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Clinical Trial Results

A Randomized, Multicenter, Phase II Study of Cetuximab With Docetaxel and Cisplatin as Induction Chemotherapy in Unresectable, Locally Advanced Head and Neck Cancer

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Author Summary

Lessons Learned

- Addition of cetuximab may affect tolerability and, in turn, affect eventual outcomes.
- The incidence of prior human papillomavirus infection has emerged as an important variable that can confound trials enrolling patients with oropharyngeal cancer.

Abstract

Background. We investigated the efficacy of cetuximab when added to induction chemotherapy followed by concurrent chemoradiotherapy (CCRT) in patients with locally advanced head and neck squamous cell carcinoma.

Methods. Patients were randomized to receive three cycles of docetaxel and cisplatin (TP regimen) with or without cetuximab (TP plus cetuximab [CTP] vs. TP) as induction chemotherapy. Patients in the CTP arm received CCRT with cetuximab and cisplatin, whereas patients in the TP arm received cisplatin alone. The primary endpoint was the objective response rate (ORR) after induction chemotherapy.

Results. Overall, 92 patients were enrolled. The ORRs for induction chemotherapy in the CTP and TP arms were not different (81% vs. 82%). Adding cetuximab lowered the completion rate of induction chemotherapy and CCRT and resulted in more frequent dose reductions of the induction chemotherapy, although this did not reach statistical significance. In the CTP and TP arms, respectively, the 3-year progression-free survival (PFS) rates were 70% and 56% ($p = .359$), and the overall survival (OS) rates were 88% and 74% ($p = .313$). When limited to patients who completed induction chemotherapy, 3-year PFS rates of 78% and 59% ($p = .085$) and OS rates of 94% and 73% ($p = .045$) were observed in the CTP and TP arms, respectively.

Conclusion. Adding cetuximab to sequential treatment did not increase the treatment efficacy and resulted in greater toxicity. In the intent-to-treat population, neither PFS nor OS was improved by the addition of cetuximab to sequential treatment; however, a suggestion of improved survival outcomes was observed in patients completing cetuximab-containing induction chemotherapy. ***The Oncologist*** 2015; 20:1119–1120

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Table 1. Treatment compliance and outcomes

Variable	CTP arm ($n = 48$)	TP arm ($n = 44$)	p value
Completion of induction chemotherapy (n)			.360
Yes	40	40	
No	8	4	
Induction completion rate (%)	83	91	
Dose reduction in induction chemotherapy[a] (n)			.001
Yes	22	6	
No	26	38	
Dose reduction in docetaxel or cisplatin (n)			.170
Yes	12	6	
No	36	38	
Response to induction chemotherapy[b] (n)			.530[c]
CR	4	4	
PR	35	32	
SD	6	7	
PD	0	1	
Objective response rate[d] (%)	81	82	
Completion of induction and CCRT (n)			.259
Yes	32	34	
No	16	10	
Protocol completion rate (%)	67	77	
Response to CCRT (n)			.506[c]
CR	22	25	
PR	11	8	
SD	0	0	
PD	1	1	
CR rate (%)	46	57	
3-years PFS rate (%)			
Total	70	56	.359
Oropharynx	87	84	.975
Nonoropharynx	53	37	.499
3-years OS rate (%)			
Total	88	74	.313
Oropharynx	92	91	.737
Nonoropharynx	86	61	.248

[a]Dose reduction in any compound among docetaxel, cisplatin, and cetuximab.
[b]Three patients in the CTP arm were not evaluable for response due to unexplained early death ($n = 1$), septic shock ($n = 1$), and hypersensitivity reaction after the first cetuximab dose ($n = 1$); all patients were evaluable for response in the TP arm.
[c]p value based on binary comparison: whether or not a patient achieved objective response.
[d]Overall response rate was defined as the proportion of patients achieving CR or PR.
Abbreviations: CCRT, concurrent chemoradiotherapy; CR, complete response; CTP, cetuximab, docetaxel, and cisplatin; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; TP, docetaxel and cisplatin.

Discussion

The epidermal growth factor receptor (EGFR) is highly overexpressed in head and neck squamous cell carcinoma (SCCHN). The addition of the EGFR inhibitor cetuximab to radiotherapy has been found to improve survival outcomes in locally advanced SCCHN (LA-SCCHN), and combining cetuximab with cytotoxic agents prolongs survival in metastatic SCCHN. Based on these additive effects of cetuximab for both radiotherapy and chemotherapy, we hypothesized that the addition of cetuximab to both induction chemotherapy and concurrent chemoradiotherapy (CCRT) phases would improve treatment outcomes. The current study represents the first randomized trial to test the effect of cetuximab integration into both the induction and CCRT phases in LA-SCCHN.

In our study, although not statistically significant, cetuximab addition to sequential treatment seemed to decrease a patient's ability to tolerate treatment. Adding cetuximab lowered the completion rate of induction chemotherapy (docetaxel plus cisplatin) and CCRT and caused more frequent dose reductions of induction chemotherapy (Table 1). Although there was no significant difference in the frequency of severe (grade ≥ 3) adverse events, overall adverse events occurred more frequently in the CTP arm. The objective response rate (the primary endpoint), progression-free survival, and overall survival were not improved by cetuximab addition in the intent-to-treat population (Table 1). Nonetheless, we found that the addition of cetuximab seemed to more favorably affect patients who completed the planned 3 cycles of induction chemotherapy (3-year PFS 78% vs. 59% [$p = .085$] and 3-year OS 94% vs. 73% [$p = .045$] in the CTP vs. TP arms).

The shortcomings of our study are as follows. Because the importance of human papillomavirus tests in oropharyngeal cancer was little known when this study was initiated and the planned sample size was small, stratification according to primary tumor site or other additional clinical variables could not be performed in the randomization process. Instead, considering possible differences in clinical practice patterns at the various participating institutions, we stratified patients only according to institution; therefore, the sex distribution was unequal between the arms ($p = .044$), and the proportion of oropharyngeal disease was slightly higher in the CTP arm than in the TP arm, although this was not statistically significant. Consequently, we cannot exclude the possibility that these unexpectedly uneven patient distributions contributed to the favorable survival outcomes in patients who completed cetuximab-containing induction chemotherapy.

In conclusion, although the addition of cetuximab to sequential treatment of LA-SCCHN may somewhat decrease patient compliance, it was tolerable overall. The primary endpoint of this study was not met, but the survival data observed in patients who completed the planned cetuximab-containing induction chemotherapy suggest that further investigation of cetuximab addition in this setting is warranted.

Author disclosures available online.