Dose-finding and efficacy confirmation trial of superselective intra-arterial infusion of cisplatin and concomitant radiotherapy for patients with locally advanced maxillary sinus cancer (JCOG1212, RADPLAT–MSC)

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Running Head

RADPLAT for maxillary sinus cancer

Abstract

A dose-finding and efficacy confirmation trial was started in Japan in April 2014 to evaluate the efficacy and safety of superselective intra-arterial infusion of cisplatin and concomitant radiotherapy for locally advanced maxillary sinus cancer. A total of 18 patients will be enrolled in the dose-finding phase for the determination of the recommended number of cisplatin cycles, and 65 patients with T4aN0M0 and 62 patients with T4bN0M0, including those who received the recommended number of or fewer cycles in the dose-finding phase, will be enrolled from 15 institutions within a 5-year period in the efficacy confirmation phase. The primary endpoints of the dose-finding and the efficacy confirmation phases are dose-limiting toxicities and three-year overall survival, respectively. This trial was registered at the UMIN Clinical Trials Registry (http://www.umin.ac.jp/ctr/) under Trial No. UMIN000013706.

Mini-Abstract

This dose-finding and efficacy confirmation trial was started in April 2014 to evaluate the efficacy and safety of superselective intra-arterial cisplatin infusion and concomitant radiotherapy for locally advanced maxillary sinus cancer.

Key words

maxillary sinus cancer, squamous cell carcinoma, chemoradiotherapy, intra-arterial, cisplatin

Introduction

Malignant tumors of the maxillary sinus are rare neoplasms accounting for 0.5% of all malignant diseases, and constituting approximately 70% of all malignancies of the paranasal sinuses and nasal cavity [1]. Most maxillary sinus cancers are at an advanced stage at the time of initial presentation because of the absence of symptoms in early stage disease. Also, only 10-20% of patients with advanced disease develop lymph node metastasis [2]. Locally advanced and resectable tumors (cT3N0M0 or cT4aN0M0) require radical surgery with or without a complete resection of the orbital contents as a standard treatment. This often results in significant disfigurement and impairment of function in patients with T4aN0M0 tumors, but this is seldom the case in those with cT3N0M0 tumors. The three-year overall survival for 30 patients with cT4aN0M0 who were mainly treated with surgery between 2006 and 2007 at the member institutions of the Head and Neck Cancer Study Group in the Japan Clinical Oncology Group (JCOG) was reported to be 81.9% [3]. This can be regarded as relatively high, but a significant number of patients refuse radical surgery because of disfigurement and functional impairment. Therefore, the development of a new, less invasive therapy that is as effective as radical surgery is critical.

On the other hand, radical surgery is not indicated for unresectable, locally advanced tumors (cT4bN0M0) and concurrent intravenous chemotherapy and radiotherapy (IV-CRT) is regarded as a community standard treatment in daily practice. However, the three-year overall survival for 7

patients in the JCOG retrospective study was 14.3% [3]. This indicates that more effective therapies are necessary for cT4bN0M0.

Chemoradiotherapy (CRT) is one of the promising treatment options for locally advanced laryngeal and pharyngeal squamous cell carcinoma. However, CRT does not necessarily lead to satisfactory treatment outcomes in cases of maxillary sinus cancer [4,5]. Recently, superselective intra-arterial infusion of high-dose cisplatin with concomitant radiotherapy (hereafter RADPLAT) has been performed for the patients with locally advanced sinonasal cancer in several institutions and has been reported to result in a favorable survival [6-9]. The feasibility and efficacy of RADPLAT were also demonstrated in a multi-institutional setting [10]. The intra-arterial infusion procedure for RADPLAT involves the introduction of a transfemoral microcatheter angiographically to the branch of the external carotid artery supplying the tumor. Cisplatin is then infused through the microcatheter to the dominant blood supply of the targeted tumor. At the same time, sodium thiosulfate is infused systemically to neutralize the cisplatin.

This procedure is now used in Japan with 100 mg/m^2 generally administered per cycle, although the number of the cycles of cisplatin infusion varies (4-7 cycles) by institution. On the other hand, in the original report by Robbins et al., 150 mg/m^2 was administered once a week for only 4 cycles [11,12]. Theoretically, repeating cisplatin infusion while patients receive radiotherapy is more effective as it increases the radiosensitization efficacy of cisplatin. However, the number of

cycles of cisplatin at a dosage of 100 mg/m^2 has not been optimized, and we have incorporated a dose-finding phase in this study to determine the recommended number of cisplatin cycles.

Against this background, we have undertaken a dose-finding and efficacy confirmation trial of the superselective intra-arterial infusion of cisplatin and concomitant radiotherapy for patients with locally advanced maxillary sinus cancer (JCOG1212, RADPLAT–MSC). The recommended number of cisplatin cycles in the dose-finding phase is to be determined by a study of patients with both T4aN0M0 and T4bN0M0 tumors. The analyses in the efficacy confirmation phase will be conducted separately for patients with T4aN0M0 and for those with T4bN0M0. Patients with lymph node metastasis were excluded to ensure homogeneity of the population and evaluate the efficacy of RADPLAT more clearly as they were reported to have a poorer prognosis than those without lymph node metastasis [6,13].

The Protocol Review Committee of the Japan Clinical Oncology Group (JCOG) approved the protocol in February 2014 and the study was activated in April 2014. This trial was registered at the UMIN Clinical Trials Registry under Trial No. UMIN000013706 (http://www.umin.ac.jp/ctr/).

PURPOSE

Dose-finding phase

The objective of the dose-finding phase is to evaluate the incidence of dose-limiting toxicity and

determine the recommended cycle of intra-arterial infusion of cisplatin in combination with concomitant radiotherapy for patients with locally advanced maxillary sinus cancer.

Efficacy confirmation phase

The objective of the efficacy confirmation phase is to confirm the efficacy and the safety of the superselective intra-arterial infusion of cisplatin and concomitant radiotherapy for patients with locally advanced maxillary sinus cancer.

STUDY DESIGN

A multi-institutional open-label dose-finding and non-randomized confirmatory trial.

ENDPOINTS

Dose-finding phase

The primary endpoint of the dose-finding phase is the incidence of dose-limiting toxicity. The secondary endpoint is the incidence of adverse events.

Efficacy confirmation phase

The primary endpoint of the efficacy confirmation phase is three-year overall survival in all eligible patients including those who received the recommended number of or fewer cycles in the dose-finding phase. The secondary endpoints are overall survival, event-free survival, local

event-free survival, clinical complete remission rate, the incidence of adverse events, and the incidence of serious adverse events.

Overall survival is defined as days from enrollment to death from any cause, and it is censored at the latest day the patient is alive. Event-free survival is defined as days from enrollment to either the first event of any disease progression such as primary disease, lymph node metastasis or distant metastasis, salvage surgery, or death from any cause. Local event-free survival is defined as days from enrollment to either the first event of primary disease progression, salvage surgery, or death from any cause. Event-free survival and local event-free survival are censored at the latest day the patient is alive without any evidence of adverse events. Clinical complete remission rate is the proportion of patients with a complete response (CR) or good partial response (good PR) among all eligible patients. A good PR is defined as a residual secondary change with tumor shrinkage, such as when the residual tissue is regarded as scar material rather than a residual tumor. Our evaluative guidelines suggested that defining good PR lesions as those 10 mm or less in size and not enhanced on contrast-computed tomography scans.

ELIGIBILITY CRITERIA

INCLUSION CRITERIA

For inclusion in the study, the patient must fulfill all of the following criteria:

1) Primary lesion located at the maxillary sinus

2) Histologically proven squamous cell carcinoma

3) Clinical stage T4aN0M0 or T4bN0M0

4) No severe carotid stenosis as evaluated by ultrasonography

5) Age between 20 and 75 years (dose-finding phase) or between 20 and 80 years (efficacy confirmation phase),

6) ECOG performance status of 0 or 1

7) No prior therapy for maxillary sinus cancer

8) No prior radiation therapy to the head and neck or the brain

9) No prior chemotherapy for any other malignancies

10) Sufficient organ function

11) Normal electrocardiogram

12) Suitability for angiography

13) Satisfying normal tissue radiation dose constraints for the ipsilateral eyeball and optic nerve, spinal cord, brainstem, and chiasma

14) Written informed consent.

EXCLUSION CRITERIA

Patients are excluded if they meet any of the following criteria:

1) Simultaneous or metachronous (within 5 years) double cancers, except *in situ* carcinoma or intramucosal tumor

2) Active infection requiring systemic therapy

3) Body temperature >= 38 degrees Celsius

4) Women during pregnancy, during breastfeeding, or within 28 days after delivery

5) Severe psychosis

6) Need for systemic steroid medication or immunosuppressant medication

7) Poorly controlled diabetes mellitus

8) Poorly controlled hypertension

9) Angina pectoris attack within 3 weeks or myocardial infarction within 6 months

10) Positive for serum HBs antigen

QUALITY CONTROL OF INTRA-ARTERIAL CHEMOTHERAPY

Fifteen institutions among the Head and Neck Cancer Study Group of the JCOG are initially participating in this trial. All participating interventional radiologists have agreed to the technical details for superselective intra-arterial chemotherapy pre-specified in the study protocol. To control the quality of the interventional technique, central review of photographs and movies in arbitrarily selected patients will be performed at a semi-annual investigators' meeting. All interventional

procedures are performed or directly supervised by interventional radiologists certified by the study chair. The major criteria for certification in this study include either i) having experienced interventional radiology (IVR) on $\geq$40 occasions with $\geq$10 occasions as the principal operator, ii) having experience with 2 patients or more requiring intervention with superselective arterial infusion of cisplatin for head and neck cancer within 2 years, or iii) being board certified in societies related to interventional radiology.

TREATMENT METHODS

CHEMOTHERAPY

The protocol treatment consists of weekly intra-arterial infusion of cisplatin with concomitant radiotherapy and salvage surgery if necessary. In the dose-finding phase, 100 mg/m^2 of cisplatin is administered intra-arterially weekly for 7 weeks. At the same time, sodium thiosulfate is administered at a dose of 20 g/m^2 intravenously to neutralize the cisplatin. The recommended number of cycles of cisplatin will be determined in the dose-finding phase and applied in the efficacy confirmation phase.

RADIATION THERAPY

Radiation therapy is administered with high-energy photons of 4–10 MV X-rays to a total dose of 70 Gy in 2-Gy fractions five times weekly. The gross tumor volume (GTV) includes the volume of the

primary tumor. The clinical target volume (CTV) includes the GTV with a 0.5 cm margin and at least the entire ipsilateral maxillary sinus. The CTV does not include potential lymph node metastasis area in the neck. The planning target volume (PTV) for the CTV is defined as a 0.5 cm margin around the CTV to compensate for set-up variations and internal organ motion. To protect normal vital structures, such as the contralateral eye ball and/or optic nerve, chiasma, spinal cord and brain, a partial reduction in the PTV margin of 0.1 cm from the initial 0.5 cm is allowed.

DOSE-FINDING METHOD

In the dose-finding phase, 100 mg/m^2 of cisplatin is administered weekly for 7 weeks with concomitant radiotherapy to 18 patients. Cisplatin is skipped in the case of adverse events that meet the skipping rule defined by the protocol. The recommended number of cycles will be determined according to the distribution of the number of cycles of administered cisplatin and the incidence of dose-limiting toxicity.

DEFINITION OF DOSE-LIMITING TOXICITY

The dose-limiting toxicity (DLT) observation period is defined as the period from the date of initiation of CRT to 28 days after the last radiotherapy session. The grade of toxicity will be assessed according to the Common Terminology Criteria for Adverse Events v 4.0. DLT will be defined

using the following criteria.

(i) Grade 3 febrile neutropenia

(ii) Grade 4 thrombocytopenia.

(iii) Estimated creatinine clearance <40 L/min.

(iv) Grade 3 non-hematologic toxicity, except for mucositis, dermatitis, electrolyte abnormalities and complications related to intervention.

(v) Radiation break of >14 days due to toxicity

(vi) Skipping chemotherapy administration for 3 or more cycles consecutively.

(vii) Treatment-related death

FOLLOW-UP

All enrolled patients are followed up for at least 5 years, while analysis of the primary endpoint of the efficacy confirmation phase is conducted 3 years after accrual completion. Efficacy and safety are to be evaluated at least every 3 months during the first year, at least every 4 months during the second year and then every 6 months during the third to fifth year.

STUDY DESIGN AND STATISTICAL ANALYSIS

This trial is a dose-finding and efficacy confirmation trial to evaluate the incidence of dose-limiting

toxicity and to determine the recommended number of cycles of intra-arterial infusion of cisplatin in combination with concomitant radiotherapy for patients with locally advanced maxillary sinus cancer in the dose-finding phase. In the efficacy confirmation phase, the objective is to evaluate the efficacy and the safety of superselective intra-arterial infusion of cisplatin and concomitant radiotherapy for patients with locally advanced maxillary sinus cancer.

We set a planned sample size for each cohort to confirm the efficacy of RADPLAT. The sample size in the efficacy confirmation phase is 65 patients with T4aN0M0 and 62 patients with T4bN0M0, including the eligible patients in the dose-finding phase but not the patients who received more than recommended number of cycles of chemotherapy in the dose-finding phase with 3 years of follow-up and an accrual period of 5 years.

In the T4aN0M0 patients, the 3-year overall survival was 81.9% in the observational study undertaken on our group. Thus, the sample size was set at 65 patients, which provided 80% power under the hypothesis of primary endpoint with an expected value of 80% and threshold value of 65% using one-sided testing at a 5% significance level.

In T4bN0M0, the 3-year overall survival was 14.3% in the observational study undertaken on our group. Thus, the sample size was set at 62 patients, which provided 80% power under the hypothesis of primary endpoint with an expected value of 35% and threshold value of 20% using one-sided testing at a 5% significance level. To test the hypothesis, we used the 3-year OS estimated

by the Kaplan–Meier method and its confidence interval based on Greenwood's formula.

INTERIM ANALYSIS AND MONITORING

No interim analysis is planned. If the number of cases with treatment-related death and severe (grade 2 or more) cerebrovascular ischemia reaches 6 and 7, respectively, registration will be suspended unless the JCOG Data and Safety Monitoring Committee approves continuation of the trial. The JCOG Data Center is responsible for data management, central monitoring and statistical analysis. JCOG Data Center also provides semi-annual monitoring reports, submitted to and reviewed by the JCOG Data and Safety Monitoring Committee. None of the physicians performing the interventions will be involved in the data analysis. For quality assurance, site-visit audits, not for a specific study basis but for the study group basis, will be performed by the JCOG Audit Committee.

PARTICIPATING INSTITUTIONS (FROM NORTH TO SOUTH)

Hokkaido University Hospital, Tohoku University Hospital, Miyagi Cancer Center, National Cancer Center Hospital East, National Hospital Organization Tokyo Medical Center, Tokyo University Hospital, Japanese Foundation for Cancer Research, Cancer Institute Hospital, Shizuoka Cancer Center, Aichi Cancer Center, Kinki University hospital, Osaka Medical Center for Cancer and Cardiovascular Diseases, Kobe University Hospital, Hyogo Cancer Center, Nara Medical University,

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Conflict of interest statement

None declared.

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