Cetuximab and Radiotherapy Versus Cisplatin and Radiotherapy for Locally Advanced Head and Neck Cancer: A Randomized Phase II Trial

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Abstract

Purpose

No randomized trials have been conducted to directly compare radiotherapy (RT) with concomitant cisplatin (CDDP) versus concomitant cetuximab (CTX) as first-line treatment of locally advanced squamous cell carcinoma of the head and neck. In this randomized trial, we compared these two treatment regimens in terms of compliance, toxicity, and efficacy.

Patients and Methods

Eligible patients were randomly assigned in a 1:1 ratio to receive either CDDP 40 mg/m2 once per Week or CTX 400 mg/m2 as loading dose followed by CTX 250 mg/m2 once per week concomitant to radical RT. For primary end points, compliance to treatment was defined as number of days of treatment discontinuation and drug dosage reduction. The acute toxicity rate was defined according to the National Cancer Institute Common Toxicity Criteria. Efficacy endpoints were local recurrence-free survival, metastasis-free survival, cancer-specific survival, and overall survival.

Results

The study was discontinued early because of slow accrual after the enrollment of 70 patients. RT discontinuation for more than10 days occurred in13% of patients given CTX and 0% given CDDP (P= .05). Drug dosage reduction occurred in 34% given CTX and 53% given CDDP (difference not sig-nificant). Toxicity profiles differed between the two arms, with hematologic, renal, and GI toxicities more frequent in the CDDP arm, and cutaneous toxicity and the need for nutritional support more frequent inthe CTX arm. Serious adverse events related to treatment, including four versus one toxic deaths, were higher in the CTX arm (19%v 3%,P=.044). Locoregionalcontrol, patterns of failure,and survivals were similar between the treatment arms.

Conclusion

CTX concomitant to RT lowered compliance and increased acute toxicity rates. Efficacy outcomes were similar in both arms.These results raise the issue of appropriately selecting patients with head and neck cancer who can benefit from CTX in combination with RT.

Introduction

The established standard treatment of patients with locoregionally advanced squamous cell carcinoma of the head and neck (LASCCHN) is chemo-radiotherapy with concomitant cisplatin (CDDP).[1] Several schedules of CDDP-based chemotherapy have beenproposed.

Bolus CDDP 100 mg/m^2 given every 3 weeks is the reference schedule.[2] However, it is associated with toxicity rates higher than that of radiation alone, and it is frequently with held from the therapeutic strategy in elderly people or in patients with poor performance status and comorbidities.[3,4] To reduce toxicity without affecting effectiveness, alternative CDDP schedules have been proposed. A feasible alternative regimen is represented by CDDP 40 mg/m^2 once per week concurrent with radiotherapy (RT),[5] which is routinely used outside of randomized clinical trials. In 2006, Bonner et al6 published preliminary results of a randomized trial in which they compared RT alone with RTplus cetuximab (CTX)for LASCCHN. They reported a 13% absolute improvement in locoregional control and a 10% absolute improvement in 3-year survival, with minimal increase in toxicity.6,7 As a consequence, CTX has increasingly been used in the treatment of patients with LASCCHN, particularly for those patients whose condition is clinically unfit for CDDP chemotherapy.3,8 Despite such recommendations, a direct com parison between concomitant CDDP and RTand

concomitant CTX and RT is lacking, particularly one to address the issue of toxicity andtolerability. Inthe5-yearupdate ofthestudybyBonneretal,7 a subgroup analysis demonstrated that the benefit of CTX was more evident for patients younger than 65 years old with a good Kar-nofsky performance status of 90% to 100%, who represent a minority of those with LASCCHN. In the updated conclusions, the authors focused on the need for a randomized trial to compare quality of life and effectiveness with CTX plus RT versus che-moradiotherapy.7 Therefore, we conceived and initiated a non-profit, multi-institutional, prospective, open-label, randomized trial designed to compare these two treatment regimens in terms of compliance, toxicity, and efficacy. The Ethical Committee of each participating institution approved the protocol and the study was activated in October 2010 (EudraCT number 2010-021552-26). This trial was also registered at ClinicalTrials.gov as NCT01216020.

Patients and methods

Eligibility criteria included an age of 18 years or older; histologically confirmed diagnosis of stage III (excluding T1N1), IVA, or IVB squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or supraglottic larynx; Eastern Cooperative Oncology Group performance status of 0 or 1; and adequate hematologic, hepatic, and renal function. Exclusion criteria included pregnancy or lactation status, unrelated malignancy within the previous 3 years, or serious comorbidities that could preclude the administration of therapy according to the protocol (Data Supplement). Patients who met the inclusion criteria were asked to provide written informed consent, and they were subsequently randomly assigned to receive RT plus CDDP in the CDDParm or RT plus CTX in the CTX arm.

Staging at Baseline and During Follow-Up

Patients were examined at baseline with magnetic resonance imaging or computed tomography (CT) and with ultrasonography of the head and neck. The same radiographic assessments were repeated during follow-up every 4 months in the first 2 years after the end of treatment (EOT), then once a year until the fifth year of follow-up. Avisit with both the radiation oncologist and an otolaryngologist was done at baseline; weekly ears, nose, and throat examinations during treatment were performed by the radi-ation oncologist in charge of

the patient; during follow-up, visits with both the radiation oncologist and the otolaryngologist were done. Radiologic assessment was anticipated if progression was suspected during follow-up. Radiologic assessments were not centrally reviewed. Similarly, baseline and follow-up visits were performed at each participating institution. A positron emission tomographic–CT scan or CT scan of the chest and the abdomen was required in the study protocol at baseline to exclude distant metastases. Systemic radiologic restaging was also performed once a year during follow-up.

Treatment

Radiation therapy (RT). A dose of 70 Gy with conventional frac-tionation of 2Gy per fraction was prescribed to the tumor and the involved lymph nodes; a dose of 50 Gy was prescribed to the remaining uninvolved neck levels. Three-dimensional conformal RT, intensity-modulated RT (IMRT), IMRT with a simultaneous integrated boost, or helical IMRT were permitted. In the case of treatment planned with a simultaneous integrated boost, slight variations in the number of fractions, total dose, and dose per fraction were allowed, with doses equivalent to normofractionation.

Medical treatment

CTX was administered according to what Bonner et al7 described in their study at a loading dose of 400 mg/m2 given intravenously (IV)a week before the startof RTand then onceper week for the duration of RT at a dose of 250 mg/m2 IV. CDDP was started simultaneously with RTat an dose of 40 mg/m2 IVonce per week for the duration of RT.5 CDDP and CTX dosage modifications and discontinuations were defined in the study protocol on the basis of hematologic, renal, cutaneous, and mucosal toxicities.

Study Design, End Point Definition, and Statistical Considerations

This was a phase II, multicenter, open-label, randomized trial to evaluate two regimens routinely used in clinical practice. The primary end point of the study was compliance and toxicity of the two treatment regimens. Treatment compliance was analyzed on the basis of breaks in RT recorded in days, percentage of drug dosage reductions, incidence and grade of drug-related adverse events (AEs), and percentage of treatment discontinuation. Toxicities,

including radiation dermatitis and acneiform rash, were graded by using the National Cancer Institute Common Toxicity Criteria scale version 4.0. If the grade was discordant, the higher one was chosen. Toxicities were assessed at specific time points: end of treatment, 30 days, 60 days, 3 to 4 months, and 6 months. Secondary end points to investigate effectiveness were 1- and 2-year local control (LC), metastasis-freesurvival (MFS), cancer-specific survival (CSS) and overall survival (OS). LC was calculated from the end of RTuntil the date of first evidence of local recurrence. MFS, CSS, and OS were calculated from the end of RTuntil the date of first evidence of metastatic disease, death from head and neck cancer, and any cause of death or date of the follow-up, respectively.

The sample-size calculation was based on compliance rate. At the time of study design, the compliance rate of concurrent CDDP and CTX were reported to be 71% and 90%, respectively.6,9 Therefore, we calculated that 65 patients per treatment arm would provide the study with a 80% power, or b, to detect a 20% difference in compliance by using a two-sided x2 test with a 5% significance level, or a. The randomization procedure, which was done with a 1:1 ratio, was centralized and managed at the institution of the scientific coordinator. Continuous data values were described by using median, mini-mum, and maximum values or the median and 25th to 75th inter-quartile range. The interarm differences were assessed using a Pearson's x2 test for categorical variables or by means of an analysis of variance for continuous variables. Kaplan-Meier survival analysis was used to estimate survival end points, and the log-rank test was used to compare differences between curves. All tests are two-sided, and a P ,.05 was considered to indicate a statistically significant difference. Statistical analysis was performed with the SPSS software (version 17.0; SPSS, Chicago, IL).

Results

Between January 2011 and August 2014, 70 patients were enrolled across six sites in Italy, 35 for each treatment arm. Recruitment was discontinued early because of slow accrual. Table 1 delineates patient and tumor characteristics at baseline. Patients were well balanced between the treatment arms, and no differences were found apart from a significant increase in alcohol consumption in the CTX arm (P = .031). Figure 1 illustrates the CONSORT flow diagram of the study. Of the 70 initially enrolled patients, 66 received treatment and four were excluded.

Table 2 summarizes the RT technique, delivered dose, and numberof concurrent CTXor CDDP cycles, whichwere not significantly different.

At the time of analysis in January 2015, median follow-up was 19.3 months (range, 0 to 48 months) for patients treated with CTX and 20.6 months (range, 0 to 39 months) for patients treated with CDDP.

Treatment Compliance

Four patients in the CTX arm versus none in the CDDP arm had a break of more than 10 days in RT (P = .05). Drug dosage reduction and drug discontinuation were not statistically different between the treatment arms.

Three patients in the CTX arm (9%) had an adverse reaction at the first infusion and were excluded from the study versus none in the CDDP arm. Two had a G3 mucositis with associated severe dysphagia; the remaining two had a severe G3 or G4 cutaneous reaction. One of these patients also had an intestinal perforation, and two more were treated for infectious complications and died from septic shock after the EOT.

Median weight losses was similar: 7% (range, 0% to 22%) in the CTX arm and 8% (range, 0% to 16%) in the CDDP arm. Patients treated with CTX needed more nutritional support during treatment (P = .032).

Acute Toxicity

Table 3 displays the toxicity scores at the EOT.

Severe cutaneous toxicity of G3 or worse was more common in the CTX arm. Patients in the CDDP arm had hematologic toxicity more frequently (G3 in five cases) than the other arm, but two episodes of G3 hematologic toxicity also occurred in the CTX arm.

No differences between thet wo treatment arms were observed in terms of mucositis. Rates of G3 events were 59% in the CTX arm and 53% in the CDDP arm.

During treatment, four patients treated with CTX developed infectious complications that evolved into septic shock later on. One patient survived, whereas three died between 18 and 100 days after the EOT.An additional patient in the CTX arm died a few days after the EOT from respiratory failure caused by aspiration pneumonia. One patient in the CDDP arm and one in the CTX arm had an intestinal perforation at the EOT and during treatment, respectively. The

patient treated with CTX survived, whereas the patient in the CDDP arm died 20 days after the EOT.

Figure 2 depicts data for the resolution of acute toxicity over time. Patients treated with CDDP lost additional weight over time after the EOT, whereas patients in the CTX arm progressively gained weight during the 6 months after the end of RT. This difference became more evident at 3 to 4 months and at 6 months (P = .009 and P = .003, respectively). Feeding-tube dependency remained similar between the treatment arms, with rates decreasing over time. Rate of feeding-tube dependency at 6months in the entire population was 11%.

More patients in the CDDP arm had hematologic (P ,.001), renal (P= .033), and GI (P= .036) toxicityof any grade at the EOT. The hematologic toxicity took longer to resolve in the CDDP arm and was reported in 8% and 3% of patients screened at 3 to 4 months and at 6 months, respectively.

Compared with patients in the CDDP arm, patients in the CTX arm needed more time to recover from cutaneous and mucosal toxicity, with higher rates of persistent toxicity at 1 month after the EOT (P = .001 and P = .039, respectively).

No differences in acute toxicity and local tumor control rates were found according to RT technique.

Patterns of Failure: LC and MFS

Respective 1- and 2-year LC rates were 64% and 53% in the CTX arm and 84% and 80% in the CDDP arm (P = .073). Respective 1- and 2-year MFS rates were 97% in the CTX arm and 90% in the CDDP arm. Median LC and MFS were not reached. Table 4 and Appendix (online only) provide data for disease pro-gression sites and the treatment given, whereas Figures 3A and 3B, depict the LC and MFS survival functions.

Survival Rates: OS and CSS

Respective 1- and 2-year OS rates were 75% and 68% in the CTXarm and 78%intheCDDParm. Respective1-and 2-yearCSS rates were 75% and 68% in the CTX arm and 81% in the CDDP arm. Median OS and CSS were not reached. Figures 3C and 3D, depict the OS and CSS survival functions.

Among patients who did not die from disease progression, four patients in the CTX arm and one patient in the CDDP arm diedfromAEspossibly relatedtotreatment, whereas onepatientin theCDDParm died the last dayof radiochemotherapy fromcauses related neither to the treatment nor to the head and neck cancer; the cause was stroke.

Discussion

To our knowledge, no published randomized trial has been conducted to directly compare the combination of CTX plus RT with concurrent chemoradiation, and data are derived only from retrospective series. Unfortunately, results from these studies are in most cases neither concordant nor comparable. The group from the Memorial Sloan-Kettering Cancer Center reported the results of a retrospective study in which it compared CDDP and CTX given concurrently with radiation for LAHNSCC. Their data showed worse locoregional control, failure-free survival, and OS in patients treated with CTX.10 The same group confirmed in a subsequent retrospective analysis the worse survival outcome of concurrent CTX compared with both concurrent CDDP or concurrent carboplatin plus fluorouracil,11 concluding that the routine use of CTX in the management of LAHNSCC should be considered cautiously. Although other retrospective series12,13 demonstrated similar results with improved survival outcomes in patients treated with standard concurrent chemotherapy, all of these analyses are admittedly flawed by the limitations deriving from their retrospective nature and by biases in patient selection and baseline characteristics. In fact, patients in the CTX arms were morelikelyolderand hadpoorer performance status, becauseCTX was often used in patients who were ineligible for standard con-current chemotherapy. In our analysis, patients and tumor characteristicsatbaselinewerewellbalancedand, withthelimits of a sample smaller than hypothesized, no statistically significant differences were detected in terms of LC, MFS, CSS, or OS. Even if survival was not a primary end point of our analysis, it should be noted that the Kaplan-Meier curves for LC, OS, and CSS main-tained a consistent separation in favor of the CDDP arm, whereas the Kaplan-Meier curve for MFS was in favor of the CTX arm. In a subgroup analysis of patients with oropharyngeal and oral cavity tumors (21 in the CDDP arm and 22 in the CTX arm) in which pretreatment characteristics were well balanced, LC, CSS, and OS rates were higher in patients treated with CDDP (P= .029, P= .015, and P = .049, respectively). In this group of patients, no other differences in terms of treatment compliance

and rates of toxicity of G3 or greater were observed. Changes in the significance of the results could, therefore, be possible in future updates with longer follow-up.

As previously reported in literature, the incidence of CTX hypersensitivity infusion reactions could be high,14,15 and the overall rate of a grade 3 or 4 reaction can reach 22%.16 Fatal events related to infusion have also been documented.17 In our series, 9% of patients in the CTX arm had an infusion reaction during administration of the loading dose. All of these patients were subsequently treated with other regimens outside of the clinical trial.

Although initially thought to have limited AEs,biologic agents have been shown to have a potential for causing adverse drug reactions, including effects on peripheral blood cell counts.18 Increased risks of grade 3 leucopenia and/or neutropenia and anemia events have been reported in patients treated with CTX plus standard chemotherapeutic agents.19 In contrast with the results of the study by Bonner et al,6,7 results from other studies suggest an overall increase in local and systemic toxicity.20 It must be noted that not all the patients in the CTX arm who had septic shock, presented with leucopenia, anemia, or thrombocytopenia and that the etiology of these fatalevents could be multifactorial.In a review by Numico et al21 it was hypothesized that some patients may be more susceptible to severe reactions such as organ failure, septic shock, or cardiac events. Treatment features and patient characteristics suchas age, weight loss, and comorbidityc ontribute to patient frailty that possibly leads to systemic inflammatory response syndrome. In our series, one of the three patients in the CTX arm who died from septic shock had G3 leucopenia, and another had G4 leucopenia and G3 anemia and thrombocytopenia. On the contrary, none of the patients in the CTX arm who did not develop a fatal event presented with hematologic toxicity of any grade (P = .03). In addition, three of the six patients in the CTX arm who developed fatal and/or severe events possibly related to treatment were also the ones who had an interruption of longer than 10 days in their course of RT. Long delays in completing the course of RT, which results in low treatment compliance,have been reported in other series20,22 and may reduce LC, possibly with an effect on survival.23,24

In summary, the incidence of both the infusion reactions and of the other severe AEs does not allow to consider CTX a safer and easy-to-use alternative to standard chemotherapy regimens. In our experience in this clinical setting, also in patients not enrolled this clinical trial, CTX toxicity remains an issue and after the start of the trial, other papers reported treatment-related severe complications (including sepsis and pulmonary complications) and deaths.25,26 This

has been also the object of a recent debate in the literature.27,28 Results of the much larger RTOG 1016 trial conducted to determine whether substitution of CDDP with CTX would result in comparable 5-year OS rates in human papillomavirus– associated oropharyngeal cancer is currently closed to accrual. Its results will probably answer some of these questions. Also, the De-ESCALaTE trial in which investigators are comparing concurrent CTX and concurrent CDDP in terms of early- and late-toxicity events is likewise addressing human papillomavirus–positive oropharyngeal squamous cell carcinoma. Its findings will hopefully provide further insight into the toxicity issue.

For LAHNSCC, biomarkers for the prediction of an improved response to CTX are also lacking. In the metastatic setting, neither epidermal growth factor receptor (EGFR) overexpression nor EGFR gene copy number were predictive of response to CTX treatment.29 Analysis of circulating tumor cells with EGFR char-acterization could possibly address this problem; it represents a method to explain different CTX response rates, but data available are, so far, insufficient.30,31

In conclusion, CTX and CDDP have different mechanisms of action and can lead to different profiles of tolerability and toxicity. In our series, CTX used concurrently with RT showed results comparable to those of the standard CDDP-RT combination in terms of survival, locoregional control, and metastatic progression. However, a subgroup analysis of oropharyngeal and oral cavity tumors showed improvedLC, CSS, and OS outcomes in the CDDP arm. The relatively high rates of infusion reactions and early death after CTX cannot be neglected. Therefore, the toxicity profile of this monoclonal antibody should be further studied. Results from other larger, prospective randomized trials are strongly needed, as well as studies to investigate bio mechanisms possibly related to systemic severe toxicity and response. The goal is to improve the selection of patients who can benefit from the CTX-RT combination.

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Final approval of manuscript: All authors

References

1. Pignon ˆJP, le Maıtre A, Maillard E, et al: MACH-NC Collaborative Group: Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update on 93 randomised trials and 17,346 patients. Radiother Oncol 92:4-14, 2009

2. Adelstein DJ, Li Y, Adams GL, et al: An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemo-radiotherapy in patients withunresectable squamous cell head neck cancer. J Clin Oncol 21:92-98, 2003

3. Harari PM, Ritter MA, Petereit DG, et al: Chemoradiation for upper aerodigestive tract cancer: Balancing evidence from clinical trials with individual patient recommendations. Curr Probl Cancer 28: 7-40, 2004

4. Trotti A, Bellm LA, Epstein JB, et al: Mucositis incidence, severity and associated outcomes in patients with head and neck cancer receiving radio-therapy with or without chemotherapy:
A systematic literature review. Radiother Oncol 66:253-262, 2003

5. Ho KF, Swindell R, Brammer CV: Dose intensity comparison between weekly and 3-weekly cisplatin delivered concurrently with radical radio-therapy for head and neck cancer: A retrospective comparison from New Cross Hospital, Wolver-
hampton, UK. Acta Oncol 47:1513-1518, 2008

6. Bonner JA, Harari PM, Giralt J, et al: Radio-therapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med 354:567-578, 2006

7. Bonner JA, Harari PM, Giralt J, et al: Radio-therapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival. Lancet Oncol 11:21-28, 2010

8. Garden AS, Asper JA, Morrison WH, et al: Is concurrent chemoradiation the treatment of choice for all patients with stage III or IV head and neck carcinoma? Cancer 100:1171-1178, 2004

9. Huguenin P, Beer KT, Allal A, et al: Con-comitant cisplatin significantly improves locoregional control in advanced head and neck cancers treated with hyperfractionated radiotherapy. J Clin Oncol 22: 4665-4673, 2004

10. Koutcher L, Sherman E, Fury M, et al: Con-current cisplatin and radiation versus cetuximab and radiation for locally advanced head-and-neck cancer. Int J Radiat Oncol Biol Phys 81:915-922, 2011

11. Shapiro LQ, Sherman EJ, Riaz N, et al: Efficacy of concurrent cetuximab vs. 5-fluorouracil/carboplatin or high-dose cisplatin with intensity-modulated radi-ation therapy (IMRT) for locally-advanced head and neck cancer (LAHNSCC). Oral Oncol 50:947-955, 2014

12. Ye AY, Hay JH, Laskin JJ, et al: Toxicity and outcomes in combined modality treatment of head and neck squamous cell carcinoma: Cisplatin versus cetuximab. J Cancer Res Ther 9:607-612, 2013

13. Ley J, Mehan P, Wildes TM, et al: Cisplatin versus cetuximab given concurrently with definitive radiation therapy for locally advanced head and neck squamous cell carcinoma. Oncology 85:290-296, 2013

14. Keating K, Walko C, Stephenson B, et al: Incidence of cetuximab-related infusion reactions in oncology patients treated at the University of North Carolina Cancer Hospital. J Oncol Pharm Pract 20: 409-416, 2014

15. Hopps S, Medina P, Pant S, et al: Cetuximab hypersensitivity infusion reactions: Incidence and risk factors. J Oncol Pharm Pract 19:222-227, 2013

16. O'Neil BH, Allen R, Spigel DR, et al: High incidence of cetuximab-related infusion reactions in Tennessee and North Carolina and the association with atopic history. Presented at the 43rd Annual Meeting of the American Society of Clinical Oncol-ogy, Chicago, IL, June 2-5, 2007

17. Grandvuillemin A, Disson-Dautriche A, Mir-emont-Salame G, et al: Reseau des Centres Regionaux de Pharmacovigilance Français: Cetux-imab infusion reactions: French pharmacovigilance database analysis. J Oncol Pharm Pract 19:130-137, 2013

18. Everds NE, Tarrant JM: Unexpected hema-tologic effects of biotherapeutics in non clinical species and in humans. Toxicol Pathol 41:280-302, 2013 19. Cui R, Chu L, Liu ZQ, et al: Hematologic tox-icity assessment in solid tumor patients treated with cetuximab: A pooled analysis of 18 randomized controlled trials. Int J Cancer 136:936-944, 2015

20. 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 32:2940-2950, 2014

21. Numico G, Franco P, Cristofano A, et al: Is the combination of Cetuximab with chemo-radiotherapy regimens worth while in the treatment of locally advanced head and neck cancer? A review of current evidence. Crit Rev Oncol Hematol 85:112-120, 2013 22. Pryor DI, Porceddu SV, Burmeister BH, et al: Enhanced toxicity with concurrent cetuximab and radiotherapy in head and neck cancer. Radiother Oncol 90:172-176, 2009

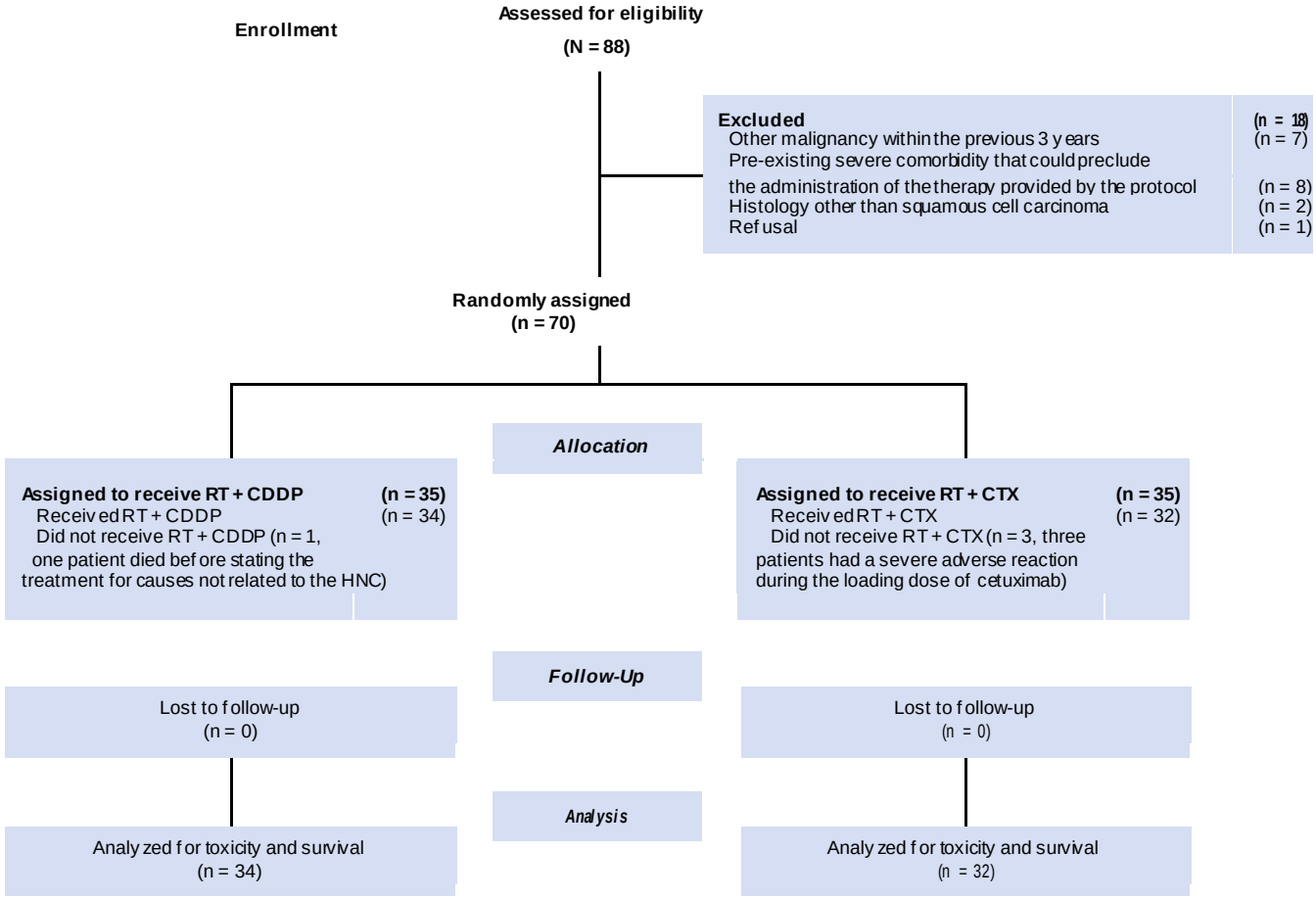

Fig 1. CONSORT flow diagram. CDDP, cisplatin; CTX, cetuximab; HNC, head and neck cancer; RT, radiotherapy.

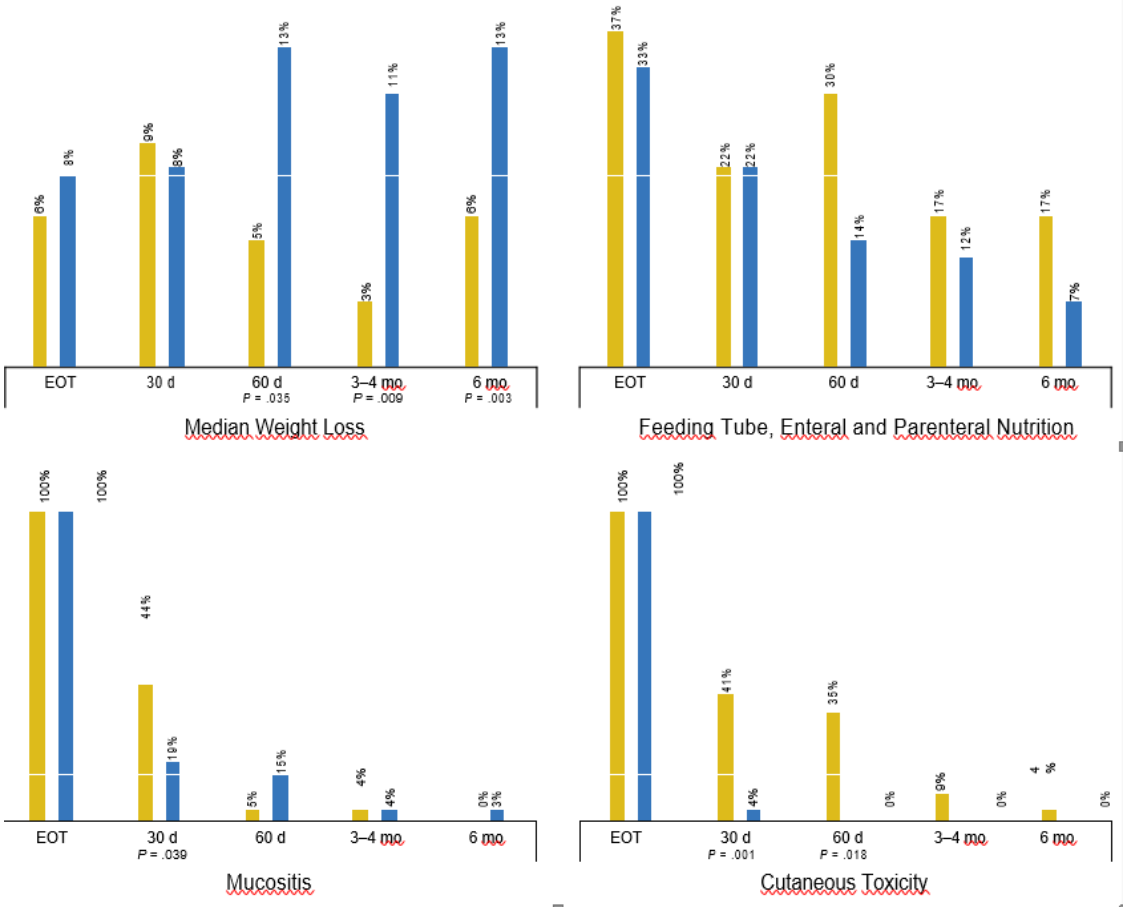

Fig 2. Weight loss, feeding-tube dependency, and acute toxicity resolution over time. EOT, end of treatment. Blue bars, cisplatin arm; gold bars, cetuximab arm.

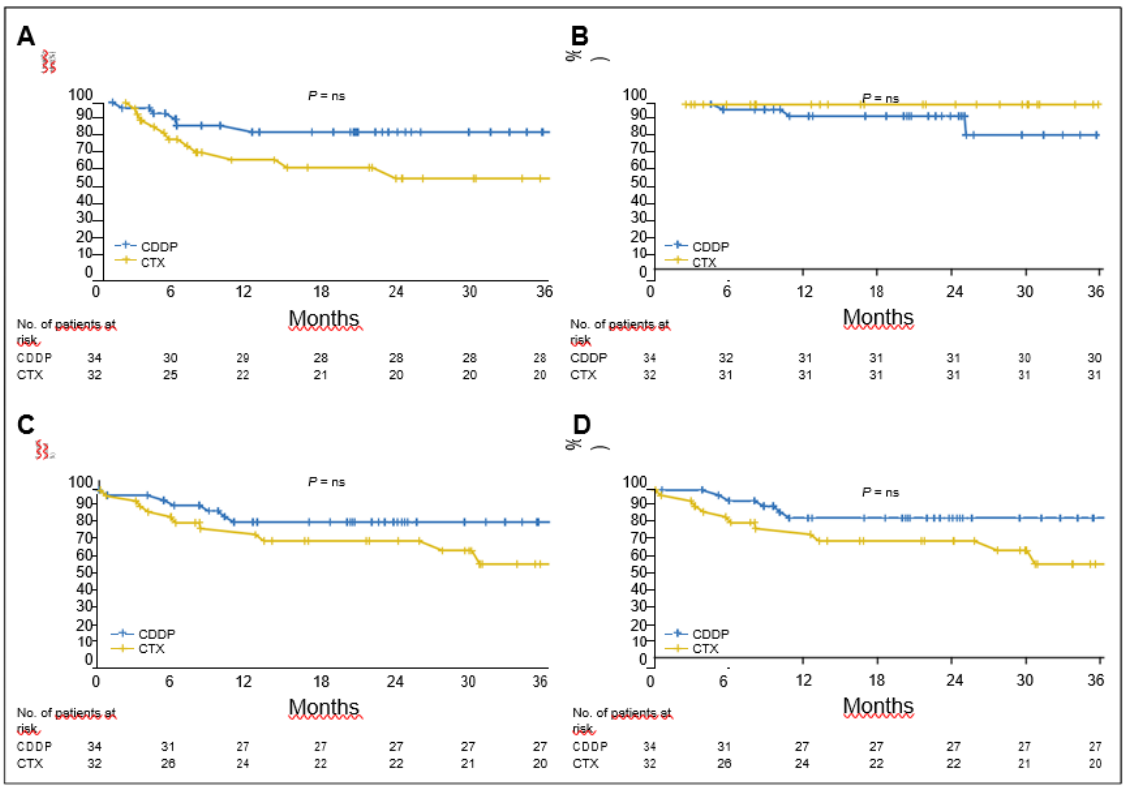

Fig 3. (A) Local control, (B) metastasis-free survival, (C) overall survival, and (D) cancer-specific survival functions. CDDP, cisplatin; CTX, cetuximab; ns, not significant.

Characteristic	RT + CT (n = 35)	RT + CDDP (n = 35)	P
Age, years*	61 (44-80)	67.5 (36-77)	ns
Sex			ns
Male	26 (74)	24 (69)	
Female	9 (26)	11 (31)	
ECOG performance status			ns
1	21 (60)	22 (63)	
2	14 (40)	13 (37)	
Smoking			ns
Yes, current	18 (52)	18 (51)	
Yes, past	13 (37)	10 (29)	
No	4 (11)	7 (20)	
Alcohol use			.031
Yes, current	22 (63)	11 (31)	
Yes, past	3 (8)	6 (17)	
No	10 (29)	18 (51)	
Cancer location			ns
Oropharynx	17 (49)	16 (46)	
Oral cavity	5 (14)	5 (14)	
Hypopharynx	6 (17)	8 (23)	
Supraglottic larynx	7 (20)	6 (17)	
Stage			ns
III	7 (20)	7 (20)	
IVA	22 (63)	24 (69)	
IVB	6 (17)	4 (11)	
T stage			ns
T1-T2	6 (17)	11 (31)	
T3	14 (40)	9 (26)	
T4a-T4b	15 (43)	15 (43)	
N stage			ns
N0-N1	15 (43)	10 (29)	
N2a-N2b	12 (34)	19 (54)	
N2c-N3	8 (23)	6 (17)	
Grade			ns
GX	9 (26)	14 (40)	
G1	3 (8)	1 (3)	
G2	14 (40)	11 (31)	
G3	9 (26)	9 (26)	

NOTE. All data are presented as No (%) unless otherwise indicated.
Abbreviations: CDDP, cisplatin; CTX, cetuximab; ECOG, Eastern Cooperative Oncology Group; ns; not significant; RT, radiotherapy.
*Data are presented as median (range).

Table 1. Patient and Tumor Characteristics

Measure	RT + CTX (n = 32)	RT + CDDP (n = 34)	P
RT technique			ns
3D	3 (9)	6 (18)	
IMRT	8 (25)	5 (15)	
IMRT-SIB	15 (47)	12 (35)	
Tomotherapy	6 (19)	11 (32)	
RT			
Total dose (T + N)*	70.00 (69.40-70.00)	70.00 (69.90-70.00)	ns
Dose/fraction (T + N)*	2.05 (2.00-2.12)	2.00 (2.00-2.12)	ns
Total prophylactic dose*	56.00 (54.00-56.00)	56.00 (54.00-56.00)	ns
RT dose/fraction (prophylactic)	1.66 (1.60-1.80)	1.60 (1.60-1.80)	ns
Interruption, days			ns
, 5	26 (81)	32 (94)	
5-10	2 (6)	2 (6)	
. 10	4 (13)	0 (0)	
Interruption, 10 days			.05
No	28 (88)	34 (100)	
Yes	4 (12)	0 (0)	
No. of concurrent cycles of CTX or CDDP			ns
# 2	1 (3)	1 (3)	
3-4	5 (16)	5 (15)	
5-6	17 (53)	21 (62)	
$ 7	9 (28)	7 (20)	
CTX or CDDP dosage reduction			ns
No	21 (66)	16 (47)	
Yes, 75%-80%	6 (19)	11 (32)	
Yes, 50%-60%	5 (15)	7 (21)	
AEs possibly related to treatment			ns
No	26 (81)	33 (97)	
Fatal	4 (13)	1 (3)	
Severe	2 (6)	0 (0)	
Severe or fatal AEs possibly related to treatment	6 (19)	1 (3)	.044
Nutritional support			ns
No	9 (28)	17 (50)	
Liquid supplements	11 (35)	6 (18)	
Enteral nutrition	10 (31)	9 (26)	
Parenteral nutrition	2 (6)	2 (6)	
Nutritional support, any	24 (75)	17 (50)	.032
Weight loss, kg†	7 (0-22)	8 (0-16)	ns

NOTE. All data are presented as No (%) unless otherwise indicated. Abbreviations: 3D, three-dimensional; AE, adverse event; CDDP, cisplatin; CTX, cetuximab; IMRT, intensity-modulated radiotherapy; ns, nonsignificant; RT, radiotherapy; SIB, simultaneous integrated boost; T + N, tumor and nodes. *Data are presented as median (interquartile range) †Data are presented as median (range

Table 2. Treatment Characteristics and Compliance

	RT + CTX (n = 32)	RT + CDDP (n = 34)	P
Cutaneous toxicity at EOT			ns
G0-G1	7 (22)	12 (36)	
G2	11 (34)	15 (44)	
G3	13 (41)	7 (20)	
G4	1 (3)	0 (0)	
Cutaneous toxicity $ G3	14 (44)	7 (21)	.039
Mucositis at EOT			ns
G0-G1	4 (13)	1 (3)	
G2	9 (28)	15 (44)	
G3	19 (59)	18 (53)	
Total WBC at EOT			.001
G0	30 (94)	17 (50)	
G1	0 (0)	7 (20)	
G2	0 (0)	6 (18)	
G3	1 (3)	4 (12)	
G4	1 (3)	0 (0)	
Hemoglobin at EOT			, .001
G0	30 (94)	17 (50)	
G1	1 (3)	13 (38)	
G2	0 (0)	4 (12)	
G3	1 (3)	0 (0)	
Platelets at EOT			.003
G0	31 (97)	21 (62)	
G1	0 (0)	9 (26)	
G2	0 (0)	3 (9)	
G3	1 (3)	1 (3)	
Hematologic toxicity $ G3	2 (6)	5 (15)	ns
Renal toxicity at EOT			.033
G0	31 (97)	27 (79)	
G1	1 (3)	3 (9)	
G2	0 (0)	3 (9)	
G3	0 (0)	1 (3)	
GI toxicity at EOT			.036
G0	27 (85)	21 (62)	
G1	3 (9)	7 (20)	
G2	2 (6)	5 (15)	
G3	0 (0)	1 (3)	

Table 3: Acute Toxicity

Arm, Site, Months After EOT	Treatment	Vital Status
CTX (n = 13)		
Local, T (n = 6)		
2	Salvage surgery	Died from septic shock after surgery
4	None, supportive care	Died
6	Salvage surgery	Alive with no evidence of disease
8	Salvage surgery	Alive with no evidence of disease
11	None, supportive care	Died
24	Salvage surgery	Alive with no evidence of disease
Local, N (n = 3)		
3	None, patient's choice	Died
7	Planned salvage surgery	Alive with evidence of disease
15	Salvage chemo-RT + surgery	Died after 13 more months (further progression)
Local, both (n = 3)		
3	Palliative chemotherapy	Died
3	None, supportive care	Died
5	Salvage surgery	Alive with no evidence of disease
Systemic, M (n = 1)		
6	Palliative chemotherapy + symptomatic RT	Died
Local + systemic, N + M (n = 0)	—	—
CDDP (n = 9)		
Local, T (n = 3)		
4	Salvage surgery	Died after 7 more months; further progression
2	None, supportive care	Died
12	Salvage surgery	Alive with no evidence of disease
Local, N (n = 1)		
6	Salvage surgery	Alive with no evidence of disease
Local, both (n = 1)		
6	Salvage surgery	Died from brain ischemic complications after surgery
Systemic, M (n = 3)		
5	None, supportive care	Died
6	None, supportive care	Died
25	Palliative surgery + RT	Alive with evidence of disease
Local-systemic, N + M (n = 1)		
1 for N, 11 for M	Palliative RT	Alive with evidence of disease

Abbreviations: CDDP, cisplatin; CTX, cetuximab; EOT, end of treatment; M, metastases; N, nodes; RT, radiotherapy; T, tumor.

Table 4: Sites of Disease Progression and Salvage Treatment Given