Received:
12 June 2017

Revised:
4 September 2017

Accepted:
11 September 2017

<https://doi.org/10.1259/bjr.20170442>

Cite this article as:

Jacinto JCK, Co J, Mejia MB, Regala EE. The evidence on effectiveness of weekly vs triweekly cisplatin concurrent with radiotherapy in locally advanced head and neck squamous cell carcinoma (HNSCC): a systematic review and meta-analysis. *Br J Radiol* 2017; **90**: 20170442.

SYSTEMATIC REVIEW

The evidence on effectiveness of weekly vs triweekly cisplatin concurrent with radiotherapy in locally advanced head and neck squamous cell carcinoma (HNSCC): a systematic review and meta-analysis

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Objective: This study aims to synthesize the current available evidences on the effectiveness of weekly vs triweekly cisplatin concurrent with radiotherapy in the primary and adjuvant treatment of locally advanced head and neck squamous cell carcinoma (HNSCC).

Methods: A systematic review and meta-analysis of literature were undertaken to assess the effectiveness of weekly vs triweekly schedule in primary and adjuvant treatment for HNSCC with adverse risk features. Search of relevant articles from electronic database from 2000 to March 2016 and appraisal of studies were done.

Results: Only one randomized controlled trial (RCT) and six retrospective studies were included in this review. The RCT showed less severe mucositis (75 vs 38.5%, $p = 0.012$) and more patients receiving at least 200 mg/m² (62.5% vs 88.5%, $p = 0.047$) of cisplatin in triweekly arm. There was no difference in 1-year progression-free survival (60% vs 71.1%, $p = 0.806$) and 1-year overall survival (OS) (71.6 vs 79.3%, $p = 0.978$) between the weekly and triweekly arm. Pooling of data from six studies showed no difference in 5-year progression-free survival (RR 0.84, 95% CI 0.67–1.07),

5-year OS (RR 0.88, 95% CI 0.73–1.07), severe renal events (RR 0.66, 95% CI 0.42–1.04), severe mucositis (RR 0.92, 95% CI 0.71–1.21), severe dermatitis (RR 0.61, 95% CI 0.37–1.03), treatment interruptions (RR 1.06, 95% CI 0.74–1.52) and number of patients receiving at least 200 mg/m² (RR 0.83, 95% CI 0.67–1.03).

Conclusion: The current evidence showed that weekly schedule is not superior to triweekly in improving oncological outcomes and decreasing early effects of treatment. In the absence of compelling data, triweekly schedule should remain the standard of care while more RCTs are warranted.

Advances in knowledge: While some have proposed that low-dose weekly cisplatin is safer and less toxic, this study emphasized that there is no difference in acute toxicity of the two schedules and it is safe to utilize high-dose cisplatin every 3 weeks to reach the threshold dose of 200 mg/m² faster. Uniquely, this study excluded nasopharyngeal cancer patients as the biology and treatment response are different with other HNSCC.

INTRODUCTION

Curative non-surgical treatment for locoregionally advanced head and neck squamous cell carcinoma (HNSCC) consists of radiotherapy concurrent with chemotherapy.¹ The latest update of meta-analysis of chemotherapy in head and neck cancer showed an absolute improvement of 4.5% in 5-year overall survival (OS) with the addition of chemotherapy to radiotherapy with greatest effect of 6.5% in the concurrent setting using platinum-based chemotherapy.² Long-term follow-up revealed benefit across all head and neck tumour

sites but was more pronounced in oropharyngeal and laryngeal cancers.³ Concurrent chemoradiation is also the standard of care in the adjuvant treatment of resectable HNSCC with presence of adverse risk features. Although single agent platinum-based chemotherapy was established as drug of choice owing to compelling evidence in several trials, there are no clear guidelines for administration of chemotherapy.⁴

Cisplatin is an alkylating agent that acts by producing DNA cross linkages and is known for its emetogenic, nephrotoxic,

ototoxic and myelosuppressive side effects. A dose of 100 mg/m² administered every 3 weeks on days 1, 22 and 43 with concurrent standard fractionated radiation therapy is the most widely utilized and studied regimen.² The advantage of triweekly adjuvant cisplatin concurrent with radiation in improving survival among resected HNSCC with positive margins and extracapsular extension has been established.⁵ Furthermore, triweekly schedule was superior in the larynx preservation trial and in the definitive treatment of nasopharyngeal carcinoma.^{6,7}

Some proponents have suggested the use of alternate schedule hypothesizing that low to moderate dose cisplatin given weekly will lessen the nephrotoxic and emetogenic effects of cisplatin without compromising oncologic outcomes. While the concept is biologically sound as prolonging the duration of cisplatin exposure with radiation will theoretically increase its radiosensitizing effect, there is paucity of evidence showing equivalence of the two chemotherapy schedules.^{8,9}

A previous meta-analysis was done that compared oncologic outcomes and side effects of weekly and triweekly cisplatin schedules across all head and neck sites including nasopharynx-only trials.¹⁰ The analysis included at least 237 nasopharyngeal cancer patients. The study concluded that oncologic outcomes were similar, with weekly schedule having higher dermatitis and treatment interruptions but lower gastrointestinal toxicity. The triweekly arm schedule showed less severe mucositis for non-nasopharynx site. This paper aims to synthesize current available evidences on the effectiveness of weekly *vs* triweekly chemotherapy concurrent with radiotherapy in the primary treatment of HNSCC or in resected HNSCC with adverse risk features. Specifically, it aims to report oncologic outcomes and toxicities of both schedules of studies from 2000 to March 2016. This analysis attempts to limit the number of nasopharyngeal carcinomas.

METHODS AND MATERIALS

Study selection

Both published and unpublished English language studies from the last 16 years (2000–March 2016) were sought using the search terms “weekly” AND “cisplatin dosage” and “head and neck cancer” in EBSCO platform (MEDLINE Complete, CINAHL Plus, Proquest Health and Medical Complete, Academic Search Complete, Biomedical Reference Collection Basic) and PubMed. Additional search using clinicaltrials.gov, International Clinical Trials Registry Platform and CENTRAL was done to look for ongoing trials. Titles of the papers were scanned for possible eligibility and subsequent review of specific abstracts were done. The reference lists of all identified publications were searched for additional studies. Google scholar search was also performed. Content experts were contacted in order to obtain additional references and unpublished trials. Electronic mail to corresponding authors for full text, data clarification and isolation were done.

Criteria for considering studies in this review

Types of participants

This review included studies of patients who underwent definitive chemoradiation for HNSCC or adjuvant chemoradiation

for resected locally advanced HNSCC with adverse risk features. Studies that included participants with non-HNSCC such as nasopharynx, paranasal sinus, thyroid and salivary gland cancer will be included as long as majority are HNSCC.

Types of interventions

The intervention investigated was the use of cisplatin-based chemotherapy concurrent with radiotherapy. The experimental arm consisted of patients who received weekly dose of cisplatin (30–40 mg/m²) and the control arm received high-dose cisplatin every 3 weeks (80–100 mg/m²). Concurrent radiotherapy was given either by conventional or intensity modulated radiotherapy. Patients supposed to receive other concurrent chemotherapeutic agents or targeted therapy aside from cisplatin were excluded.

Outcomes

The main outcomes were 5-year OS and 5-year progression-free survival (PFS). OS was defined as the number of patients alive for the specified time from the date of randomization or initiation of treatment. PFS was defined as the number of patients with cancer-related progression for a specified time from the date of randomization or initiation of treatment.

Secondary outcomes were occurrence of (1) severe renal events, (2) severe mucositis, (3) severe dermatitis, (4) radiotherapy treatment interruptions and (5) number of patients receiving greater than 200 mg/m² of cumulative cisplatin dose.

Severe renal events, mucositis and dermatitis were defined as Grade 3–4 in both Radiation Therapy Oncology Group, European Organisation for Research and Treatment of Cancer or National Cancer Institute Common Terminology Criteria for Adverse Events.^{11,12} Radiation treatment interruption is defined as any disruption in radiotherapy treatment course for any reason.

Types of studies

This review included one RCT and retrospective comparative studies in the background of scarcity of evidence as to be able to obtain at least Level III evidence. This is in consonance with the Oxford Center for Evidence-based Medicine wherein retrospective cohorts are considered as Level III evidence.¹³

With the majority of the studies having a retrospective design, the risk of selection bias cannot be eliminated. Three retrospective studies allocated patients with poorer performance status and older age to the weekly cisplatin arm.

Assessment of methodological quality

Two reviewers (JM, JLC) conducted independent critical appraisals of the eligible studies using a standardized critical appraisal form McMaster critical review form—quantitative studies.¹⁴ There was no disagreement on the decision to include or exclude a study.

Data collection and synthesis

Data were extracted independently by the two reviewers using a purpose built Microsoft excel sheet. Data extraction included author, year, title, study design, sample size, study population,

Figure 1. Preferred reporting items for systematic reviews and meta analyses flowchart.

intervention, control and outcomes. Statistical pooling of outcomes was done using Review Manager Software 5.3 (Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Heterogeneity was assessed using χ^2 analysis through the same software. An overall summary of recommendation was developed using the National Health and Medical Research Council of Australia Body of Evidence framework. This framework has five components (evidence base, consistency, clinical impact, generalizability and applicability) and an overall body of recommendation.¹⁵

RESULTS

Search results

The search yielded 180 abstracts from EBSCO platform and 193 abstracts from PubMed (Figure 1). 161 studies were excluded owing to duplication. Upon review of the titles, 196 studies were excluded owing to one-arm study (54), use of targeted treatment (22), intraarterial chemotherapy (19), review (4), protocol study (1), basic science (5), non-head and neck site (8), RT technique (4), other planned chemotherapy aside from cisplatin (45), recurrence and palliation (14), chemotherapy sequence (2), use of primary radiotherapy alone (3), use of hyperthermia (1),

sensorineural effect (1), surgical neck dissection (3), use of intra-tumoral cisplatin (3), use of interferon (1), use of antifolates (1), use of stealth liposome (1). The full texts of the 16 remaining abstracts were reviewed. 10 papers were removed as they were one-arm studies (3), use of other planned chemotherapy other than cisplatin (6), use of hyperfractionation (1). Three papers were identified using purling.¹⁶⁻¹⁸ Two studies are only available in abstract form.^{17,18} A total of seven papers were eligible^{16,19-23} (Figure 1).

Appraisal results

All studies included in this review were of sound methodological quality (Table 1). All studies have clear purpose, relevant background and justification for conducting the study. One RCT and six retrospective two-arm studies were included in the analysis. The RCT and two retrospective studies had similar population characteristics on each arm in terms of age, tumour characteristics and TNM staging, sites of disease, rates of extracapsular extension and positive margins and performance status. The remaining studies had older and of poor performance status in the weekly arm. Three trials were minimally contaminated with nasopharyngeal cancer

Table 1. National Health and Medical Research Council evidence statement form

Components	Grade	Comments
Evidence base		
Overall survival (OS)	C	Only one study was a randomized controlled trial (RCT) and two studies were retrospective arm design. ^{19,24}
Progression-free survival (PFS)	C	Two studies were retrospective arm design. ^{19,24}
Severe renal event	C	Five studies were retrospective arm design. ^{16,19,20,23,24} and one RCT. ²²
Severe mucositis	C	Five studies were retrospective arm design. ^{16,19,20,23,24} and one RCT. ²²
Severe dermatitis	C	Four studies were retrospective arm design ^{20,21,23,24} and one RCT. ²²
Radiotherapy treatment interruption	C	Four studies were retrospective arm design ^{20,21,23,24} and one RCT. ²²
Received > 200 mg/m ² cumulative cisplatin dose	C	Three studies were retrospective arm design ^{19,23,24} and one RCT. ²²
Consistency		
OS	A	Figure 2 showed data from both studies crossed the line of no effect. ^{19,24} Overall estimate showed no significant difference in OS.
PFS	A	Figure 3 showed data from both studies crossed the line of no effect. ^{19,24} Overall estimate showed no significant difference in PFS.
Severe renal event	A	Figure 4 showed data from all included studies crossed the line of no effect. ^{16,19,20,23,24} Overall estimate showed no significant difference in occurrence of severe renal events.
Severe mucositis	C	In Figure 5 , five studies were included in measuring severe mucositis. Three studies showed no significant difference between two regimens. ^{16,19,23} One study had more severe mucositis in the triweekly arm ²⁴ while the other had more in the weekly arm. ²⁰ Overall estimate showed no significant difference in occurrence of severe mucositis. While in the randomized trial included, there is more severe mucositis in the weekly arm. ²²
Severe dermatitis	B	In Figure 6 , four studies were included in measuring severe dermatitis. Four studies showed no significant difference between two regimens. ^{20,21,23} One study had more severe dermatitis in the triweekly arm. ²⁴ Overall estimate showed no significant difference in occurrence of severe dermatitis.
Radiotherapy treatment interruption	A	Figure 7 showed data from all included studies crossed the line of no effect. ^{20,21,23,24} Overall estimate showed no significant difference in occurrence of radiotherapy treatment interruption.
Received > 200 mg/m ² cumulative cisplatin dose	B	Figure 8 showed data from two included studies crossed the line of no effect. ^{21,23} Overall estimate showed no significant difference in number of patients who received > 200 mg/m ² cumulative cisplatin dose. One RCT showed more patients in the triweekly arm received > 200 mg/m ² cumulative cisplatin dose.
Clinical impact		
OS	B	Both cisplatin dose schedule can be confidently used without compromising OS and PFS. Clinical decision will depend on which schedule is more applicable in one's setting.
PFS	B	
Severe renal event	B	There is no significant difference in toxicity profile (severe renal event, mucositis and dermatitis) of both schedules. Clinical decision will depend on which schedule is more applicable in one's setting.
Severe mucositis	B	
Severe dermatitis	B	
Radiotherapy treatment interruption	B	Both schedules will not affect completion of radiotherapy and receipt of acceptable cumulative cisplatin dose. Clinical decision will depend on which schedule is more applicable in one's setting.
Received > 200 mg/m ² cumulative cisplatin dose	B	
Generalizability		
OS	B	The studies had similar samples included. On review of baseline characteristics, both studies had older population in the weekly arm. One study had difference in performance status, pre-treatment weight and creatinine clearance. Findings may be generalizable to all patients with head and neck squamous cell carcinoma (HNSCC) for chemoradiation.
PFS	B	
Severe renal event	B	Among five studies, two gave weekly cisplatin to older patients and with poorer performance status. ^{23,24} Findings on severe renal event may be generalizable to all patients with HNSCC for chemoradiation.

(Continued)

Table 1. (Continued)

Components	Grade	Comments
Severe mucositis	B	Among five studies, two gave weekly cisplatin to older patients and with poorer performance status. ^{23,24} Findings on severe mucositis may be generalizable to all patients with HNSCC for chemoradiation.
Severe dermatitis	B	Among four studies, two gave weekly cisplatin to older patients and with poorer performance status. ^{23,24} Findings on severe dermatitis may be generalizable to all patients with HNSCC for chemoradiation.
Radiotherapy treatment interruption	B	Among four studies, two gave weekly cisplatin to older patients and with poorer performance status. ^{23,24} Findings on the incidence of radiotherapy treatment interruption may be generalizable to all patients with HNSCC for chemoradiation.
Received > 200 mg/m ² cumulative cisplatin dose	B	Among three studies, one gave weekly cisplatin to older patients and with poorer performance status. ²³ Findings on the more than 200 mg/m ² cumulative cisplatin dose may be generalizable to all patients with HNSCC for chemoradiation.
Applicability		
OS	A	The equivalence of triweekly and weekly cisplatin schedule in this systematic review shows the value of using triweekly regimen in a limited-resource setting as this schedule is more cost-effective without compromising survival and PFS benefit of chemoradiation and without incurring more toxicity.
PFS	A	
Severe renal event	A	
Severe mucositis	A	
Severe dermatitis	A	
Radiotherapy treatment interruption	A	
Received > 200 mg/m ² cumulative cisplatin dose	A	
Overall		
OS	B	The body of evidence in this study can be trusted to guide practice in most situations.
PFS	B	
Severe renal event	B	
Severe mucositis	B	
Severe dermatitis	B	
Radiotherapy treatment interruption	B	
Received > 200 mgm ⁻² cumulative cisplatin dose	B	

HNSCC, head and neck squamous cell carcinoma; OS, Overall survival; PFS, progression-free survival; RCT, randomized controlled trial.

patients. One study was contaminated with seven patients who received carboplatin than cisplatin. All studies had measurable outcomes.

Main results

Randomized controlled trial

Only one RCT investigated the role of concurrent chemoradiation either with weekly (40 mg/m²) or triweekly (100 mg/m²) cisplatin in locally advanced HNSCC. The study included post-operative oral cavity cancers with pathological documentation for extracapsular spread of lymph node, positive surgical margin or N2 disease. Initially, study was expected to accrue 371 patients but was only able to randomize 50 patients. Results showed that 1-year locoregional recurrence-free survival and OS were not significantly different for both arm, with 60% vs 71.1% ($p = 0.806$) and 71.6% vs 79.3% ($p = 0.978$) for weekly and triweekly, respectively.

More patients were able to receive > 200 mg/m² cumulative cisplatin dose in triweekly arm 88.5% vs 62.5% ($p = 0.047$). Toxicity profile showed more severe mucositis for weekly 75% vs 38.5% ($p = 0.012$), while no difference in acute renal toxicity and dermatitis.²²

Retrospective studies

Pooled analysis from the trials showed no difference in all outcomes comparing weekly and triweekly cisplatin schedules. Pooled data from two studies showed that the benefit ratio of OS and PFS at 5 years are 0.88 (CI 0.73–1.07) and 0.84 (CI 0.67–1.07), respectively. The risk of development of severe renal event, severe mucositis and severe mucositis are 0.66 (0.42–1.04), 0.92 (0.71–1.21) and 0.61 (0.37–1.03), respectively. Risk of treatment interruptions from four studies showed risk ratio of 1.06 (CI 0.74–1.52). While the benefit of receiving at least 200 mg/m² is 0.83 (CI 0.67–1.03) (Figures 2–8).

Figure 2. Weekly vs triweekly cisplatin arm. Overall survival at 5-year follow up.

DISCUSSION

This review presented the current overall evidence on using weekly cisplatin vs triweekly cisplatin on primary treatment of HNSCC and as adjuvant treatment for adverse risk HNSCC. In the pooled analysis, 5-year OS, PFS, renal toxicity, severe mucositis, treatment interruptions and number of patients receiving at least 200 mg/m² were similar in both arms.

Based on the National Health and Medical Research Council, additional levels and grades for recommendations for developers of guidelines, this review recommends that the findings in this review in terms of PFS, OS, severe renal event, severe mucositis, severe dermatitis, radiation treatment interruption and patients receiving at least 200 mg/m² cumulative cisplatin dose can be trusted to guide clinical decision in most situations.

This review concurred with the previous meta-analysis done in terms of oncologic outcomes, dermatitis and mucositis.²⁵ Our systematic review differed as we included one RCT and one recent large retrospective study. We analysed the data differently. We excluded studies with population of pure nasopharyngeal cancer, as the biology and behavior of this malignancy are different from other HNSCC. We likewise included longer oncologic follow-up up to 5 years, treatment interruptions and number of patients receiving 200 mg/m² cumulative cisplatin dose.

One study from India by Noronha *et al*²⁶ presented at the 2017 Annual ASCO Meeting randomized 300 HSNCC patients who will undergo definitive or adjuvant chemoradiation to weekly 30 mg/m² or triweekly 100 mg/m² cisplatin. About 87% of patients had oral cavity cancer and 93% had adjuvant intent. Results showed significantly more Grade 3–4 toxicity with the weekly regimen, specifically hearing dysfunction, while mucositis was the same. The study did not report on nephrotoxicity, dermatitis and cumulative cisplatin dose. In terms of oncologic outcomes, after 2-years follow up, both OS and PFS were the same. There were significantly more locoregional failures with the weekly

regimen although recognizing the lower than typical dose employed in the weekly regimen of the trial (30 mg/m² instead of 40 mg/m²). This concluded that triweekly regimen remains the standard of care.

Concurrent chemoradiation was established as the standard of care in locally advanced HNSCC. The same regimen is used as adjuvant treatment for patients with positive margins and presence of extracapsular extension post-operatively. It is associated with early treatment interruptions and lower compliance rate compared with radiotherapy alone.^{5,27,28} Attempts have been made by changing cisplatin schedule to lessen toxicity profiles while maintaining the same oncologic outcome.

Platinum-based antineoplastic agents are chemotherapeutic drugs that exert their anticancer effect by causing cross-linking of DNA leading to inhibition of its synthesis and induction of apoptosis.²⁹ Amongst all members of this class, cisplatin is the most commonly used and studied for HNSCC and three studies have shown its superiority over carboplatin.^{30,31} Several dosing schedules have been used in among studies on concurrent chemoradiation in the definitive and adjuvant setting, however, efficacy has not been compared to show superiority of one over the other.⁴

The high emetic, nephrotoxic, neurotoxic and ototoxic potential of bolus cisplatin lead to the assumption that moderate dose of cisplatin given weekly could lead to better tolerability, less systemic toxicities and improvement in compliance. Review on pharmacokinetics of cisplatin has showed possible preference on weekly schedule over triweekly as more frequent administration could provide more radiosensitizing effect and lesser toxicity profile without compromising efficacy.³² This has been supported by modeling studies wherein in murine fibroblast, the radiosensitization of cisplatin is optimal at 1 µg ml⁻¹ concentration and decreases with increasing dose given less frequently.³³ Daily administration of cisplatin concurrent with radiotherapy

Figure 3. Weekly vs triweekly cisplatin arm. Progression-free survival at 5year follow up.

Figure 4. Weekly vs triweekly cisplatin arm. Occurrence of severe renal events.

increased local control to 35% vs 6% compared with weekly cisplatin.^{34,35} While triweekly schedule could prevent development of distant metastasis by addressing micrometastatic disease, no data has supported this hypothesis at the moment. In other malignancies such as cervical and esophageal, weekly schedule has been standard of care.

There is a paucity of data from RCTs investigating weekly vs triweekly cisplatin schedule. Previous one arm study trials that investigated the use of moderate dose of cisplatin concurrent with radiation showed good compliance rate from 59% to up to 100% compliance rate for chemotherapy.^{36–40} Good disease-free survival and OS comparative to triweekly arm were reported. However, one trial reported lower 3year disease-free survival and OS at 29 and 34%, respectively.⁴

The two regimens seem to have similar oncologic outcomes as these may be affected by the cumulative cisplatin dose rather than the dosing schedule.⁴² However, it should be noted that older, alcohol consumers and patients with less pretreatment and creatinine clearance were likely to be given weekly cisplatin, while those patients with high T and N stage were likely to be assigned in triweekly arm.

One of the main reasons of shifting from triweekly to weekly schedule is when it will be given to patients with low renal reserve. Previous studies have shown that the use of high dose triweekly cisplatin is associated with more acute toxicities up to 41% to 77% including renal toxicities.^{5,28} Our review showed that there is no difference in the incidence of severe renal events in either arm. This may be explained by selection bias in which those who had decreased initial renal function was assigned to

weekly arm but the risk or lack thereof will not be confirmed unless new randomized clinical trials are performed. Another reason for the lack of difference is the aggressive hydration for patients given with high dose triweekly chemotherapy.

The occurrence of dermatitis and mucositis is expected during the course of radiotherapy, but is earlier in the concomitant chemoradiation setting. Current trials have mixed results on the occurrence of mucositis among patients being treated with either weekly or triweekly cisplatin. In the trials done comparing chemoradiation, with chemotherapy given every 3 weeks, to radiation treatment alone, rates of severe mucositis were relatively high ranging from 41 to 65%.^{6,28} In contrast, one-arm study on the tolerability of weekly cisplatin has acceptable severe mucositis occurrence ranging from 18 to 35.2%.^{37,39} In the review, most of the trials showed no significant difference in the occurrence of severe mucositis and dermatitis, except for two trials.^{20,24} This may be owing to difference in baseline characteristics in the included patients.

Decreased compliance to treatment owing to intolerable early effects of treatment may prolong overall treatment time that may in turn decrease local control and overall survival. Studies on adjuvant radiotherapy with concurrent triweekly chemotherapy also reported that only 49 to 61% of the patients received the planned three cycles of cisplatin.^{5,28}

Some trials reported the value of cumulative cisplatin dose and showed that patients receiving two doses of cisplatin at 100 mg/m² vs three doses showed no significant difference in oncologic outcomes suggesting that the cisplatin threshold dose is 200 mg/m².^{2,42} One study reviewed evidences on this and suggested that

Figure 5. Weekly vs triweekly cisplatin arm. Occurrence of severe mucositis.

Figure 6. Weekly vs triweekly cisplatin arm. Occurrence of severe dermatitis.

the total dose of cisplatin administered is more important than the schedule in HNSCC and NPC. Among the five trials dealing with HNSCC, four had total cisplatin dose ranging from 210 to 300 mg/m² and all showed improvement in OS. The only one of the five trials that did not show survival benefit had cisplatin cumulative dose at 140 mg/m².⁴

One retrospective study suggested weekly 50 mg/m² to have higher cumulative cisplatin dose compared with triweekly 100 mg/m² with comparable toxicity, however, significantly more patients in the weekly regimen have better performance status that could tolerate more cisplatin. The triweekly arm's mean cisplatin dose is 199.4 mg/m², approaching the minimum threshold. For efficacy of regimens, this study recognized that it did not have the power to compare and no conclusions can be drawn owing to significant differences among patients.⁴³ Our pooled data showed trend favouring triweekly regimen in reaching the threshold dose compared with more conventional weekly dose of 30–40 mg/m².

Alternative regimens have been proposed aside from alteration of cisplatin schedule for certain subset of patients considered to be intolerant of cisplatin such as replacement with carboplatin. This has been tested in several studies but did not show superiority over cisplatin based chemotherapy but is well tolerated by elderly patients.^{44–46} Another option is the use of cetuximab instead of chemotherapy. The addition of cetuximab with radiotherapy increases OS compared with radiotherapy alone, with same rates of toxicities except occurrence of acneiform rash with cetuximab. Other strategies such as aggressive hydration and medical management may also be investigated.

Financial consideration has been an issue in the delay of administration of optimal treatment in the low to middle income

countries. While weekly regimen may be perceived as more economical than triweekly arm, in our local setting, the total cost of triweekly schedule is around \$900 or Php45,000 including overnight hospital admissions, hydration, pre and post chemotherapy medications while average total cost for weekly schedule is around \$1500 or Php75,000 as an outpatient basis. While this may suggest cost-effectiveness of triweekly arm, a thorough analysis and formal cost-effectiveness study is necessary to arrive at conclusion.

The major limitation of this systematic analysis is the inclusion of only one RCT and the rest are retrospective studies. This mirrors the lack of completed RCTs despite the vast number of HNSCC. Retrospective studies are limited by selection bias as assignment of patients in either arm reflects institutional practice. Older, poor-performing and medically unfit patients are usually assigned to weekly arm while better-performing and higher stage patients are assigned to triweekly arm.^{19,23,24} Patients who underwent weekly cisplatin initially presented with significantly lower weight prior to treatment with mean weight of 65 kg compared with the triweekly arm with mean weight of 71 kg ($p = 0.021$).²⁴ Patients who presented with advanced stage were more likely to receive triweekly cisplatin.²⁰

There may be the existence of a novel clinical pathway for selecting patients appropriate for each regimen. Currently, the choice of regimen relies on the clinical judgment of the attending physician/s and/or local practice guidelines. While there may be a specific subset of patients in whom weekly concurrent cisplatin is more appropriate, this population is yet to be determined.

Toxicities of cisplatin are not limited to mucositis and renal events. Studies have documented the occurrence of neutropenia, neurotoxicity and ototoxicity. However, these were

Figure 7. Weekly vs triweekly cisplatin arm. Number of patients with radiation treatment interruptions.

Figure 8. Weekly vs triweekly cisplatin arm. Number of patients receiving at least 200 mg/m² cumulative cisplatin dose.

not emphasized by published studies comparing weekly and triweekly regimen. Also, to our knowledge, no studies have been published presenting the late effects and long-term sequelae of addition of cisplatin with radiation. A RCT is recommended to eliminate selection bias and be able to report, aside from oncologic outcomes and side effects, patient reported outcomes such as quality of life and symptom assessment while on treatment and thereafter.

No large Phase III study has validated the superiority of triweekly or weekly concurrent cisplatin schedule with radiotherapy. We are in anticipation of the publication of the study by Noronha et al²⁶ and the final results of the two ongoing RCTs by Japan Clinical Oncology Group and Italian Association of Head and Neck Oncology. Until more RCTs are completed, in the absence

of superiority of weekly cisplatin, triweekly cisplatin still remains the standard of care for HNSCC.

CONCLUSION

This review showed no difference in outcomes between weekly and triweekly cisplatin schedules in terms of OS, PFS, incidence of severe renal events, severe mucositis, severe dermatitis, radiotherapy treatment interruption and patients receiving at least 200 mg/m² cumulative cisplatin dose. In a limited resource setting, triweekly regimen can be confidently adopted without compromising outcomes and toxicity profiles, with it being more economical, hence, subsequently increasing compliance rate. In the absence of superiority of weekly cisplatin schedule and until the release of more clinical trials, triweekly cisplatin schedule should remain the standard of care for locally advanced HNSCC.

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