDDP group. This result led to the recommendation in the NCCN guidelines that CDDP should not be used in CRT following platinum-based ICT.

Treatment of R/M-SCCHN

In the NCCN guidelines [5], CDDP and carboplatin (CBDCA) + 5-FU + cetuximab combination therapy is described as a treatment for R/M-SCCHN at the level of category 1. The results of a phase III randomized control study of the CDDP + 5-FU combination therapy (PF therapy) and the PF therapy + cetuximab combination therapy (EXTREME study) [10] conducted in 442 patients with R/M-SCCHN in 80 facilities in 27 European countries were reported. The median OS of the PF therapy + cetuximab group was 10.1 months, which was significantly longer than that of the PF-alone therapy by 7.4 months (HR 0.80, $p = 0.04$), demonstrating an additional survival benefit of cetuximab.

A CDDP + cetuximab therapy is described as combination chemotherapy. Burtness et al. [11] compared the CDDP + cetuximab combination group and the CDDP + placebo combination group in 117 patients with R/M-SCCHN in the ECOG-E5397 study (phase III study). The response rate of the cetuximab combination group was 26 %, which was significantly higher than that of the placebo combination group (10 %) ($p = 0.03$); however, no significant difference was observed in the median progression-free survival (PFS) (4.2 vs. 2.7 months). Grade 3

or higher hematotoxicity was observed more frequently in the cetuximab combination group than in the placebo combination group (36 vs. 18 %); however, survival in patients with skin symptoms was longer than in those without skin symptoms.

Cetuximab as a monotherapy is described. Vermorken et al. [12] reported that, in a phase II study of cetuximab monotherapy in CDDP-resistant patients, the response rate was 13 % and the tolerability was good.

Clinical study results of cetuximab in Japan

Studies in LA-SCCHN

CRT is the most effective treatment for unresectable LA-SCCHN, and its additional survival benefits compared with RT alone have been confirmed [13, 14]. In Japan, CDDP alone or PF therapy is frequently used as a regimen concomitantly with RT; recently, however, a study using cetuximab concomitantly with RT has been conducted in Japan as well. The results of this study have been published as summarized below.

A phase II study (053 study) using cetuximab [400 mg/m^2 (1st week), 250 mg/m^2 (2nd–7th week)] + RT [72.0 Gy (42 times, 6 weeks), simultaneous additional irradiation method] in 22 Japanese patients with LA-SCCHN was conducted, and tolerability (treatment completion rate), safety (adverse events), and efficacy (antitumor effects) were evaluated [15]. As a result, all 22 patients completed the study (treatment completion rate 100 %), and adverse events fell within the predicted range and were tolerable. The grade 3/4 adverse events included mucosal inflammation (16 cases 72.7 %), dermatitis (6 cases 27.8 %), infections (5 cases 22.7 %), stomatitis (5 cases 22.7 %), and radiation skin injury (5 cases 22.7 %). The response rate [complete response (CR) plus PR] at 8 weeks after the completion of the study was 81.8 %, and the efficacy and safety profiles in the Japanese patients were similar to those obtained in foreign phase III studies. Therefore, cetuximab + RT combination therapy is considered to be a well-tolerated, effective treatment for Japanese patients with recent onset of LA-SCCHN.

Studies in R/M-SCCHN

A phase II study of a weekly treatment with the combination of CDDP + 5-FU and cetuximab in 33 patients with R/M-SCCHN (056 study) was conducted in Japan as well, and the efficacy and safety [antitumor effects, efficacy persistence, PFS, and time to progression (TTP)] were evaluated [16]. The study was completed in December 2011. The best overall response rate was 36 % (95 % CI 20, 55), with a CR in one patient; three patients with stable disease according to modified WHO criteria were considered to have a PR according to RECIST (Response Evaluation Criteria In Solid Tumors). The median PFS was 4.1 (95 % CI 4.0, 5.5) months. The PFS rate was 70 % (95 % CI 53, 86) at 3 months and 23 % (95 % CI 7, 39) at 6 months. The median OS was 14.1 (95 % CI 10.2, 15.4) months. The OS rates at 3, 6, 9 and 12 months were 100, 85 (95 % CI 73, 97), 67 (95 % CI 51, 83) and 61 % (95 % CI 44, 77), respectively. The disease control rate was 88 %. The median duration of response [first assessment of CR or PR until progressive disease (PD)] was 2.8 (95 % CI 2.8, 5.5) months, with a median time-to-treatment failure of 4.2 (95 % CI 4.1, 5.6) months. There were no unexpected safety concerns. Grade 3 or 4 adverse events were experienced by nearly all patients (32, 97 %). No adverse events were fatal. The demonstrated efficacy and safety of cetuximab in combination with CDDP and 5-FU for the first-line treatment of Japanese patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck justify the further use of this combination treatment in this patient population.

The results of major clinical studies

The number of clinical studies of the multidisciplinary approach with cetuximab in patients with SCCHN reported or registered was 603 in PubMed (as of July 2012), 1,440 at ASCO meetings (by the end of 2012), and 203 on http://ClinicalTrials.gov.

Clinical studies in patients with LA-SCCHN (Tables 1, 2)

Combination with chemoradiotherapy

Bonner et al. [17] reported that the 5-year survival rate is improved when cetuximab is used in combination with RT. However, because the standard therapy for LA-SCCHN is not RT alone but CRT with CDDP, a large-scale clinical study (RTOG0522 study; planned to be completed in June 2014) to investigate additional survival benefits of the combination of cetuximab with CRT was started. The CRT (RT + CDDP) + cetuximab group (447 patients) and the CRT (RT + CDDP)-alone group (448 patients) are being compared. According to the interim report [18], the 2-year PFSs of the cetuximab combination group and the CRT-alone group were 63.4 and 64.3 % ($p = 0.67$), respectively, and their 2-year overall survival rates (OSs) were 82.6 and 79.7 % ($p = 0.17$), respectively. No significant differences were observed in either of the comparisons. No between-group differences in the incidence of grade 3 or higher adverse events were observed; however, the frequencies of grade 3/4 mucositis (45 vs. 35 %) and grade

Table 1 Clinical trials with cetuximab and radiotherapy for LA-SCCHN

	Phase	No. of patients	Regimen	Results			
				ORR	OS	PFS	
Combination with RT or CRT							
UAB-9901 [7, 17]	III	424	RT + CEX vs. RT		49.0 vs. 29.3 months[a] 3 years: 55 vs. 45 % 5 years: 45.6 vs. 36.4 %[a]	17.1 vs. 12.4 months[a] 2 years: 46 vs. 37 %	LRC 24.4 vs. 14.9 months[a]
RTOG 0522 [18]	III	895	RT + CDDP + CEX vs. RT + CDDP		2 years: 83 vs. 80 %	2 years: 63 vs. 64 %	
Combination with RT after ICT							
TREMPLIN [9]	II	116	RT + CEX vs. RT + CDDP after TPF		18 months: 86 vs. 85 %		18 months Larynx preserved: 82 vs. 86 %
H&N07 [20, 21]	II/III	413	RT + CDDP/5-FU vs. RT + CEX, RT + CDDP/5-FU vs. RT + CEX after TPF				Median dose of RT: 66 vs. 70 Gy[a] Median time of RT: 7.2 vs. 8.4 weeks[a] Completion rate: 91.3 vs. 78.2 %[a]
Combination with re-RT for local recurrence							
Balermpas et al. [37]	I	18	RT (IMRT) + CEX	47 %	Median: 8.38 months 1 year: 44%	Median 7.33 months	
Comet et al. [34]	I	40	RT (SBRT: 36 Gy; 6 Gy/fr), CEX/CDDP	79.40 % (CR 44.1 %)	Median: 13.6 months		
Combination with postoperative RT							
RTOG0234 [30]	II	203	CRT (RT + CDDP vs. RT + DTX) + CEX		2 years: 69 vs. 79 %		2 years DFS: 57 vs. 66 % 2 years distant: 26 vs. 13 %
Matuschek et al. [31]	II	80	CRT (RT + CDDP/5-FU) + CEX → CEX				CRT completion: 68.8 % CEX maintenance (6 months) completion: 48 %

RT radiotherapy, *ICT* induction chemotherapy, *CEX* cetuximab, *CDDP* cisplatin, *5-FU* 5-fluorouracil, *DTX* docetaxel, *TPF* DTX + CDDP + 5-FU, *IMRT* intensity modulated radiotherapy, *SBRT* stereotactic body radiotherapy, *OS* overall survival, *ORR* overall response rate, *CR* complete response, *LRC* locoregional control, *CRT* chemoradiotherapy, *PFS* progression-free survival, *DFS* disease-free survival

3/4 skin symptoms (40 vs. 17 %) were higher in the cetuximab combination group (the incidence rate of grade 3/4 dermatitis in the cetuximab combination group was 19 %).

Concomitant use in sequential chemoradiotherapy

Sequential CRTs in which ICT is performed before RT or CRT are described in the NCCN guidelines [5] and ESMO [8] guidelines. As for the ICT to be used, TPF (DTX + CDDP + 5-FU) is described as the first-line regimen. Because deterioration of renal function etc. can occur after CDDP-based ICT, such as TPF, use of CDDP again in the CRT is difficult and tolerability becomes a concern. For this reason, concomitant use of CBDCA or cetuximab is also described [5]. Although the antitumor effect of TPF therapy is high, its effect on survival is still unclear at the moment. However, in the ESMO guidelines, ICT is classified as the grade A recommendation for patients who want laryngeal preservation as with CRT and, therefore, often used especially in Europe. For this reason,

Table 2 Clinical trials of induction chemotherapy with cetuximab for LA-SCCHN

	Phase	No. of patients	Regimen	Results		
				ORR	OS	PFS
Kies et al. [24]	II	47	PCC followed by RT or CRT	96 % after ICT (CR 19 %)	3 years: 91 %	3 years: 87 %
Adkins et al. [27]	II	30	ACCF (nab-PTX + CEX + CDDP + 5FU) vs. TPF + CEX	After ICT: 100 vs. 83 % CR 53 vs. 27 %		
Combination with ICT and post-ICT						
Argiris et al. [25]	II	39	TPE (DTX + CDDP + CEX) → RT + CDDP + CEX(XPE) → CEX	After TPE 86.5 % after XPE 100 % (CR 24 %)	3 years: 74 %	3 years: 70 %
ECOG-E2303 [22, 23]	II	68	PCC → CRT (RT + PTX + CBDCA) + CEX	pCR 91 %	1 year: 97 % 2 years: 82 %	1 year: 82 % 2 years: 66 %
Suntharalingam et al. [26]	II	43	PCC → RT + CEX	After CRT CR 84 %	3 years: 59 %	3 years LRC: 72 % 3 yearrs DFS: 58 % 2 years local control: 83 %
Seiwert et al. [29]	II	110	PCC → RT + 5FU/HU + CEX/ RT + CDDP + CEX	After ICT 91.8%	1 year: 98.3 vs. 94.2 % 2 years: 89.5 vs. 91.4 %	1 year: 86.0 vs. 95.9 % 2 years: 82.3 vs. 89.7 %

RT radiotherapy, *ICT* induction chemotherapy, *CEX* cetuximab, *CDDP* cisplatin, *CBDCA* carboplatin, *5-FU* 5-fluorouracil, *DTX* docetaxel, *PTX* paclitaxel, *HU* hydroxyurea, *TPF* DTX + CDDP + 5-FU, *PCC* paclitaxel + carboplatin + CEX, *ACCF* nab-PTX + CET + CDDP + 5FU, *nab-RTX* nanoparticle albumin-bound pacritaxel, *TPE* dosetaxel + CDDP + CEX, *XPE* RT + CDDP + CEX, *OS* overall survival, *ORR* overall response rate, *CR* complete response, *pCR* pathological confirmed CR, *DCR* disease control rate, *LRC* locoregional control, *PFS* progression-free survival, *DFS* disease-free survival, *CRT* chemoradiotherapy, *LRC* locoregional control

efforts are being made actively to develop effective and safe regimens by using cetuximab in ICT or CRT following ICT; however, the combination regimen with RT following ICT has not been established at this point.

Efforts have been made to use cetuximab in combination with RT following ICT. The results of a phase II randomized control study (TREMPLIN study) [9] comparing CRT simultaneously using CDDP and cetuximab + RT after TPF as an ICT in patients with resectable laryngeal and hypopharyngeal cancer requiring total laryngectomy were reported. After 3 courses of TPF, the patients were assigned to total laryngectomy + postoperative irradiation if not responsive (<PR) or randomly assigned to CDDP + RT or cetuximab + RT if responsive (≥PR). One hundred and fifty-three patients with LA-SCCHN were treated with TPF as ICT, and then 116 responsive (≥PR) patients were treated with cetuximab + RT or CDDP + RT. This resulted in similar laryngeal preservation rates, survival rates, and locoregional control, while incidences of acute toxicity and late effects were more frequently observed in the RT + CDDP group than in the cetuximab + RT group. On the other hand, the local recurrence rate tended to be higher in the cetuximab combination group, although statistically non-significant (21.4 vs. 11.7 %, $p = 0.14$). In the cetuximab group, the ratio of patients in whom remedy procedures were safely and successfully performed was high; however, for patients wanting laryngeal preservation, a therapy with less local recurrence is more appropriate than a therapy in which remedy procedures are performed more safely. Regarding the concomitant use of RT following ICT, verification with a large-scale phase III study is warranted.

Jordan et al. [19] used cetuximab in combination with CRT (RT + CDDP) following TPF in 152 patients, where, in order to reduce toxicity, the usual dose of CDDP (75 or 80 mg/m^2) in TPF was reduced to less than half (35 mg/m^2) and the dose of CDDP in CRT was reduced to 40 mg/m^2. As a result, the response rate after TPF was 82 % (CR 22 %) and that after CRT was 89 % (CR 57 %); grade 3/4 adverse events after completing CRT were observed in 34 of 142 patients (24 %); and 15 patients were unable to complete CRT because of incidences of dermatitis, although the authors reported that the study was performed relatively safely on the whole. Ghi et al. [20] and Paccagnella et al. [21] are conducting phase II/III studies (H & N07 studies). In these studies, they have divided the patients into a total of 4 groups [2 groups in which CRT (RT + CDDP + 5-FU) or RT + cetuximab administration is performed after ICT (TPF therapy) and 2 groups in which CRT (RT + CDDP + 5-FU) or RT + cetuximab administration is performed without ICT] and are comparing the 4 groups regarding whether ICT (TPF therapy) has or has not been performed and also comparing the results of CRT and

RT + cetuximab regarding whether ICT has or has not been performed. According to the interim report, the treatment completion rate of the CRT (RT + CDDP + 5-FU) therapy group (91.3 %) was higher than that of the RT + cetuximab therapy group (78.2 %) ($p < 0.01$); no differences in the incidence rates of grade 3/4 adverse events in the irradiation field were observed. The studies to evaluate OS will continue, and the differences between the groups with and without ICT (TPF therapy) will be analyzed.

Results of studies investigating concomitant use of cetuximab with TP (DTX + CDDP), TPF (DTX + CDDP + 5-FU), or PF (CDDP + 5-FU) were reported. For concomitant use with TP, Wanebo et al. [22, 23] used cetuximab in CRT after ICT as well. They reported as follows: the clinically evaluated complete response (cCR) rate after ICT was 65 % (41/63); based on the biopsy findings, the pathologically confirmed complete response (pCR) rate after ICT was 38 % (24/63); the pCR rate after completion of CRT was 90 % (57/63); the 2-year PFS was 66 %; and the 2-year OS was 82 % (ECOG-E2303 study). According to later studies by Kies et al. [24] (RT or surgery after ICT), Argiris et al. [25] (concomitant use also after ICT and additional maintenance therapy with cetuximab), and Suntharalingam et al. [26] (cetuximab + RT after ICT), the response rate after ICT was about 87 %, the 3-year PFS was 58–87 %, and the 3-year OS was 59–91 %.

For concomitant use with TPF, Adkins et al. [27] used cetuximab in combination with ICT [nab-paclitaxel (PTX) + CDDP + 5-FU] and compared the results with those of their past study (TPF + cetuximab therapy). The result showed that the response rate after ICT was 100 % (CR 53 %, PR 47 %), which was comparable or superior to their previous results (response rate 83 %, CR 27 %, PR 56 %).

For concomitant use with PF, D'Angelillo et al. [28] used cetuximab concomitantly with ICT (CDDP + 5-FU) and then performed RT + cetuximab after ICT. They reported that the response rate after ICT was 89.4 % and the CR rate after the median follow-up period of 13 months was 73.7 %, and that safety was higher than with the DTX-based TPF regimen.

A combination regimen with CRT after ICT with concomitant cetuximab was reported by Seiwert et al. [29]. After CBDCA + PTX + cetuximab treatment as an ICT, they compared concomitant cetuximab therapies with 2 types of CRT with different chemotherapeutic regimens in 110 patients with LA-SCCHN. The locoregional control rate after ICT was 91.8 %. The 2-year OSs of the RT + 5-FU/hydroxyurea (HU) + cetuximab (CetuxFHX) group and the RT + CDDP + cetuximab (CetuxPX) group were 89.5 and 91.4 %, respectively, and their 2-year PFSs were 82.3 and 89.7 %, respectively. The incidence rates of grade 3 or higher mucositis of the CetuxFHX group and the CetuxPX group were 91.9 and 94.3 %, respectively, and those of dermatitis were 82.1 and 50.9 %, respectively. Comparable efficacy and safety were observed in both groups, suggesting that 5-FU/HU and CDDP are interchangeable. However, the significance for the concomitant use of cetuximab in CRT is still unclear and warrants further clinical study data.

Concomitant use with postoperative RT

With regard to concomitant use with postoperative RT in resectable cases, Kies et al. [30] compared the effects of the postoperative CRTs [RT + cetuximab + CDDP group (group A) or RT + cetuximab + DTX group (group B)] with those of a past study [the results of the CRT group of RT + CDDP therapy (RTOG9501 study)]. The results showed that the 2-year OSs of group A and group B were 69 and 79 %, respectively, and that the 2-year disease-free survival rates (DFSs) of the same groups were 57 and 66 %, respectively. The DFS of group B was significantly improved compared with the previous result ($p = 0.031$), indicating that 2-year DFS was improved 11 % by RT + cetuximab + DTX combination therapy compared with RT + CDDP (RTOG0234 study: NCT00084318). Later, Matuschek et al. [31] and Benezery et al. [32] also examined the concomitant use of cetuximab with postoperative CRT and reported that the combination therapy was effective and safe.

Cetuximab is also used concomitantly at the time of retreatment with RT for locally recurrent unresectable cases, and combined use with intensity modulated radiotherapy [33] or with stereotactic body radiotherapy (SBRT) [34, 35] has been reported. It has also been reported that combination therapy with cetuximab is less toxic than conventional CRT [36, 37], and that the combination of cetuximab with short-term SBRT is an effective salvage therapy [38].

Maintenance therapy

Ferris et al. [38] used cetuximab concomitantly with CRT (RT + CDDP) after ICT (CDDP + DTX + cetuximab), performed 6 months of maintenance therapy with cetuximab thereafter, and obtained a 3-year PFS of 67 % as a result. Mesia et al. [39, 40] compared the cetuximab + RT group (group A) with the group in which maintenance therapy (12 weeks) was performed after cetuximab + RT (group B). The CR rate of group A was 55.6 %, and that of group B (after 12 weeks) was 69.6 %. Other results of group A and group B after 1 year were 56.8 and 60.5 % for locoregional control rate, 55.6 and 60.9 % for event-free survival, and 75.6 and 87 % for OS, respectively.

Ongoing or planned clinical studies

Many large-scale comparative studies are being planned or conducted in the world, and most protocols, including those of the US, have adopted sequential CRT in which ICT is performed before CRT. Planned studies in the US include studies of concomitant use of cetuximab with postoperative RT in high-risk, postoperative patients (target number of patients 700) and studies in human papillomavirus (HPV)-positive patients.

To examine the possibility of laryngeal preservation, Lefebvre et al. [41] investigated the effects on survival in patients who received total surgical resection of the affected area and those who received CT (CDDP + 5-FU), and performed a 10-year follow-up of the EORTC-24891 study in patients with hypopharyngeal squamous cell carcinoma (SCC). Among the 194 evaluable patients, transitions to PD of the surgery group (94 patients) and the CT (ICT) group (100 patients) were observed in 54 patients and 49 patients, respectively. Similarly, deaths were observed in 81 patients and 83 patients; the 10-year OSs were 13.8 and 13.1 %; and 10-year PFSs were 8.5 and 10.8 %; respectively. The rate of preservation of laryngeal function for 10 years in the CT group was 8.7 %. In other words, it was revealed that the prognoses were comparable in both treatment groups and that laryngeal function was preserved in more than half of the survivors after CT. This suggests that, even in operable patients, multidisciplinary treatment aiming at preserving laryngeal function, especially drug therapy with CRT and cetuximab etc., will be positioned as an important method for LA-SCCHN treatment in the future.

Treatment of R/M-SCCHN

Primary therapies (Table 3)

The usefulness of cetuximab in prognosis has been shown by phase III studies in R/M patients, such as the EXTREME study by Vermorken et al. [10] and the ECOG-E5397 study by Burtness et al. [11], and thus cetuximab has been positioned as a primary therapy for R/M patients. Following these studies, Mesía et al. [42] investigated the effect on quality of life (QOL) in the subanalysis of the EXTREME study, and reported that the CDDP + 5-FU + cetuximab combination group was superior to the CDDP + 5-FU group in some evaluation items (pain, swallowing, conversation, and dietary habits).

Regimens that do not use drugs containing platinum (Pt) in patients contraindicated for Pt have been investigated. Hitt et al. [43] examined the combination with taxanes in 46 patients and reported that weekly administration of PTX + cetuximab gave the following results: response rate, 54 % (CR rate 22 %); disease control rate, 80 %; and median PFS and OS, 4.2 and 8.1 months, respectively. Guigay et al. [44, 45] also investigated a regimen in which cetuximab was administered as a maintenance therapy after treatment with DTX + CDDP + cetuximab (in which 5-FU had been replaced by a taxane) as a possible alternative regimen.

Secondary (and succeeding) therapies (Table 4)

Regarding patients non-responsive to Pt, Baselga et al. [46] and Herbst et al. [47] reported on the significance of Pt + cetuximab as a secondary therapy, and Péron et al. [48]

Table 3 Clinical trials of first-line treatment with cetuximab for R/M-SCCHN

	Phase	No. of patients	Regimen	Results			
				ORR	OS	PFS	
ECOG-E5397 [11]	III	117	CDDP + CEX vs. CDDP	26 vs. 10 %[a]	9.2 vs. 8.0 months 2 years: 15.8 vs. 9.4 %	4.2 vs. 2.7 months	
EXTREME [10]	III	442	Pt + 5-FU + CEX vs. Pt + 5-FU	36 vs. 20 %[a]	10.1 vs. 7.4 months[a]	5.6 vs. 3.3 months[a]	
Mesia et al. [43]	III	291	Pt + 5-FU + CEX vs. Pt + 5-FU				Pt + 5-FU + CEX: better for functional QOL
Hitt et al. [44]	II	46	PTX + CEX	54 %	8.1 months	4.2 months	DCR: 80 %
GORTEC2008-03 [45, 46]	II	54	DTX + CDDP + CEX → CEX	BestORR: 54 %	15.3 months	7.1 months after maintenance: 4.2 months	

Pt platinum, *CEX* cetuximab, *CDDP* cisplatin, *DTX* docetaxel, *PTX* paclitaxel, *ORR* overall response rate, *OS* overall survival, *PFS* progression-free survival, *DCR* disease control rate, *QOL* quality of life, *5-FU* 5-fluorouracil

[a] Statistically significant

Table 4 Clinical trials of second-line treatment with cetuximab after initial treatment for R/M-SCCHN

	Phase	No. of patients	Regimen	Results			
				ORR	OS	PFS	
Baselga et al. [47]	II	96	Pt + CEX	10 %	183 days		DCR: 53 %TTP: 85 days
Herbstet al. [48]	II	131	Pt + CEX	13.10 %	SD/PD/PD 6.1/ 4.3/ 11.7 months		Duration: SD/PD/PD 4.2/4.1/7.4 months
Vermorken et al. [12]	II	103	CEX; PD → CEX + Pt		178 days		CEX phase: DCR: 46 %, TTP: 70 days CEX + Pt phase: DCR: 26 %, TTP: 50 days
Massaet al. [51]	II	24	VNR + CEX			5.8 months	DCR: 69.5 % duration:5.2 months
Fury et al. [50]	II	26	CEX: 500 or 750/mg/m^2 bi-weekly	11 vs. 11 %	Total: 8.1 months	65 vs. 57 days	
Peron et al. [49]	II	42	PTX + CEX	38 %	7.6 months	3.9 months	DCR: 74 %

Pt platinum, *CEX* cetuximab, *PTX* paclitaxel, *VNR* vinorelbine, *ORR* overall response rate, *OS* overall survival, *PFS* progression-free survival, *DCR* disease control rate, *TTP* median time to progression, *SD* stable disease, *PD* progressive disease

reported that the combination of PTX and cetuximab exhibits good efficacy and tolerability. Vermorken et al. [12] and Fury et al. [49] examined the efficacy of cetuximab alone and reported that doses at 250/400–500 mg/m^2 can be administered without a problem. Massa et al. [50] examined the effect of the combination of vinorelbine and cetuximab, and reported that it exhibited good tolerability.

Other ongoing or planned clinical studies with cetuximab

Many new regimens aiming at enhancing the efficacy of cetuximab or overcoming resistance to cetuximab are being studied. Enhanced efficacy by combining it with tyrosine kinase inhibitors [51, 52], recovery of sensitivity of the SCCHN cell line to cetuximab [53], etc. have been observed in non-clinical studies, and clinical studies investigating combination regimens with other molecularly targeted drugs, such as tyrosine kinases inhibitors, are underway.

Because the upregulation of vascular endothelial growth factor (VEGF) is associated with tolerance to EGFR inhibitors, Argiris et al. [54] conducted a phase II clinical study of the combination of anti-VEGF monoclonal antibody bevacizumab and cetuximab, and they reported that the study of R/M-SCCHN in previously treated patients resulted in a PR rate of 18 %, a median PFS of 2.8 months, and a median OS of 7.6 months, and that the treatment was effective and well tolerated. Vermorken et al. [55] investigated the additional benefits of cilengitide, a selective integrin inhibitor, because αvβ5 integrin is overexpressed in SCCHN. A combination of PFE (CDDP + 5-FU + cetuximab) and once- and twice-weekly cilengitide was compared with PFE alone in patients with R/M-SCCHN. The results of the PFE alone and the once- and twice-weekly cilengitide were as follows: median PFS, 5.7, 6.4, and 5.6 months, respectively; median OS, 11.6, 12.4, and 10.6 months, respectively; and response rates, 35.5, 46.8, and 26.7 %, respectively. Safety results were comparable among these groups. Based on these results, they reported that the combination group did not have merits over the PFE alone in PFS (ADVANTAGE study). Chung et al. [56] considered that activation of the AKT/mTOR pathway was important for the mechanism of EGFR inhibition in SCCHN, and examined the effect of concomitant use of the everolimus, a selective inhibitor of mTOR, with CDDP + cetuximab, in an attempt to overcome resistance to cetuximab, an inhibitor of EGFR due to mTOR inhibition. They examined the maximum tolerated dose of everolimus when used in combination with CDDP + cetuximab in patients with R/M-SCCHN. However, because toxicity was observed even with the lowest everolimus dose (2.5 mg) group, they reported that care should be taken when using the combination of CDDP + cetuximab + everolimus in patients with R/M-SCCHN.

Conclusions

The multidisciplinary treatment has been developing over many clinical trials. CRT, proven standard treatment for advanced head and neck cancer, improves the prognosis and locoregional control of LA-SCCHN and also improves functional preservation, such as laryngeal preservation compared with RT alone. However, late toxicities of chemotherapeutic drugs plus RT are of great concern for long survival. Effective treatments with low toxicities are

focused on multidisciplinary treatment. Many of the clinical studies in this review are still insufficient to confirm the evidence. However, combinations with molecular targeted drugs will play the key role in head and neck cancer treatments for next decade.

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