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# 2012 年度後期定期モニタリングレポート
# JCOG1008(phase Ⅱ/Ⅲ)

**局所進行頭頸部扁平上皮癌術後の再発ハイリスク患者に対する 3-Weekly CDDP を同時併用する術後補助化学放射線療法と Weekly CDDP を同時併用する術後補助化学放射線療法に関するランダム化第Ⅱ/Ⅲ相試験**

| | | | |
|---|---|---|---|
| 研究グループ: | | 試験進捗: | 登録中 |
| 頭頸部がんグループ | | | |
| 研究代表者: | | 登録開始日: | 2012 年 10 月 16 日 |
| 田原 信 | 国立がん研究センター東病院 | | |
| 研究事務局: | | 登録終了予定: | 2017 年 10 月 |
| 清田 尚臣 | 神戸大学医学部附属病院 | | |
| データマネージャー: | | 追跡終了予定: | 登録終了後 5 年 |
| 山田 英申/今井美恵子 | JCOG データセンター | | |
| 医学的コメント: | | プロトコール改正: | なし |
| 中村 健一/國枝 太史 | JCOG 運営事務局 | プロトコール改訂: | なし |
| 江場 淳子 | | | |

**提出日:2013 年 2 月 15 日**

## 0. 研究概要

### 0.1. 研究目的

局所進行頭頸部扁平上皮癌術後の再発ハイリスク患者に対する Weekly Cisplatin(CDDP)を同時併用する化学放射線療法(Weekly CDDP+RT)の臨床的有用性を標準治療である 3-Weekly CDDP を同時併用する化学放射線療法とのランダム化比較にて評価する。

### 0.2. 対象

1) 切除標本で原発巣が組織学的に扁平上皮癌と確認されている。
2) 口腔、中咽頭、下咽頭、喉頭のいずれかに原発巣を有する。原発巣の部位は切除標本にて判断する。
3) 術後病理診断にて Stage III、IVA、IVB(UICC 第 7 版)のいずれかと診断されている。
4) 術後病理組織標本にて以下の①、②のいずれかまたは両方を満たす。
   ① 顕微鏡的切除断端陽性である
   ② 頸部リンパ節転移*の節外浸潤を認める
   *頸部リンパ節の定義:「3.2.2. N-所属リンパ節 UICC 第 7 版」を参照
5) 根治切除後 56 日以内である。
6) 登録前 28 日以内に行われた CT にて明らかな遠隔転移を認めない。
7) 登録時の年齢が 20 歳以上 75 歳以下である。
8) PS(ECOG)が 0 または 1 である。
9) 他のがん種に対するものも含めて、放射線治療、化学療法、ホルモン療法いずれの既往もない。
10) 主要臓器機能が保たれている。
11) 登録 28 日以内の安静時 12 誘導心電図で正常、または治療を必要とする異常が認められない。
12) 本試験参加について患者本人より文書による同意が得られている。

### 0.3. エンドポイント

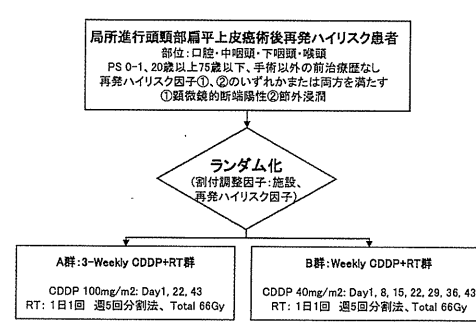
Primary endpoint :第Ⅱ相部分:治療完遂割合
第Ⅲ相部分:全生存期間

Secondary endpoints :第Ⅱ相部分:有害事象
第Ⅲ相部分:無再発生存期間、局所無再発生存期間、無栄養補助生存割合、有害事象、許容治療期間中の非入院治療期間

### 0.4. 治療

**A 群(3-Weekly CDDP+RT):**
CDDP 100 mg/m$^2$ :day 1、22、43
RT:1 日 1 回、週 5 回分割法、Total 66 Gy

**B 群(Weekly CDDP+RT):**
CDDP 40 mg/m$^2$ :day 1、8、15、22、29、36、43
RT:1 日 1 回、週 5 回分割法、Total 66 Gy



### 0.5. 割付調整因子

施設、再発ハイリスク因子(顕微鏡的断端陽性かつ節外浸潤陽性/顕微鏡的断端陽性かつ節外浸潤陰性/顕微鏡的断端陰性かつ節外浸潤陽性)

### 0.6. 予定登録数、登録期間、追跡期間

予定登録数:260 名、登録期間:5 年、追跡期間:5 年

### 0.7. 解析

1) 中間解析:
   1 回目:登録数が第 II 相部分の予定登録数である 66 例に達した時点で、中間解析を行えるデータが得られる解析時期を予想し、両群の治療完遂割合について評価する(第 II 相部分)。
   2 回目:予定登録数の半数の登録が得られた時点で、第 III 相部分の登録中に登録を続けることが妥当かどうかを判断する目的で行う。原則として登録は停止しない。
   3 回目:登録終了後早期に、予定した期間の追跡を続けるかどうかを判断する目的で行う。
2) 主たる解析:中間解析により試験中止となった場合。
3) その他解析:なし

### 0.8. プロトコール改正・改訂

改正:なし
改訂:なし

### 0.9. 進捗状況

なし

## 1. 登録状況

登録例 **4** 例(2013 年 2 月 14 日 現在)

### 1.1. 参加施設別登録数

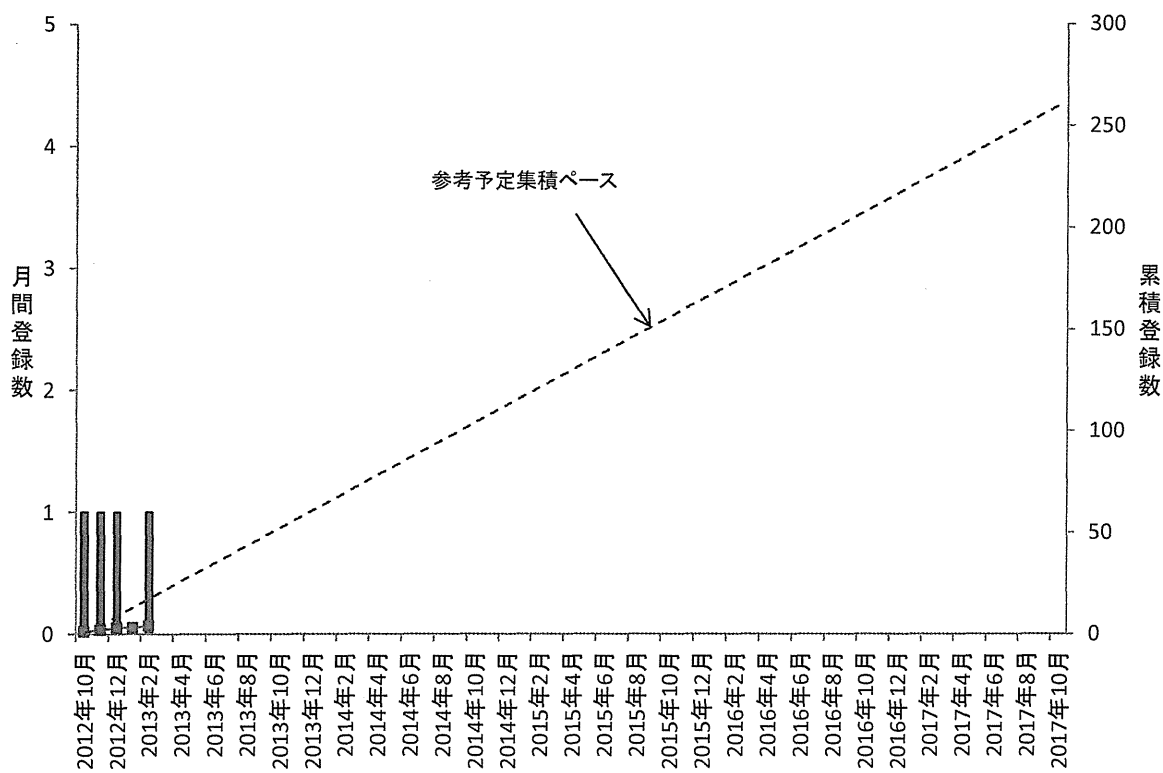
| 施設名 | A 群 | B 群 | 計 |
|---|---|---|---|
| 北海道大学病院 | 0 | 0 | 0 |
| 東北大学病院 | 0 | 0 | 0 |
| 宮城県立がんセンター | 0 | 0 | 0 |
| 自治医科大学 | 0 | 0 | 0 |
| 国立がん研究センター東病院 | 0 | 0 | 0 |
| 国立病院機構東京医療センター | 0 | 0 | 0 |
| 東京慈恵会医科大学附属病院 | 0 | 0 | 0 |
| がん研究会有明病院 | 1 | 0 | 1 |
| 東海大学医学部 | 0 | 0 | 0 |
| 静岡県立静岡がんセンター | 0 | 0 | 0 |
| 愛知県がんセンター中央病院 | | | |
| 名古屋大学医学部 | 0 | 0 | 0 |
| 近畿大学医学部 | 0 | 0 | 0 |
| 大阪府立病院機構大阪府立成人病センター | 0 | 0 | 0 |
| 神戸大学医学部 | 1 | 0 | 1 |
| 兵庫県立がんセンター | 1 | 1 | 2 |
| 奈良県立医科大学 | 0 | 0 | 0 |
| 国立病院機構四国がんセンター | 0 | 0 | 0 |
| 計 | **3** | **1** | **4** |

網掛け:IRB 未承認施設(2013 年 2 月 14 日現在)

### 1.2. 登録時の個人識別情報使用不可の施設

なし

### 1.3. 集積ペース



# II. 研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

書籍
なし

雑誌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# III. 研究成果の刊行物・別刷

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Original Article

# Phase I/II Study of S-1 plus Cisplatin Combination Chemotherapy in Patients with Advanced/Recurrent Head and Neck Cancer

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**Objective:** The objectives of this study were to determine the maximum tolerated dose (MTD) and recommended dose (RD) of S-1 plus cisplatin (CDDP) and to evaluate safety and efficacy using the defined RD in advanced/recurrent head and neck cancer (HNC).
**Methods:** S-1 was administered orally at 40 mg/m$^2$ twice daily for 14 consecutive days, and CDDP was infused on day 8 at a dose of 60 and 70 mg/m$^2$. Each course was repeated every 4 weeks.
**Results:** A total of 38 patients were registered, 10 patients for the Phase I study and an additional 28 patients for the Phase II study. Although no dose-limiting toxicity (DLT) was observed in the CDDP 60 mg/m$^2$ (Level 1) group, two of six patients in the CDDP 70 mg/m$^2$ (Level 2) group exhibited DLT (fatigue/diarrhea). The MTD was not achieved in the Phase I study. Level 2 was therefore determined as the RD. In the Phase II study, 34 patients, including 6 patients from the Phase I study, were evaluated. At the termination of treatment, the confirmed response rate was 44.1% (15/34, 95% CI: 27.4–60.8). The best response rate without an adequate duration time was 67.6% (95% CI: 51.9–83.4). The median survival period was 16.7 months, and the 1-year survival rate was 60.1%. The main toxicities of Grade 3 or above were anorexia (26.5%), nausea (14.7%), neutropenia/thrombocytopenia (11.8%) and anemia/fatigue (8.8%).
**Conclusions:** This is considered to be an effective regimen with acceptable toxicities for HNC.

*Key words: head and neck cancer – S-1 – CDDP – chemotherapy*

## INTRODUCTION

As clinical characteristics of head and neck cancer (HNC), ~90% of the cases are squamous cell carcinoma, and two-thirds of the patients suffer from locoregional advanced (Stages III and IV) disease. Although the prognosis for early-stage (Stages I and II) HNC is satisfactory with 5-year survival rates of 70–90% after standard therapy such as surgery, radiotherapy or both (1), the 5-year survival rate falls to <50% in the locoregional advanced stage, even if radical treatment such as surgery, radiotherapy or chemotherapy [at the induction/concurrent chemoradiotherapy (CCRT)] is performed.

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For patients suffering from incurable cancer or recurrent disease, either locoregionally or in the form of distant metastasis, the prognosis is particularly poor, with a median survival period of only 6 months with conventional palliative chemotherapy (1). Some combination therapies, including cisplatin (CDDP), were devised after Wittes et al. (2) reported the efficacy of CDDP for HNC in 1977, and the efficacy became clear (3,4). Since Kish et al. (5) reported the efficacy of CDDP plus 5-fluorouracil (5-FU) combination therapy (CDDP/5-FU) in 1982, moreover, CDDP/5-FU has been considered the most common combination chemotherapy, and it has been widely employed as the first-line chemotherapy for advanced/recurrent HNC. The response rate for CDDP/5-FU has been reported to be 50–90% (6–8) when used as the first-line induction chemotherapy and to be 32–48% (3,9) when used as second-line or later recurrent chemotherapy. CDDP/5-FU requires long-term hospitalization, however, because it involves continuous infusion of 5-FU and requires adequate support for mucosal and renal toxicity.

S-1 (Taiho Pharmaceutical Co., Ltd, Tokyo, Japan) is a novel oral anticancer agent consisting of tegafur (FT), 5-chloro-2,4-dihydroxypyridine (CDHP) and potassium oxonate (Oxo) at a molar ratio of 1:0.4:1, based on biochemical modulation of 5-FU (10). S-1 showed high response rates of 28.8–46.2% with acceptable toxicity in Phase II studies for advanced/recurrent HNC conducted in Japan (11,12). It was approved for HNC in Japan under the approval regulation system in 2001. If the efficacy and toxicities of S-1 plus CDDP combination therapy (S-1/CDDP) were similar to those of CDDP/5-FU in this study, it is thought that it would become one of the potential choices as chemotherapy for advanced/recurrent HNC.

## PATIENTS AND METHODS

### Patient Selection

The following eligibility criteria were used: histologically or cytological confirmed HNC (excluding thyroid cancer), unresectable locally advanced (Stage III/IV disease) and recurrent or distant metastasis, at least measurable disease after prior treatment. If the patients had received prior treatment, radiotherapy more than 28 days, surgery and chemotherapy or adjuvant chemotherapy more than 14 days was required before registration. Other eligibility criteria included the following: age 20–80 years, Eastern Cooperative Oncology Group (ECOG) performance status 0–1, life expectancy >3 months, adequate bone marrow, hepatic and renal functions (reflected by an absolute hemoglobin level of >9.0 g/dl, leukocyte count > lower limit of normal, platelet count $>100 \times 10^{-9}$ cells/l, normal bilirubin level of <1.5 mg/dl, aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase levels <2.5 times the upper limit of normal, serum creatinine level < upper limit of normal and creatinine clearance >70 ml/min). Within 14 days before registration, all patients underwent a complete physical examination that included their medical history, blood count, serum biochemistry tests (hepatic and renal function tests and electrolytes), urinalysis and echocardiography; a chest radiograph (X-ray) and computed tomography (CT) or magnetic resonance imaging scans of all disease sites were obtained during the 28 days before registration. Patients who had undergone induction chemotherapy with CDDP/5-FU or platinum-based chemotherapy were excluded from the Phase II study unless it used a lower dose as a sensitizer of CCRT. The exclusion criteria were as follows (summary): severe drug hypersensitivity, pulmonary fibrosis or interstitial pneumonia, severe heart disease, difficult-to-control diabetes, active infection or acute inflammation, active concomitant malignancy, and other serious medical conditions. Patients were required to give written informed consent before admission to the study. The study protocol was approved by the instruction review board of each participating hospital, and the study was conducted in accordance with the Japanese Good Clinical Practice guideline.

### Treatment and Dose-escalation Schedule

#### Phase I Study

S-1 was administered orally at the dose of 40 mg/m$^2$ twice a day, after the morning and evening meals between days 1 and 14. Three initial doses were established according to the body surface area (BSA): <1.25 m$^2$, 80 mg/day; 1.25–1.5 m$^2$, 100 mg/day; >1.5 m$^2$, 120 mg/day. CDDP was administered intravenously over 2 h on day 8. The treatment was repeated every 4 weeks. The starting dose of CDDP was 60 mg/m$^2$ as Level 1 with a planned increase to 70 mg/m$^2$ as Level 2. We did not establish a Level 3, because the approved dose of CDDP in Japan is 70 mg/m$^2$. For the first step, three patients were treated at the Level 1 dose. They would then go to Level 2 if no patient showed dose-limiting toxicity (DLT). If one or two of the three patients in the first step showed any DLT, three additional patients were to be enrolled at the same dose level. A dose level would be determined as maximum tolerated dose (MTD) if more than three of six patients showed DLT. The recommended dose (RD) was to be one level below the MTD level.

#### Phase II Study

A treatment regimen with the RD determined in the Phase I study was repeated every 4 weeks at least two cycles unless progression or unacceptable toxicity occurred. The next course was started for patients whose organ biological parameters had been maintained at the level of the eligibility criteria (leukocyte count >3000 mm$^{-3}$, platelet count $>75 \times 10^{-9}$ cells/l and non-hematologic toxicity >Grade 2).

If these criteria were satisfied 3 weeks after day 1 of each cycle of chemotherapy, the next cycle could be administered. The doses of S-1 were adjusted according to the degree of

hematologic and non-hematologic toxicities. The dose was reduced by one level, 20 mg/day, in patients whose BSA was $>1.25$ m$^2$, with evidence of Grade 4 hematologic toxicity or Grade 3 or greater non-hematologic toxicity during any phase of the administration cycle. If a patient with a BSA of $<1.25$ m$^2$ experienced the above toxicities, no further treatment with S-1 was conducted. If treatment was stopped for $\geq 4$ weeks, the patient was withdrawn from the study.

### Definitions of DLT and MTD

Toxicity was evaluated according to the National Cancer Institute-Common Toxicity Criteria (NCI-CTC), version 2.0. DLT was defined as Grade 4 leukocytopenia or thrombocytopenia, Grade 4 neutropenia lasting for 4 days, occurrence of neutropenic fever ($\geq 38$°C) with Grade 3 leukocytopenia or neutropenia, any Grade 3 non-hematologic toxicity except nausea, vomiting or anorexia following related events occurring in the first course. Patients were also categorized in the DLT group when the second course of treatment was not resumed within 21 days after the first course. The MTD was defined as the dose at which 50% (3/6) or more patients experienced DLT during the first course.

### Evaluation and Follow-up

Examinations of blood chemistry and symptoms of toxicity were repeated weekly. The clinical response was measured for each course based on the CT scans or X-ray findings that initially had been used to define the tumor extent. Toxicities were graded according to the NCI-CTC, version 2.0. Tumor responses were evaluated according to the criteria of the World Health Organization (1979), which was an evaluation standard in Japan at the time of the start of this study. Complete response (CR) was defined as the disappearance of all measurable and assessable diseases for at least 4 weeks. Partial response (PR) was defined as a $\geq 50\%$ reduction in the sum of the products of the largest diameters of the measurable disease for at least 4 weeks. Stable disease (SD) was defined as failure to observe a PR or CR or progression of the disease for at least 4 weeks. Progressive disease (PD) was defined as a $\geq 25\%$ increase in the sum of the products of the largest diameters of the measurable disease or the appearance of new lesions. We conducted assessment meetings for mutual assessment of patient's eligibility and their response to treatment.

### Statistical Analysis

The primary objective of the Phase I study was to determine the MTD and RD, and the secondary objective was evaluation of the safety. In the Phase II study, the primary objective was to evaluate efficacy using the defined RD, and the secondary objective was evaluation of the safety and survival.

The number of the Phase II study patients to be enrolled in this study was calculated as $\geq 26$, which was required to offset the null hypothesis that the lower bound of 95% CI of the expected response rate (65%) would be $<35\%$ under conditions of an $\alpha$ error of 0.05 and a $\beta$ error of 0.2. The overall survival of eligible patients was defined from the start of treatment to death or the last follow-up visit and was estimated by the Kaplan–Meier method.

## RESULTS

Between July 2002 and June 2004, 10 patients were entered in the Phase I study and 28 were entered in the Phase II study to confirm the efficacy and toxicities at the RD.

All patients were eligible for the toxicity evaluation for the total course and for objective response evaluations (Table 1). In the Phase I study, because one patient might have contravened the exclusion criteria, active infection or acute inflammation after registration, four patients were enrolled in the Level 1 group. In the Phase II study at the RD including six patients of the Phase I study, 18 patients with unresectable advanced HNC were enrolled, which included 1 patient with distant metastasis (lung and liver). Twenty patients with recurrent HNC included five patients with distant metastasis (lung, skin and bone) who had received prior therapy (surgery, radiation, chemotherapy or more than one) and 10 patients had previously received CCRT with the docetaxel or platinum anticancer agents (carboplatin and CDDP) and other anticancer agents (5-FU, tegaful/uracil and methotrexate). A total of 75 courses were administered: a total of 6 courses at Level 1 in the Phase I study (median: 2 courses, range: 1–2) and a total of 69 courses at the RD (median: 2 courses, range: 1–3).

### Determination of MTD and DLT

The toxicities (drug-related adverse events) observed during the first course are shown in Table 2. DLT was not observed at Level 1. At dose level 2, two of six patients showed DLT, one of them Grade 3 diarrhea and the other Grade 3 fatigue. The MTD was not achieved in the Phase I study. Dose level 2 was therefore determined to be RD in the subsequent Phase II study according to the provisions stated in the protocol.

### Safety

The toxicities observed among 34 patients, including 6 patients in Level 2 in the Phase I study, are shown in Table 2. The most common toxicities and incidences were hematologic toxicities (64.7–94.1%), gastrointestinal (GI) dysfunction (79.4–82.4%) and fatigue (58.8%). The toxicities of Grade 3 or above observed were anorexia (26.5%), nausea (14.7%) and fatigue (8.8%). The hematologic toxicities of Grade 3 or above observed were 11.8% in this study,