

MINI-REVIEW

Three Weekly Versus Weekly Cisplatin as Radiosensitizer in Head and Neck Cancer: a Decision Dilemma

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Abstract

Cisplatin-based concurrent chemoradiation plays an undisputed key role as definitive treatment in unresectable patients with locally advanced squamous cell carcinoma head and neck or as an organ preservation strategy. Treatment with 100 mg/m² 3-weekly cisplatin is considered the standard of care but is often associated with several adverse events. The optimum drug schedule of administration remains to be defined and presently, there is insufficient data limiting conclusions about the relative tolerability of one regimen over the other. This review addresses regarding the optimal dose schedule of cisplatin focusing mainly on three-weekly and weekly dose of cisplatin based concurrent chemoradiotherapy in locally advanced head and neck cancer with an emphasis on mucositis, dermatitis, systemic toxicity, compliance, and treatment interruptions. To derive a definitive conclusion, large prospective randomized trials are needed directly comparing standard 3-weekly cisplatin (100 mg/m²) with weekly schedule (30 - 40 mg/m²) of concurrent cisplatin based chemoradiotherapy in locally advanced squamous cell carcinoma head and neck.

Keywords: Head and neck cancer - cisplatin - radiosensitization - treatment schedule decisions

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Introduction

Head and neck cancer is the sixth most common cancer worldwide with an estimated annual burden of 6, 33,000 incident cases and 3, 55,000 deaths (Jemal et al., 2011). Overall 57.5% of the total head and neck cancers occur in Asia, accounting for approximately 30% of all cancers in India (Kulkarni et al., 2013). In developing countries approximately 80% of cases present with locally advanced head and neck cancer (LA-HNC) (Mohanty et al., 2000). The treatment of these patients has evolved since the introduction of combined modality treatment (Sambargi et al., 2012).

For patients with locally advanced disease not amenable to surgical resection, concurrent chemoradiotherapy (CCRT) is now recognized worldwide as a standard treatment option (Adelstein et al., 2003). Most of the randomized controlled trials have accepted cisplatin in a dose of 100 mg/m² given every 3-weeks concurrent with RT as a standard reference regimen in the definitive and adjuvant setting (Adelstein et al., 2003; Bernier et al., 2004; Cooper et al., 2004). Despite this, still uncertainties exist regarding appropriate chemoradiotherapy (CRT) regimens because of significant heterogeneity in published data with respect to patient selection, chemotherapy (CT) schedules and RT fractionation (Browman et al.,

2001; Hao et al., 2006). In addition, the use of 3-weekly schedule has been an area of concern for the clinicians as well as for the patients in view of challenges imposed by this schedule such as acute toxicities, treatment compliance and hospitalization for supportive care. Moreover, suboptimal compliance with this schedule could jeopardize the treatment outcome, resulting in poorer loco-regional control and shorter survival (Pajak et al., 1991; Browman et al., 2001; Adelstein et al., 2003). In an effort to overcome these challenges, splitting the 3-weekly cisplatin into a weekly cisplatin schedule with dosage ranging from 20 to 40 mg/m² has been investigated with some promising results achieving better antitumor efficacy, fewer side effects, and lower cost and hospitalization rates. Considering the controversial nature of the available research regarding the optimal scheduling of cisplatin - based concurrent chemoradiotherapy in LA-HNC, we undertook this comprehensive review to focus on the question regarding the use of standard 3-weekly cisplatin (100 mg/m²) in comparison to the more popular weekly cisplatin (20 to 40 mg/m²) concurrent with radiation therapy.

After thoroughly searching the published medical literature using internet and PubMed we found that the experience with "Comparison between three-weekly versus weekly schedule of cisplatin based concurrent

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chemoradiotherapy in head and neck cancer” is mainly limited to less than 10 original articles mainly retrospective institutional reports. We could not find any review article on this debatable topic.

Historical Background

The success story of cisplatin began when Dr. Barnett Rosenberg and his colleagues (Rosenberg et al., 1965) found that certain electrolysis products of platinum mesh electrodes were capable of inhibiting cell division dramatically in *Escherichia coli* creating lot of interest in the possible use of these products in the treatment of cancer. This led to the accidental identification of cis-dichloro-diammine-platinum (cisplatin; CDDP) as the agent responsible for this activity. Since then it opened a new era for the use of platinum compounds in the treatment of various solid malignant tumours, especially squamous cell cancers of the head and neck region, in both pediatric and adult age groups (Goncalves et al., 2013) also including testicular, ovarian, bladder, esophageal, small and non-small cell lung, breast, cervical, stomach and prostate cancers, as well as Hodgkin's and non-Hodgkin's lymphomas, neuroblastoma, sarcomas, multiple myeloma, melanoma, and mesothelioma (Florea et al., 2011).

Cisplatin as Radiosensitizer

Over the last several years cisplatin has received the maximum attention as radiosensitizer in head and neck cancer. Cisplatin is a platinum compound with complex mechanism of action when it comes to radiation-drug interactions thereby leading to increased cell damage and cell kill. Cisplatin demonstrates radiosensitizing properties through inhibition of DNA repair and cell cycle arrest (Lawrence et al., 2003). Furthermore, it exhibits radiosensitization of hypoxic cells due to scavenging of hydrated electrons by the platinum complex and formation of local concentrations of OH radicals, which eventually damage the DNA. Cisplatin was shown to have cytostatic properties by blocking the cells in the G2 phase of the mitotic cycle. Moreover, ionizing radiation can also increase cellular uptake of platinum (Yang et al., 1995). To date, the most important property of cisplatin as confirmed by preclinical and clinical studies is the ability to form DNA adducts. Cisplatin can form both intrastrand and interstrand adducts with the DNA; thereby distorting the DNA structure and blocking nucleotide replication and transcription (Bagri et al., 2014).

Combined Modality Treatment for Locally Advanced Head and Neck Carcinoma

Concurrent chemoradiation has been widely adopted as standard of care for LA-HNC after the publication of a large and most comprehensive meta-analysis based on individual patient data of 10,741 patients in 63 randomized trials (Pignon et al., 2000). The meta-analysis was updated and extended to include 16,640 patients treated in 87 trials (Pignon et al., 2007) confirming that concurrent chemoradiation conferred an absolute survival benefit

of 8% at 2 and 5 years. Regarding the type of drugs to be combined concomitantly with radiotherapy (RT), cisplatin alone, platinum with 5-Fluorouracil (5-FU) or other poly-chemotherapy including either platinum or 5-FU gave a benefit of the same magnitude. In contrast, mono-chemotherapy with a drug other than cisplatin led to inferior results and is not recommended in routine practice (Pignon et al., 2009).

The choice of particular regimen given at various institutions varies markedly from every 3 weeks (100 mg/m²) to low-dose daily (6 mg/m²) administration. Among the weekly schedule, doses as low as 20 mg/m² concurrent with RT have been tried. An Intergroup randomized trial (Quon et al., 2011) of 307 eligible patients comparing 20 mg/m² of cisplatin with RT to the same RT alone demonstrated no improvement in overall survival (OS) or freedom from failure, suggesting that 20 mg/m² (weekly) was too low a dose. Unfortunately, the study also revealed increased risk of late laryngeal and esophageal toxicities. In the face of recognized toxicity, institutional practices favouring a weekly schedule have typically favoured doses of ≥ 30 mg/m². Asif et al. subjected 30 patients to Inj. Cisplatin at an intermediate dose of 30 mg/m² intravenously once a week with RT compared to RT alone group (Asif et al., 2003). None of the patients in the weekly CRT group developed systemic toxicity and only 13.3% patients developed grade III mucositis. The same regimen has been employed with altered fractionation RT either hyperfractionation or concomitant boost technique and was found to be safe and effective (Newlin et al., 2010). Maqbool et al. (2012) prospectively investigated the feasibility and acute toxicity patterns of 40 mg/m² weekly cisplatin with conventionally fractionated external beam radiotherapy (EBRT) in head and neck squamous cell carcinoma (HNSCC) patients (Maqbool et al., 2012). The authors concluded that use of weekly cisplatin as an outpatient treatment is an attractive schedule from the standpoint of delivery, tolerance, compliance and cost-effectiveness.

Acute Toxicity (Mucositis, Dermatitis)

Mucositis is the commonest dose-limiting non-hematological toxicity associated with cisplatin use whether 3-weekly or weekly schedule. Maqbool et al. reported mucositis to be the predominant toxicity requiring interruptions in radiation therapy and chemotherapy dose modifications (Maqbool et al., 2012). In a study by Tsan et al. the patients receiving low dose weekly cisplatin (40 mg/m²) suffered more severe (\geq grade 3) mucositis than patients receiving 3-weekly cisplatin (100 mg/m²) (75% vs. 38.5%; $p=0.012$). The main reasons for this observation of some difference in toxicity could have been forced hydration and post-CT care of patients which was mandatory only for 3-weekly arm as suggested by the authors (Tsan et al., 2012). Similar findings were seen in a retrospective analysis of 55 patients by Kose et al. demonstrating a higher incidence of grade III - IV mucositis with the weekly regimen (Kose et al., 2011). They reported that patients with grade III - IV mucositis during CRT had significantly higher median OS than those

with grade I - II mucositis. An unusually low incidence (29%) of grade III or worse mucositis has also been demonstrated with the weekly regimen mostly in patients receiving more intense treatment i.e. doses \geq 66 Gy and 6 or more cycles of chemotherapy (Gupta et al., 2009). Different results have on the contrary been published (Geeta et al., 2006; Mitra et al., 2011) showing a trend to decreased toxicity with 3-weekly cisplatin than weekly cisplatin, as their weekly cisplatin schedule resulted in a higher rate of severe mucositis, significant in both univariate and multivariate analysis. In a retrospective analysis comparing the two regimens of concurrent chemotherapy with intensity-modulated radiotherapy, no statistically significant difference in the incidence of grade III - IV mucositis was found (32.5% for weekly group vs. 16.6% for 3-weekly group; $p=0.08$) (Espeli et al., 2012).

Radiation dermatitis is experienced to various degrees by the majority of patients undergoing RT for LA-HNC (Wendt et al., 1998; Calais et al., 1999; Bourhis et al., 2006). In most patients, the radiation dermatitis is mild to moderate (grades 1 and 2), but according to Bonner et al. ~ 20% - 25% of patients experience severe reactions on receiving combination of Cetuximab and RT (Bonner et al., 2006). Espeli et al. reported higher incidence of grade II - III skin toxicity for 3-weekly group as compared to weekly group ($p=0.5$) (Espeli et al., 2012). Similarly, Ho et al. found that patients treated with 3-weekly cisplatin seemed to suffer more grade 3 radiation dermatitis (56% vs. 26%), although not statistically significant (Ho et al., 2008).

Systemic Toxicities (Hematological, Auditory, Renal Impairment)

Most published reports have described the incidence of Grade 3 / 4 neutropenia as approximately 30%

with 3-weekly cisplatin compared with 10 - 15% with weekly cisplatin concurrent with RT, thus highlighting the importance of delivery of fractionated doses of chemotherapy (Cooper et al., 2004; Zenda et al., 2009; Homma et al., 2011; Mitra et al., 2011; Kiyota et al., 2012; Osman et al., 2014). Contradictory to this, various studies have reported no difference in terms of hematological toxicities between the two comparative arms (Kose et al., 2011; Tsan et al., 2012).

Auditory impairment after cisplatin therapy has been reported to be dose dependent, schedule dependent, and frequency dependent (Rademaker-Lakhai et al., 2006). De Jongh et al. described the toxicity of weekly high-dose cisplatin (70 to 85 mg/m²) in 400 patients with advanced solid tumours treated in the period 1990-2001 who took part in phase I / II trials (De Jongh et al., 2003). They observed ototoxicity in 2.5% of the patients. In the RTOG 95-01 study, the incidence of Grade 3 or more auditory disorders was 10% after 3-weekly cisplatin concurrent with RT (Cooper et al., 2004). However, we could not find any reports on Grade 3 or more auditory disorders with the weekly cisplatin schedule.

Although rare, there have been reports of renal disorders with concurrent cisplatin-based CRT. It is suggested that as the 3rd - 4th week of treatment is reached, oral mucosal reactions increase affecting oral intake further adding to the cisplatin-induced nephrotoxicity (Bagri et al., 2014). In a retrospective overseas study reported by Uygun et al. the incidence of Grade 3 / 4 renal disorders was lower with weekly cisplatin than with 3-weekly cisplatin (Uygun et al., 2009). A Japanese study reported that, although no difference was observed in the incidence of Grade 3 / 4 renal toxicity, the incidence of Grade 2 or more, for which dose reduction or discontinuation of cisplatin must be considered, was 30 - 32% in 3-weekly cisplatin compared with 2 - 15% in weekly cisplatin concurrent

Table 1. Published Series of Concurrent Cisplatin Schedules Compiling Patients Receiving 3-Weekly Versus Weekly Cisplatin Regimes for Locally Advanced Squamous Cell Carcinoma Head and Neck

S.No.	Name & Year of Publication	No. of Patients	RP / PP	Definitive / Adjuvant	3-weekly vs weekly CDDP dose (mg/m ²)	Mucositis	Neutropenia	Response	Compliance	Survival (OS) 3w vs w
1	Geeta et al, 2006	83	RP	Definitive	100 vs 40	↑ in weekly	↑ in weekly	NE	↑ in 3 weekly	NE
2	Ho et al, 2008	51	RP	Definitive	80 - 100 vs 33 - 40	NE	Similar	Similar	↑ in weekly	NE
3	Uygun et al, 2009	50	PP	Definitive	100 vs 40	↑ in 3 weekly	↑ in 3 weekly	Similar	NE	NE
4	Mitra et al, 2011	90	PP	Definitive	100 vs 30	Similar	↑ in 3 weekly	□ in 3 weekly	Similar	NE
5	Kose et al, 2011	55	RP	Definitive	100 vs 30	↑ in weekly	↑ in 3 weekly	NE	NE	Almost Similar
6	Tsan et al, 2012	55	PP	Adjuvant	100 vs 40	↑ in weekly	Similar	NE	↑ in 3 weekly	NE
7	Espeli et al, 2012	94	RP	Both	100 vs 40	↑ in weekly	NE	NE	NE	44% vs 42%
8	Geiger et al, 2014	104	RP	Adjuvant	100 vs 30 - 40	NE	NE	NE	NE	91% vs 86%
9	Fayette et al, 2015	266	RP	Adjuvant	100 vs 40	↑ in 3 weekly	↑ in 3 weekly	NE	NE	62.3% vs 52.6%

RP = Retrospective, PP = Prospective, NE = not evaluated, ↑ = Higher, OS = Overall survival, 3w = 3 weekly, w=weekly

with RT, showing a significantly lower incidence with the weekly schedule (Kiyota et al., 2012). In a phase III randomized study on post-operative patients of carcinoma oral cavity, no difference in \geq grade 3 renal toxicity was observed among the patients receiving low dose weekly cisplatin (40 mg/m²) and the patients receiving 3-weekly cisplatin (100 mg/m²) (Tsan et al., 2012). In a retrospective analysis of treatment outcome and nephrotoxicity of RT concurrent with either 3-weekly or weekly cisplatin in 94 patients with stage III / IV HNC (Espeli et al, 2012), the difference in the incidence of acute renal failure did not reach statistical significance (35% for weekly group vs. 53.7% for 3-weekly group; p=0.07). The frequency of chronic renal failure was significantly higher in 3-weekly group (12.5% for weekly group vs. 29.6% for 3-weekly group; p=0.04). Although no patients developed irreversible renal failure requiring dialysis.

Overall Survival and Response Rates

Concerns about the survival benefit of either schedule should be balanced against the incidence of grade 3 or 4 drug toxicities. However, very few comparative studies have commented on this important end point of survival. Weekly cisplatin (40 mg/m²) with concurrent RT reported an impressive 2-year OS and local progression-free rates (PFR) of 93.7% and 88.0%, respectively with complete response in the primary site in 98.1% patients (Homma et al., 2011). A large single institutional retrospective audit from India included 264 patients of LA-HNC treated with weekly cisplatin 30 mg/m² concurrent with conventional RT. The estimated 5-years loco-regional control (LRC) and disease-free survival (DFS) were 46% and 43% respectively, while the OS was not computed (Gupta et al., 2009). Inferior 2-year local relapse-free, regional relapse-free, locoregional relapse-free, DFS, and OS rates of 48.8%, 57.8%, 33.2% and 49.7%, respectively were reported by Krstevska et al. in 65 patients of oropharyngeal carcinoma treated with weekly cisplatin at 30 mg/m² concurrent with 3-dimensional conformal RT (3D-CRT) (Krstevska et al., 2012). Kang et al. reported median OS of 42.7 months and 3-year DFS rate of 72.8% in stage IV HNSCC patients treated with low dose weekly cisplatin (20 to 30 mg/m²) concurrent with RT (Kang et al., 2015).

In a retrospective review by Geiger et al. on 104 patients with Stage III /IV HNSCC who had surgery followed by adjuvant chemoradiation therapy determining whether weekly cisplatin could be a safe and effective alternative as compared to standard 3-weekly chemotherapy. The authors concluded that there was no significant survival difference with high-dose or weekly cisplatin and weekly cisplatin in the adjuvant setting may be a better treatment for patients with HPV-positive oropharynx cancer to preserve survival and minimize toxicity (Geiger et al., 2014). In a report of 50 patients which included majority of patients with advanced laryngeal cancer, compared administration of bolus cisplatin at 100 mg/m² every 3 weeks in younger patients with more favourable performance status (PS) to a schedule of weekly cisplatin at 40 mg/m² given to older patients with less favourable PS, combined with conventionally fractionated RT to 70

Gy. At short-term follow-up, loco-regional disease control rates were comparable, but the follow-up was too short to make any firm conclusions (Uygun et al., 2009). In addition, no significant difference in the efficacy of the regimens (similar response rates and loco-regional control) was demonstrated by a randomized study comparing daily (6 mg/m²), weekly (40 mg/m²), and three-weekly (100 mg/m²) schedule of cisplatin with conventionally fractionated RT (Gladkov et al., 2007). The retrospective study of Espeli et al. suggested that 3-weekly schedule can be combined to IMRT atleast in the fit subset of patients. Moreover, patients treated with the standard 3-weekly regimen had a longer OS but this has been related to the selection of a fit and younger population rather than to a better antitumour activity; indeed, progression-free survival rates were not statistically different (Espeli et al., 2012).

Compliance

Achieving a good compliance with any form of treatment is necessary in order to minimize the interruption to the oncological treatment. With concurrent cisplatin-based CRT, compliance is a clinical challenge affecting 5-year local control, LRC and DFS. One of the largest single-centre experiences with 264 patients by Gupta et al. found that patients receiving > 85% of the planned dose (6 or more cycles of weekly CT) had a significantly superior 5-year local control (64.5% vs 41.8%, p=0.022); LRC (54.5% vs 26.8%, p=0.009); and DFS (49.6% vs 25.8%, p=0.011) as compared to lesser dose intensity cisplatin (1 - 5 cycles of CT) concurrent with RT (Gupta et al., 2009). In the RTOG 9501 study, 61% of patients received all 3 planned cycles of cisplatin, 23% received 2 cycles, 13% received 1 cycle, and 2% received no chemotherapy (Cooper et al., 2004). In the EORTC 22931 study, compliance to chemotherapy decreased according to the courses delivered, as the first, second, and third cycles were administered to 88%, 66%, and 49% of patients, respectively (Bernier et al., 2004). A retrospective review conducted by Bahl and co-workers. on 75 patients with carcinoma nasopharynx reported that only 43% patients received all three cycles of concurrent CT and 33.3% patients received the intended dose without a cumulative delay of atleast 7 days through the three cycles respectively (Bahl et al., 2004).

In an Indian trial 83 patients were randomized to receive either 3-weekly cisplatin 100 mg/m² (group A) for 3 cycles or weekly cisplatin 40 mg/m² (group B) for 6 cycles concurrent with RT. Treatment compliance was similar at 64% and 66% in groups A and B respectively (Geeta et al., 2006). Number of studies (Huguenin et al., 2004; Wee et al., 2005) showed that a substantial fraction of patients could not receive the third planned dose of cisplatin and suggested that a cumulative dose of 200 mg/m² might be adequate to yield same beneficial effect. However, weekly cisplatin dose ranging from 30 - 35 mg/m² had shown CT completion rate (7 cycles) to be from 64% to as high as 87% in the literature (Glaser et al., 1993; Mitra et al., 2011). It is worth noting that weekly cisplatin

schedule is easier to manage than three-weekly cisplatin because of the regular monitoring of patients for toxicity allowing the schedule to be altered if required (Homma et al., 2011). Al-Sarraf et al. (2007) found that weekly cisplatin regimens have been mainly used for elderly unfit patients, while 3-weekly 100 mg/m² cisplatin has been considered the standard systemic treatment in CRT programs (Al-Sarraf et al., 2007).

Treatment Interruption

Finally, another concern that has been discussed is the treatment interruptions during RT as it affects the local control of the disease. In the first comparative study in 2006, 51 patients received cisplatin (100 mg/m² every 3-weekly), while 32 patients received cisplatin (40 mg/m² weekly) during definitive RT. Contrary to expectations, the incidence of treatment interruptions was significantly higher (41% vs 22%; p=0.005) in the weekly cisplatin arm (Geeta et al., 2006). Frequent omission of weekly cisplatin (40 mg/m²) due to haematological toxicity has also been reported by Pala et al. (2012). Similar to this, Mitra et al. found more number of treatment interruptions in weekly CT group, which might be explained by higher percentage of patients with significant weight loss in the weekly group. These studies prompted the authors to suggest CT dose reduction and the need for prophylactic feeding tube placements for all patients receiving weekly cisplatin (Mitra et al., 2011).

Even as concerns to treatment interruptions depending on the CT schedule employed the data in the literature are contradictory. Three-weekly regimen was found to be associated with more delays (41% vs 29%) and omissions of CT (17.4% vs 5.6%) resulting in lesser patients achieving cumulative doses beyond 200 mg/m², potentially lowering dose-intensity (Ho et al., 2008). The average dose intensity of weekly cisplatin (26.5mg/m²/week) has been reported to be equivalent to that of three-weekly regimen (28.9 mg/m²/week) (Homma et al., 2011). Fayette et al. found higher incidence of secondary hospitalizations and RT interruptions (≥ 3 days) with 3-weekly cisplatin; although with a significantly better OS with 3-weekly regimen (5 years OS: 62.3%; 95% CI [51.6-71.3]) than with weekly cisplatin (5 years OS: 52.6%; 95% CI [44.5-66.0]) (Fayette et al., 2015). Several other institutional reports have described their results with weekly cisplatin at 40 mg/m² (Beckmann et al., 2005; Steinmann et al., 2009) and 30 mg/m² (Traynor et al., 2010). Overall, these results suggests comparable efficacy at 30 - 40 mg/m², with a potentially more favourable acute systemic toxicity profile with weekly cisplatin. Despite these benefits with the weekly schedule, it is important to note that the most widely accepted standard of care, supported by level I evidence, remains the bolus cisplatin schedule.

Combined modality chemoradiation therapy has taken a 'central place' in the treatment of locally advanced squamous cell carcinoma of head and neck. The optimal scheduling of cisplatin with regard to efficacy and safety profile is very much in question. Unfortunately, till date no level I evidence exists to support the use of weekly

cisplatin towards improving local control or survival with reduced toxicities. In this review, after scrutinizing the literature, we cannot assume that one treatment schedule is superior to the other. However, in view of toxicities associated with the standard three-weekly cisplatin based chemoradiation regime specially in developing countries like India, with limited resources and the cost of hospitalization for inpatient care for the management of acute toxicities, it's the right time to search for better alternative schedules substituting the "contemporary standard of care three-weekly concurrent cisplatin". Unfortunately, before replacing the standard three-weekly schedule there are still many questions to be answered suggesting a need to conduct head-to-head phase III randomized trial examining high-dose three-weekly versus weekly cisplatin schedule concurrent with radiation therapy in LA-HNC.

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