Weekly versus every three weeks cisplatin as concurrent chemoradiotherapy in locally advanced head and neck cancer: single institution experience

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Abstract:

Background: In locally advanced head and neck squamous cell carcinoma, chemo-radiation with cisplatin 100 mg/m2 administered once every three weeks is the standard of treatment. Because of its presumed reduced toxicity and convenience, low-dose weekly cisplatin is increasingly being replaced. There is, however, no level 1 proof of effectiveness equivalent to cisplatin / 3weeks.

Patient and methods: This is a retrospective comparative analysis. We compare the response, side effect and survival functions of cisplatin in low dose and high dose with concurrent radiotherapy in locally advanced head and neck carcinoma.

Results: In our study, there's no statistically difference between the two groups as regard the patients and tumor criteria. As regarding the side effect was tolerated but statistically significant difference in hematological toxicities anemia and leucopenia (p= 0.029, 0.001) between both groups and dysphagia (p= 0.054). There's no significant difference in response and 3-year local control in both groups. The 3-year overall survival was better in the 3-weekly dose schedule than the low weekly dose with significant difference.

Conclusion: No significant differences between both treatment groups regarding response rates, loco-regional free survival and most of treatment toxicities. So, the weekly dose can be a good substitution to the three-weekly dose with accepted toxicities, ease of administration and adequate cumulative total dose.

Keywords: head and neck cancer, cisplatin, high dose, low dose, concurrent chemoradiotherapy,
retrospective.

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Introduction:

Head and neck cancer is the sixth most frequent malignancy worldwide [1]. Asia accounts for 57.5% of all head and neck cancers [2]. In Egypt, at our department in Mansoura University Hospital at Clinical Oncology and Nuclear Medicine department; we had 146 cases of head and neck cancers (5.6%) out of 2620 cases totally at 2015 [3]. Approximately 80% of individuals in underdeveloped nations have locally advanced head and neck cancer [4]. Since the introduction of combined modality treatment has progressed [5]. Cisplatin based concurrent chemo-radiotherapy (CRT) protocols is the standard of care in treating locally advanced head and neck squamous cell carcinoma (HNSCC). An improvement of loco-regional control and survival has been observed with administrating cisplatin every 3 weeks using the high dose (HD) regimen (100 mg/m^2) in randomized clinical trials [6].

One of the major concerns of using HD cisplatin is the high incidence of acute toxicity during the treatment course which led to many patients receive suboptimal cumulative cisplatin dose and dose intensity, thus compromising outcomes in nearly three quarters of the patients in some clinical studies [7, 8].

On the other hand, the low dose (LD) weekly cisplatin (40 mg/m^2) is more tolerable regarding toxicity profile [9] ease of administration, and lower necessity for supportive care and inpatient admissions [6]. The weekly regimen is widely accepted and included in

official international guidelines [10] but its toxicity and efficacy compared to HDC across several retrospective and prospective clinical studies was evaluated on a small number of patients [6]. To our knowledge, once-a-week cisplatin has never been compared with once-every-3-weeks cisplatin in a large randomized trial [8].

We aimed to assess and compare our experience in our department with the two different doses regarding response, loco-regional control, toxicity and survival of patients to try to standardize one of them with the least side effects, better survival and tumor control.

Patients and Methods:

This is a retrospective comparative study conducted to the cases of locally advanced head and neck squamous cell carcinoma (HNSCC) attended to the Clinical Oncology and Nuclear Medicine department, Mansoura University from January 2015 to December 2017 inclusive and divided in 2 groups,: the 1st group (group I) who received low dose weekly cisplatin 40mg /m² and the 2nd one (group II) who received high dose cisplatin 100 mg/ m² every 3 weeks concurrently with three-dimensional conformal radiation therapy (3D-CRT). The main objectives of our study were to compare and evaluate treatment toxicities, loco-regional control, tumor response and survival functions.

The cases included were locally advanced head and neck carcinoma stages III and IV, not operated, squamous cell carcinoma of the oral cavity, oropharynx, and hypopharynx/ larynx. All cases assessed pathologically, radiological and laboratory before starting treatment. We excluded the cases of nasopharyngeal carcinoma, metastatic cases and abnormal kidney functions. All patients underwent staging work up which included detailed physical examination, (ENT) examination, Computed Tomography (CT), or Magnetic Resonance Imaging (MRI) of the head and neck. Metastatic workup included chest X-ray or CT Chest in all patients. Routine blood examination included complete blood count and biochemical tests for renal and hepatic functions before CTH administration.

All patients underwent radiation treatment. The radiation fields used were as of that for the conventional treatment according to each tumor site with three dimensional conformal (3-D) techniques. The total dose was 66 Gy in 33 fractions with 2 Gy per fraction one fraction per day, and 5 days a week treatment with concern to the critical nearby structures.

Response assessment was routinely done for all patients at completion of treatment with RECIST (Response Evaluation Criteria in Solid Tumors) criteria (11).

Toxicities were reported according to the Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0 (12).

Study protocol was submitted for approval by the Institutional Research Board (IRB), Faculty of Medicine at Mansoura University and approved by code (R.21.08.1417).

Statistical analysis

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). The Kolmogorov-Smirnov was used to verify the normality of distribution of variables, Comparisons between groups for categorical variables were assessed using Chi-square test (Fisher's Exact or Monte Carlo correction). Student t-test was used to compare two groups for normally distributed quantitative variables while Mann Whitney test was used to compare between two groups for not normally distributed quantitative variables. Kaplan-Meier Survival curve was used for the significant relation with overall survival and loco-regional free survival. Significance of the obtained results was judged at the 5% level.

Results:

Our study is a single institution experience. It is retrospective comparative analysis of patients with locally advanced squamous cell carcinoma of the head and neck (LAHNSCC) undergoing concomitant radiotherapy and chemotherapy with cisplatin. We recruited 120 patients presented to Clinical oncology and nuclear medicine department, Faculty of medicine, Mansoura University Hospital from January 2015 up to December 2017 inclusive. We divided the patients into 2 groups I (80 patients) and II (40 patients). In group (I): cisplatin 40 mg/m² given once a week while in group (II): cisplatin 100 mg/m² given once every 3 weeks, both are administered concurrently with curative intent radiotherapy.

Patient's characteristics:

The two groups were balanced with no statistical difference between both of them regarding patients and tumor characteristics as shown in Table (1). The median age of both groups was 59 ys and 60 ys respectively with no statistical significance between both of them. No statistically significant difference regarding sex between both groups (P=0.288) and there was male predominance between both treatment groups. The majority of cases were smokers in both groups (57.5% & 65% respectively). The tumor sites were oral cavity (7.5%), oropharynx (62.5%), larynx and hypopharynx (30%) in group I while 10%, 65% and 25% respectively in group II with no significant difference (P= 0.79). The most presenting T stages in both groups are T1 and T2, while the most N stage is N2. The stages of the tumors were (III) in 25% of cases, (IV a) in 65% and (IV b) in 10% of group (I) while in Group (II) 25%, 60% and 15% respectively with no statistical difference. IV. In both groups, more than 70 % of the patients were ECOG 0 and1. The median number of chemotherapy cycles in group I was 4 cycles (2-6) (median dose for group I was 160 mg/ m²) while in group II was 2 cycles (1-3) (median dose for group II was 200 mg/ m²).

Tumor response, Loco-regional free survival and overall survival function:

The median follow-up for the patients was 24 months (range 15-37 months). Complete response (CR) assessed in all cases 3 months after the end of treatment. CR occurs in 52 patients (65%) of group I and in 28 patients of group II (70%). Partial response (PR) occurs in 28 patients (35%) of group I and in 12 patients (30%) of group II with no statistical differences between both groups (P=0.584). Local recurrences occur in 40% of cases in group I while in 30% of patients in group II with no difference statistically (P=0.28) as shown in Table (2).

The median loco-regional free survival for group I was 44.6 months while in group II was 49.7 months. The 3-year loco-regional free survival in patients treated with high dose cisplatin (group II) was 72.5 % versus 63.8 % in the patients treated with low dose cisplatin weekly (group I) (P=0.051) as in Figure (1), Table (3) with an absolute difference of 8.7 % in both arms regarding the loco-regional recurrence.

The median overall survival for group I was 45.6 months while in group II was 49.7 months. The median 3-year overall survival for group II treated with high dose cisplatin was 100% versus 98.7% in group I treated with low dose cisplatin weekly with significant difference between both of them (P=0.003) as shown in Figure (2), Table (4).

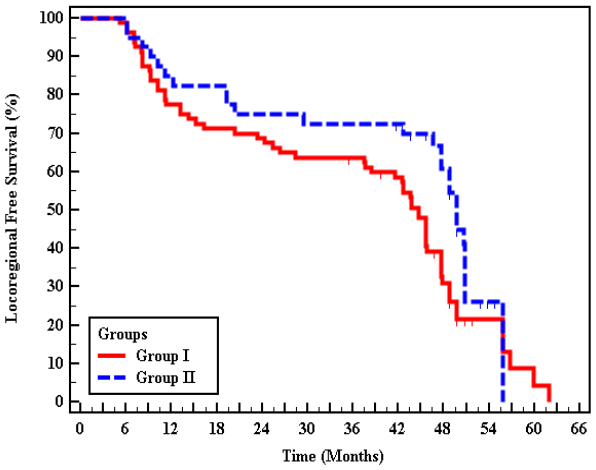

Figure (1): Kaplan-Meier survival curve for Loco-regional free survival with the 2 groups

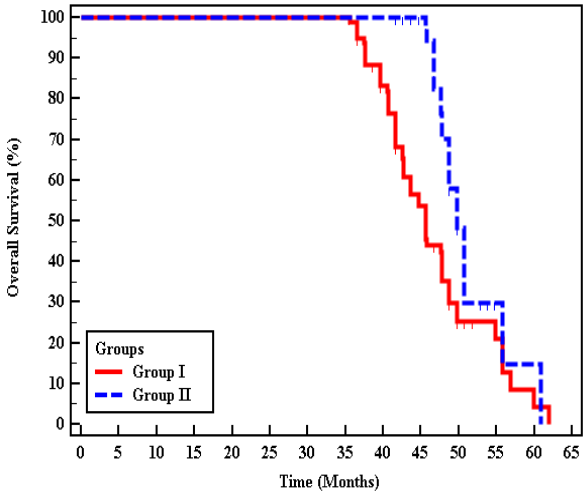

Figure (2): Kaplan-Meier survival curve for overall survival with 2 groups

Toxicity:

Regarding non-hematological toxicities, the most common grade of dysphagia in group (I) was grade II (52.5%) while in (group II) was grade III (55%) but with no statistical difference (P= 0.54). Nausea and vomiting were commonly mild of grade II in both groups (87.5% and 90% respectively). Mucositis was nearly equal in both groups and mostly of grade II (45% and 55% respectively). Xerostomia and dermatitis were mostly of grade II and comparable between both groups nearly in 85% of patients while grade III in less than 20 % of them in both groups. The acute renal toxicity was comparable between both groups and occurred only in less than 30% of patients as mentioned in Table (2).

Concerning the hematological toxicities, anemia grade I and II occurred in 85% of patients of group (I) while in 75% of group (II) with statistically significant difference (P=0.29). Leucopenia of grade I and II occurred in 80% of group (I) patients while occurred in 65% of group (II) patients with strong significant difference (P< 0.001) as shown in Table (2).

Table (1): Comparison between the two studied groups according to different parameters

	Group I (n = 80)	**Group II (n = 40)**	**p**
Age (years)			
Mean ± SD.	59.4 ± 2.4	60.1 ± 3.7	0.248
Median (Min. – Max.)	59 (56 – 64)	60 (54 – 67)	
Sex			
Male	52 (65%)	22 (55%)	0.288
Female	28 (35%)	18 (45%)	
Tobacco smoking			
Current	46 (57.5%)	26 (65%)	0.687
Former	26 (32.5%)	10 (25%)	
Never	8 (10%)	4 (10%)	
Primary anatomical site of tumor			
Oral cavity	6 (7.5%)	4 (10%)	0.794
Oropharynx	50 (62.5%)	26 (65%)	
Hypopharynx/larynx	24 (30%)	10 (25%)	
T			
T1	22 (27.5%)	12 (30%)	0.990
T2	24 (30%)	12 (30%)	
T3	8 (10%)	4 (10%)	
T4	26 (32.5%)	12 (30%)	
N			
N0	16 (20%)	8 (20%)	$^{MC}p=$
N1	12 (15%)	6 (15%)	1.000
N2	48 (60%)	24 (60%)	
N3	4 (5%)	2 (5%)	
Staging			
III	20 (25%)	10 (25%)	0.713
IVa	52 (65%)	24 (60%)	
IVb	8 (10%)	6 (15%)	
ECOG			
0	32 (40%)	16 (40%)	0.946
1	26 (32.5%)	12 (30%)	
>1	22 (27.5%)	12 (30%)	
Start treatment			
2015	30 (37.5%)	16 (40%)	0.553
2016	36 (45%)	20 (50%)	
2017	14 (17.5%)	4 (10%)	
No of chemotherapy cycles			
Mean ± SD.	4.3 ± 1	2.3 ± 0.8	$<0.001^{*}$
Median (Min. – Max.)	4 (2 – 6)	2 (1 – 3)	

SD: Standard deviation t: Student t-test U: Mann Whitney test MC: Monte Carlo
p: p value for comparing between the studied groups *: Statistically significant at $p \leq 0.05$

Table (2): Comparison between the two studied groups according to toxicity

	Group I (n = 80)	**Group II (n = 40)**	**p**
Dysphagia			
Grade II	42 (52.5%)	12 (30%)	0.054
Grade III	32 (40%)	22 (55%)	
Grade IV	6 (7.5%)	6 (15%)	
Nausea/vomiting			
Grade II	70 (87.5%)	36 (90%)	$^{FE}p=$
Grade III	10 (12.5%)	4 (10%)	0.772
Mucositis			
Grade II	36 (45%)	22 (55%)	0.542
Grade III	32 (40%)	14 (35%)	
Grade IV	12 (15%)	4 (10%)	
Xerostomia			
Grade II	66 (82.5%)	32 (80%)	$^{MC}p=$
Grade III	14 (17.5%)	6 (15%)	0.195
Grade IV	0 (0%)	2 (5%)	
Dermatitis			
Grade II	66 (82.5%)	36 (90%)	0.278
Grade III	14 (17.5%)	4 (10%)	
Laryngeal oedema			
Grade II	66 (82.5%)	32 (80%)	$^{MC}p=$
Grade III	14 (17.5%)	6 (15 %)	0.195
Grade IV	0 (0%)	2 (5%)	
Anemia			
Grade I	42 (52.5%)	12 (30%)	$^{MC}p=$
Grade II	26 (32.5%)	18 (45%)	0.029*
Grade III	12 (15%)	8 (20%)	
Grade IV	0 (0%)	2 (5%)	
Leucopenia			
Grade I	32 (40%)	2 (5%)	^{MC}p
Grade II	32 (40%)	24 (60%)	<0.001*
Grade III	16 (20%)	12 (30%)	
Grade IV	0 (0%)	2 (5%)	
Thrombocytopenia			
Grade I	66 (82.5%)	30 (75%)	$^{MC}p=$
Grade II	12 (15%)	6 (15%)	0.243
Grade III	2 (2.5%)	4 (10%)	
Acute renal toxicity			
No	60 (75%)	28 (70%)	0.559
Yes	20 (25%)	12 (30%)	
Response 3M after end of ttt			
Complete Response	52 (65%)	28 (70%)	0.584
Partial Response	28 (35%)	12 (30%)	
Local recurrence			
No	48 (60%)	28 (70%)	0.284
Yes	32 (40%)	12 (30%)	

FE: Fisher Exact **MC: Monte Carlo**

p: p value for comparing between the studied groups *: Statistically significant at $p \leq 0.05$

Table (3): Kaplan-Meier survival curve for overall survival with groups

	Mean	Median	% 3 years	% 5 years	% End of study	Log rank χ^2	Log rank p
Groups							
Group I	46.84	45.67	98.7	4.2	0.0	9.027*	0.003*
Group II	51.51	49.73	100.0	14.9	0.0		

Group I: Dose per cycle is 40 mg/m^2 Group II: Dose per cycle is 100 mg /m^2

Table (4): Kaplan-Meier survival curve for Loco-regional free survival with groups

	Mean	Median	% 3 years	% 5 years	% End of study	Log rank χ^2	Log rank p
Groups							
Group I	36.37	44.63	63.8	4.3	0.0	3.824	0.051
Group II	41.16	49.73	72.5	0.0	0.0		

Group I: Dose per cycle is 40 mg/m^2 Group II: Dose per cycle is 100 mg /m^2

Discussion:

Locally advanced Head and neck cancer accounts for 50–60% of all head and neck cancers, Chemoradiotherapy has been shown to be the gold standard of care in the non-surgical treatment of these individuals. The advantages of employing combined modality therapy for the treatment of locally advanced HNC come with a significant increase in acute toxicity. As a result, combining various protocols of concurrent cisplatin with EBRT has become a focus of research to solve the problem of increased acute toxicity.

Our study is a retrospective observational analysis that compared the two groups of concurrent chemo-radiation in which group I: (cisplatin at a dose of 100 mg/m^2) administered every three weeks and group II: (cisplatin at a dose of 40 mg/m^2) administered every week to assess the toxicity, response and survival.

In our study the most common non-hematological side effect in both study groups was G II nausea and vomiting (87.5%, 90%) in group I & II respectively but statistically not significant (p= 0.772) followed by xerostomia, dermatitis and laryngeal edema with p value (0.195, 0.278 and 0.195 respectively). Dysphagia was statistically non-significant with different grades (p= 0.054), grade II was common in group I in 42 cases (52.5%) and grade III was common in group II in 22 cases (55%). Grade II mucositis developed in 45% in group I while 55% in group II which statistically not significant (p=0.542) while in other studies as Panihar et al. reported in 2021, the mucositis is the common non hematological side effect but also without significant difference. Three weekly cisplatin arm, 63% of the patients had grade III mucositis while 52% of the patients had grade III mucositis in weekly cisplatin arm [13]. Also, Fayette et al. at 2015 in other study reported that mucositis was slightly higher in three weekly arm but it was not statistically significant (p = 0.714) [14].

As regard the hematological toxicity, anemia developed in both groups with statistically significant p value equal 0.029 and leucopenia with p value <0.001. In the others studies, anemia was observed to be in 73% patients of three weekly arm and in 68% patients of weekly cisplatin arm. Leukopenia was significantly higher in three weekly cisplatin arm (p= 0.05), 93% of three weekly cisplatin arm developed leukopenia during the course of treatment while 64% patients in weekly cisplatin arm [14,15]. Thrombocytopenia was also observed to be higher in three weekly cisplatin arm, 41% patients developed thrombocytopenia in three weekly cisplatin arm and 23% in weekly cisplatin arm.

The acute renal toxicity is known side effect of cisplatin and it is dose dependent toxicity. In our study renal toxicity was not statistically significantly but was higher in three weekly cisplatin arm patients (p= 0.559), twenty patients developed acute renal toxicity in three weekly arm and only twelve in weekly cisplatin arm but in others study the acute renal toxicity is significant with p value 0.05 and also more common in the group of cisplatin every 3 weeks [8,16].

Regarding the response, there is no statistically significant difference in response (65% in the 1st group and 70% in 2nd group achieve complete as well as partial response 35% & 30% respectively) between the two arms with (p=0.584), which was similar to the most of the trials with less toxicity in the weekly group [17-19].

Concerns regarding either schedule's survival advantage should be weighed against the incidence of grade III or IV toxicity. In this study, The median 3-year loco-regional free survival in patients treated with high dose cisplatin (group II) was 72.5% versus 63.8% in the patients treated with low dose cisplatin weekly (group I) (P= 0.051) with an absolute difference of 8.7 % in both arms regarding the loco-regional recurrence and the median 3-year OAS for group II treated with high dose cisplatin was 100% versus 98.7% in group I treated with low dose cisplatin weekly with significant difference between both of them (P= 0.003).

However, just a few comparative studies have addressed this critical survival criterion. Homma and his colleagues at 2011 studied weekly cisplatin (40 mg/m²) combined with concurrent RT and resulted in outstanding 2-year OS and local progression-free rates (PFR) of 93.7% and 88.0%, respectively, with complete response in the main site in 98.1% of patients [20].

Gupta et al. at 2009 studied 264 patients with LAHNC. They were treated with weekly cisplatin 30 mg/m^2 combined with conventional RT in a large single institutional retrospective audit from India. The projected 5-year LRC and DFS were 46% and 43%, respectively, whereas the OS was not calculated [17]. In 65 patients with oropharyngeal carcinoma treated with weekly cisplatin at 30 mg/m^2 concurrent with 3D-CRT, Krstevska et al. reported inferior 2-year local relapse-free, regional relapse-free, loco-regional relapse-free, DFS, and OS rates of 48.8%, 57.8%, 33.2%, and 49.7%, respectively [21]. In stage IV HNSCC patients treated with low dose weekly cisplatin (20 to 30 mg/m²) concurrent with RT, Kang et al. reported a median OS of 42.7 months and a 3-year DFS rate of 72.8 % [22].

Conclusion:

Concurrent chemo-radiotherapy with cisplatin in HNSCC is associated with different acute toxicities. With concurrent chemo-radiation, the weekly cisplatin is more tolerable alternative for the standard every 3 weeks cisplatin with more favorable toxicity profile, ease of administration, adequate cumulative total dose, and same response rate and loco-regional control rate while the other arm (every 3 weeks cisplatin) is better than the weekly one in the overall survival rate.

Ethical considerations

Study protocol was submitted for approval by the Institutional Research Board (IRB), Faculty of Medicine at Mansoura University (R.21.08.1417).

Conflict of interest

The authors declare that there is no conflict of interest.

Authors' contributions

All authors read and approved the final manuscript.

References:

1. Jemal A, Bray F, Center MM, et al. Global cancer statistics. CA: a cancer journal for clinicians. 2011;61(2):69-90.
2. Kulkarni MR. Head and neck cancer burden in India. Int J Head Neck Surg. 2013;4(1):29-35.
3. Abo-Touk NA, editor Cancer Registry Report in Mansoura University Hospital, Egypt in 2015. Forum of Clinical Oncology; 2020: Sciendo.
4. Mohanti B, Bahadur S, Lal P, et al. Cancers of the head and neck. Textbook of Radiation Oncology, Principles and Practice New Delhi: BI Churchill Livingstone. 2000:131-99.
5. Sambargi UC, Mahesh D, Pai A, et al. Recent advances in chemotherapy for head and neck cancers. Journal of Orofacial Sciences. 2012;4(1):15.
6. Mashhour K, Hashem W. Cisplatin Weekly Versus Every 3 Weeks Concurrently with Radiotherapy in the Treatment of Locally Advanced Head and Neck Squamous Cell Carcinomas: What Is the Best Dosing and Schedule? Asian Pacific journal of cancer prevention: APJCP. 2020;21(3):799.
7. Otty Z, Skinner MB, Dass J, et al. Efficacy and tolerability of weekly low-dose cisplatin concurrent with radiotherapy in head and neck cancer patients. Asia-Pacific Journal of Clinical Oncology. 2011;7(3):287-92.
8. Noronha V, Joshi A, Patil VM, et al. Once-a-week versus once-every-3-weeks cisplatin chemoradiation for locally advanced head and neck cancer: a phase III randomized noninferiority trial. Journal of Clinical Oncology. 2018;36(11):1064-72.
9. Rawat S, Srivastava H, Ahlawat P, et al. Weekly versus three-weekly cisplatin-based concurrent chemoradiotherapy as definitive treatment in head and neck cancer-where do we stand? The Gulf journal of oncology. 2016;1(21):6-11.
10. Network NCC. NCCN clinical practice guidelines in oncology, NCCN Evidence Blocks: Head and neck cancers version 2.2017. 2017.
11. Schwartz LH, Litière S, De Vries E, et al. RECIST 1.1—Update and clarification: From the RECIST committee. European journal of cancer. 2016;62:132-7.
12. Savarese D. Common terminology criteria for adverse events. UpToDate Waltham, MA: UpToDate. 2013.
13. Panihar C, Rawat S, Singotia L, et al. A Prospective Randomised Comparative Study Between Weekly Cisplatin Versus Three Weekly Cisplatin with Radiotherapy in Unresectable Locally Advanced Head and Neck Cancer. Indian Journal of Otolaryngology and Head & Neck Surgery. 2021:1-6.
14. Fayette J, Molin Y, Lavergne E, et al. Radiotherapy potentiation with weekly cisplatin compared to standard every 3 weeks cisplatin chemotherapy for locoregionally advanced head and neck squamous cell carcinoma. Drug design, development and therapy. 2015;9:6203.
15. Espeli V, Zucca E, Ghielmini M, et al. Weekly and 3-weekly cisplatin concurrent with intensity-modulated radiotherapy in locally advanced head and neck squamous cell cancer. Oral oncology. 2012;48(3):266-71.

16. Colevas AD. Commentary on "Weekly Low-Dose Versus Three-Weekly High-Dose Cisplatin for Concurrent Chemoradiation in Locoregionally Advanced Non-Nasopharyngeal Head and Neck Cancer: A Systematic Review and Meta-Analysis of Aggregate Data". The oncologist. 2017;22(9):1022.
17. Gupta T, Agarwal JP, Ghosh-Laskar S, et al. Radical radiotherapy with concurrent weekly cisplatin in loco-regionally advanced squamous cell carcinoma of the head and neck: a single-institution experience. Head & neck oncology. 2009;1(1):1-12.
18. Helfenstein S, Riesterer O, Meier UR, et al. 3-weekly or weekly cisplatin concurrently with radiotherapy for patients with squamous cell carcinoma of the head and neck–a multicentre, retrospective analysis. Radiation Oncology. 2019;14(1):1-10.
19. Rades D, Seidl D, Janssen S, et al. Comparison of weekly administration of cisplatin versus three courses of cisplatin 100 mg/m 2 for definitive radiochemotherapy of locally advanced head-and-neck cancers. BMC cancer. 2016;16(1):1-8.
20. Homma A, Inamura N, Oridate N, et al. Concomitant weekly cisplatin and radiotherapy for head and neck cancer. Japanese journal of clinical oncology. 2011;41(8):980-6.
21. Krstevska V, Stojkovski I, Zafirova-Ivanovska B. Concurrent radiochemotherapy in locally-regionally advanced oropharyngeal squamous cell carcinoma: analysis of treatment results and prognostic factors. Radiation Oncology. 2012;7(1):1-14.
22. Kang MH, Kang JH, Song H-N, et al. Concurrent chemoradiation with low-dose weekly cisplatin in locally advanced stage IV head and neck squamous cell carcinoma. Cancer research and treatment: official journal of Korean Cancer Association. 2015;47(3):441.