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Review Article

Comparing Cisplatin Dosing Schedules in Concurrent Chemoradiotherapy for Locally Advanced Head-and-Neck Cancer: A Comprehensive Review of Weekly Versus 3-Weekly Regimens

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Abstract

Objective: There are approximately 900,000 new cases of head-and-neck cancer (HNC) annually, with a significant proportion presenting as locally advanced head-and-neck cancer (LA-HNC). Cisplatin-based concurrent chemoradiotherapy (CCRT) has become widely accepted, particularly for patients deemed inoperable. The standard regimen is a high-dose 3-weekly cisplatin schedule, however, this can lead to considerable toxicities. This review evaluates the efficacy, safety, and compliance associated with an emerging alternative: a weekly cisplatin dosing schedule. **Data Sources:** The review of current literature included randomized controlled trials, meta-analyses, and retrospective studies within the past decade, comparing weekly, and 3-weekly cisplatin CCRT regimens for LA-HNC. **Study Selection:** Studies comparing 3-weekly and weekly cisplatin-based CCRT were included. **Results:** Weekly cisplatin regimens demonstrated comparable efficacy to the traditional 3-weekly schedule, with lower toxicity and improved compliance. Key studies suggested that weekly cisplatin may have a more favorable safety profile, with reduced risks of neutropenia, renal impairment, and ototoxicity. However, the potential for slightly better locoregional control with the 3-weekly regimen remains a point of ongoing investigation. Novel agents including immune checkpoint inhibitors, xevinapant, and berzosertib are being actively investigated as combinational therapies with cisplatin-based CCRT. **Conclusion:** Weekly cisplatin-based CCRT is a viable alternative to the traditional 3-weekly regimen for treating LA-HNC, particularly in patients at higher risk of toxicities. Further randomized controlled trials are required to confirm the optimal cisplatin schedule and efficacy of combinational therapies with novel agents. These findings underline the importance of exploring treatment protocols that balance therapeutic benefits with reduced adverse effects and improved compliance.

Keywords: Chemotherapy, cisplatin, locally advanced head-and-neck cancer, medical oncology, therapeutic uses

Introduction

Globally, there are approximately 900,000 incident cases of head-and-neck cancer (HNC) with over 400,000 associated

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deaths per year.[1] In Taiwan, between 2010 and 2018, 16,894 patients aged ≥20 years received a primary diagnosis of HNC, with declines in the incidence of nasopharynx, sinus, and oropharynx cancers.[2] Approximately 80% of HNC cases are locally advanced (LA-HNC) when diagnosed in developing countries.[3] Treatment strategies for these patients have evolved, especially with the introduction of combined modality treatments.[4]

For patients with LA-HNC who are deemed surgically inoperable, concurrent chemoradiotherapy (CCRT) is globally recognized as the standard treatment.[5] Most randomized controlled trials have endorsed using cisplatin at a dose of 100 mg/m^2 every 3 weeks alongside radiation therapy as the standard regimen for both definitive treatment and adjuvant therapy.[6] However, there is still uncertainty about the optimal chemoradiotherapy regimen due to variations in patient selection, chemotherapy schedules, and radiation fractionation.[6] Concerns associated with the 3-weekly cisplatin regimen include acute toxicities, treatment compliance, and the need for hospitalization for supportive care.[7] Suboptimal compliance with this regimen can negatively impact treatment outcomes, leading to reduced locoregional control and shorter survival.[7]

To address these issues, researchers have explored splitting the 3-weekly cisplatin dose into smaller weekly doses, ranging from 20 to 40 mg/m^2.[7,8] This approach has shown promise, potentially leading to better antitumor efficacy, fewer side effects, and lower hospitalization costs.[7,8] Several significant randomized controlled trials have been published in the past 2 years comparing the traditional 3-weekly cisplatin schedule (100 mg/m^2) with the emerging weekly schedule (20–40 mg/m^2).[7-11] Since these publications postdate the most recent systematic review and meta-analysis on the subject, endorsed by the Italian Association of Radiotherapy and Clinical Oncology,[12] an updated review is warranted. Therefore, to summarize the current knowledge and explore the optimal cisplatin schedule for CCRT in patients with LA-HNC[6] with regards to the efficacy, safety, and compliance, we conducted an extensive review of the medical literature.

Cisplatin as a Radiosensitizing Agent

Cisplatin has gained significant attention in recent years as a radiosensitizer in the treatment of HNC.[4] Cisplatin forms covalent bonds with DNA, leading to the formation of DNA adducts which impair the cell's ability to repair radiation-induced DNA damage.[13] Cisplatin also arrests cells in the G2 phase of the cell cycle, a key state for radio sensitivity.[13] In addition, it enhances radio sensitization in hypoxic cells by scavenging hydrated electrons through its platinum complex, creating localized concentrations of hydroxyl (OH) radicals that damage DNA.[13] Interestingly, ionizing radiation can increase the cellular uptake of cisplatin.[13]

Cisplatin-based Combined Chemoradiotherapy for LA-HNC

Due to the aforementioned properties, cisplatin-based CCRT has become the standard of care for LA-HNC.[14] Different institutions employ various dosing schedules for cisplatin,[15] ranging from a high-dose 3-weekly regimen (100 mg/m^2) to low-dose daily regimen (6 mg/m^2).[15] For weekly dosing, doses of 30 mg/m^2 or more are most commonly used concurrently with radiotherapy.[15] The lowest effective dose of weekly concurrent cisplatin was empirically determined by an intergroup trial of 308 patients comparing 20 mg/m^2 weekly cisplatin chemoradiation to radiotherapy alone, which found no improvement in progression-free survival (7.2 months vs. 6.5 months, $P = 0.030$) by the addition of 20 mg/m^2 weekly cisplatin to radiotherapy.[15] Intermediate doses such as 30 mg/m^2 weekly have shown better safety with minimal systemic toxicity and reduced severe mucositis.[4] Other studies have highlighted the feasibility and attractiveness of 40 mg/m^2 weekly cisplatin in terms of delivery, tolerance, compliance, and cost-effectiveness.[16] Intermediate cisplatin doses can also be adapted for use with altered fractionation radiotherapy techniques such as hyperfractionation or concomitant boost.[17]

Cisplatin-based Concurrent Chemoradiotherapy as Adjuvant Treatment for LA-HNC

Current clinical guidelines recommend that cisplatin-based CCRT can be administered under two treatment settings for LA-HNC.[17] For LA-HNCs deemed surgically inoperable, cisplatin-based CCRT is used as definitive or primary treatment.[18] Where LA-HNC is considered amenable to curative surgery, surgical tumor excision is carried out first, with varying degrees of organ preservation.[18] Cisplatin-based CCRT in this scenario is administered as adjuvant treatment aimed at eradicating minimal residual disease.[19]

High-risk clinicopathologic features indicate the need for adjuvant CCRT.[5,14] These features include extranodal extension (ENE), positive or close surgical margins, primary tumors classified as pT3/pT4, nodal involvement at the pN2/N3 level, clinically enlarged level IV/V nodes in cases of tumors arising in the oral cavity or oropharynx, and lymphovascular or perineural invasion.[5,14] Combined chemoradiation is only currently recommended in high-risk patients because the benefit of adding adjuvant chemotherapy to adjuvant radiation therapy remains controversial, fraught with conflicting evidence from randomized studies weighed against considerable increase in acute toxicity.[19]

The recommendations for adjuvant cisplatin CCRT in patients with postoperative LA-HNC and high-risk features are based on two randomized studies, EORTC 22931 and RTOG 9501, which specifically addressed the feasibility of adjuvant cisplatin by comparing adjuvant CCRT with cisplatin at 100 mg/m^2 for three cycles to radiation therapy alone.[20,21] The

EORTC trial showed a survival benefit with adjuvant CCRT across the entire cohort,[20] but this finding was not replicated in the RTOG study.[21] A later combined analysis of the two trials suggested a significant survival benefit with CCRT in patients with ENE or positive margins. Based on these data, the current practice is to reserve chemoradiation for these high-risk patients.[22] A long-term follow-up of the RTOG study also indicated a significant overall survival benefit for patients with positive margins or ENE.[23]

Cisplatin-based Concurrent Chemoradiotherapy as Definitive Treatment for LA-HNC

As primary treatment for inoperable LA-HNC, the MACH-NC meta-analysis and its subsequent updates conclusively showed that adding definitive chemotherapy to definitive locoregional radiotherapy improved overall survival in patients with LA-HNC.[24] Originally based on 10,741 patients across 63 randomized trials, the first iteration of the MACH-NC meta-analysis addressed the optimal timing of chemotherapy in the primary treatment setting.[24] The benefit of chemotherapy was observed only when it was administered concurrently with radiation therapy.[24] The hazard ratio (HR) for this group was 0.81, with a 95% confidence interval (CI) of 0.76–0.88 and an 8% absolute benefit at 5 years ($P < 0.001$).[24] In terms of the primary chemoradiation, cisplatin alone, platinum-based or 5-fluorouracil-based polychemotherapy offered similar therapeutic efficacy, whereas monotherapy with other drugs yielded poorer results.[24] Overall survival was not affected by the addition of induction (HR = 0.96, 95% CI [0.90–1.01]) or adjuvant chemotherapy (HR: 1.02, 95% CI [0.92–1.13]).[24]

An updated analysis in 2009 revealed a 6.5% absolute benefit for definitive cisplatin CCRT over radiotherapy alone at 5 years (HR: 0.81, 95% CI: 0.78–0.86, $P < 0.001$), with no significant heterogeneity among the studies.[25] The benefit of CCRT was less pronounced in older patients (over 70 years) and those with an Eastern Cooperative Oncology Group performance status of ≥2.[25] Overall, CCRT showed a 3.5% absolute benefit in 5-year survival compared to induction chemotherapy, with a more noticeable effect in preventing locoregional failure (HR: 0.74, 95% CI: 0.70–0.79, $P < 0.001$).[25] Although induction chemotherapy demonstrated better systemic control (HR: 0.73, 95% CI: 0.61–0.88, $P = 0.001$), it did not offer a survival advantage across the general population, likely due to its inferior local control.[25] This analysis thus established definitive CCRT as the standard of care for most patients with inoperable LA-HNC.

A 2021 update to the meta-analysis confirmed a 6.5% absolute survival benefit for CCRT over radiotherapy alone at 5 years, and a 3.6% benefit at 10 years.[26] Compared to induction chemotherapy (including taxane-based triplet regimens), definitive CCRT showed an absolute benefit of 6.2% at 5 years for overall survival, 3.7% at 5 years for event-free survival (EFS), and 5.8% at 5 years for locoregional failure.[26] A site-specific meta-analysis published in 2011 indicated that while the benefit of chemotherapy was observed across all sites, primary CCRT was superior to neoadjuvant and adjuvant chemotherapy only in oropharyngeal and laryngeal cancers, with absolute benefits of 8.4% and 5.4% in overall survival at 5 years, respectively.[27] Despite similar numerical benefits in oral cavity and hypopharynx cancers (6.9% and 3.2% in overall survival at 5 years, respectively), the lack of statistical significance could be due to limited power in the analysis for these subsites.[27]

Weekly versus Three-Weekly Cisplatin Concurrent Chemoradiotherapy—Therapeutic Outcomes and Response Rates

Published randomized controlled trials have examined the comparative merits of 3-weekly versus weekly cisplatin chemoradiation therapy for LA-HNC, in both adjuvant and definitive treatment settings [Table 1]. Major randomized controlled trials and large population-based studies have so far not demonstrated significant differences in overall and distant metastasis-free survival between the 3-weekly and weekly cisplatin CCRT regimens.[8,10,11,28,29] The main factor affecting the efficacy of weekly versus 3-weekly cisplatin appears to be in regards to local disease control. Noronha *et al*. examined weekly versus 3-weekly cisplatin chemoradiation therapy for LA-HNC in which 90% of the treatments were administered as adjuvant therapy. LA-HNC in this study was defined as nonnasopharyngeal head-and-neck squamous cell carcinomas (HNSCCs), i.e., arising from the oral cavity, oropharynx, hypopharynx, larynx, or metastatic cervical lymphadenopathy of unknown primary.[8] Locally advanced disease was defined as stage III or IV without distant metastases, and planned for curative chemoradiation.[8] Adjuvant CCRT was prescribed for patients with one or more high-risk features (extracapsular extension, close [<5 mm] or positive margins, more than two positive lymph nodes, or T4 primary) according to the guidelines, with a minority of patients receiving definitive CCRT for unresectable disease or organ preservation. In terms of locoregional control, after a median follow-up of 22 months (range, 3–51 months), 24% of the patients in the 3-weekly arm and 38% in the weekly arm developed locoregional relapse (HR: 1.76, 95% CI [1.11–2.79], $P = 0.014$).[8] In the published 6-year follow-up of the same study,[28] Noronha *et al*. reported that after a median follow-up of 77.3 months, the median time to locoregional failure was 46.1 months (95% CI: 31.6–60.6) in the weekly cisplatin arm, and 57.9 months (95% CI: 47.1–68.6) in the 3-weekly arm, respectively (HR: 1.43, 95% CI: [1.01–2.02], $P = 0.042$).[28] However, the estimated 5-year locoregional control rates were 48.2% in the weekly cisplatin arm and 55.2% in the 3-weekly cisplatin arm. This resulted in an absolute difference of 7%, with a 95% CI ranging from − 2.5 to 16.5. As such, Noronha and colleagues suggested that while broadly similar across multiple clinical parameters, locoregional control may be better achieved with a 3-weekly cisplatin schedule in patients with LA-HNC.

Table 1: Evidence for weekly cisplatin-based combined chemoradiotherapy for LA-HNC

Study	Patient number	Study design	Tumor site	Clinical setting	Weekly CDDP dose (mg/m²)	Locoregional control	Overall survival	Reference
Noronha *et al*., 2018	300	Phase III randomized noninferiority trial	90% oral cavity	90% adjuvant CCRT	30	2-year LRC 59.3% (QW) versus 75.3% (Q3W), absolute difference 16% (95% CI: 7.19–24.81)	5-year OS 43.1% (QW) and 48.6% (Q3W)	[8]
Xia *et al*., 2021 (ChiCTR-TRC-12001979 trial)	510	Phase III randomized noninferiority trial	100% nasopharynx	100% definitive CCRT	40	Local relapse-free survival HR: 0.88 (95% CI: 0.47–1.63); *P*=0.68	OS HR: 1.35 (95% CI: 0.70–2.63), *P*=0.37	[9]
Shama *et al*., 2021 (ConCERT trial)	278	Open-label phase III randomized noninferiority trial	60% oral cavity; 20% larynx	100% definitive CCRT	40	2-year LRC 61.53% (QW) versus 57.69% (Q3W), absolute difference 3.84% (95% CI: −6.15–13.80)	OS 25.46 months (QW) versus 30.50 months (Q3W); *P*=0.59	[10]
Kiyota *et al*., 2022 (JCOG1008 trial)	261	Phase II/III randomized noninferiority trial	45% oral cavity; 35% hypopharynx	100% adjuvant CCRT	40	Local relapse-free survival HR: 0.71 (95% CI: 0.48–1.06)	OS HR: 0.69 (99% CI: 0.37–1.32), *P* for noninferiority=0.0043	[11]

CCRT: Combined chemoradiotherapy, HR: Hazard ratio, LRC: Locoregional control, OS: Overall survival, QW: Once every week, Q3W: Once every 3 weeks, CI: Confidence interval, LA-HNC: Locally-advanced head-and-neck cancer

Following the study by Noronha and colleagues, JCOG1008 was a multicenter, noninferiority, phase II/III randomized controlled trial comparing weekly and 3-weekly adjuvant cisplatin CCRT for postoperative LA-HNC [Table 1].[11] This trial showed that in the postoperative setting, weekly cisplatin was noninferior to 3-weekly cisplatin in terms of overall survival (HR: 0.69, 95% CI [0.37–1.270], *P* for noninferiority = 0.0027) and local relapse-free survival (HR: 0.73; 95% CI: [0.47–1.13]).[11] In other words, this study found that weekly cisplatin CCRT was a noninferior adjuvant treatment option for LA-HNC compared with 3-weekly cisplatin.

The ConCERT trial is an ongoing open-label, noninferiority phase III randomized controlled trial investigating weekly versus 3-weekly cisplatin CCRT as definitive therapy for LA-HNC.[10] In the published interim report, the primary tumor locations were as follows: 59.6% in the oropharynx, 17.5% in the larynx, and 11.6% each in the hypopharynx and oral cavity.[10] The locoregional control rates at 2 years were 57.7% for the 3-weekly cisplatin arm and 61.5% for the weekly cisplatin arm, with an absolute difference of 3.8% (one-sided 95% CI: −6.15–13.80), which fell within the predefined noninferiority margin of −10.0%.[10] There was no significant difference in the median time to locoregional failure (21.2 months for the 3-weekly arm vs. not reached for the weekly cisplatin arm; *P* = 0.45), overall survival (30.5 months for the 3-weekly arm vs. 25.5 months for the weekly cisplatin arm; *P* = 0.59), and progression-free survival (20.6 months for the 3-weekly cisplatin arm vs. 20.7 months for the weekly cisplatin arm; *P* = 0.46).[10] Taken together, emerging level 1 evidence suggests that a weekly cisplatin regimen is not inferior to 3-weekly cisplatin, although more studies are required to confirm the outcomes, especially in relation to locoregional disease control.

Another randomized controlled trial, ChiCTR-TRC-1200197921, compared weekly and 3-weekly cisplatin specifically for locally advanced nasopharyngeal carcinoma (LA-NPC).[9] In this open-label, randomized noninferiority phase III trial,[9] patients with LA-NPC were randomly assigned to receive six cycles of weekly or two cycles of 3-weekly definitive cisplatin CCRT [Table 1]. The results showed no significant difference between the treatment arms in terms of overall survival (HR: 1.35, 95% CI: [0.70–2.63], *P* = 0.37), local failure-free survival (HR: 0.88, 95% CI [0.47–1.63], *P* = 0.68), and distant metastasis-free survival (HR: 1.06, 95% CI [0.61–1.84], *P* = 0.84).[9]

Treatment Compliance

Achieving high compliance in any treatment is crucial to minimize interruptions in cancer therapy.[17] In CCRT, compliance is a significant parameter that can impact 5-year local control, locoregional control, and disease-free survival.[17] A large single-center study with 264 patients showed that those who received more than 85% of the planned dose (six or more cycles of weekly chemotherapy) had significantly better 5-year local control (64.5% vs. 41.8%), locoregional control (54.5% vs. 26.8%), and disease-free survival (49.6% vs. 25.8%) compared to patients with lesser dose intensity (1–5 cycles).[30]

In the JCOG1008 study[11] [Table 2], the two different cisplatin treatment arms both achieved high treatment compliance, as measured by cumulative dose of cisplatin (280 mg/m² for 3-weekly cisplatin; 239 mg/m² for weekly cisplatin), proportion of actual-to-planned delivery of cisplatin (88.9% for 3-weekly cisplatin; 84.1% for weekly cisplatin), and proportion of treatment completion (93.2%, 95% CI: [87.5–96.8] for 3-weekly cisplatin; 86.8%, 95% CI: [79.7–92.1] for weekly

Table 2: Treatment compliance of weekly cisplatin-based combined chemoradiotherapy for LA-HNC

Study	Treatment compliance	Reference
Noronha *et al*., 2018	Median cumulative cisplatin dose 210 mg/m^2 (QW) versus 300 mg/m^2 (Q3W)	[8]
Xia *et al*., 2021 (ChiCTR-TRC-12001979 trial)	Median cumulative cisplatin dose 200 mg/m^2 (QW) versus 220 mg/m^2 (Q3W)	[9]
Shama *et al*., 2021 (ConCERT trial)	More treatment delays (P=NS) and treatment interruptions (P=0.035) in the Q3W treatment arm	[10]
Kiyota *et al*., 2022 (JCOG1008 trial)	Median cumulative dose of cisplatin 239 mg/m^2 (QW) versus 280 mg/m^2 (Q3W)	[11]

QW: Once every week, Q3W: Once every 3 weeks, LA-HNC: Locally-advanced head-and-neck cancer

cisplatin).[11] The total radiotherapy dose received was 66 Gy for the patients in both treatment arms.[11]

In Noronha *et al*.'s study[8] [Table 2], in the 3-weekly cisplatin arm, 94% of the patients completed the planned CCRT, with a dose reduction required in 8% of the patients, and dose delay in 28% of the patients.[8] The median cumulative cisplatin dose was 300 mg/m^2, with a median cumulative dose intensity of 42 mg/m^2/week. In the weekly cisplatin arm, 88.7% of the patients completed the planned CRT. 9.3% of patients required dose reduction, and 24.7% of the patients had a dose delay.[8] The median cumulative cisplatin dose was 210 mg/m^2, and the median dose intensity was 30.7 mg/m^2/week. Overall, in terms of treatment completion and compliance, no significance differences were found between the two arms (P = 0.1).[8]

In the ChiCTR-TRC-12001979 trial,[9] 99.6% of the patients received two cycles of 3-weekly cisplatin, while in the weekly cisplatin arm, 36.8% of the patients received 5 cycles, and 53.6% of the patients received 6 cycles.[9] In addition, 90% of the patients in the 3-weekly arm and 86.4% of the patients in the weekly arm received >200 mg/m^2 of cisplatin, and the median cisplatin doses were 220 mg/m^2 (interquartile range [IQR] 198–240) and 200 mg/m^2 (IQR 200–200), respectively.[9]

In real-world practice, a weekly cisplatin schedule may also be easier to manage compared to a 3-weekly regimen, because it involves more frequent monitoring, allowing for adjustments as needed.[31] A 3-weekly cisplatin regimen at 100 mg/m^2 remains the standard treatment in CCRT programs, while weekly cisplatin is often favored in older or less fit patients.[14]

Acute Toxicities of Cisplatin

In terms of safety [Table 3], mucositis is the most common nonhematologic side effect that limits cisplatin dosing, regardless of whether it is administered in a 3-weekly or weekly schedule.[17] Mucositis is also a leading cause of interruption in radiation therapy and the need to adjust chemotherapy dose.[3] In the JCOG1008 study,[11] which was a phase II/III randomized controlled trial investigating adjuvant weekly cisplatin chemoradiation versus 3-weekly cisplatin chemoradiation therapy for postoperative HNSCC, mucositis of any grade occurred in 118/129 (92%) patients receiving 3-weekly cisplatin, and 113/122 (93%) patients receiving weekly cisplatin.[11] Grade 3–4 mucositis occurred in 30/129 (23%) and 34/122 (28%), respectively.[11] In the randomized noninferiority trial conducted by Noronha *et al*.[8] which compared weekly and 3-weekly cisplatin chemoradiation for LA-HNSCC, grade 2 mucositis occurred in 98/148 (65.3%) patients receiving weekly cisplatin, and in 108/149 (72.5%) patients receiving 3-weekly cisplatin, with comparable grade 3 or higher mucositis events. In the ChiCTR-TRC-12001979 trial,[9] grade 3 mucositis occurred in 89/249 (35.7%) patients receiving weekly cisplatin, and in 85/260 (32.7%) patients receiving 3-weekly cisplatin (P = 0.53).[9] In summary, in the setting of randomized controlled trials, weekly cisplatin resulted in the same number or fewer events of mucositis compared to 3-weekly cisplatin. These results were supported by another retrospective analysis that compared the two dosing schedules in conjunction with intensity-modulated radiotherapy, which found no significant difference in the incidence of grade III-IV mucositis (32.5% in the weekly group vs. 16.6% in the 3-weekly group, P = 0.08).[32]

Radiation dermatitis is another common side effect among patients undergoing radiotherapy for LA-HNC [Table 3].[24] Most cases are mild to moderate (grades 1 and 2), however, clinical trials have reported that up to 8% of patients can experience severe reactions when combining cisplatin with radiotherapy.[33] The JCOG1008 trial found no significant difference in grade 3–4 radiation dermatitis with the 3-weekly regimen compared to the weekly regimen (15% and 12%, respectively).[11] Similarly, Noronha *et al*. noted that the patients on the 3-weekly cisplatin regimen appeared to have similar grade 3 radiation dermatitis to the patients on the weekly cisplatin regimen (6.7% vs. 7.4%, P = 0.670). The ChiCTR-TRC-12001979 trial also found no significant difference in grade 3–4 dermatitis with the 3-weekly regimen compared to the weekly regimen (8.5% and 6.0%, respectively, P = 0.29).[8]

Systemic Toxicities of Cisplatin

Most studies have reported that the incidence of severe neutropenia (grade 3/4) is around 30% with 3-weekly cisplatin, compared to 10%–15% with weekly cisplatin in conjunction with radiotherapy.[3] This highlights the potential benefit of fractionated doses in reducing hematologic toxicity.[17] These findings are supported by randomized controlled trials [Table 3]. In the JCOG1008 trial, grade 2–3 neutropenia occurred in 14% of LA-HNC patients who received weekly cisplatin, and in 44% of the patients who received 3-weekly cisplatin (P < 0.001).[11] Febrile neutropenia occurred in 0.7% of the patients receiving weekly cisplatin, and

Table 3: Toxicity profile of weekly cisplatin-based combined chemoradiotherapy for LA-HNC

Study	Toxicity	Reference
Noronha *et al*., 2018	Any acute toxicity grade 3 or higher 71.6% (QW) versus 84.6% (Q3W); *P*=0.006	[8]
Xia *et al*., 2021 (ChiCTR-TRC-12001979 trial)	Any acute grade 3 toxicity 60.2% (QW) versus 53.1% (Q3W); *P*=0.015	[9]
Shama *et al*., 2021 (ConCERT trial)	Q3W arm had more mucositis (*P*=0.029), myelosuppression (*P*=0.021)	[10]
Kiyota *et al*., 2022 (JCOG1008 trial)	Neutropenia 35% (QW) versus 49% (Q3W); creatinine increase 30% (QW) versus 40% (Q3W)	[11]

QW: Once every week, Q3W: Once every 3 weeks, LA-HNC: Locally-advanced head-and-neck cancer

4.7% of the patients receiving 3-weekly cisplatin ($P = 0.019$).[11] Similarly, Noronha *et al*. reported that grade 3–4 neutropenia occurred in 35% of the patients receiving weekly cisplatin, and 49% of the patients receiving 3-weekly cisplatin.[8] These findings indicate that, as expected, high-dose cisplatin is associated with more neutropenic toxicity in LA-HNC.

Cisplatin-induced auditory impairment is influenced by dosage, schedule, and frequency.[34] A study on weekly high-dose cisplatin (70–85 mg/m^2) involving 400 patients with advanced solid tumors showed ototoxicity in 2.5% of the patients.[35] In the JCOG100817 trial, grade 2–3 early deafness (within 3 months of receiving cisplatin CCRT) occurred in 19.5% of the patients who received 3-weekly cisplatin, and in 8.0% of the patients who received weekly cisplatin ($P = 0.013$).[11] Grade 2–3 late deafness occurred in 28.6% of the patients given 3-weekly cisplatin, and 7.8% of the patients receiving weekly cisplatin ($P = 0.004$).[11] Noronha *et al*., reported that hearing disturbance of any grade occurred in 17% of the patients who received 3-weekly cisplatin, and in 7% of the patients who received weekly cisplatin.[8] In summary, these studies showed significant dose-dependent ototoxicity in LA-HNC patients who received cisplatin-based CCRT, which favors the use of weekly low-dose cisplatin regimens.

Renal toxicity is another concern with cisplatin-based chemoradiotherapy.[36] It has been suggested that as treatment progresses to the 3rd or 4th week, oral mucosal reactions can worsen, potentially leading to cisplatin-induced nephrotoxicity.[36] In a phase III study involving postoperative oral cancer patients, no significant difference was observed in ≥ grade 3 renal toxicity between low-dose weekly cisplatin (40 mg/m^2) and 3-weekly cisplatin (100 mg/m^2).[37] In addition, Noronha *et al*. reported that serum creatinine increased in 40% of LA-HNC patients receiving 3-weekly cisplatin, and in 30% of the patients receiving weekly cisplatin.[8] A retrospective analysis of treatment outcomes and nephrotoxicity in 94 patients with stage III/IV HNC showed no statistically significant difference in acute renal failure (35% for weekly vs. 53.7% for 3-weekly), but a significantly higher incidence of chronic renal failure in the 3-weekly group (12.5% for weekly vs. 29.6% for 3-weekly; $P = 0.04$).[32] In the JCOG1008 trial, grade 3 hyponatremia occurred in 49.7% of the patients given 3-weekly cisplatin, and in 22.7% of the patients given weekly cisplatin.[11] Therefore, weekly cisplatin appears to offer superior renal safety compared with 3-weekly cisplatin in patients with LA-HNC. Despite these findings, none of the patients developed irreversible renal failure requiring dialysis.[8,11,37]

Role of Immune Checkpoint Blockade in Cisplatin Concurrent Chemoradiotherapy for LA-HNC

Over the past decade, immune checkpoint blockade (ICB) has become a crucial component in the treatment of HNCs.[14] The KEYNOTE-048 phase 3 trial provided category 1 evidence that both pembrolizumab alone and combined with cisplatin and 5-fluorouracil significantly improved overall survival compared to cetuximab plus cisplatin and 5-fluorouracil in first-line systemic therapy for recurrent and metastatic HNSCC.[38,39] In addition, the CHECKMATE-141 and KEYNOTE-012 trials demonstrated that nivolumab and pembrolizumab alone were superior to standard second-line treatments, including methotrexate, docetaxel, and cetuximab, in prolonging overall survival for recurrent and metastatic HNSCC.[40,41] These results have prompted the exploration of PD-1 and PD-L1 inhibitors in combination with standard cisplatin CCRT regimens for LA-HNC.

However, unlike the success seen in metastatic recurrent HNSCC, recent phase 3 trials have not demonstrated the efficacy of combining immune checkpoint inhibitors with primary cisplatin CCRT for LA-HNC.[42] In the KEYNOTE-412 trial, 804 patients with newly diagnosed, high-risk unresected LA-HNC were randomly assigned to receive either the anti-PD-1 monoclonal antibody pembrolizumab plus two doses of 3-weekly cisplatin 100 mg/m^2 with concurrent accelerated fractionation radiotherapy (70 Gy) followed by 1 year of 3-weekly maintenance pembrolizumab, or placebo plus the same 3-weekly cisplatin CCRT and placebo maintenance regimen.[42] EFS did not significantly differ between the two study arms (median EFS not reached in the pembrolizumab arm vs. 47.7 months in the placebo arm; HR: 0.83 [95% CI: 0.68–1.03]; $P = 0.043$ [significance threshold, $P < 0.024$]).[42] Similarly, in the JAVELIN head and neck 100 phase III randomized controlled trial, avelumab, an anti-PD-L1 monoclonal antibody, was unable to prolong progression-free survival when combined with 3-weekly CCRT given as three doses of standard-of-care cisplatin 100 mg/m^2 with intensity-modulated radiotherapy of 70 Gy.[43] The median progression-free survival was not reached in either the avelumab or placebo arm (HR: 1.21, [95% CI: 0.93–1.57], $P = 0.92$).[43]

Machiels *et al*. suggested several reasons for the lack of efficacy for Programmed Death-1 (PD-1) and Programmed Death-Ligand 1 (PD-L1) blockade combined with cisplatin CCRT in LA-HNC.[42] One potential contributing factor could be the timing of ICB, which was administered concurrently with cisplatin CCRT.[42] Concurrent chemoradiation may deplete working T cells due to the inclusion of tumor-involved and high-risk regional lymph nodes in the clinical target volume, thereby rendering ICB less effective.[44] Comparative studies on non-small cell lung cancer (NSCLC) support this idea. The PACIFIC trial showed that consolidative durvalumab treatment significantly improved progression-free survival in patients with unresectable stage III NSCLC who did not progress after primary cisplatin-based CCRT (HR: 0.52; 95% CI: [0.42–0.65], $P < 0.001$).[45] Assuming the experience with NSCLC is at least in part generalizable to LA-HNSCC, a sequential ICB-CCRT strategy may be more rewarding. However, a recent update of the IMvoke010 trial reported that consolidative atezolizumab after multimodal definitive treatment in patients with high-risk LA-HNSCC did not significantly improve overall survival compared with placebo (HR: 0.94; 95% CI: 0.70–1.26).[46] Therefore, more research is required to optimize the timing of ICB in relation to primary cisplatin CCRT for LA-HNSCC.

The authors also pointed out that KEYNOTE-412 did not select patients based on PD-L1 expression levels, although *post hoc* analysis indicated that only those with a PD-L1 expression of combined positive score ≥ 20 benefited from the addition of pembrolizumab to cisplatin CCRT.[42] Therefore, PD-L1 expression may play a predictive role in determining the outcome of ICB combined with cisplatin CCRT for LA-HNC, which may need to be considered in future study designs. Another critical factor is the cumulative toxicity of adding concurrent ICB to high-dose 3-weekly cisplatin CCRT.[42] The KEYNOTE-412 trial reported serious adverse events in 245 of 398 (62%) of patients treated with pembrolizumab-CCRT compared to 197/398 (49%) treated with placebo-CCRT, with grade 4 and 5 adverse events occurring in 138/398 (35%) and 102/398 (26%) patients, respectively.[42] This marginal difference in adverse events was associated with higher dose discontinuation rates in the pembrolizumab arm (149/398 patients [38%]) compared to the placebo arm (128/398 patients [32%]),[42] which may have confounded the measurable therapeutic effects. Given the emerging noninferiority outcomes with low-dose weekly cisplatin CCRT for LA-HNC as discussed above,[9-11] it may be worth considering whether future clinical trial designs could benefit from incorporating ICB or placebo with weekly 40 mg/m^2 cisplatin-based CCRT instead of the standard 3-weekly 100 mg/m^2 cisplatin to lower the absolute toxicity burden in patients receiving ICB-CCRT enough to reveal any significant therapeutic benefit that could be derived from concurrent or sequential ICB. However, it should be noted that optimizing the ICB therapeutic strategy is challenging when the dose toxicity of cisplatin CCRT itself continues to be an area of active research in LA-HNSCC.

Where Next? Novel Medications on the Horizon for Combinational Therapy with Cisplatin Concurrent Chemoradiotherapy for LA-HNC

In addition to optimizing the cisplatin dosing schedule of CCRT treatment for LA-HNC, new drugs are being investigated in this area and could significantly impact the treatment landscape.[47] Xevinapant, an oral inhibitor of apoptosis proteins,[48] showed promising results in a randomized, placebo-controlled phase II trial when used with cisplatin CCRT.[49] The study was a double-blind trial involving 96 patients with unresectable LA-HNC and a smoking history of at least 10 pack-years. The participants were randomly assigned in a 1:1 ratio to receive either xevinapant at a dosage of 200 mg taken once daily (from days 1 to 14 of a 3-week cycle) every 3 weeks for three cycles, in addition to cisplatin CCRT, or a placebo with the same CCRT regimen. The CCRT regimen consisted of the standard 3-weekly cisplatin at 100 mg/m^2 for 3 cycles, along with intensity-modulated radiotherapy at a total dose of 70 Gy over 7 weeks. The study found that the xevinapant arm met the primary endpoint, achieving an odds ratio for locoregional tumor control of 2.74 ($P = 0.0232$).[49] In addition, there was a significant improvement in the secondary endpoint of progression-free survival.[49] The median progression-free survival was not reached in the xevinapant group, compared to 16.9 months in the placebo group (HR = 0.33; $P = 0.0019$).[49] At the 2022 European Society for Medical Oncology (ESMO) conference, updated 5-year survival data confirmed that patients with unresectable LA-HNC had improved 5-year overall survival when treated with xevinapant plus 3-weekly cisplatin CCRT compared to the placebo group (53% vs. 28%).[50] A larger, international phase III trial is now underway to validate these findings (NCT04459715).

Berzosertib (formerly known as M6620 or VX-970) is another novel drug, noted for being a highly potent and selective first-in-class inhibitor of ataxia-telangiectasia and Rad3-related protein kinase.[51] A phase I trial combining berzosertib with weekly cisplatin CCRT (40 mg/m^2 and 70 Gy) in locally advanced HNSCC also reported promising initial efficacy and safety results at the ESMO 2022 conference.[52]

Conclusion

Weekly cisplatin-based CCRT has emerged as a viable alternative to the traditional 3-weekly schedule in treating LA-HNC. Evidence from recent studies suggests that weekly cisplatin offers comparable therapeutic outcomes with potentially lower toxicity, improved compliance, and reduced interruptions.[8-11] Despite indications that 3-weekly cisplatin may provide marginally better locoregional control, ongoing trials such as ConCERT are set to further clarify the optimal therapeutic regimen.[10] Taken together, future LA-HNC treatment may benefit from these evolving CCRT protocols, along with emerging treatment modalities such as

combinational ICB, xevinapant, and berzosertib,[49,52] offering new opportunities for improved patient outcomes.

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Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Conflicts of interest

There are no conflicts of interest.

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