Dose Escalation of Lobaplatin Concurrent with IMRT for the Treatment of Stage III-IVb NPC: A Phase I Clinical Trial$^2,3$

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Abstract
The maximum tolerated dose (MTD) of lobaplatin as a single agent chemotherapy concurrent with intensity-modulated radiotherapy (IMRT) in Asian population with nasopharyngeal carcinoma (NPC) remains unclear. From June 2016 to December 2017, 17 patients diagnosed with stage III-IVb NPC from an Asian population were prospectively enrolled. Patients were administered lobaplatin with 25-50 mg/m$^2$ escalation of dosage on day 1. Every 21 days (days 1, 22, and 43) during radiotherapy, cycles were repeated. We administered radiotherapy as 2.12-2.27 Gy per fraction with five daily fractions each week for 6 to 7 weeks. The evaluation of lobaplatin-related toxic effects was based on the Common Terminology Criteria for Adverse Events version 4.0. During the weekly treatment period, complete blood counts and biochemistry were performed. Dose-limiting toxicities (DLTs) were determined by the following events during any cycle in which lobaplatin was administered. Each dose group consisted of at least three cases. We proceeded to the subsequent dose group in the absence of DLT with a dose increment of 5 mg/m$^2$ until DLT occurred. Periods from 1 week prior to the chemotherapy initiation to 3 weeks after the last chemotherapy were defined as DLT observation periods. MTD was determined by the dose that was immediately below the dose that produced DLT. After analysis, DLT occurred in three patients, including a group with two of three patients in 45 mg/m$^2$ lobaplatin and another group with one of five patients in 40 mg/m$^2$ lobaplatin. No grade 3-4 toxicity was observed in patients treated with lobaplatin $<$40 mg/m$^2$. The tumor response rate at 12 weeks after treatment was 100%. In summary, lobaplatin concurrent with IMRT was active in stage III-IVb NPC, and the MTD for the lobaplatin as single-agent chemotherapy was 40 mg/m$^2$ when combined with IMRT in an Asian population. This trial is registered with ClinicalTrials.gov, number NCT03188497.

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Introduction
In Southern China, nasopharyngeal carcinoma (NPC) is highly prevalent, where the annually incidence rate ranges 20-50 cases per 100,000 population $[1]$. Currently, in our daily practice, approximately 60%-70% of NPC patients show locoregionally advanced disease (stage III-IVb) at the time of diagnosis. Presently, the standard treatment modality is concurrent chemoradiotherapy for locoregionally advanced NPC. Platinum-based drugs are the most widely used for concurrent chemotherapy combined with radiotherapy. Cisplatin has shown to have a strong antitumor activity in NPC and is also a first-generation platinum agent. Although cisplatin plus intensity-modulated radio-
therapy (IMRT) shows positive prognosis in NPC [2], the adverse effects of cisplatin such as vomiting, renal toxicity, ototoxicity, and neurotoxicity have limited clinical application [3]. As a result, a need to explore new effective platinum agents with improved effectiveness and favorable toxicity will have important clinical significance.

The third-generation platinum complex lobaplatin presents active antitumor action in numerous solid tumors, such as hepatocellular carcinoma, cervical cancer, and breast cancer [4–6]. Literature has reported that lobaplatin is more soluble and stable in water and not as toxic compared to cisplatin [3]. A recent phase II study conducted by Ke and colleagues [7] evaluated the efficiency and safety of lobaplatin plus 5-fluorouracil as induction chemotherapy followed by lobaplatin-radiotherapy in locoregionally advanced NPC patients. In that study, Ke and colleagues [7] suggested that lobaplatin-based chemotherapy combined with radiotherapy presented promising antitumor effects with tolerable toxicities. However, few studies reported maximum tolerated dose (MTD) of lobaplatin as a single agent combined with radiotherapy among an Asian population.

To date, a phase I clinical trial conducted among a Western population established the MTD of 50 mg/m² for lobaplatin chemotherapy [8]. Considering tolerance differences between Asian and Western populations given the same doses of agent, the lobaplatin dose may not be applicable to Asian patients. Therefore, a dose escalation trial was conducted to determine MTD of lobaplatin as a single agent combined with radiotherapy among an Asian population.

Materials and Methods

Participants

Patients were included in this clinical trial if they were pathologically diagnosed type II or III NPC in accordance with the World Health Organization; ages 18-65 years; stage III-IVb; 0 or 1 Eastern Cooperative Oncology Group performance status (ECOG PS); marrow conditions (white blood cell count ≥4.0 × 10⁹/l; absolute neutrophil of 2.0 × 10⁹/l; hemoglobin concentrations ≥90 g/l; platelet ≥10 × 10⁹/l); normal cardiopulmonary function; satisfactory hepatic function (total bilirubin and alanine aminotransferase <2 times the normal values); and satisfactory renal function (creatinine <1.5 times the normal value). If patients had distant metastasis, previous malignant disease, or previously received therapy for NPC, they were excluded. We excluded patients if they were pregnant or breastfeeding, had serious comorbidities, or had cardiac disease that was unstable and required treatment.

Fifth Affiliated Hospital of Sun Yat-sen University’s institutional review board approved the study protocol. All patients provided informed consent prior to participation. The present clinical trial was registered with the Chinese Clinical Trials Registry (registration number: NCT03188497).

Pretreatment Evaluation

All Patients included in the study had undergone pretreatment evaluations consisting of full medical history and physical examination, nasopharynx and neck magnetic resonance imaging, abdominal sonography, chest radiography, and bone scan or whole-body fluorodeoxyglucose positron emission tomography. Additionally, we collected information from tests on renal and liver function tests and complete blood count. We staged patients in accordance to International Union Against Cancer/American Joint Committee on Cancer staging system for NPC (seventh edition, 2009) based on clinical and radiography data [9].

Trial Design and Treatment Assessment

The present study was a phase I single-arm clinical trial on dose escalation. Each group in this study maintained a minimum of three patients. Our main study end point was MTD of lobaplatin combined with concurrent IMRT for stage III-IVb NPC treatment, and our secondary end points were DLT and tumor response rates. Utilizing the Response Evaluation Criteria in Solid Tumors version 1.1, we recorded tumor responses [10] where first assessment was 12 weeks following radiotherapy. For evaluations, magnetic resonance imaging results were used as the primary image-based evidence. The evaluation of acute toxic effects was based on the Common Terminology Criteria for Adverse Events version 4.0.

The Definition of DLT and MTD

Periods from 1 week prior to the chemotherapy initiation to 3 weeks after the last chemotherapy were defined as DLT observation periods. During the treatment period, we performed complete blood counts and biochemistry weekly. If the following events occurred during any cycle in which lobaplatin was administered, we determined DLT: a) grade ≥3 anemia; b) grade ≥3 thrombocytopenia; c) grade ≥3 neutropenia no less than 5 days; d) grade 3 febrile neutropenia (absolute neutrophil count <1.0 × 10⁹/l, fever ≥38.5°C) despite therapy with granulocyte colony-stimulating factor; and e) any other grades 3–4 toxicity (except alopecia and nausea). MTD was determined by the dose that was immediately lower than the dose that produced DLT.

Treatment and Dose Escalation

We treated patients with 2.12–2.27 Gy per fraction with five daily fractions each week for 6 to 7 weeks, administered by IMRT. The cumulative radiation doses to the primary tumor were 68–70 Gy and to positive cervical lymph nodes were 64–68 Gy. Sites identified as potential local infiltration and bilateral cervical lymphatics were irradiated to ≥54 Gy. Concurrent chemotherapy regimen consisted of lobaplatin administered as a 2-hour intravenous infusion every 3 weeks for three cycles, starting on the initial date of radiotherapy. An initial lobaplatin dose of 25 mg/m² with modified Fibonacci method was used [11] and a following increase of 5 mg/m² for each group. Participant enrollment gradually progressed from a low-dose group to a high-dose group. Treatment specified by the study protocol was provided to patients. In each group, there were a minimum of three patients. The following dose group was started if DLT did not occur in three cases within the dose group. If a case of DLT occurred in a group, two more patients were enrolled in the same dose group. Enrollment into subsequent dose group would only begin in the event the two additional patients did not experience DLT. In contrast, the trial was terminated if DLT occurred in the two patients additionally included. Moreover, the trial will also be terminated if at least two cases of DLT initially occurred in a group as well. In the final group, the dosage considered to produce DLT was the dosage used, and MTD was identified as the dosage immediately lower than the one that produced DLT.

Statistical Analysis

Data for all end points were analyzed in all eligible patients who completed protocol treatment. SPSS 18.0 was used to perform all data analysis, and adverse events were presented with descriptive statistics.
Results

Patient Characteristics

From June 2016 to December 2017, patients were enrolled and analyzed. Table 1 shows the characteristics of these patients. The study population included 7 female patients and 10 male patients where the median age was 48 years (range: 27-64). The body surface areas of the patients ranged from 1.36 to 1.98 m² (median, 1.77 m²). We observed 11 cases (65%) of stage III, 4 cases (24%) of stage IVa, and 2 cases (12%) of stage IVb. Median radiation dose was 69.2 Gy (range 68-70 Gy). We did not identify any cases of lost to follow-up (100%) until March 5 2018.

Determination of MTD

The first three enrolled patients were administered an initial lobaplatin dose of 25 mg/m²; however, among these patients, DLT did not occur (Table 2). The remaining three patients were enrolled in the 30-mg/m² lobaplatin group where DLT did not occur as prior. The three patients in the third group were enrolled in 35 mg/m², and as with the prior group, DLT did not occur as well. Subsequently, three patients were enrolled in the dose group of 40 mg/m². In this group, DLT (in the form of grade 3 thrombocytopenia) was detected after the third course lobaplatin in one case. We consequently enrolled another two patients into the 40-mg/m² lobaplatin group; however, we did not observe any other cases of DLT. Our findings suggest that this dose is not continuously associated with DLT. In the next dose group of 45 mg/m², three patients were enrolled in adherence with the dose escalation method. At this dose level, grade 3 thrombocytopenia was experienced in one patient with a PLT of 47 × 10⁹/l on day 16 following one cycle of lobaplatin. Grade 3 thrombocytopenia with a PLT of 35 × 10⁹/l was experienced in another patient on day 12 following the second cycle of lobaplatin. Therefore, MTD was determined for tested lobaplatin as single-agent chemotherapy concurrent with radiotherapy as 40 mg/m² in an Asian population, and the most frequent DLT of lobaplatin is thrombocytopenia.

Compliance and Tumor Response Rates

Among the 17 patients, 48 cycles of lobaplatin were administered. Fifty (88%) patients completed 3 lobaplatin cycles, 1 (6%) patient completed 2 lobaplatin cycles, and 1 (6%) patient completed 1 lobaplatin cycle. In addition, for these two patients who did not

Table 1. Characteristics of 17 Patients

| Characteristic          | No. of Patients (%) |
|-------------------------|---------------------|
| Age, years              | 48                  |
| Median                  | 27-64               |
| Gender                  | 10.58.8             |
| Male                    | 7 (41.2)            |
| Female                  | 10.58.8             |
| Body surface area, m²   | 1.77                |
| Median                  | 1.36-1.98           |
| T stage                 | 4 (23.5)            |
| T1                      | 2 (11.8)            |
| T2                      | 7 (41.2)            |
| T3                      | 4 (23.5)            |
| N stage                 | 11 (64.7)           |
| N0                      | 2 (11.8)            |
| N1                      | 3 (17.6)            |
| N2                      | 1 (5.9)             |
| N3                      | 3 (17.6)            |
| N4                      | 11 (64.7)           |
| Overall stage           | 4 (23.5)            |
| III                     | 2 (11.8)            |
| IVa                     | 11 (64.7)           |
| IVb                     | 4 (23.5)            |

Table 2. Hematological Toxicities

| Adverse Events | 25 mg/m² | 30 mg/m² | 35 mg/m² | 40 mg/m² | 45 mg/m² |
|----------------|----------|----------|----------|----------|----------|
| Anemia         | 0 1      | 3 3      | 67 1     | 33 2     | 40 1     |
| Thrombocytopenia| 0 2      | 67 2     | 67 2     | 67 3     | 60 0     |
| Neutropenia    | 0 2      | 67 2     | 67 2     | 67 3     | 60 0     |
| Leukopenia     | 0 2      | 67 2     | 67 2     | 67 3     | 60 0     |

Table 3. Nonhematological Toxicities

| Adverse Events | 25 mg/m² | 30 mg/m² | 35 mg/m² | 40 mg/m² | 45 mg/m² |
|----------------|----------|----------|----------|----------|----------|
| Diarrhea       | 0 3      | 100 3    | 100 3    | 100 5    | 100 3    |
| Nausea         | 0 3      | 100 3    | 100 3    | 100 4    | 80 2     |
| Vomiting       | 0 3      | 100 3    | 100 3    | 100 4    | 80 2     |
| Stomatitis (mucositis) | 0 3      | 100 3    | 100 3    | 100 4    | 80 2    |
| Transaminases  | 0 3      | 100 3    | 100 3    | 100 4    | 80 2    |
| Nephrotoxicity | 0 3      | 100 3    | 100 3    | 100 4    | 80 2    |
| Otoxicity      | 0 3      | 100 3    | 100 3    | 100 4    | 80 2    |
complete three cycles of lobaplatin, we subsequently used cisplatin (80 mg/m$^2$ for 4 hours on day 1 intravenously, once every 3 weeks) instead of lobaplatin to complete the remaining chemotherapy. Thrombocytopenia, leukopenia, and anemia were the most commonly observed hematological adverse events (Table 2). As for nonhematological events, we observed vomiting, stomatitis, and nausea were commonly logged (Table 3). In addition, tumor response was assessed at 12 weeks after treatment. Among these patients, we observed 12 (71%) cases of complete response, 5 (29%) case of partial response, no stable disease, and no cases of progressive disease cases. Thus, the tumor response rate (complete response + partial response) was 100% (17/17).

**Discussion**

This is the first study in which MTD of lobaplatin in combination with IMRT has been explored in treatment of NPC as first-line therapy. Our data showed for the examined lobaplatin that MTD was 40 mg/m$^2$ on day 1 given in weeks 1, 4, and 7 of radiotherapy. Moreover, for treatment of locoregionally advanced NPC, low incidence of adverse effects was associated with lobaplatin concurrent with IMRT, and the treatment achieved a high response rate.

In many cancer types, lobaplatin has exhibited antitumor properties for lung, breast, colorectal, and cervical cancers [5,6,12,13]. Currently, there are few clinical studies on lobaplatin concurrent with IMRT for NPC treatment; however, the MTD of lobaplatin as a single-agent chemotherapy in the Asian population remains unclear. A Phase I clinical trial by Peng and colleagues investigated increase of lobaplatin plus fixed-dose docetaxel (60 mg/m$^2$) for recurrent or metastatic tumors treatment [14]. They suggested that the MTD for tested lobaplatin was 35 mg/m$^2$, which is lower than that reported in the present study (40 mg/m$^2$). Inconsistency is potentially attributed to differences between patients enrolled in the study [14] in comparison to the present. For this study, eligible patients were only those who were treatment-naive. In comparison, patients in Peng et al. [14] were administered intensive chemotherapy before disease recurrence, potentially reducing patients' tolerance to salvage chemotherapy. Another possible reason for lower MTD of lobaplatin in the study by Peng et al. [14] is that the combination regimen of lobaplatin and docetaxel had the additive effect of chemotherapy toxicity, which may result in the reduction of the MTD of lobaplatin in their study.

In Germany, Fiebig and colleagues reported that the tolerated dose of lobaplatin was 50 mg/m$^2$ in a Western population [8]. As compared with Fiebig’s study, the tolerated dose of lobaplatin in the current study was much lower (40 mg/m$^2$). The primary reason may be due to ethnic differences and the different tolerances for lobaplatin between Asian and Western populations. To support this, previous studies [15,16] have demonstrated that the tolerated doses of chemotherapy among Asian populations are comparable to 70%-80% of corresponding doses in Western populations. This phenomenon can potentially be explained in Asian populations, as there is a lack of CYP3A isoenzymes. Among lower active metabolites, these enzymes are a part of chemotherapy metabolism [17].

Regarding toxicity, we found that the most frequent DLT of lobaplatin is thrombocytopenia; similar findings were reported by Welink et al. [18] in a previous series. In the current study, among the 45-mg/m$^2$ lobaplatin group, two out of three patients experienced grade 3 thrombocytopenia, while no grade 3-4 thrombocytopenia was observed among patients treated with lobaplatin less than 40 mg/m$^2$; this may indicate that the occurrence of lobaplatin-induced myelosuppression primarily correlated with the lobaplatin dose. Additionally, no grade 3-4 nausea or vomiting was detected, which may elevate patient compliance to achieve chemotherapy. In addition, high-volume fluid infusion is not required during chemotherapy due to lobaplatin having limited renal toxicity [18], which may shorten inpatient period allowing patients with either cardiac, renal, or dysfunction to be administered lobaplatin.

In the present study, tumor response rate of NPC patients treated with lobaplatin concurrent with IMRT was 100%. Considering our research design type, we could not draw any conclusions whether lobaplatin could be used as a candidate for cisplatin directly. However, Zhang et al. [19] reported excellent short-term outcomes in high-risk NPC patients for combined lobaplatin and docetaxel as neoadjuvant chemotherapy with concurrent lobaplatin and IMRT. Another study [20] reported that the tumor response rate of lobaplatin plus docetaxel was 67.6%, which is similar with cisplatin plus docetaxel (response rate, 61.5%) in recurrent and metastatic NPC. This may suggest that lobaplatin could be used as a candidate for cisplatin in the future. Similarly, a randomized control trial conducted by Wang et al. [3] suggested a comparable response rate for cervical cancer stage II and III in accordance with FIGO staging system between cisplatin- and lobaplatin-based chemoradiotherapy (100% vs. 100%). Though it is difficult to directly compare our findings with other clinical trials, lobaplatin combined with concurrent radical IMRT provides an encouraging tumor response rate in the current study. However, we still need to enroll more patients and follow up patients closely to fully evaluate both survival and toxic effects.

In summary, lobaplatin plus IMRT given every 21 days for 3 cycles showed a positive effect for locoregionally advanced NPC treatment. Our results suggested that the MTD of lobaplatin was 40 mg/m$^2$ in Chinese population, and the most common and frequent DLT of lobaplatin is thrombocytopenia. Further studies are needed to confirm our observed findings and long-term efficacy.

**Authors’ Contributions**

Z. L. and S. Y. W. were responsible for study design. S. Y. W., X. W. X., and J. J. Y. drafted the manuscript. P. J. P. and B. Z. participated in the data interpretation. Q. D. L. and X. P. H. participated in the data collection and analysis. All authors have read and approved the final manuscript.

**References**

[1] Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, and Bray F (2015). Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 136(5), E359–386.

[2] Tham IW, Hee SW, Yeo RM, Salleh PB, Lee J, Tan TW, Fong KW, Chua ET, and Wee JT (2009). Treatment of nasopharyngeal carcinoma using intensity-modulated radiotherapy-the national cancer centre singapore experience. Int J Radiat Oncol Biol Phys 75(5), 1481–1486.

[3] Wang JQ, Wang T, Shi F, Yang YY, Su J, Chai YL, and Liu Z (2015). A Randomized controlled trial comparing clinical outcomes and toxicity of lobaplatin- versus cisplatin-based concurrent chemotherapy plus radiotherapy and high-dose-rate brachytherapy for FIGO stage II and III cervical cancer. Asian Pac J Cancer Prev 16(14), 5957–5961.

[4] Zhao C, Wang XJ, Wang S, Feng WH, Shi L, and Yu CP (2014). Lobaplatin combined fluorouridine/pirarubicin-based transcatheter hepatic arterial chemomobilization for unresectable primary hepatocellular carcinoma. Asian Pac J Cancer Prev 15(9), 2057–2060.

[5] Engel JB, Martens T, Hanke JC, Häusler SF, Kockenberger M, Segerer S, Djakovic A, Meyer S, Dietl J, and Wischhusen J, et al (2012). Effects of
lobaplatin as a single agent and in combination with TRAIL on the growth of triple-negative p53-mutated breast cancers in vitro. Anticancer Drugs. Anti-Cancer Drugs 23(4), 426–436.

[6] Li X, Ran L, Fang W, and Wang D (2014). Lobaplatin arrests cell cycle progression, induces apoptosis and alters the proteome in human cervical cancer cell Line CaSkis. Biomed Pharmacother 68(3), 291–297.

[7] Ke LR, Xia WX, Qiu WZ, Huang XJ, Yang J, Yu YH, Liang H, Liu GY, Ye YF, and Xiang YQ et al (2017). Safety and efficacy of lobaplatin combined with 5-fluorouracil as first-line induction chemotherapy followed by lobaplatin-radiotherapy in locally advanced nasopharyngeal carcinoma: preliminary results of a prospective phase II trial. BMC Cancer 17(1), 134–142.

[8] Fiebig HH, Henß H, and Mross K (1994). Phase I clinical trial of lobaplatin (D-19466) after intravenous bolus injection. Onkologie 17, 142–148.

[9] Edge SB and Compton CC (2010). The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol 17, 1471–1474.

[10] Duffaud F and Therasse P (2000). New guidelines to evaluate the response to treatment in solid tumors. Bull Cancer 87(12), 881–886.

[11] Ratain MJ, Mick R, Schilsky RL, and Steigler M (1993). Statistical and ethical issues in the design and conduct of phase I and II clinical trials of new anticancer agents. J Natl Cancer Inst 85(20), 1637–1643.

[12] Zhang H, Chen R, Yang S, Liu W, Li K, Zhang H, Zhu X, and Chen B (2016). Lobaplatin for the treatment of SK-MES-1 lung squamous cell line in vitro and in vivo. Oncol Targets Ther 9, 4215–4224.

[13] Dai HY, Liu L, Qin SK, He XM, and Li SY (2011). Lobaplatin suppresses proliferation and induces apoptosis in the human colorectal carcinoma cell Line LOVO in vitro. Biomed Pharmacother 65(3), 137–141.

[14] Peng Y, Liu YE, Ren XC, Chen XJ, Su HL, Zong J, Feng ZL, Wang DY, Lin Q, and Gao XS (2015). A phase I clinical trial of dose escalation of lobaplatin in combination with fixed-dose docetaxel for the treatment of human solid tumours that had progressed following chemotherapy. Oncol Lett 9(1), 67–74.

[15] Lin Q, Gao XS, Qiao XY, Zhou ZG, Zhang P, Chen K, Zhao YN, and Asaumi J (2008). Phase I trial of escalating-dose cisplatin with 5-fluorouracil and concurrent radiotherapy in Chinese patients with esophageal cancer. Acta Med Okayama 62(1), 37–44.

[16] Lin Q, Liu Y, Chang CL, Wang N, Fu JM, Ren XC, Chen XJ, Hu J, Tian YS, and Guo ZJ, et al (2012). Phase I trial of dose escalation of capecitabine combined with fixed docetaxel in previously treated patients with non-small cell lung cancer. Chin-Ger J Clin Oncol 11, 6–10.

[17] Lai CL, Tsai CM, Chiu CH, Wang GS, Su WJ, Chen YM, and Perng RP (2005). Phase II randomized trial of tri-weekly versus days 1 and 8 weekly docetaxel as a second-line treatment of advanced non-small cell lung cancer. Jpn J Clin Oncol 35, 700–706.

[18] Welink J, Pechstein B, and van der Vijgh WJ (1996). Determination of the two diastereoisomers of lobaplatin (D-19466) in plasma ultrafiltrate of cancer patients with a normal or an impaired kidney or liver function by high-performance liquid chromatography with ultraviolet detection. J Chromatogr B Biomed Appl 675(1), 107–111.

[19] Zhang S, Lin S, and Hu L (2016). Lobaplatin combined with docetaxel neoadjuvant chemotherapy followed by concurrent lobaplatin with intensity-modulated radiotherapy increases the survival of patients with high-risk lymph node positive nasopharyngeal carcinoma. J BUON 21(1), 161–167.

[20] Long GX, Lin JW, Liu DB, Zhou XY, Yuan XL, Hu GY, Mei Q, and Hu GQ (2014). Single-arm, multi-centre phase II study of lobaplatin combined with docetaxel for recurrent and metastatic nasopharyngeal carcinoma patients. Oral Oncol 50(8), 717–720.