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Weekly Cisplatin Plus Radiation for Postoperative Head and Neck Cancer (JCOG1008): A Multicenter, Noninferiority, Phase II/III Randomized Controlled Trial

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abstract

PURPOSE The standard treatment for postoperative high-risk locally advanced squamous cell carcinoma of the head and neck (LA-SCCHN) is chemoradiotherapy with 3-weekly cisplatin (100 mg/m²). However, whether chemoradiotherapy with weekly cisplatin (40 mg/m²) yields comparable efficacy with 3-weekly cisplatin in postoperative high-risk LA-SCCHN is unknown.

PATIENTS AND METHODS In this multi-institutional open-label phase II/III trial, patients with postoperative high-risk LA-SCCHN were randomly assigned to receive either chemoradiotherapy with 3-weekly cisplatin (100 mg/m²) or with weekly cisplatin (40 mg/m²) to confirm the noninferiority of weekly cisplatin. The primary end point of phase II was the proportion of treatment completion, and that of phase III was overall survival. A noninferiority margin of hazard ratio was set at 1.32.

RESULTS Between October 2012 and December 2018, a total of 261 patients were enrolled (3-weekly cisplatin, 132 patients; weekly cisplatin, 129 patients). At the planned third interim analysis in the phase III part, after a median follow-up of 2.2 (interquartile range 1.19-3.56) years, chemoradiotherapy with weekly cisplatin was noninferior to 3-weekly cisplatin in terms of overall survival, with a hazard ratio of 0.69 (99.1% CI, 0.374 to 1.273 [< 1.32], one-sided P for noninferiority = .0027 $< .0043$). Grade 3 or more neutropenia and infection were less frequent in the weekly arm (3-weekly v weekly, 49% v 35% and 12% v 7%, respectively), as were renal impairment and hearing impairment. No treatment-related death was reported in the 3-weekly arm, and two (1.6%) in the weekly arm.

CONCLUSION Chemoradiotherapy with weekly cisplatin is noninferior to 3-weekly cisplatin for patients with postoperative high-risk LA-SCCHN. These findings suggest that chemoradiotherapy with weekly cisplatin can be a possible treatment option for these patients.

ASSOCIATED CONTENT

Data Supplement Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

The global incidence of squamous cell carcinoma of the head and neck (SCCHN) is estimated at more than 700,000 cases newly diagnosed annually.¹ A majority of patients present with locally advanced SCCHN (LA-SCCHN), and surgery is a mainstay of treatment for resectable cases. Postoperative chemoradiotherapy with 3-weekly cisplatin at 100 mg/m² is standard treatment for patients with high-risk factors for recurrence.²⁻⁴ However, the 3-weekly dosage has raised concerns about insufficient cisplatin delivery because of

high-dose-related toxicity,^{2,3,5} and chemoradiotherapy with weekly cisplatin is widely used as a possible alternative with a better safety profile.⁶⁻¹³ Although some results have conflicted, meta-analyses of comparisons between the 3-weekly and weekly cisplatin suggest that the two approaches have equal efficacy.¹⁴⁻¹⁹

Here, we conducted a multi-institutional open-label phase II/III trial to investigate whether chemoradiotherapy with weekly cisplatin at 40 mg/m² was noninferior to 3-weekly cisplatin at 100 mg/m² in terms of overall survival (OS) for postoperative high-risk LA-SCCHN (JCOG1008).

CONTEXT

Key Objective

Chemoradiotherapy with 3-weekly cisplatin at a dose of 100 mg/m² is the standard treatment for patients with postoperative locally advanced squamous cell carcinoma of the head and neck (LA-SCCHN) with high risk for recurrence. However, the 3-weekly dosage has attracted concern with regard to insufficient cisplatin delivery because of high-dose–related toxicities. Chemoradiotherapy with weekly cisplatin at a dose of 40 mg/m² is widely used as a possible alternative, albeit without sufficient evidence. This clinical trial was conducted to prove the noninferiority of weekly cisplatin to 3-weekly cisplatin plus radiation therapy (RT).

Knowledge Generated

This randomized phase II/III trial showed that chemoradiotherapy with weekly cisplatin is noninferior to 3-weekly cisplatin plus RT for postoperative high-risk LA-SCCHN, with a favorable toxicity profile.

Relevance

The result provides evidence that weekly cisplatin plus RT can be a possible treatment option for patients with postoperative high-risk LA-SCCHN.

PATIENTS AND METHODS

Eligibility

Eligibility criteria included the following: the presence of histologically proven squamous cell carcinoma in the resected specimen; primary lesion located in the oral cavity, oropharynx, hypopharynx, or larynx; pathologic stages III, IVA, or IVB (UICC seventh edition); high-risk factors for recurrence (microscopically positive margin and/or extranodular extension); within 56 days of surgery; without distant metastasis; age 20–75 years; an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1; adequate organ function; no clinically significant abnormal findings on electrocardiography; and written informed consent. A microscopically positive margin was defined as an invasive cancer at or close to the resection margin (< 5 mm) on microscopic evaluation, with no evidence of residual gross tumor. The exclusion criteria are described in detail in the Protocol (online only).

Study Design

JCOG1008 is a multi-institutional, open-label, randomized, noninferiority phase II/III trial conducted in 28 institutions in Japan. This trial was registered with the Japan Registry of Clinical Trials (Number: jRCTs031180135) and approved by the National Cancer Center Hospital–Certified Review Board (CRB3180008). All patients provided written informed consent. Patients were randomly assigned in a 1:1 ratio to chemoradiotherapy with 3-weekly cisplatin or weekly cisplatin by the minimization method using a random component, with adjustment to balance high-risk factors for recurrence and institution.

End Points

The primary end point of the phase II part was the proportion of treatment completion among all eligible patients. Cumulative cisplatin dose during radiation therapy (RT) for SCCHN has a significant correlation with survival,²⁰ with

200 mg/m² suggested to be sufficient to achieve an additive effect with RT, irrespective of the method of administration.²¹

On the basis of these results, treatment completion was defined as follows: for the 3-weekly arm, completion of RT within 66 days and administration of two of three courses of 3-weekly cisplatin during RT or within 14 days from the last day of completion of radiation; for the weekly arm, completion of RT within 66 days and administration of five of seven courses of weekly cisplatin during the RT period.

The primary end point of the phase III part was OS, and secondary end points were relapse-free survival (RFS), local relapse-free survival, nutrition support–free survival, nonhospitalized treatment period during the permissible treatment period, and adverse events (AEs). Definitions of end points are given in the Protocol. Incidence of AEs was evaluated using CTACE version 4.0. Per-protocol disease assessment (physical examination, computed tomography or magnetic resonance imaging of head and neck, and upper abdominal computed tomography) and adverse event data were required every 3 months for a year, every 4 months from 1 to 2 years, every 6 months from 2 to 3 years, and then annually through 5 years.

Treatment

In the 3-weekly arm, cisplatin was administered at 100 mg/m² once every 3 weeks for three cycles during the RT period or once within 14 days from the day of completion of radiation. In the weekly arm, cisplatin was administered at 40 mg/m² once a week for seven cycles during the RT period. Criteria for dose reduction or delay were prespecified. RT was administered with high-energy photons of 4–10 MV x-rays to a total dose of 66 Gy in 33 fractions over 6.5 weeks. Three-dimensional conformal radiation therapy or intensity-modulated radiation therapy was chosen at institutional discretion. Details of RT planning are given in the Protocol. For quality control and assurance of RT, compliance with protocol-specified RT

planning was examined for all enrolled patients at completion of RT.

Statistical Analysis

This trial aimed to confirm the noninferiority of chemoradiotherapy with weekly cisplatin to chemoradiotherapy with 3-weekly cisplatin for postoperative high-risk patients with LA-SCCHN. The planned accrual period was 5 years, and the follow-up period was 5 years. In the phase II part, corresponding to the first interim analysis, the planned sample size was 33 patients in each arm, calculated on the basis of an expected proportion of treatment completion of 80% and a threshold of 50%, with a one-sided alpha of .025 and a power of 90%.^{2,3,5,6,9,22-26} Arms were not compared in phase II. In the phase III part, we planned to include 260 patients to observe 161 deaths, considering an accrual period of 5 years, a follow-up of 5 years, a one-sided alpha of .05, a power of 75%, and a noninferiority margin of 1.32 (corresponding to 10% for 5-year OS). Because the weekly arm was expected to be marginally better than the 3-weekly arm on the basis of the reports available at the time that the trial was planned,^{2,3,6-9,27} we used a hybrid noninferiority approach.²⁸ Thus, the expected OS of the 3-weekly and the weekly arms was 49% and 52%. Noninferiority of the weekly arm in terms of OS was tested with regard to the hazard ratio (HR) and CI between arms, as estimated using a Cox proportional hazards model stratified by the high-risk factors. Noninferiority would be concluded if the upper limit of the CI of the HR did not exceed 1.32 in the intention-to-treat population.

Three interim analyses were planned, the third after accrual completion to determine continuation of follow-up. The Data and Safety Monitoring Committee (DSMC) of the Japan Clinical Oncology Group independently reviewed the interim analysis reports to recommend continuation or early termination in consideration of efficacy and futility. Multiplicity was adjusted by the Lan and DeMets method with the O'Brien-Fleming-type alpha spending function.²⁹ The significance level for the third interim analysis was 0.0043 with an information fraction of 47.2% (76 of 161) at the data cutoff of July 2, 2019. Additional follow-up analyses for efficacy were performed with the data cutoff of June 25, 2021. All analyses were performed using SAS version 9.4.

RESULTS

Patient Characteristics

Between October 16, 2012, and December 21, 2018, 261 patients were enrolled. All patients were allocated to the treatment groups (132 in the 3-weekly arm and 129 in the weekly arm) and included in the intention-to-treat analyses. Three patients in the 3-weekly arm and seven in the weekly arm were excluded from safety analysis, leaving 251 in the per-protocol analyses (Fig 1).

Treatment arms were generally balanced with respect to demographic and clinical characteristics (Table 1 and the Data Supplement, online only). Immunohistochemistry information on p16 status was collected after the third interim analysis and reported for 34 of 35 patients with oropharyngeal cancer (Data Supplement).

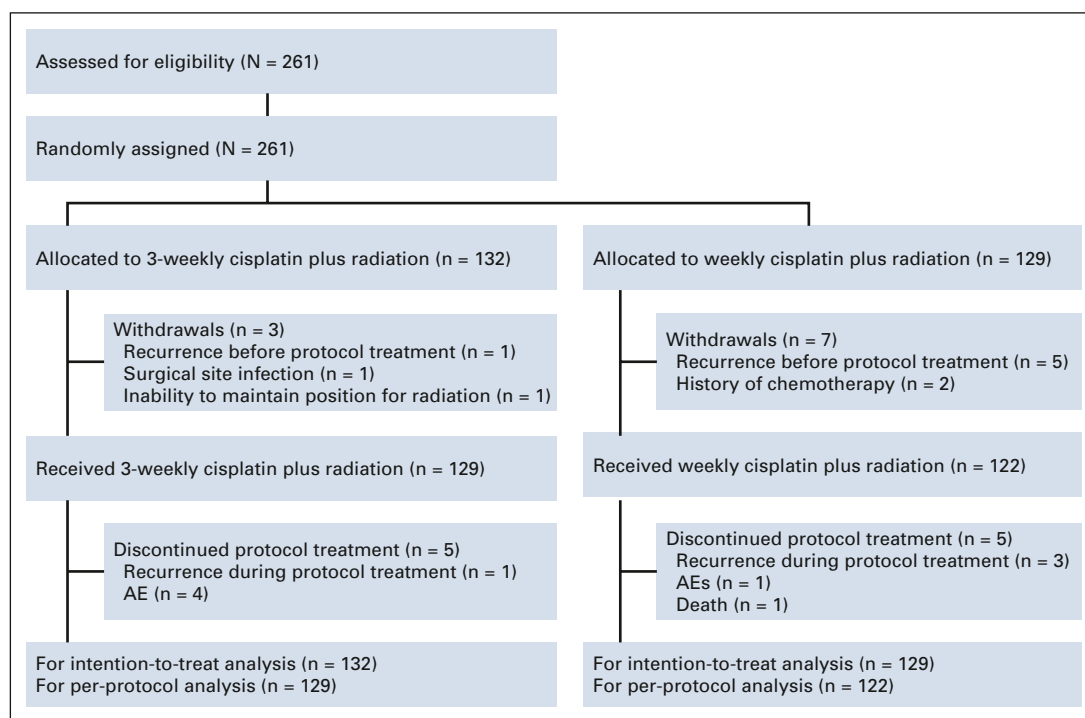


FIG 1. CONSORT diagram. AE, adverse event.

TABLE 1. Baseline Characteristics

Characteristic	3-Weekly Cisplatin (n = 132)	Weekly Cisplatin (n = 129)	Total (N = 261)
Age			
Median, years (IQR)	62 (55-68)	61 (53-66)	62 (54-67)
Sex, No. (%)			
Male	110 (85)	110 (85)	220 (84)
Female	22 (15)	19 (15)	41 (16)
ECOG performance status, No. (%)			
0	92 (70)	93 (72)	185 (71)
1	40 (30)	36 (28)	76 (28)
Primary site, No. (%)			
Oral cavity	61 (46)	60 (46)	121 (46)
Larynx	12 (9)	11 (9)	23 (9)
Oropharynx	14 (11)	21 (16)	35 (14)
Hypopharynx	45 (34)	37 (29)	82 (31)
High-risk factors, No. (%)			
Positive margin	43 (33)	42 (35)	85 (35)
Extranodal extension	112 (85)	109 (85)	221 (85)
Pathologic T stage, No. (%)			
T1	13 (10)	7 (5)	20 (8)
T2	26 (20)	40 (31)	66 (25)
T3	25 (19)	23 (18)	48 (18)
T4	68 (51)	59 (46)	127 (49)
Pathologic N stage, No. (%)			
N0	9 (7)	6 (5)	15 (5)
N1	10 (7)	15 (12)	25 (10)
N2	107 (81)	104 (81)	211 (81)
N3	5 (4)	2 (1)	7 (3)
Nx	1 (1)	2 (1)	3 (1)
Pathologic stage, No. (%)			
III	9 (7)	11 (9)	20 (8)
IVA	117 (88)	113 (88)	230 (88)
IVB	5 (4)	3 (2)	8 (3)
Unknown	1 (1)	2 (1)	3 (1)

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

Efficacy

At the time of the third interim analysis in the phase III part, 44 patients (33%) in the 3-weekly arm had died versus 32 (25%) in the weekly arm. The median follow-up was 2.2 years (2.8 years for survivors). In terms of OS, the weekly arm was noninferior to the 3-weekly arm with a HR of 0.69 (99.1% CI, 0.37 to 1.27) since the upper limit of CI was below the prespecified noninferiority margin of an HR of 1.32 (one-sided *P* value for noninferiority = .0027 < .0043; Fig 2A). The estimated 2- and 3-year OS was 74.2%/59.1% in the 3-weekly arm and 77.7%/71.6% in the weekly arm. For the preplanned subgroup analyses for OS, most

subgroups were more favorable in the weekly arm (Fig 2B). The OS result in the per-protocol subset showed the same trend (Data Supplement). The HR of death adjusted with known confounders of pT, pN, and primary site was 0.79 (95% CI, 0.50 to 1.26).

Regarding RFS, 88 patients (33.7%) experienced disease recurrence. Of the 51 with recurrence in the 3-weekly arm, recurrence was at locoregional sites only in 15, distant sites only in 31, and both in five. Of 37 patients with recurrence in the weekly arm, recurrence was at locoregional sites only in 14, distant sites only in 21, and both in two. The HR of RFS was 0.71 (95% CI, 0.48 to 1.06; Fig 3A). The HR of

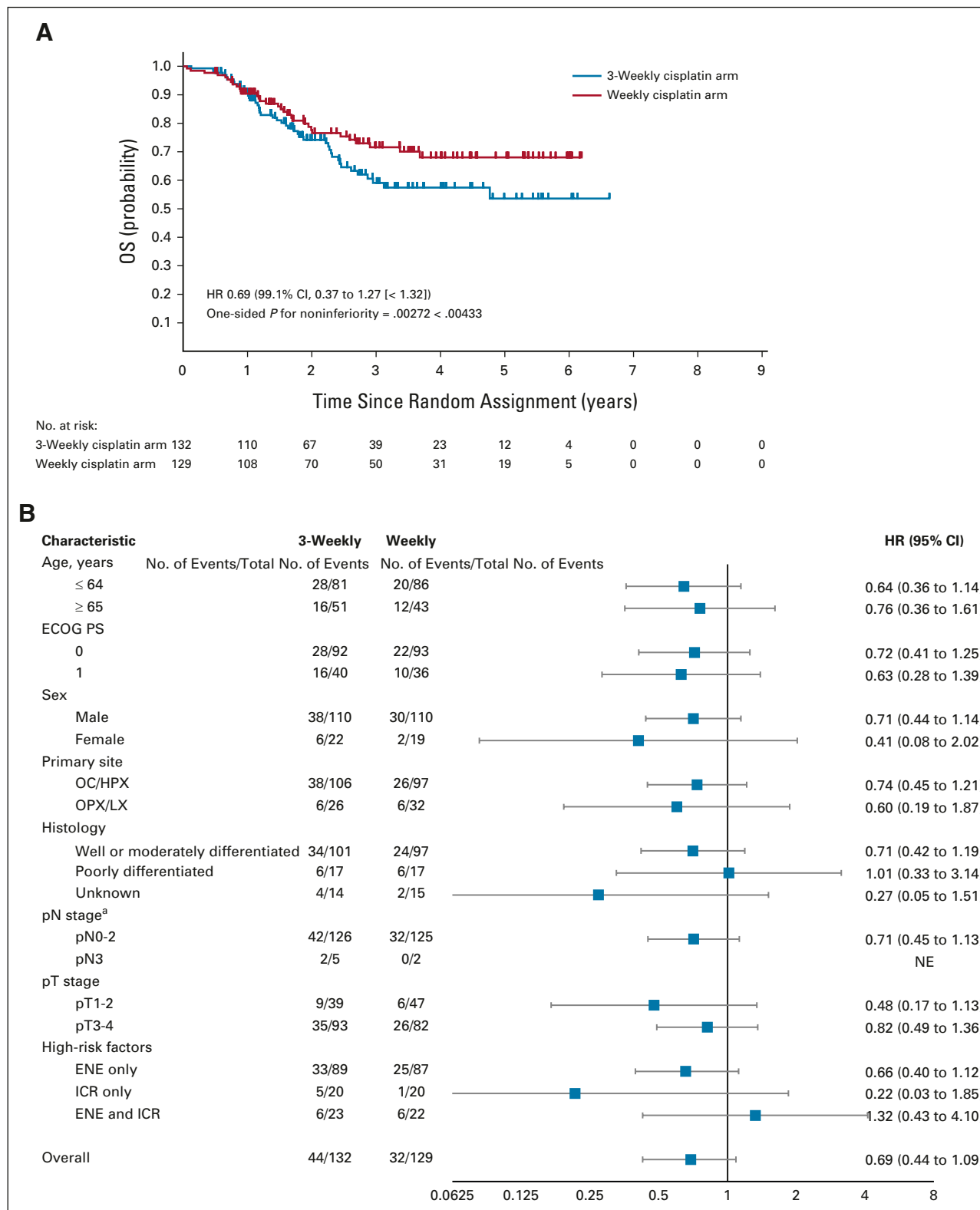


FIG 2. (A) The Kaplan-Meier curve for OS for all randomly assigned patients at the third interim analysis. The symbols indicate censored observations. The boundary for statistical significance of noninferiority for OS required a P value of $< .00433$ (CI 99.1%). HRs were computed using a stratified Cox proportional hazards model and the P values were from a stratified log-rank test. (B) The plot of unstratified HRs for death in the analysis of treatment, with effect according to baseline demographic and clinical subgroups. (C) The Kaplan-Meier curve for OS for all randomly assigned patients at the updated analysis. ^aOne patient in each arm is missing. ECOG PS, Eastern Cooperative Oncology Group performance status; ENE, extranodal extension; HPX, hypopharynx; HR, hazard ratio; ICR, incomplete resection; LX, larynx; NE, not evaluable; OC, oral cavity; OPX, oropharynx; OS, overall survival. (continued on following page)

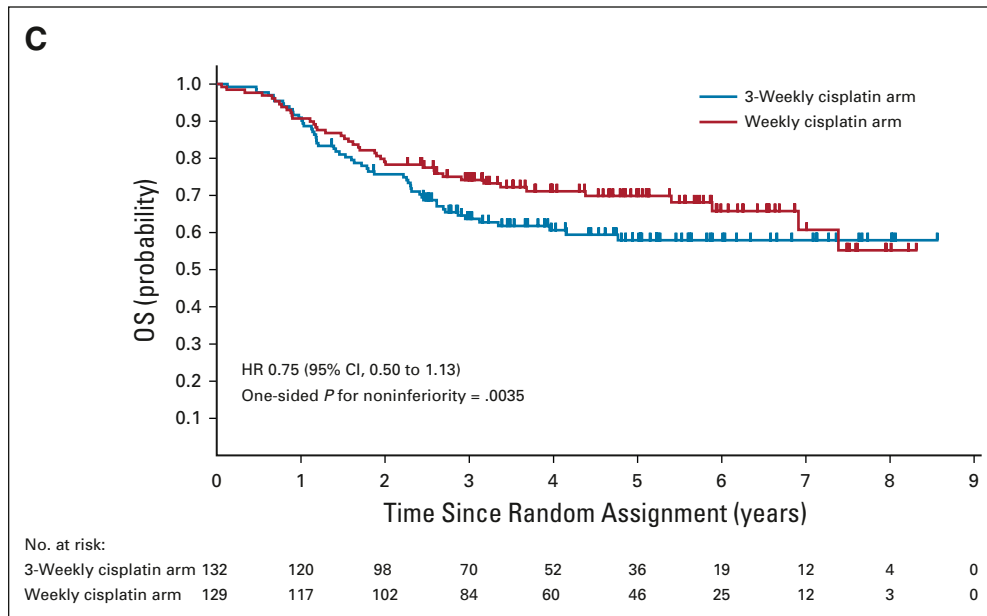


FIG 2. (Continued)

local relapse-free survival was 0.73 (95% CI, 0.47 to 1.13; Data Supplement). Preplanned subgroup analyses are shown in [Figure 3B](#) and the Data Supplement.

From additional data with a median follow-up of 3.5 years (4.8 years for survivors), the HR for death was 0.75 (95% CI, 0.50 to 1.13; *P* for noninferiority of .0035), which maintained the noninferiority of the weekly arm ([Fig 2C](#)). Regarding the cause of death, although two treatment-related deaths were observed in the weekly arm, the total number of deaths was lower and cancer-specific deaths were less frequent in the weekly arm (Data Supplement). All other additional analyses are shown in the Data Supplement.

Safety

The proportion of treatment completion in both arms in the phase II part met the prespecified criteria (Data Supplement). Hence, the DSMC allowed continuation to the phase III part. Treatment delivery and compliance with radiation therapy and chemotherapy were sufficient and as planned in both arms ([Table 2](#)). Regarding safety, acute hematologic and nonhematologic AEs occurring in 15% and 5% of patients or more are shown in [Table 3](#) and the Data Supplement, respectively. Late toxicities occurring in 1% of patients or more are shown in the Data Supplement. AEs of special interest, including neutropenia, infection, hearing impairment, and renal impairment, were prespecified in the protocol since these were anticipated to be less frequent in the weekly arm as the primary merit of weekly administration. Regarding acute hematologic AEs of special interest, grade 3 or more neutropenia was less frequent in the weekly arm (3-weekly cisplatin v weekly cisplatin, 49% v

35%) although thrombocytopenia of any grade was less frequent in the 3-weekly arm (3-weekly cisplatin v weekly cisplatin, 66% v 84%). Among acute nonhematologic AEs of special interest, grade 3 or more infection was less frequent in the weekly arm (3-weekly cisplatin v weekly cisplatin, 12% v 7%), as was any grade of renal impairment (3-weekly cisplatin v weekly cisplatin, 40% v 30%) and hearing impairment (3-weekly cisplatin v weekly cisplatin, 17% v 7%), including tinnitus (3-weekly cisplatin v weekly cisplatin, 25% v 5%). The proportion of patients with at least one grade 3 or more AE (3-weekly v weekly) was 79.8% versus 81.1% (*P* = .87), and that of grade 4 AEs was 18.6% versus 8.2% (*P* = .017). In terms of hematologic toxicities, that of grade 3 or more AEs was 61.2% versus 64.8% (*P* = .60) and that of grade 4 AEs was 14.7% versus 7.4% (*P* = .07). In the 3-weekly arm, three patients discontinued protocol treatment because of treatment-related AEs, one each for xerostomia, mucositis, and persistent nausea. In the weekly arm, two patients discontinued protocol treatment, one each for anorexia and febrile neutropenia. Two treatment-related deaths were reported in the weekly arm, one each because of febrile neutropenia and laryngeal edema.

DISCUSSION

To our knowledge, this multi-institutional open-label randomized phase II/III trial is the first to show that chemoradiotherapy with weekly cisplatin at 40 mg/m² is noninferior to 3-weekly cisplatin at 100 mg/m², with a favorable toxicity profile, in postoperative high-risk LA-SCCHN.

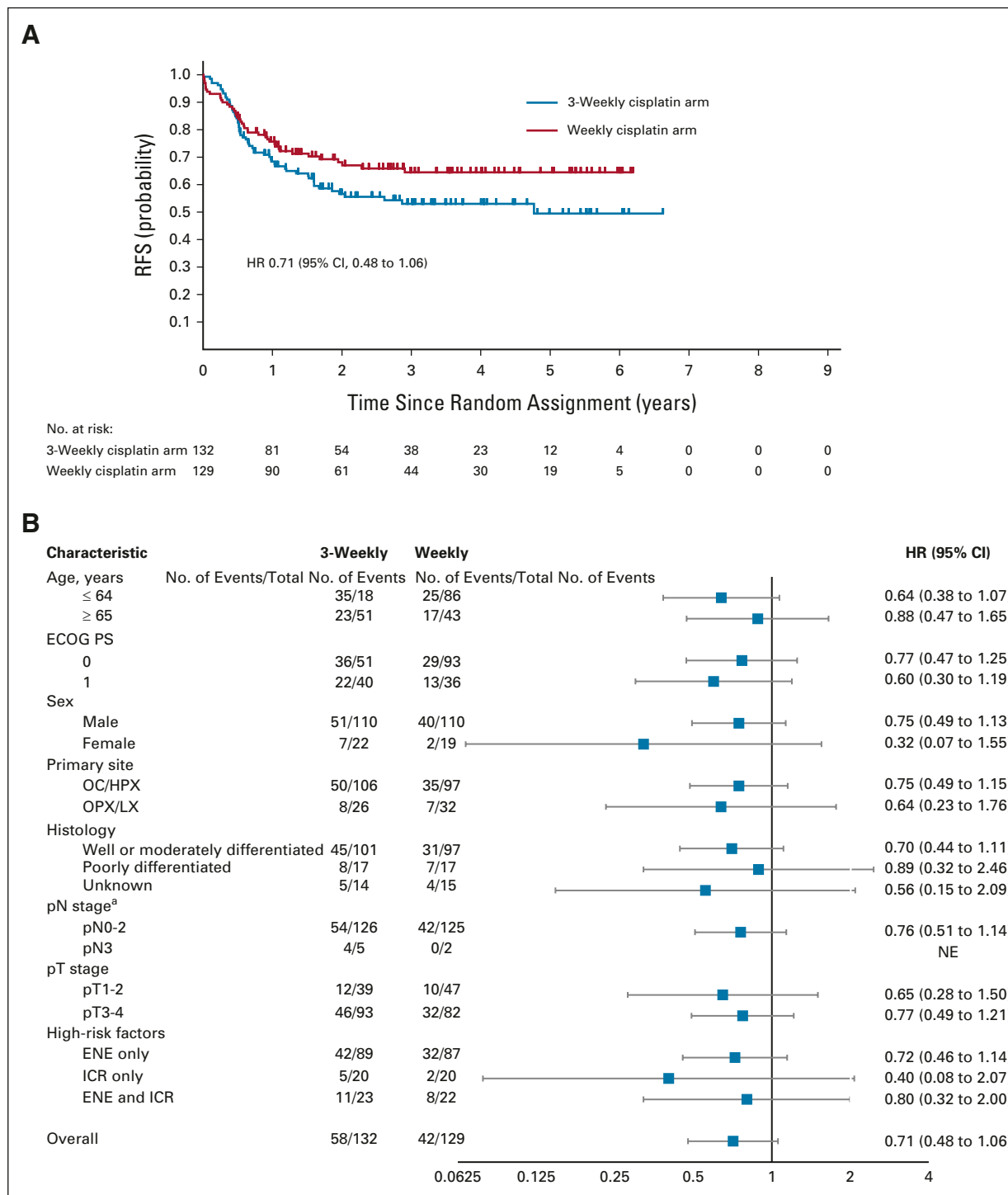


FIG 3. (A) The Kaplan-Meier curve for RFS for all randomly assigned patients. The symbols indicate censored observations. HRs were computed using a stratified Cox proportional hazards model. (B) The plot of unstratified HRs for death or recurrence in the analysis of the treatment effect according to baseline demographic and clinical subgroups. ^aOne patient in each arm is missing. ECOG PS, Eastern Cooperative Oncology Group performance status; ENE, extranodal extension; HPX, hypopharynx; HR, hazard ratio; ICR, incomplete resection; LX, larynx; NE, not evaluable; OC, oral cavity; OPX, oropharynx; RFS, relapse-free survival.

After two pivotal randomized trials, the standard treatment for patients with postoperative high-risk LA-SCCHN has been chemoradiotherapy with 3-weekly cisplatin at 100 mg/m².^{2,3} Clinical benefit was estimated to be an

approximately 10% absolute survival benefit and a 30% decrease in risk of death compared with RT alone.⁴ However, concerns about this treatment were raised after finding that only around 60% of patients completed

TABLE 2. Treatment Delivery and Compliance

Parameter	3-Weekly Cisplatin (n = 132)	Weekly Cisplatin (n = 129)
Total RT dose (Gy), median (IQR)	66 (66-66)	66 (66-66)
Duration of RT (days), median (IQR)	49 (47-51)	49 (46-50)
Interval from surgery to RT initiation (days), median (IQR)	49 (42-56)	50 (43-56)
Cycles of cisplatin, median (IQR)	3 (3-3)	6 (5-7)
Cumulative dose of cisplatin (mg/m ²), median (IQR)	280 (250-299)	239 (199-277)
Proportion of actual to planned delivery of cisplatin (%), mean (SD)	88.9 (15.1)	84.1 (17.6)
Proportion of treatment completion (%), median (95% CI)	93.2 (87.5 to 96.8)	86.8 (79.7 to 92.1)

Abbreviations: IQR, interquartile range; RT, radiation therapy; SD, standard deviation.

three cycles of 3-weekly cisplatin because of high-dose–related toxicities, such as myelosuppression, renal impairment, and hearing impairment.^{2,3,5} On the other hand, although chemoradiotherapy with weekly cisplatin at 40 mg/m² is an established standard treatment for locally advanced nasopharyngeal carcinoma and cervical cancer,^{26,30} chemoradiotherapy with weekly cisplatin has been widely used as a possible alternative regimen for LA-SCCHN.^{6-8,10-14,16-19,25} Regarding the postoperative high-risk setting, a small randomized trial suggested that chemoradiotherapy with weekly cisplatin at a flat dose of 50 mg was superior to RT alone.⁹ Furthermore, other studies of chemoradiotherapy with weekly cisplatin indicated equivalence with 3-weekly cisplatin in terms of treatment outcomes and greater safety, albeit without a direct prospective comparison on the basis of a sufficient and plausible clinical trial design.^{10-12,16-18}

However, researchers from a single institution in India reported a phase III trial of chemoradiotherapy with 3-weekly cisplatin at 100 mg/m² compared with weekly cisplatin at 30 mg/m² for patients with LA-SCCHN.¹⁵ Patients in both the definitive and postoperative settings were eligible. The primary end point—2-year locoregional control—of chemoradiotherapy with weekly cisplatin was 58.5%, which was significantly worse than 73.1% seen with 3-weekly cisplatin (HR 1.76; 95% CI, 1.11 to 2.79; *P* = .014). Hence, the trial failed to demonstrate the noninferiority of chemoradiotherapy with weekly cisplatin at a dose of 30 mg/m². In stark contrast, our trial was a multi-institutional randomized phase III trial conducted in 28 participating institutions of the Japan Clinical Oncology Group Head and Neck Cancer Study Group in Japan, and eligibility was strictly restricted to postoperative high-risk patients. Regarding the weekly cisplatin dose, we adopted seven administrations of 40 mg/m² during RT for a total of 280 mg/m² to maintain comparability with the planned total dose of 3-weekly cisplatin of 300 mg/m². Results showed a cumulative dose of cisplatin of 239 mg/m² in the weekly cisplatin arm (interquartile range [IQR]: 199-277) versus 280 mg/m² in the 3-weekly cisplatin arm (IQR: 250-299). The cumulative cisplatin dose during RT for SCCHN has a significant correlation with survival,²⁰ and 200 mg/m² is

suggested to be sufficient to achieve an additive effect with RT.²¹ Accordingly, about 75% of our patients in the weekly arm achieved a cumulative cisplatin dose of more than 200 mg/m². This contrasts with the median cumulative dose of cisplatin of 210 mg/m² (IQR: 180-210) with weekly cisplatin at a dose of 30 mg/m² in the Indian trial. This difference in cumulative dose with weekly cisplatin might explain the conflicting results between our present and the Indian trial. In addition, a possible explanation for the better outcome with weekly cisplatin in our trial is that the dose intensity of weekly cisplatin at 40 mg/m² is theoretically higher than that of 3-weekly cisplatin at 100 mg/m² and of weekly cisplatin at 30 mg/m² (40 mg/m²/week *v* 33 mg/m²/week *v* 30 mg/m²/week). In our study, administration of cisplatin within 14 days from the last day of completion of radiation was allowed for the 3-weekly arm, but not for the weekly arm. In other words, the permissible duration of administration of cisplatin differed between the two arms. Therefore, we could not formally calculate dose intensity. However, the mean proportion of actual to planned delivery of cisplatin was 84.1% in the weekly cisplatin arm and 88.9% in the 3-weekly cisplatin arm, indicating higher estimated dose intensity in the weekly than in the 3-weekly cisplatin arm (33.6 mg/m² *v* 29.3 mg/m²). We therefore propose that our maintenance of dose intensity in the weekly cisplatin arm provides proof of noninferiority.

Our trial has several limitations, mostly owing to its statistical design. Our trial is a noninferiority trial with a relatively wide noninferiority margin of 10% for 5-year OS, corresponding to a noninferiority margin of HR of 1.32. In practice, this would allow for a possible 32% increase in risk of death in chemoradiotherapy with weekly cisplatin. Given the nature of our relatively small noninferiority trial, care is required for potential subgroups, such as those with poorly differentiated subtypes and large tumors (pT3-4), which could affect treatment outcomes. Furthermore, given that survival curves overlapped early after random assignment, proportionality might have been violated, which would indicate that the HRs may not be robust. In addition, it is unclear whether these merits in the safety profile on weekly administration were simply derived from the weekly dosing or from the lower total dose of cisplatin in this arm. However, we prespecified the merit of weekly administration of

TABLE 3. Acute Adverse Events in $\geq 15\%$ of Patients

Adverse Event	3-Weekly Cisplatin (n = 129), No. (%)		Weekly Cisplatin (n = 122), No. (%)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Hematologic				
Anemia	129 (100)	18 (14)	122 (100)	16 (13)
Leukocytopenia	123 (95)	71 (55)	114 (93)	75 (62)
Neutropenia	118 (92)	63 (49)	106 (87)	43 (35)
Thrombocytopenia	85 (66)	3 (2)	102 (84)	4 (3)
Nonhematologic				
Hypoalbuminemia	129 (100)	0 (0)	117 (96)	0 (0)
Hyponatremia	119 (92)	13 (10)	100 (82)	13 (11)
Mucositis	118 (92)	30 (23)	113 (93)	34 (28)
Radiation dermatitis	118 (92)	19 (15)	112 (92)	14 (12)
Dysgeusia	97 (75)	—	81 (66)	—
Nausea	87 (67)	17 (13)	57 (47)	6 (5)
Xerostomia	81 (63)	1 (1)	81 (66)	2 (2)
Hypocalcemia	80 (62)	5 (4)	67 (55)	7 (6)
Hyperkalemia	79 (61)	6 (5)	77 (63)	2 (2)
Dysphagia	75 (58)	24 (19)	59 (48)	14 (12)
ALT increased	74 (57)	4 (3)	37 (30)	3 (3)
AST increased	66 (51)	4 (3)	36 (30)	0 (0)
Hypomagnesemia ^a	65 (51)	0 (0)	64 (54)	1 (1)
Constipation	63 (49)	0 (0)	56 (46)	0 (0)
Creatinine increased	51 (40)	0 (0)	36 (30)	0 (0)
Fatigue	50 (39)	5 (4)	41 (34)	1 (1)
Hypokalemia	46 (36)	7 (5)	25 (21)	3 (3)
Tinnitus	32 (25)	0 (0)	6 (5)	0 (0)
Hypermagnesemia ^a	26 (20)	3 (2)	10 (8)	1 (1)
Diarrhea	26 (20)	0 (0)	14 (12)	1 (1)
Infection	25 (19)	15 (12)	18 (15)	8 (7)
Fever	25 (19)	1 (1)	27 (22)	2 (2)
Alopecia	23 (18)	—	14 (12)	—
Vomiting	22 (17)	1 (1)	16 (13)	0 (0)
Hearing disturbance	22 (17)	5 (4)	9 (7)	2 (2)
Neck edema	21 (16)	1 (1)	16 (13)	0 (0)

^aData missing for one patient in the 3-weekly arm and three patients in the weekly arm.

cisplatin in terms of safety, and the AEs of special interest were neutropenia, infection, hearing impairment, and renal impairment. As expected, grade 3 or more neutropenia and infection were less frequent in the weekly cisplatin arm, as was any grade of hearing impairment, including tinnitus, and renal impairment. Moreover, grade 4 AEs were less frequent in the weekly arm and grade 4 hematologic toxicities appeared to be less frequent in this arm. Other AEs listed in Table 3 were also generally equally or less frequent in the weekly cisplatin arm. By contrast, thrombocytopenia was frequent in the weekly arm and one of two treatment-

related deaths in this arm was due to febrile neutropenia. A recent report from China found that leukopenia and thrombocytopenia were more frequent in a weekly cisplatin arm compared with a 3-weekly cisplatin arm although the planned total dose of the weekly cisplatin arm was higher than that of the 3-weekly arm (240 mg/m² v 200 mg/m²).³¹ While recognizing this difference, these findings indicate the need for care in avoiding hematologic toxicities in the safety management of this regimen. More particularly, they suggest the importance to safety of dose selection, which takes account of both total and individual dosage. Viewed

overall, we propose that the safety merit of chemoradiotherapy with weekly cisplatin can be traded off against its possibly adverse noninferiority margin. Moreover, an updated analysis with longer follow-up showed that the noninferiority of the weekly cisplatin arm was maintained with an HR for OS of 0.75.

In summary, chemoradiotherapy with weekly cisplatin at a dose of 40 mg/m² for patients with postoperative high-risk

LA-SCCHN is noninferior to chemoradiotherapy with 3-weekly cisplatin at a dose of 100 mg/m² and has a favorable acute safety profile. Chemoradiotherapy with weekly cisplatin can be a possible treatment option for these patients. Follow-up is ongoing in both arms, with confirmation of final treatment outcomes and late toxicities expected at final analysis, 5 years after final registration.

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DATA SHARING STATEMENT

Anonymized individual participant data that underlie the results reported in this Article will not be shared because patient follow-up will be continued until December, 2023. After publication of the final follow-up, using data as of December 2023, the individual participant data that underlie the results will be shared after deidentification to investigators whose proposed data use has been approved by investigators of the JCOG Head and Neck Cancer Study Group identified for that purpose. Proposals should be directed to matahara@east.ncc.go.jp.

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