The Oncologist®

Clinical Trial Results

A Phase II Study of Genexol-PM and Cisplatin as Induction Chemotherapy in Locally Advanced Head and Neck Squamous Cell Carcinoma

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Trial Information

- **Trial Identifier**: NCT01689194
- **Sponsor(s)**: Investigator-initiated trial
- **Principal Investigators**: Keun-Wook Lee, Se-Hoon Lee
- **IRB Approved**: Yes

Lessons Learned

- Induction chemotherapy with Genexol-PM and cisplatin demonstrated modest tumor response in locally advanced head and neck squamous cell carcinoma.
- Considering favorable toxicity profiles and promising survival data, further studies on this regimen are warranted in patients with head and neck squamous cell carcinoma.

Abstract

Background. Genexol-PM is a polymeric micellar formulation of paclitaxel without Cremophor EL. We investigated the efficacy and safety of Genexol-PM plus cisplatin as induction chemotherapy (IC) in patients with locally advanced head and neck squamous cell carcinoma (LA-HNSCC).

Methods. Patients received Genexol-PM (230 mg/m^2) and cisplatin (60 mg/m^2) every 3 weeks as IC. After three cycles of IC, definitive treatment of either concurrent chemoradiotherapy (CCRT) with weekly cisplatin (30 mg/m^2) or surgery was performed. The primary endpoint was overall response rate (ORR) after IC.

Results. Of 52 patients enrolled, 47 completed three cycles of IC, and the ORR was 55.8% (95% confidence interval, 42.3–69.3). Although there was one treatment-related death, toxicity profiles to Genexol-PM and cisplatin were generally favorable, and the most common grade 3 or 4 toxicities were neutropenia (15.4%), anorexia (7.7%), and general weakness (7.7%). Fifty-one patients received definitive treatment (CCRT [*n* = 44] or radical surgery [*n* = 7]). The rate of complete response following CCRT was 81.8% (36/44). After a median follow-up of 39 months, estimates of progression-free survival (PFS) and overall survival (OS) at 3 years were 54.3% and 71.3%, respectively.

Conclusion. IC with Genexol-PM and cisplatin demonstrated modest tumor response with well-tolerated toxicity profiles for patients with LA-HNSCC. ***The Oncologist*** 2019;24:751–e231

Discussion

Although there have been debates on the role of induction chemotherapy in LA-HNSCC, recent studies have suggested that a sequential approach using induction chemotherapy can yield survival benefit. However, the most effective regimen of docetaxel, cisplatin, and 5-fluorouracil (TPF) has significant toxicity, and some patients cannot receive planned definitive CCRT because of toxicity during induction chemotherapy. Hence, an alternative regimen is needed to reduce toxicity. In this phase II study, we evaluated the efficacy and safety of Genexol-PM (a novel formulation of paclitaxel without Cremophor EL) and cisplatin as induction chemotherapy in LA-HNSCC.

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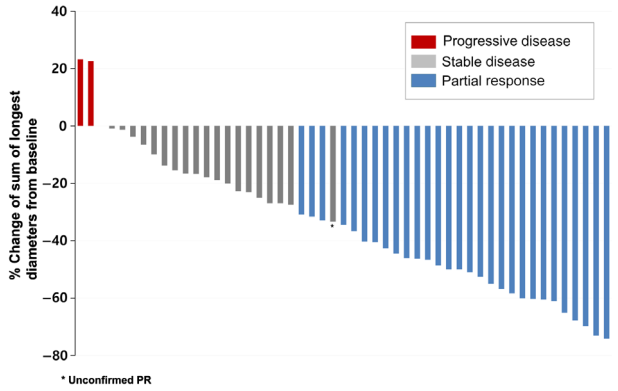

Figure 1. Waterfall plots of best percentage changes in the sum of the longest diameters of target lesions.
Abbreviation: PR, partial response.

Genexol-PM showed significant antitumor activity without increasing toxicity compared with conventional Cremophor EL-based paclitaxel in several malignancies. We hypothesized that the use of Genexol-PM plus cisplatin in LA-HNSCC would reduce the toxicity without compromising the efficacy. Of the 52 patients enrolled, the ORR was 55.8% (Fig. 1); toxicity profiles were favorable, and the most common grade 3 or 4 toxicity was neutropenia (15.4%). Estimates of PFS and OS at 3 years were 54.3% and 71.3%, respectively (Table 1).

Although the ORRs of Genexol-PM/cisplatin (55.8%) seemed somewhat lower compared with those reported for TPF (64%–80%), 3-year PFS and OS rates (54.3% and 71.3%, respectively) were within a similar range as those reported from previous studies. Moreover, the toxicity profiles of Genexol-PM/cisplatin look very favorable with fewer grade 3 or 4 adverse events compared with TPF. In our study, 47 out of 52 patients (90.4%) completed the three scheduled cycles of induction chemotherapy, and the proportion of patients who were able to receive the definitive treatment was 98.1%. As previously reported, the proportion of patients who completed the planned concomitant treatment was approximately 50% because of the severe toxicities from TPF-based induction chemotherapy. The treatment compliance rate during induction chemotherapy followed by CCRT in our study was in marked contrast to the low compliance rate obtained from the TPF regimen.

Table 1. Treatment outcomes

	***n* = 52, *n* (%)**
Completion of induction chemotherapy	
Yes	47 (90.4)
No	5 (9.6)
Response to induction chemotherapy	
CR	0 (0.0)
PR	29 (55.8)
SD	20 (38.5)
PD	2 (3.8)
NE	1 (1.9)
Overall response rate (95% CI)	55.8% (42.3%–69.3%)
Disease control rate (95% CI)	94.2% (87.8%–100.0%)
Definitive treatment after induction chemotherapy	
CCRT	44 (84.6)
Surgery	7 (13.5)
Not done	1 (1.9)
Response to CCRT (*n* = 44)	
CR	36 (81.8)
Non-CR	6 (13.6)
Not evaluated	2 (4.5)
3-years PFS rate	
In total population	54.3%
In oropharyngeal cancer	68.8%
In nonoropharyngeal cancer	44.2.6%
3-years OS rate	
In total population	71.3%
In oropharyngeal cancer	75.0%
In nonoropharyngeal cancer	58.9%

Abbreviations: CCRT, concurrent chemoradiotherapy; CI, confidence interval; CR, complete response; NE, not evaluable; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

In conclusion, induction chemotherapy with Genexol-PM/cisplatin demonstrated modest ORR in LA-HNSCC. However, toxicity profiles were very favorable, and survival outcomes look promising.

Trial Information	
Disease	Head and neck cancers
Stage of Disease/Treatment	Neo-adjuvant
Prior Therapy	None
Type of Study – 1	Phase II
Type of Study – 2	Single arm
Primary Endpoint	Overall response rate (ORR)
Secondary Endpoint	Progression-free survival (PFS)
Secondary Endpoint	Overall survival (OS)
Secondary Endpoint	Toxicity

Additional Details of Endpoints or Study Design

The primary endpoint of this study was ORR after induction chemotherapy. Secondary endpoints included PFS, OS, and toxicities. Responses were classified as a complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) according to the RECIST, version 1.0 [1]. ORR was defined as the proportion of patients achieving CR or PR after induction chemotherapy. Among patients receiving subsequent CCRT, PFS was defined as the period from the starting date of induction chemotherapy to disease progression or recurrence or death from any cause. Among patients receiving subsequent radical surgery, PFS was defined as the period from the starting date of induction chemotherapy to disease recurrence or death from any cause. OS was calculated from the starting date of induction chemotherapy to death from any cause.

The sample size was calculated with the assumption that the null hypothesis $P_0 = 0.50$ and alternative hypothesis $P_1 = 0.70$. With a given power of 0.80 and α-error of 0.05, 47 patients were needed. Considering a 10% drop-out rate, a total of 52 patients were planned to be enrolled. Statistical analyses on categorical variables in tables were performed using Pearson's χ^2 test. The Kaplan-Meier method was used for the analysis of PFS and OS. All statistical tests were two-sided with significance defined as $p < .05$. All analyses were performed using SPSS for Windows version 23.0 (IBM Corp., Armonk, NY). The study protocol was reviewed and approved by the institutional review boards of each hospital and the Ministry of Food and Drug Safety, a Korean regulatory authority. The study was conducted in accordance with the tenets of the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice. Written informed consent was obtained from all the patients before participation. The trial is registered with ClinicalTrials.gov (NCT01689194).

Investigator's Analysis	Active and should be pursued further

Drug Information

Drug 1	
Generic/Working Name	Paclitaxel
Trade Name	Genexol-PM
Company Name	Samyang Biopharmaceuticals Co., Seoul, Korea
Drug Type	A sterile lyophilized polymeric micellar formulation of paclitaxel without Cremophor EL
Drug Class	Mitotic - Kinetic spindle protein
Dose	230 mg/m^2
Route	Intravenous (IV)
Schedule of Administration	
Patients were scheduled to receive induction chemotherapy in the form of IV Genexol-PM at a dose of 230 mg/m^2 over 3 hours, followed by cisplatin 60 mg/m^2 IV over 1 hour with adequate hydration. All patients received antiemetic premedication with the 5-HT$_3$ antagonist, aprepitant and dexamethasone. Treatment was repeated every 3 weeks up to three cycles.	
Drug 2	
Generic/Working Name	Cisplatin
Drug Type	Small molecule
Drug Class	Platinum compound
Dose	60 mg/m^2
Route	IV
Schedule of Administration	
Patients were scheduled to receive induction chemotherapy in the form of IV Genexol-PM at a dose of 230 mg/m^2 over 3 hours, followed by cisplatin 60 mg/m^2 IV over 1 hour with adequate hydration. All patients received antiemetic premedication with the 5-HT$_3$ antagonist, aprepitant and dexamethasone. Treatment was repeated every 3 weeks up to three cycles.	
After three cycles of induction chemotherapy, the multidisciplinary team assessed the resectability and the applicability of definitive treatment of CCRT or radical surgery to individual patients. CCRT was started 4–8 weeks after the last administration of the induction chemotherapy cycle. Cisplatin (30 mg/m^2) was given every week during CCRT. RT was administered via conventional fractionation (1.8–2.0 Gy/day; 5 days per week; total dose, 66–70 Gy). If the patients received radical surgery, postoperative adjuvant therapy was given according to the associated risk factors.	

Patient Characteristics	
Number of Patients, Male	47
Number of Patients, Female	5
Stage	
T stage	
T1	6
T2	14
T3	10
T4	22
N stage	
N0	2
N1	7
N2	37
N3	6
Stage	
III	3
IVA	42
IVB	7
Age	Median (range): 60 years (range, 43–74 years)
Number of Prior Systemic Therapies	Median (range): 0
Performance Status: ECOG	0 — 23 1 — 29 2 — 0 3 — 0 Unknown — 0

Other

From July 2013 to April 2016, a total of 52 patients with nonmetastatic LA-HNSCC were enrolled. Of 52 patients, more than 90% were male with a median age of 60 (range, 43–74) years. The Eastern Cooperative Oncology Group (ECOG) performance status was ≤1 in all patients. Forty-nine patients (94.3%) had stage IV and 43 (82.7%) had N2 to N3 disease. The primary tumors were located in the oropharynx (*n* = 17), oral cavity (*n* = 16), larynx (*n* = 13), and hypopharynx (*n* = 6). The median time between the diagnosis of LA-HNSCC and initiation of induction chemotherapy was 12 (range, 1–41) days.

Cancer Types or Histologic Subtypes	Oropharynx, 17; Oral cavity, 16; Larynx, 13; Hypopharynx, 6

Primary Assessment Method	
Title	Efficacy
Number of Patients Screened	54
Number of Patients Enrolled	52
Number of Patients Evaluable for Toxicity	52
Number of Patients Evaluated for Efficacy	52
Evaluation Method	RECIST 1.0
Response Assessment CR	*n* = 0 (0%)
Response Assessment PR	*n* = 29 (55.8%)
Response Assessment SD	*n* = 20 (38.5%)
Response Assessment PD	*n* = 2 (3.8%)
Response Assessment OTHER	*n* = 1 (1.9%)

Outcome Notes

Tumor assessments were performed based on the RECIST, ver. 1.0 [1] at the baseline and after two and three cycles of induction chemotherapy. All cases with responses to two cycles (CR or PR) were confirmed with repeated imaging after the third cycle, at least 4 weeks after the tumor assessment after the second cycle. Before the initiation of the next cycle, laboratory tests, weight, and ECOG performance status were checked. Adverse events (AEs) were graded according to the National

Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). After completion of definitive treatment (CCRT or surgery), tumor assessments for recurrence or progression were performed every 3 months.

Baseline tumor measurements prior to induction chemotherapy were obtained for all 52 patients, and tumor shrinkage was observed in 48 patients (Fig. 1). The ORR to induction chemotherapy was 55.8% (95% confidence interval [CI], 42.3–69.3). All responses were PRs. The rates of SD and PD after induction chemotherapy were 38.5% and 3.8%, respectively. Therefore, the disease control rate after induction chemotherapy was 94.2% (95% CI, 87.8–100.0; Table 1).

The median PFS and OS were not reached. The estimated 3-year PFS and OS rates were 54.3% (95% CI, 47.0–61.6) and 71.3% (95% CI, 63.8–78.8), respectively. PFS and OS are shown in Figures 2 and 3, respectively.

Adverse Events

The hematological and nonhematological AEs of all grades are summarized in Table 2.

Serious Adverse Events

Name	Grade	Attribution
Generalized muscle weakness (one patient; two events)	3	Probable
Anorexia and emesis (one patient; two events)	3	Possible
Febrile neutropenia (one patient)	3	Definite
Neutropenia and sepsis (one patient)	5	Definite

A total of six serious adverse events were reported in four patients during induction chemotherapy: one patient developed two events of generalized muscle weakness (grade 3 in both events); another patient developed two events of anorexia and emesis (grade 3 in both events). There was one treatment-related mortality (neutropenia and sepsis).

Assessment, Analysis, and Discussion

Completion	Study completed
Investigator's Assessment	Active and should be pursued further

Local therapy including platinum-based concurrent chemoradiotherapy (CCRT) or radical surgery is the key component of the treatment of locally advanced head and neck squamous cell carcinoma (LA-HNSCC) [2]. To improve survival and functional outcomes in LA-HNSCC, chemotherapy has been integrated into various multimodality approaches. Although CCRT has improved the local control rate with organ preservation, distant metastasis has become a more frequently recognized cause of treatment failure [3], suggesting that additional systemic chemotherapy directed at improving distant control might now be important to improve the overall success of treatment in LA-HNSCC.

Therefore, the use of systemic chemotherapy before definitive CCRT or radical surgery, so-called induction chemotherapy or sequential approach, has been a theoretically attractive approach. This sequential approach has been shown to reduce the incidence of distant metastasis and to support organ preservation [2, 4]. Although there has been a long debate on the effect of induction chemotherapy on overall survival (OS), a recent meta-analysis [5] and phase III trial [6] suggested that a sequential approach could yield survival benefit. However, the most effective regimen in this setting, docetaxel, cisplatin, and 5-fluorouracil (TPF), has frequent severe adverse events (AEs) including febrile neutropenia [7–9]. Some patients are unable to receive definitive CCRT because of clinical deterioration during induction TPF.

Hence, an alternative regimen is needed to reduce toxicity while maintaining the efficacy. Genexol-PM (Samyang Biopharmaceuticals Co., Seoul, Korea) is a sterile lyophilized polymeric micellar formulation of paclitaxel without Cremophor EL (CrEL; polyoxyethylated castor oil). CrEL is known to induce histamine release and may, therefore, be responsible for hypersensitivity reactions [10, 11]. In previous Korean phase II and III trials of non-small cell lung cancer, breast cancer, thymic carcinoma, and ovarian cancer [12–15], Genexol-PM showed promising antitumor activity with relatively good tolerability. In metastatic breast cancer, Genexol-PM demonstrated noninferior and even superior clinical efficacy compared with paclitaxel [15]. Based on those studies, Genexol PM has been approved in lung, breast, and ovarian cancers in Korea. In the U.S., two clinical trials were performed in breast cancer (NCT02064829) and pancreas cancer (NCT00111904), and further investigations are ongoing.

Therefore, we designed an open-label, single-arm, phase II study of Genexol-PM plus cisplatin in patients with LA-HNSCC. The purpose of this study was to evaluate the efficacy and safety of Genexol-PM and cisplatin as induction chemotherapy in LA-HNSCC. This trial was conducted at three institutions in Korea: Seoul National University Hospital, Seoul National University Bundang Hospital, and Seoul Metropolitan Government Seoul National University Boramae Medical Center. Adult (age ≥ 18 years) patients

with measurable, previously untreated, pathologically proven, and unresectable nonmetastatic LA-HNSCC were eligible. Patients with undifferentiated carcinoma were also allowed. The primary tumors were located in the oral cavity, oropharynx, hypopharynx, or larynx. Unresectable disease was defined as follows: (a) technically unresectable tumor due to tumor fixation, lymph node fixation, or involvement of the skull base or cervical spine; (b) LA-HNSCC with low surgical curability and/or high probability of severe postoperative functional deficit on the basis of advanced disease (T3–4) or regional lymph node extension (N2–3, except for T1 N2). Disease was staged according to the criteria of the American Joint Committee on Cancer (version 7.0). Additional eligibility criteria were Eastern Cooperative Oncology Group performance status of 0–1, and adequate bone marrow, renal, and hepatic function. Exclusion criteria included any previous chemotherapy or radiotherapy for LA-HNSCC, diagnosis of other cancer within 5 years, peripheral neuropathy or hearing disorder of grade ≥ 2 by National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0), or comorbidities contraindicating administration of systemic chemotherapy and/or radiotherapy.

Patients were scheduled to receive induction chemotherapy with Genexol-PM and cisplatin. Treatment was repeated every 3 weeks up to three cycles. Primary prophylactic granulocyte colony-stimulating factor (G-CSF) was not allowed. During the induction phase, prophylactic G-CSF use was only allowed if grade 4 neutropenia persisted for ≥7 days or neutropenic fever developed in the preceding cycle of chemotherapy. Dose modification was executed according to the severity of hematological and nonhematologic AEs other than nausea, vomiting, and alopecia. The dose of Genexol-PM was reduced to 175 mg/m^2 in grade 4 thrombocytopenia or second occurring cases with grade 4 neutropenia or any grade of febrile neutropenia, although prophylactic G-CSF was used. If absolute neutrophil count and platelet count did not recover to 1.5×10^9/L and 100×10^9/L within 3 weeks from the scheduled date of the next chemotherapy cycle, induction chemotherapy was stopped and CCRT or surgery was performed. If alanine transaminase/aspartate transaminase or alkaline phosphatase level increased to >5 times the upper limit of normal and did not improve within 3 weeks, induction chemotherapy was stopped and CCRT or surgery was performed. The dose of cisplatin was reduced to 40 mg/m^2 if the creatinine clearance ranged from 40 to <60 mL/minute or grade 2 peripheral neuropathy was present. If the creatinine clearance decreased to <40 mL/minute or peripheral neuropathy of grade ≥ 3 developed, induction chemotherapy was stopped and the subject was withdrawn from this trial.

After three cycles of induction chemotherapy, the multidisciplinary team assessed the resectability and the applicability of definitive treatment of CCRT or radical surgery to individual patients. CCRT was started 4–8 weeks after the last administration of the induction chemotherapy cycle. Cisplatin (30 mg/m^2) was given every week during CCRT. RT was administered via conventional fractionation (1.8–2.0 Gy/day; 5 days per week; total dose, 66–70 Gy). If the patients received radical surgery, postoperative adjuvant therapy was given according to the associated risk factors.

All 52 patients received at least one cycle of induction chemotherapy with Genexol-PM and cisplatin. Five patients discontinued chemotherapy because of progressive disease, patients' refusal, and septic shock. Based on intent-to-treat analysis, all 52 patients were included in response and survival evaluation, and toxicity analysis. The median number of induction chemotherapy cycles was 3 (range, 1–3) with mean relative dose intensities of 92.4% (standard deviation, 13.8%) for Genexol-PM and 92.3% (standard deviation, 14.0%) for cisplatin. Forty-seven (90.4%) patients fully completed the three cycles of induction therapy. One dose reduction to 175 mg/m^2 of Genexol-PM was performed in five patients. Baseline tumor measurements prior to induction chemotherapy were obtained for all 52 patients, and tumor shrinkage was observed in 48 patients (Fig. 1). The overall response rate (ORR) was 55.8% (95% confidence interval [CI], 42.3–69.3). All responses were partial responses. The rates of stable disease and progressive disease were 38.5% and 3.8%, respectively. Therefore, the disease control rate was 94.2% (95% CI, 87.8–100.0; Table 1).

Regarding treatment after induction chemotherapy (Table 1), 51 patients (98.1%) received the subsequent definitive treatment with either CCRT (n = 44) or radical surgery (n = 7). The median total dose of radiation therapy was 65 (range, 40–70) Gy, and the median number of cycles of weekly cisplatin combined with radiotherapy was 6 (range, 4–6). Three patients who started CCRT received fewer than the planned six cycles of cisplatin and received less than the planned RT dose, because of disease progression during CCRT or intolerable mucositis. Among patients who received CCRT (n = 44), the complete response (CR) rate following CCRT was 81.8% (n = 36) and six patients (13.6%) showed non-CR response. At the time of data analysis with a median follow-up of 39 months (data cutoff: December 2016), 12 patients died and tumor progression was the most common cause of death (occurring in 91.7%). The median progression-free survival (PFS) and overall survival (OS) were not reached. The estimated 3-year PFS and OS rates were 54.3% (95% CI, 47.0–61.6) and 71.3% (95% CI, 63.8–78.8), respectively. PFS and OS are shown in Figures 2 and 3, respectively. Although there was a trend for favorable prognosis among patients with oropharyngeal cancer, the difference in OS rates was not statistically significant with respect to the primary tumor locations (oropharynx vs. nonoropharynx: 75.0% vs. 58.9%, p = .056).

The hematological and nonhematological AEs of all grades are summarized in Table 2. The most common AEs associated with the study treatment were anorexia (38.5%), myalgia (30.8%), fatigue (26.9%), peripheral neuropathy (25.0%), and nausea (23.1%). Treatment-related grade 3 or 4 toxicities included neutropenia (15.4%), anorexia (7.7%), general weakness (7.7%), hypocalcemia (3.8%), and so on. Grade 4 neutropenia and hypocalcemia occurred in five (9.6%) and one (1.9%) patients, respectively. One patient died of grade 4 neutropenia and sepsis. Overall, almost all the AEs occurring during the study treatment were reversible and manageable.

In this study, induction chemotherapy with Genexol-PM and cisplatin demonstrated modest tumor response (ORR = 55.8%) with well-tolerated toxicity profiles for patients with LA-HNSCC. Although numerous studies on induction chemotherapy followed by CCRT had established its role in organ preservation and distant metastasis control in

LA-HNSCC [2, 4, 16], its role in improving the survival outcome has been demonstrated by recent meta-analysis and a phase III study [5, 6]. So far, the TPF regimen has been regarded as a standard induction regimen. However, the significant toxicity associated with TPF led to clinical deterioration in some patients during induction TPF therapy, which rendered those patients unable to receive definitive treatments such as CCRT. Hence, doublet regimens such as docetaxel plus cisplatin (TP) are being used as an alternative for TPF in the Asian population [17]. We hypothesized that the use of Genexol-PM instead of docetaxel in LA-HNSCC would reduce the toxicity without compromising the efficacy. The present study is the first phase II trial to evaluate the efficacy and toxicity of Genexol-PM plus cisplatin integrated into the induction regimen in treating patients with LA-HNSCC.

Among four recent phase III trials, only one (the Italian study) showed the survival benefit of induction chemotherapy followed by concomitant treatment (radiotherapy with concurrent chemotherapy or cetuximab) over concomitant treatment alone. In the Italian study group trial, patients with LA-HNSCC were randomized to receive three cycles with TPF followed by concomitant treatment, or concomitant treatment alone. The ORR to induction TPF therapy was 76%. PFS and OS were significantly higher in the TPF arm; 3-year PFS and OS rates in the TPF arm were 47.0% and 57.5%, respectively [6]. Three other phase III trials (DeCIDE [18], PARADIGM [19], and a Spanish study [20]) failed to show superior OS with induction chemotherapy followed by CCRT over CCRT alone. In the DeCIDE study [18], the ORR to induction TPF was 64%. With a minimum follow-up of 30 months, no difference in PFS and OS was observed between TPF followed by CCRT and CCRT alone; median durations of PFS and OS were not reached, and 3-year PFS and OS rates were not reported. In the PARADIGM and Spanish studies, no difference in survival outcomes was also observed between patients treated with induction chemotherapy followed by CCRT and those who received CCRT alone. In the PARADIGM study [19], the 3-year PFS and OS rates were 67% and 73%, respectively, in the induction TPF arm. The Spanish study [20] was a three-arm study; patients with LA-HNSCC were randomly assigned to induction chemotherapy with either TPF or cisplatin/5-fluorouracil (PF) followed by CCRT or CCRT alone. In the induction chemotherapy arms (either TPF or PF), the ORR was 77.7%–80.1% and the median PFS and OS were 14.3–14.6 months and 27.0–27.2 months, respectively. In our previous phase II study [21], we compared the efficacy of induction chemotherapy using cetuximab, docetaxel, and cisplatin (CTP; experimental arm) versus docetaxel and cisplatin (TP; control arm) among patients with LA-HNSCC. In the TP arm (n = 44), 40 patients (90.9%) completed the planned three cycles of induction TP therapy and the ORR to TP was 81.8%. Thirty-five patients (79.5%) were able to receive definitive CCRT, and the CR rate after CCRT was 71.4% (25/35) among these patients. Three-year PFS and OS rates after induction chemotherapy with TP followed by CCRT were 56% and 74%, respectively [21]. In the present study, 47 out of 52 patients (90.4%) completed the planned three cycles of Genexol-PM plus cisplatin therapy. The sequential treatment of induction chemotherapy (Genexol-PM plus cisplatin) followed by CCRT or surgery showed promising treatment outcomes. Although the ORR to Genexol-PM plus cisplatin (55.8%) seems somewhat lower compared with the ORRs (64%–82%) to the above-mentioned TP or TFP, toxicity profiles look very favorable with fewer grade 3 or 4 AEs. After CCRT, the CR rate was 81.8% (36/44). The 3-year PFS and OS rates achieved with Genexol-PM/cisplatin followed by CCRT or surgery were 54.3% and 71.3%, respectively. The direct comparison of data from our study with the above-mentioned previous data might be difficult because of the heterogeneous features such as different proportions of primary tumors, TNM stages, and different drugs concomitantly used during radiotherapy. The authors agree that it remains to be further investigated whether the efficacy of the induction chemotherapy might be influenced by the subsequent concomitant treatment. Nonetheless, the OS data of our sequential approach (Genexol-PM/cisplatin followed by CCRT or surgery) seems at least similar to those of previous studies. In addition, the result of our current study is in agreement with the view that the benefit of taxane plus cisplatin or taxane plus PF as induction chemotherapy does not seem to be affected by the taxane used, be it docetaxel or paclitaxel [16].

As previously reported, the proportion of patients with LA-HNSCC who were able to complete the planned concomitant treatment was approximately 50% because of the severe toxicities resulting from TPF-based treatment [16, 22]. Furthermore, the recent meta-analysis by Kim et al. [5] also reported that there was a significant increase in the risk of grade 3–4 hematologic toxicities associated with TPF induction such as anemia, thrombocytopenia, and neutropenia. This unfavorable toxicity profile often resulted in the poor compliance of patients with LA-HNSCC to the subsequent treatments (surgery or CCRT), which contributed to the lower treatment efficacy. However, the serious grade 3 or 4 AEs observed in this trial using Genexol-PM and cisplatin were less frequent than those in previous phase III trials using the standard TPF-based regimen [7, 8]. For example, the incidence rates of grade 3–4 neutropenia, thrombocytopenia, and anemia in our study were only 15.4%, 0%, and 0%, respectively, which is much lower than those from other previous phase II and III studies using the TPF regimen [20, 22]. In our trial, the proportion of patients who were able to receive the definitive treatment (CCRT [n = 44] or surgery [n = 7]) was 98.1%; among 44 patients who initiated CCRT, 41 (93.2%) completed CCRT as initially planned and the CR rate following CCRT was 81.8% (36/44). The treatment compliance rate during induction chemotherapy and CCRT in our study was in marked contrast to the low compliance rate obtained from the induction TPF regimen.

The limitations of our study are as follows. First, this was a single-arm phase II study in which the clinical benefit of Genexol-PM and cisplatin during the induction phase could not be directly assessed in comparison with the TPF induction regimen. Moreover, given the ORR of 55.8% (95% CI, 42.3–69.3), the current study did not meet the primary endpoint of ORR 70.0%. Consequently, this study does not provide evidence of a noninferior efficacy of Genexol-PM plus cisplatin compared with conventional TPF regimen.

Second, we did not obtain the results of human papillomavirus (HPV) testing. HPV-associated oropharyngeal cancer is well known to have a favorable outcome [23]. However, HPV testing was not routinely conducted in this trial, and this could be a confounding factor.

In conclusion, induction chemotherapy with Genexol-PM plus cisplatin showed moderate tumor response. However, considering the promising survival data and favorable toxicity profiles with this regimen, further investigations such as randomized trials are warranted to verify the efficacy of induction Genexol-PM plus cisplatin therapy in LA-HNSCC and to identify and/or select patients more likely to benefit from this induction regimen.

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(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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Figures and Table

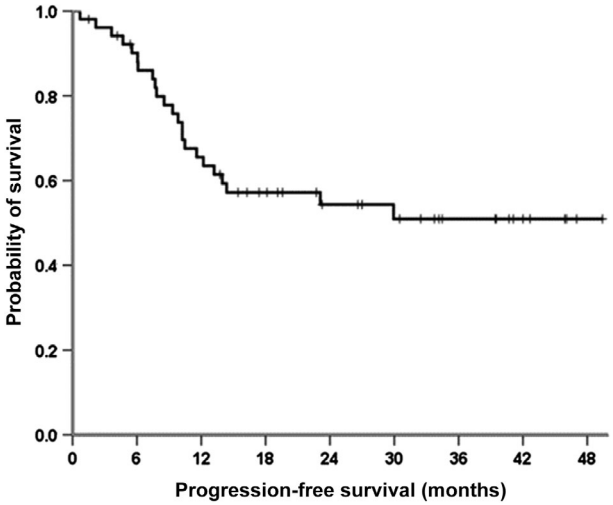

Figure 2. Kaplan-Meier curve for progression-free survival.

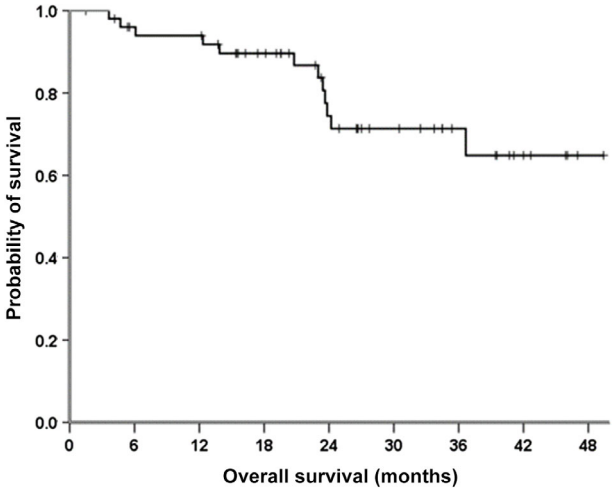

Figure 3. Kaplan-Meier curve for overall survival.

Table 2. Adverse events during induction chemotherapy

Per person (*n* = 52)	All grades, *n* (%)	Grade 1, *n* (%)	Grade 2, *n* (%)	Grade 3, *n* (%)	Grade 4, *n* (%)
Anorexia	20 (38.5)	15 (28.8)	1 (1.9)	4 (7.7)	0 (0.0)
Myalgia	16 (30.8)	15 (28.8)	1 (1.9)	0 (0.0)	0 (0.0)
Fatigue	14 (26.9)	12 (23.1)	2 (3.8)	0 (0.0)	0 (0.0)
Peripheral neuropathy	13 (25.0)	12 (23.1)	1 (1.9)	0 (0.0)	0 (0.0)
Nausea	12 (23.1)	10 (19.2)	2 (3.8)	0 (0.0)	0 (0.0)
General weakness	9 (17.3)	4 (7.7)	1 (1.9)	4 (7.7)	0 (0.0)
Neutropenia	9 (17.3)	0 (0.0)	1 (1.9)	3 (5.8)	5 (9.6)
Constipation	8 (15.4)	7 (13.5)	1 (1.9)	0 (0.0)	0 (0.0)
Cough	7 (13.5)	7 (13.5)	0 (0.0)	0 (0.0)	0 (0.0)
Dizziness	6 (11.5)	4 (7.7)	2 (3.8)	0 (0.0)	0 (0.0)
Hypertension	5 (9.6)	0 (0.0)	4 (7.7)	1 (1.9)	0 (0.0)
Fever	4 (7.7)	4 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)
Diarrhea	4 (7.7)	3 (5.8)	1 (1.9)	0 (0.0)	0 (0.0)
Vomiting	4 (7.7)	2 (3.8)	1 (1.9)	1 (1.9)	0 (0.0)
Hypocalcemia	4 (7.7)	1 (1.9)	1 (1.9)	1 (1.9)	1 (1.9)
Febrile neutropenia	2 (3.8)	0 (0.0)	0 (0.0)	2 (3.8)	0 (0.0)
Thrombocytopenia	2 (3.8)	1 (1.9)	1 (1.9)	0 (0.0)	0 (0.0)
Hyponatremia	2 (3.8)	1 (1.9)	0 (0.0)	1 (1.9)	0 (0.0)
Mucositis	2 (3.8)	1 (1.9)	0 (0.0)	1 (1.9)	0 (0.0)
Anemia	1 (1.9)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)
Acute kidney injury	1 (1.9)	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)
Allergic reaction	1 (1.9)	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)