Hong Kong J Radiol. 2016;19:96-102 | DOI: 10.12809/hkjr1615340

ORIGINAL ARTICLE

Treatment Outcome of Cetuximab Compared with Cisplatin during Radical Radiotherapy for Locally Advanced Head and Neck Cancer

KS Law[1], RKY Wong[1], E Yu[2], ACK Cheng[1]

[1]Department of Oncology, [2]Clinical Research Centre, Princess Margaret Hospital, Laichikok, Hong Kong

ABSTRACT

Objectives: *To assess whether cetuximab (C225) is equivalent to cisplatin (CDDP) with concurrent radical radiotherapy (RT) for locally advanced head and neck squamous cell carcinoma (LAHNSCC) by comparing the treatment outcome of two patient cohorts treated in our institute.*

Methods: *Patients with LAHNSCC treated with weekly C225 and intensity-modulated radiotherapy (IMRT) with radical dose 70 Gy between March 2008 and June 2014 were retrospectively reviewed. Another cohort of patients with LAHNSCC treated with weekly CDDP and IMRT was selected for comparison, with matched age, sex, and primary tumour site. Treatment outcomes including crude local control rate, median duration of locoregional control, median overall survival, and toxicities were compared.*

Results: *The study cohort comprised 20 (95.2%) males and 1 (4.8%) female in each treatment arm. Their median age was similar in each cohort with 67 years in C225 group and 65 years in CDDP group. The median number of cycles received was 6 in C225 group versus 5 in CDDP group. Crude local control rate was 52.3% (11/21) in C225 group versus 61.9% (13/21) in CDDP group. The median duration of locoregional control was 15 months in C225 group and 48 months in CDDP group (hazard ratio [HR] = 1.19; 95% confidence interval [CI], 0.71-3.39; p = 0.747). The median overall survival was 27 months in C225 group versus 49 months in CDDP group (HR = 1.21; 95% CI, 0.48-3.07; p = 0.678). Acute severe skin toxicity (≥grade 3) was observed in 19% (n = 4) of the C225 group and 0% (n=0) of the CDDP group, while 38.1% (n = 8) of the CDDP group had grade 2 radiation dermatitis versus 14.3% (n = 3) of the C225 group. Two patients in the C225 group developed a grade 4 acute skin reaction with full-thickness dermis ulceration and bleeding. No grade 4 skin toxicity was observed in the CDDP group. Severe bone marrow toxicity (≥grade 3) occurred in 4.8% (n = 1) of the CDDP group, and CDDP-induced vomiting (grade 1-2) developed in 14.3% (n = 3) of patients and none had grade 3 or above toxicity. No bone marrow toxicity or vomiting occurred with C225 treatment. More treatment-induced renal toxicity was observed in the CDDP cohort (42.9%) compared with the C225 cohort (9.5%).*

Conclusion: *The results showed a trend of superior treatment outcomes for CDDP than C225 when combined with radical IMRT. If patients had good tolerance, CDDP concurrent with IMRT remains the standard of care for the treatment of LAHNSCC. C225 should be reserved for patients with poor functional status who cannot tolerate CDDP or where there are contraindications. In general, C225 concurrent with RT is well-tolerated, but there is a chance of grade 4 skin reactions. Prevention, early detection, and management of skin reaction to C225 are therefore vital. Whenever possible, C225 or CDDP should be added to radical RT for LAHNSCC for a gain in clinical outcome since evidence has shown poorer treatment results with RT alone.*

Key Words: *Carcinoma, squamous cell; Cetuximab; Head and neck neoplasms; Radiotherapy; Treatment outcome*

Correspondence: *Dr Ka-suet Law, Department of Oncology, Princess Margaret Hospital, Laichikok, Hong Kong.*
Email: snowlaw@gmail.com

Submitted: 24 Jun 2015; Accepted: 18 Nov 2015.

Disclosure of Conflicts of Interest: All authors have no relevant conflicts of interest to disclose.

中文摘要

比較西妥昔單抗（C225）和順鉑（CDDP）作為治療局部晚期頭頸部腫瘤的根治性放療結果

羅家雪、黃家仁、余洛汶、鄭志堅

目的：為局部晚期頭頸部鱗狀細胞癌（LAHNSCC）患者作根治性放療時，比較使用C225和CDDP的治療效果。

方法：回顧分析2008年3月至2014年6月期間每週接受強度調控放射治療（IMRT）並使用70 Gy C225的LAHNSCC患者。另一組年齡、性別及原發腫瘤位置相若的LAHNSCC患者則每週接受IMRT並使用CDDP。比較兩組患者的治療結果，包括粗局部控制率、局部控制的中位時間、總生存率中位數和毒性。

結果：每組患者包括20名（95.2%）男性和1名（4.8%）女性，患者年齡中位數相若（C225組67歲，CDDP組65歲）。放療週期中位數C225組6週，CDDP組5週。粗局部控制率C225組52.3%（11/21），CDDP組61.9%（13/21）。局部控制時間中位數C225組15個月，CDDP組48個月（風險比= 1.19；95%置信區間0.71-3.39；p=0.747）。總生存率中位數C225組27個月，CDDP組49個月（風險比= 1.21；95%置信區間0.48-3.07；p=0.678）。急性放射性皮炎（3級或以上）C225組19%（4例），CDDP組0%（0例）；CDDP組中38.1%（8例）有2級放射性皮炎，CDDP組則只有14.3%（3例）。C225組中兩名患者有4級急性放射性皮炎，並出現全層真皮潰瘍及出血。CDDP組則沒有4級急性放射性皮炎。CDDP組中4.8%（1例）出現骨髓毒性（3級或以上），14.3%（3例）因CDDP而誘發嘔吐（1-2級），但症狀均為輕微，並無3級或以上。C225組沒有出現骨髓毒性或嘔吐。與C225（9.5%）組相比，CDDP組有較多因治療引起的腎毒性病例（42.9%）。

結論：研究結果顯示CDDP結合根治性IMRT的治療效果，在數字上比C225結合根治性IMRT較佳。如果合適，應使用CDDP結合根治性IMRT治療LAHNSCC患者。對於那些功能狀態不佳、不能耐受CDDP或有禁忌症的患者，則可使用C225結合根治性IMRT治療。雖然一般來說，大多數患者能接受C225結合根治性IMRT，4級急性放射性皮炎仍可能發生。所以，接受C225治療前防止和及早發現並訂立治理方法至關重要。由於單單接受放療的治療效果不佳，可以的話，都應該加入C225或CDDP來改善治療效果。

INTRODUCTION

Squamous cell head and neck cancer accounts for 2.5% of new cancer cases annually, and is the 10th most common cancer newly diagnosed in Hong Kong.[1] Definitive chemo-irradiation is the standard of care for treatment of locally advanced squamous cell carcinoma of the head and neck (LAHNSCC). A meta-analysis of chemotherapy in head and neck cancer (MACH-NC) demonstrated a 6.5% absolute improvement in 5-year overall survival (OS) with concurrent chemo-irradiation compared with radiotherapy (RT) alone.[2] Cisplatin (CDDP) was considered as the most effective agent for concurrent RT. CDDP, however, is associated with both short-term adverse effects and long-term toxicity.

Cetuximab (C225), an antibody against epidermal growth factor receptor, appears to offer a less toxic alternative. The Bonner study randomly assigned patients with LAHNSCC to C225 and RT or RT alone. It found that C225 improved locoregional control and OS[3] without worsening quality of life.[4] A 5-year update demonstrated a continuous improvement in OS,[5] although locoregional control and disease-free survival data were not available. Nonetheless, this study was conducted before concurrent chemo-irradiation was proven superior to RT alone. Therefore, C225 was not directly compared with CDDP.

To date, there is no mature evidence that C225 can

replace CDDP when combined with RT in terms of treatment efficacy. A retrospective study from the US Memorial Sloan-Kettering Cancer Center (MSKCC) showed inferior local control in C225 arm, with 2-year locoregional failure rate of 5.7% for CDDP/RT versus 39.9% for C225/RT ($p < 0.0001$), and 2-year failure-free survival and OS rates of 87.4% versus 44.5% ($p < 0.0001$) and 92.8% versus 66.6% (P=0.0003), respectively.[6] Another retrospective study from the MSKCC with CDDP/RT (n = 49) and C225/RT (n = 125) in LAHNSCC patients also determined that CDDP/RT had a superior 2-year locoregional failure rate (5.7% vs. 39.9%; $p < 0.001$), failure-free survival (87.4% vs. 44.5%; $p < 0.001$), and OS (92.8% vs. 66.6%; $p < 0.001$).[7] In addition, a prospective TREMPLIN phase 2 study[8] compared induction chemotherapy followed by either CDDP (n = 60) or C225 (n = 56) concurrent with radiation in patients with locally advanced squamous cell carcinoma of the larynx or hypopharynx. In this study, 12 (21%) patients in the C225 arm developed a local recurrence compared with five (8%) patients in the CDDP arm ($p = 0.08$). Two phase III randomised controlled trials in the US (RTOG 1016) and the UK (NCT 01874171) directly compared concurrent weekly C225 and RT versus concurrent CDDP and without neoadjuvant and adjuvant treatment. The US trial stopped recruiting patients in 2013 while the UK trial is still in recruitment phase till September 2017. A review of the local data is valuable to guide our practice.

METHODS

This was a retrospective analysis to compare clinical outcomes of LAHNSCC treated with concurrent C225 versus CDDP with RT in our institution. Data of patients with stage III and IV disease without distant metastases treated with RT and C225 from 1 March 2008 to 30 June 2014 were collected. Treatment comprised a C225 loading dose (400 mg/m^2) via intravenous infusion 1 week prior to the start of RT, followed by a weekly infusion (250 mg/m^2) alongside with RT. Intensity-modulated radiotherapy (IMRT) technique with 70 Gy in 33 daily fractions over 7 weeks was used. Data of another group of patients treated with weekly CDDP (40 mg/m^2) and RT with matched age, sex, and primary tumour site were subsequently collected for comparison.

Patients were monitored and their toxicities were graded weekly during treatment using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Any C225 infusion reaction was traced from the chemotherapy day-ward medical record. Blood was collected for complete blood count and renal function tests were conducted every week in clinic.

The Statistical Package for the Social Sciences (Windows version 19.0; SPCC Inc., Chicago [IL], USA) was used for statistical analysis. Median duration of local control, disease recurrence, and survival were generated by Kaplan-Meier method and compared in two different patient groups by log rank test. Treatment toxicities of the two patient cohorts were compared by Fisher's exact test.

RESULTS

The characteristics of the 42 patients from two cohorts are summarised in Table 1. There were 21 patients treated with RT and weekly C225, and another 21

Table 1. Patient characteristics.

Characteristic	No. (%) of patients		p Value*
	C225 (n = 21)	CDDP (n = 21)	
Gender			1.000
Female	1 (4.8)	1 (4.8)	
Male	20 (95.2)	20 (95.2)	
Age (years)‡	67 (59-71)	65 (59-68.5)	0.351†
Cycles received‡	6 (4-7)	5 (4-6)	0.227†
ECOG status			0.007
PS0	0	1 (4.8)	
PS1	5 (23.8)	14 (66.7)	
PS2	15 (71.4)	6 (28.6)	
PS3	1 (4.8)	0	
FU time (months)‡	16 (7.8-37.0)	21 (10-38)	0.392†
Sub-sites			0.729
Larynx	11 (52.4)	13 (61.9)	
Stage II	0	1	
Stage III	4	3	
Stage IVA	7	6	
Stage IVB	0	3	
Hypopharynx	7 (33.3)	7 (33.3)	
Stage III	3	1	
Stage IVA	2	4	
Stage IVB	2	2	
Oropharynx	3 (14.3)	1 (4.8)	
Stage IVA	2	1	
Stage IVB	1	0	
Stage§			0.697
II-IVa	18 (85.7)	16 (76.2)	
IVb	3 (14.3)	5 (23.8)	
Stage§			0.734
II-III	7 (33.3)	5 (23.8)	
IVa-IVb	14 (66.7)	16 (76.2)	

Abbreviations: C225 = cetuximab; CDDP = cisplatin; ECOG = Eastern Cooperative Oncology Group; FU = follow-up; PS = Performance Status.
* Fisher's exact test.
† Mann-Whitney *U* test.
‡ Shown as median (interquartile range).
§ Stage II-IVa = potentially operable; stage IVb = inoperable.

patients were treated with RT and weekly CDDP during the same period. The predominant primary sites were larynx with 11 (52.4%) cases and 13 (61.9%) cases in the C225 and CDDP group, respectively, followed by hypopharynx with seven (33.3%) cases in both groups. There were seven (33.3%) cases of stage II and III patients in the C225 group and five (23.8%) cases of stage II and III patients in the CDDP group. If we classify patients depending on surgical operability, either potentially operable stages (stage II-IVa) or inoperable (stage IVb), there were 18 (85.7%) cases in the C225 group and 16 (76.2%) cases in the CDDP group who were potential candidates for surgery. Regarding performance status, in the CDDP group there were more ECOG 1 (14/21, 66.7%) patients, whereas in the C225 group there were more ECOG 2 (15/21, 71.4%) patients. The median number of cycles tolerated was 6 and 5 cycles in the C225 and CDDP groups, respectively. The median duration of RT was 50 days (interquartile range [IQR], 46.5-52.0) in the CDDP group versus 48 days (IQR, 42.3-49.8) in the C225 group.

The median follow-up was 16 months for the C225 group and 21 months for the CDDP group. The crude local control rate was 52.3% (11/21) in the C225 cohort versus 61.9% (13/21) in the CDDP cohort. The median duration of locoregional control was 15 months in the C225 group and 48 months in the CDDP group (hazard ratio [HR] = 1.19; 95% confidence interval [CI], 0.71-3.39; and p = 0.747) [Figure 1]. The median time to disease recurrence was 15 months in the C225 group versus 48 months in the CDDP group, HR being 1.90 (95% CI, 0.73-4.91) and p = 0.168 (Figure 2). The median OS was 27 months in the C225 group versus 49 months in the CDDP group, HR being 1.21 (95% CI, 0.48-3.07) and p = 0.678 (Figure 3).

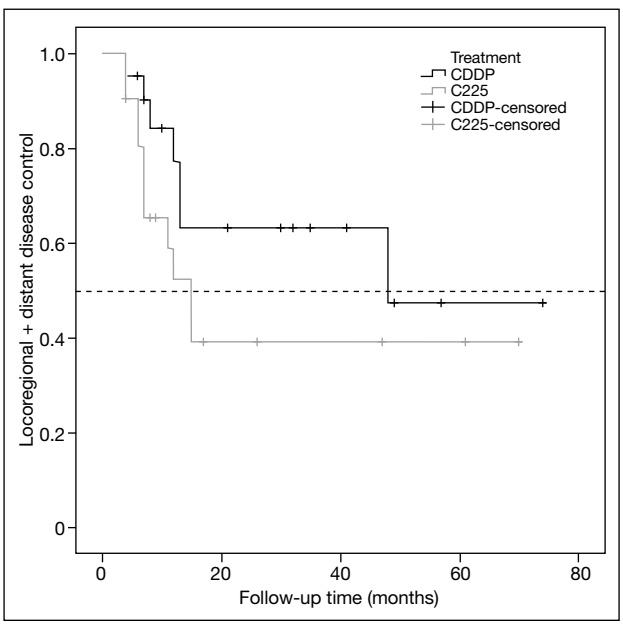

Figure 2. Kaplan-Meier curves for disease control (locoregional + distant disease control) [p = 0.168].

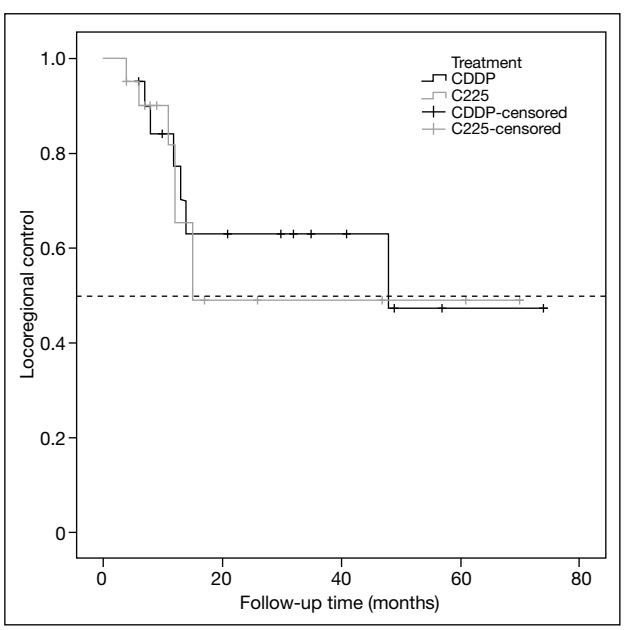

Figure 1. Kaplan-Meier curves for locoregional control (p = 0.747).

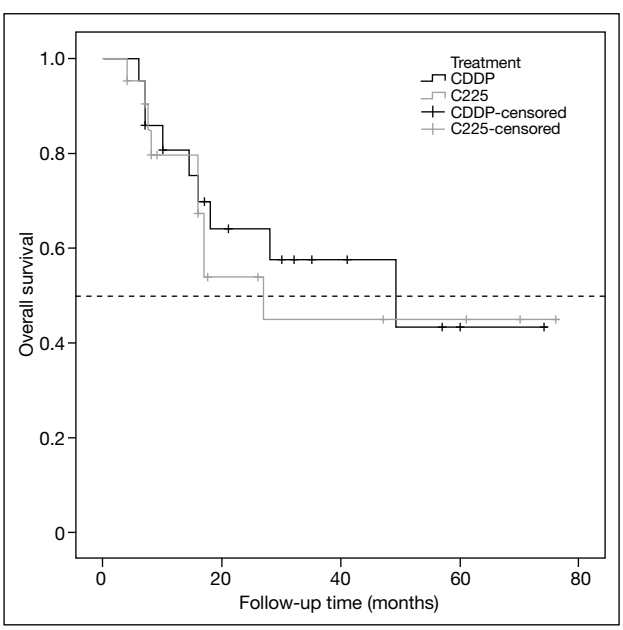

Figure 3. Kaplan-Meier curves for overall survival (p = 0.678).

A summary of the treatment toxicities is shown in Table 2. Acute severe skin toxicities (≥grade 3) were 19% (n = 4) in the C225 group and 0% (n = 0) in the CDDP group (p = 0.142). Nonetheless, 38.1% (n = 8) of the CDDP group had grade 2 radiation dermatitis versus only 14.3% (n = 3) in the C225 group. Two (9.5%) patients in the C225 group developed grade 4 acute skin reaction with full-thickness dermis ulceration and bleeding. No grade 4 skin toxicity was observed in the CDDP group. Severe bone marrow toxicities (≥grade 3) occurred in 4.8% (n = 1) of the CDDP group (p < 0.001); and CDDP-induced vomiting developed in 14.3% (n = 3) of patients of whom none had ≥grade 3 toxicity (p = 0.003). No bone marrow toxicity or vomiting was observed from the C225 treatment. More treatment-induced renal toxicity was observed in the CDDP group compared with the C225 group (42.9% vs. 9.5%; p = 0.032). The gastrointestinal, bone marrow, and renal toxicities which had statistically significant differences in both groups are shown in Table 2.

Table 2. Treatment toxicities of C225 and CDDP patient cohorts.

Treatment toxicity	No. (%) of patients		p Value*
	C225 (n = 21)	CDDP (n = 21)	
Severity of skin toxicity			0.142
Grade 0	4 (19.0)	2 (9.5)	
Grade 1	10 (47.6)	11 (52.4)	
Grade 2	3 (14.3)	8 (38.1)	
Grade 3	2 (9.5)	0	
Grade 4	2 (9.5)	0	
Severity of mucosities			0.073
Grade 0	0	1 (4.8)	
Grade 1	8 (38.1)	8 (38.1)	
Grade 2	8 (38.1)	12 (57.1)	
Grade 3	5 (23.8)	0	
Severity of BM			<0.001
Grade 0	21 (100.0)	10 (47.6)	
Grade 1	0	5 (23.8)	
Grade 2	0	5 (23.8)	
Grade 3	0	1 (4.8)	
Severity of vomit			0.003
Grade 0	21 (100.0)	13 (61.9)	
Grade 1	0	5 (23.8)	
Grade 2	0	3 (14.3)	
Grade 3	0	0	
Severity of renal toxicity			0.032
Grade 0	19 (90.5)	12 (57.1)	
Grade 1	2 (9.5)	9 (42.9)	
Grade 2	0	0	
Grade 3	0	0	

Abbreviations: BM = bone marrow toxicity; C225 = cetuximab; CDDP = cisplatin.
* Fisher's exact test.

DISCUSSION

The trend shown in this study for better local control and OS for CDDP compared with C225 echoes the findings from MSKCC.[6,7] The number of patients in current study was too small and limited the statistical power to obtain significant results. Results from retrospective single-institution studies with intrinsic limitations should be interpreted with caution. A prospective randomised controlled trial TREMPLIN phase 2 study also demonstrated inferior local control when using C225,[8] although the TREMPLIN trial integrated induction chemotherapy in both groups of patients. In the current study, no patients received any neoadjuvant or adjuvant chemotherapy and target agent. All patients in this study received 70 Gy/33 daily fractions over 7 weeks using IMRT with simultaneous concomitant boost. This eliminates the confounding effect of different RT fractionation schedule.

The median number of cycles of C225 was 6 while full compliance should complete 8 cycles. There were four patients in the C225 group who were switched from prior CDDP used concurrently with RT, including two patients who had a persistently low absolute neutrophil

Table 3. Comparison of MACH-NC and Bonner trial.[2,5]

	MACH-NC[2]	Bonner trial[5]
Study design	Meta-analysis of 50 trials (n = 9615)	Single trial (n = 424)
HR (95% CI) of death	0.74 (0.67-0.82)	0.74 (0.57-0.97)
Effect on local failure	Main effect	Only effect
Effect on distant metastasis	Modest effect	No effect
Efficacy	Efficacy irrespective of site and fractionation schedule	? RT schedule specific
Toxicity	Significant acute toxicity which may inflict on late toxicity, in particular swallowing dysfunction	Grade III-IV mucositis and radiation dermatitis not significantly increased; toxicity seems not increased; high compliance; QOL not decreased

Abbreviations: CI = confidence interval; HR = hazard ratio; QOL = quality of life; RT = radiotherapy.

count after only one cycle of CDDP, and two other patients with impaired renal function after one cycle of CDDP. There were also two patients in the C225 group who had grade 4 skin toxicity, and C225 was withheld after the 4th week and 5th week of RT.

When we compared the MACH-NC meta-analysis with the Bonner study as shown in Table 3,[2,5] both CDDP and C225 showed efficacy in local control, but distant cancer control for C225 was inconspicuous. The current study exhibited similar results with three (14.3%) patients developing distant metastases in the C225 group, while only one (4.7%) patient having subsequent distant metastasis in the CDDP group. These results are consistent with those of the MACH-NC meta-analysis,[2] suggesting that CDDP may have a modest effect on distant control. The Bonner study failed to show statistically significant efficacy of C225 on distant control.[5]

We should be mindful that although the HR of death for C225 and CDDP concurrent with RT compared with RT alone was 0.74 (Table 3), the MACH-NC meta-analysis was a pooled analysis of 50 trials with 9615 patients included.[2] The Bonner study was a single phase III randomised controlled trail with only 424 patients included.[5] It should be cautious during interpretation of the equivalence of the HRs. In addition, the RT fractionation schedule in our patients was uniformly prescribed to 70 Gy in 33 fractions over 7 weeks using IMRT technique, while in MACH-NC meta-analysis, various RT fractionation schedules were used in the 50 trials. This may suggest that the efficacy of CDDP was demonstrated irrespective of the RT fractionation schedule, while we could not confirm such an effect in our retrospective review. In addition, patients with oral squamous cell carcinoma were included in the MACH-NC meta-analysis, while our retrospective review did not include such group of patients, nor were they included in the Bonner study. Biomarkers, such as human papillomavirus (HPV)/P16 status of tumour,[9] were not fully analysed in the current report. Only 10 out of the total 42 patients had been tested, with none being HPV positive.

There is no phase III randomised controlled trial to prove that the local control, distant control, and OS of C225 is inferior to CDDP used concurrently with RT. However, current available evidence, including this study, shows a trend of inferior clinical outcome for C225 compared with CDDP. This provides evidence that supports concurrent CDDP and RT as the gold standard of treatment for LAHNSCC whenever the patient can tolerate CDDP. Results from ongoing phase III randomised controlled trials to compare both drugs directly in this setting are needed for verification. Nonetheless, if the patient has poor premorbid renal or cardiac function, and cannot tolerate side-effects of CDDP treatment, switching to concurrent C225 and RT remains a better option than using RT alone as supported by the Bonner study data.[2] Whenever possible, C225 or CDDP should be added to radical RT for LAHNSCC for optimal clinical outcomes, since evidence has shown poor treatment results by RT alone.

Although there were slightly more patients in the CDDP group who experienced grade 2 or 3 radiation dermatitis, there were two patients in the C225 group who had grade 4 radiation dermatitis with full-thickness skin ulceration and bleeding. Early identification of patients with severe C225-induced skin toxicity is crucial and some earlier reports suggest early use of antibiotics[10] in treating head and neck cancer with C225 and RT. The late toxicity of our two groups of patients in this retrospective study remains to be determined for comparison.

There are a number of caveats for this retrospective review. In this review, although two groups of patients were matched with age, sex, and tumour subsites (Table 1), selection bias exists. Patients with poor performance status and suboptimal renal or cardiac function were treated with C225. Twelve patients in this group had deranged renal function (two had impaired function probably due to prior exposure to CDDP), five patients had borderline performance status, and two had congestive heart failure. Two patients had a persistent low absolute neutrophil count after one cycle of CDDP so they were also subsequently switched to C225 concurrent with RT.

CONCLUSION

There is a trend to show that use of CDDP concurrent with RT can attain better local control and survival compared with C225 concurrent with RT. Concurrent CDDP and RT remains the standard treatment of LAHNSCC. For patients in whom CDDP is contraindicated or not tolerated, concurrent use of C225 with RT can achieve a better clinical outcome than RT alone. C225 is well tolerated in general but early detection and management of patients with severe grade 4 skin toxicity during treatment is of utmost importance.

REFERENCES

1. Hong Kong Cancer Registry. Available from: http://www3.ha.org.hk/cancereg/e_a1b.asp. Accessed Jun 2015.
2. Pignon JP, le Maître A, Maillard E, Bourhis J; 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. 2009;92:4-14. cross ref
3. Bonner JA, Harari PM, Giralt J, Azarnia N, Shin DM, Cohen RB, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med. 2006;354:567-78. cross ref
4. Curran D, Giralt J, Harari PM, Ang KK, Cohen RB, Kies MS, et al. Quality of life in head and neck cancer patients after treatment with high-dose radiotherapy alone or in combination with cetuximab. J Clin Oncol. 2007;25:2191-7. cross ref
5. Bonner JA, Harari PM, Giralt J, Cohen RB, Jones CU, Sur RK, et al. Radiotherapy 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. 2010;11:21-8. cross ref
6. Koutcher L, Sherman E, Fury M, Wolden S, Zhang Z, Mo Q, et al. Concurrent cisplatin and radiation versus cetuximab and radiation for locally advanced head-and-neck cancer. Int J Radiat Oncol Biol Phys. 2011;81:915-22. cross ref
7. Riaz N, Sherman EJ, Fury M, Lee N. Should cetuximab replace Cisplatin for definitive chemoradiotherapy in locally advanced head and neck cancer? J Clin Oncol. 2013;31:287-8. cross ref
8. Lefebvre J, Pointreau Y, Rolland F, Alfonsi M, Baudoux A, Sire C, et al. Sequential chemoradiotherapy (SCRT) for larynx preservation (LP): Results of the randomized phase II TREMPLIN study [abstract]. J Clin Oncol. 2012;30(Suppl 15):S360.
9. Rosenthal DI, Harari PM, Giralt J, Bell D, Raben D, Liu J, et al. Impact of p16 status on the results of the phase III cetuximab (cet)/radiotherapy (RT) [abstract]. J Clin Oncol. 2014;32(Suppl):S5.
10. Melosky B, Burkes R, Rayson D, Alcindor T, Shear N, Lacouture M. Management of skin rash during EGFR-targeted monoclonal antibody treatment for gastrointestinal malignancies: Canadian recommendations. Curr Oncol. 2009;16:16-26. cross ref