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Safety of S-1 as Adjuvant Chemotherapy after Curative Treatment in Head and Neck Cancer Patients who are ≥75 years old

Yasuaki KATSUBE, Isaku OKAMOTO, Hiroki SATO, Takahito KONDO, Takuro OKADA, Kiyoaki TSUKAHARA

Department of Otorhinolaryngology, Head and Neck Surgery, Tokyo Medical University

Abstract

All large-scale clinical studies of S-1 to date have only included patients <75 years old. The purpose of this study was to retrospectively investigate the safety of S-1 as adjuvant chemotherapy after curative treatment in head and neck cancer patients who are ≥75 years old. The study investigated 20 patients (18 men, 2 women) with head and neck cancer ≥75 years old. Mean age was 77 years. One-year of treatment was completed in 8 of 20 patients (40%). Grade III/IV adverse events were observed in 6 of 20 patients (30%). 3 years overall survival was 55%. This study suggested that S-1 could also be a treatment option as adjuvant chemotherapy after curative treatment in head and neck cancer patients who are ≥75 years old.

Introduction

In aging societies, the number of older patients with head and neck cancer is increasing. Older individuals have decreased physical strength and often present with a complex medical history. Such patients also tend to be less tolerant of treatments and more susceptible to developing complications. For these reasons, performing cancer treatments similar to those given to younger individuals can be difficult. S-1 (Taiho Pharmaceutical, Tokyo, Japan) is a fluoropyrimidine preparation that combines tegafur with gimeracil and oteracil potassium in a molar ratio of 1 : 0.4 : 1. A meta-analysis did not provide convincing evidence of any benefits of adjuvant chemotherapy on head and neck cancer patients[1]. Given the current situation, ACTS-HNC (adjuvant chemotherapy with S-1 after curative treatment in patients with head and neck cancer) study was performed[2]. And S-1 improves overall survival (OS) when used as an adjuvant chemotherapy after curative treatment for advanced head and neck cancer. However, all previous large-scale clinical studies to date have only included patients <75 years old[2-5]. The safety of S-1 in older patients is thus unclear. The purpose of this study was to retrospectively investigate the safety of S-1 as adjuvant chemotherapy after curative treatment in head and neck cancer patients who are ≥75 years old.

Materials and Methods

The study was conducted from September 2001 to August 2016 and included patients ≥75 years old with head and neck cancer who underwent adjuvant chemotherapy with S-1 after curative treatment in the Department of Otolaryngology, Head and Neck Surgery of Tokyo Medical University Hospital or the Department of Otolaryngology, Head and Neck Surgery of Tokyo Medical University Hachioji Medical Center. Twenty patients with data available from medical records were investigated in this study.

The standard S-1 dose was defined as 80 mg/body/day for a body surface area (BSA) <1.25 m^2, 100 mg/body/day for BSA ≥1.25 to <1.5 m^2, or 120 mg/body/day for

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Corresponding author : Kiyoaki Tsukahara, Department of Otorhinolaryngology, Head and Neck Surgery, Tokyo Medical University, 6-7-1 Nishishinjuku, Shinjuku-ku, Tokyo 160-0023, Japan
TEL : +81-(0)3-3342-6111 E-mail : tsuka@tokyo-med.ac.jp

BSA ≥1.5 m^2. The patient received one of these oral dosage divided into two equal doses. One cycle consisted of a two-week treatment period followed by one week of rest[6]. When the attending physician determined the treatment to be difficult, the dose was reduced by one level at a time, as appropriate. The duration of adjuvant chemotherapy after curative treatment was set at one year. In all patients, S-1 was given until treatment could not be continued due to Grade III/IV adverse events, recurrence/distant metastasis, patient request for discontinuation of treatment protocol, or on the decision of the attending physician. Before starting the treatment, we explained the medical condition including the standard treatment. Then, when the patient desired S-1 administration, S-1 administration was started. There are no financial or other interests related to S-1 administration.

The one-year treatment rate, reason for discontinuation, incidence of Grade III/IV adverse events and 3 years overall survival rate were investigated. Adverse events were evaluated using Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. The tumour-node-metastasis classification was determined based on the fifth edition of Unio Internationalis Contra Cancrum (UICC) criteria. This study was approved by the Ethics Committee of Tokyo Medical University (T2019-0196).

Results

Background characteristics of patients

Patient characteristics are shown in Table 1. The 20 patients comprised 18 men and 2 women, ranging in age from 75 to 83 years old (mean age, 77 years). Primary sites were the hypopharynx (*n*=9), oral cavity (*n*=4), nasal cavity/paranasal sinus (*n*=2), larynx (*n*=4), oropharynx (*n*=1). The tumour was classified as stage I in two patients, stage II in three patients, stage III in three patients, and stage IV in 12 patients.

Of the 20 patients, 11 (55%) received the standardized dose, while 9 (45%) received a reduced dose from initial therapy based on the decision of their attending physician.

One-year treatment rate

Table 2 shows that 1 year of treatment was completed in 8 of 20 patients (40%).

Table 1 Patients Background

		number
Sex	male	18
	female	2
Age		75～83（mean 77）
Primary site	oral cavity	4
	oropharynx	1
	hypopharynx	9
	larynx	4
	Nasal cavity/para nasal sinus	2
Stage	I	2
	II	3
	III	3
	IV	12

Table 3 Adverse events（Grade 3/4）

Number of patients with Grade 3/4 adverse events	6 cases（30%）
Anemia	1 cases（ 5%）
Diarrhea	4 cases（20%）
Anorexia	1 cases（ 5%）

Reasons for discontinuation

Table 3 shows the reasons for discontinuing treatment. Twelve patients in Group A discontinued treatment due to the appearance of Grade III/IV adverse events (*n*=6, 30%), recurrence/distant metastasis (*n*=5, 25%), and patient request (*n*=1, 5%).

Grade III/IV adverse events

As shown in Table 3, Grade III/IV adverse events were observed in 6 of 20 patients (30%). These events included anemia (*n*=1, 5%, onset at 2nd week), diarrhea (*n*=4, 20%, onset at 2nd, 3rd, 8th and 11th week), and anorexia (*n*=1, 5%, onset at 2nd week).

3 years overall survival

As shown in Fig. 1, 3 years overall survival was 55% (*n*=20).

Discussion

Since older patients have decreased organ function, adverse events from drugs are more likely compared to younger patients. Moreover, once an adverse event develops, recovery tends to be more problematic. One study reported that concurrent chemoradiotherapy was

Table 2 Treatment rates for 1 year, and Reasons to stop S-1 therapy

		n=20
Patients who have received S-1 therapy for 1 year		8 cases（40%）
Reasons to stop S-1 therapy	Adverse events（Grade 3/4）	6 cases（30%）
	Recurrence/distant metastasis	5 cases（25%）
	Patients request	1 cases（ 5%）

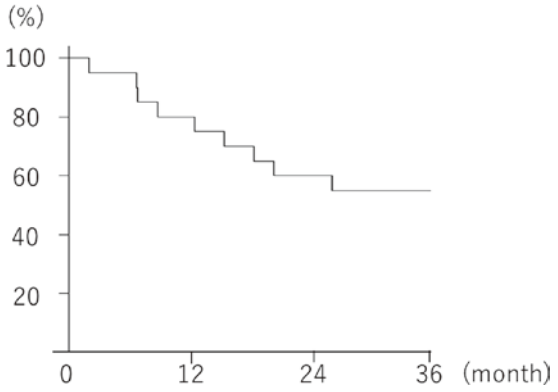

Fig. 1 3 years overall survival rate (n=20)

performed in less than 2% of patients ≥70 years old[7]. On the other hand, S-1 has been reported as an effective adjuvant chemotherapy after curative surgery for head and neck cancer[2]. The effectiveness of S-1 for unresectable, recurrent, and metastatic cases has also been reported[8)9)]. Since S-1 can be used in various situations, ascertaining the treatment effects in older patients is important. However, some previous studies have only included a small number of patients 75-78 years old[8)9)]. Furthermore, no reports from actual clinical practice have described completion rates or adverse events limited to older patients with head and neck cancer. The present study was retrospective in design, but has the significance from the perspective of only patients ≥75 years old were included. The results showed that the 1-year completion rate was 40%. These percentages were similar as the 43.3% completion rate in <75-year-old patients undergoing S-1 treatment in the ACTS-HNC trial[2]. Based on these findings, it was suggested that S-1 could be used as adjuvant chemotherapy after curative treatment for head and neck cancer even in patients who are ≥75 years old. We believe that adjuvant therapy, which was shown to be effective in the ACTS-HNC trial[2], is good indication for older patients as well as for those under 75 years.

Aging is associated with several physiological changes in organ function that could alter drug pharmacokinetics and impact on the tolerability and toxicity of cytotoxic chemotherapy[10]. The most commonly observed Grade III/IV adverse event was diarrhea (20%), followed by anemia and anorexia (5% each). Grade III/IV anorexia was observed in 0-5.1% of patients in previous reports[2)8)9)] and diarrhoea was observed in 0-0.8%[2)8)11)], indicating a greater frequency of adverse events in our study. This may be related that the subjects of this study were the elderly with relatively impaired organ function. Important future directions include investigation of the relationship between the effects of S-1 cancer treatment, adverse events, and dosing in older patients. Supportive care is also important in the treatment of malignant tumors. Oral care, in particular, is one of the most important supportive treatments for head and neck cancer treatment. Oral mucositis during myelosuppression is a strong risk factor for systemic infections. Therefore, infection control by oral care is important[12]. We now also require oral care intervention before the start of head and neck cancer treatment. However, supportive care interventions including oral care were not sufficient during the study period. We think that an increase in completion rate can be expected by strengthening supportive care.

Physical conditions vary from person to person, even among older individuals. Conceptually, older patients can be categorized into three types[13] : fit older patients (FiOPs) who can receive the same standard therapy as younger patients ; vulnerable older patients (VOPs) who can receive treatment at reduced doses even if the same treatment as a younger patient cannot be administered ; and frail older patients (FrOPs) who are ineligible for treatment. In the present study, FiOPs and VOPs are mixed. Because gradual dose reduction was acceptable for ACTH-HNC trial[1], we think that it is acceptable to reduce the dose depending on the general condition of elderly patients. Limitation to this study was selection bias. In other words, doctors were choosing elderly people whose organ function was maintained. In the future, a prospective study using a geriatric assessment tool is necessary.

Conclusion

We investigated the 1-year completion rate of adjuvant chemotherapy with S-1 after curative treatment in patients with 20 head and neck cancer who were ≥75 years old. Eight of 20 patients (40%) completed the 1-year treatment and 3 years survival rate was 55%. This study suggested that S-1 could also be a treatment option as adjuvant chemotherapy for older patients.

References

1) Pignon JP, le Maitre A, Maillard E, Bourhis J, MACH-NC Collaborative Group : Meta-analysis of chemotherapy in head and neck cancer (MACH-NC) : an update on 93 randomised trials and 17,346 patients. Radiother Oncol **92** : 4-14, 2009
2) Tsukahara K, Kubota A, Hasegawa Y, Takemura H, Terada T, Taguchi T, Nagahara K, Nakatani H, Yoshino K, Higaki Y, Iwae S, Beppu T, Hanamure Y, Tomita K, Kohno N, Kawabata K, Fukushima M, Teramukai S, Fujii M, ACTS-HNC group : Randomized phase III trial of adjuvant chemotherapy with S-1 after curative treatment in patients with squamous-cell carcinoma of the head and neck (ACTS-HNC). Plos One. doi : 10.1371/journal.pone.0116965. eCollection 2015

3) Sakuramoto S, Sasako M, Yamaguchi T, Kinoshita T, Fujii M, Nashimoto A, Furukawa H, Nakajima T, Ohashi Y, Imamura H, Higashino M, Yamamura Y, Kurita A, Arai K, ACTS-GC Group : Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. N Engl J Med **357** : 1810-1820, 2007
4) Sasako M, Sakuramoto S, Katai H, Kinoshita T, Furukawa H, Yamaguchi T, Nashimoto A, Fujii M, Nakajima T, Ohashi Y : Five-year outcomes of a randomized phase III trial comparing adjuvant chemotherapy with S-1 versus surgery alone in stage II or III gastric cancer. J Clin Oncol **29** : 4387-4393, 2011
5) Uesaka K, Boku N, Fukutomi A, Okamura Y, Konishi M, Matsumoto I, Kaneoka Y, Shimizu Y, Nakamori S, Sakamoto H, Morinaga S, Kainuma O, Imai K, Sata N, Hishinuma S, Ojima H, Yamaguchi R, Hirano S, Sudo T, Ohashi Y, JASPAC 01 Study Group : Adjuvant Chemotherapy of S-1 Versus Gemcitabine for Resected Pancreatic Cancer : A Phase 3, Open-Label, Randomised, Non-Inferiority Trial (JASPAC 01). Lancet **388** : 248-257, 2016
6) Tsukuda M, Kida A, Fujii M, Kono N, Yoshihara T, Hasegawa Y, Sugita M, Chemotherapy Study Group of Head and Neck Cancer : Randomized scheduling feasibility study of S-1 for adjuvant chemotherapy in advanced head and neck cancer. Br J Cancer **93** : 884-889, 2005
7) van der Schroeff MP, Derks W, Hordijk GJ, de Leeuw RJ : The effect of age on survival and quality of life in elderly head and neck cancer patients : a long-term prospective study. Eur Arch Otorhinolaryngol **264** : 415-422, 2007
8) Yokota T, Onozawa Y, Boku N, Hamauchi S, Tsushima T, Taniguchi H, Todaka A, Machida N, Yamazaki K, Fukutomi A, Yasui H : S-1 monotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck after progression on platinum-based chemotherapy. Jpn J Clin Oncol **41** : 1351-1357, 2011
9) Maeda M, Yamashita T, Matsunobu T, Araki K, Tomifuji M, Shiotani A : Outpatient oral chemotherapy with S-1 for unresectable or distant metastatic head and neck cancer. Anticancer Res **33** : 3285-3289, 2013
10) Wildiers H, Highley MS, de Bruijn EA, van Oosterom AT : Pharmacology of anticancer drugs in the elderly population. Clin Pharmacokinet **42** : 1213-1242, 2003
11) Peng PJ, Cheng H, Ou XQ, Zeng LJ, Wu X, Liu YM, Lin Z, Tang YN, Wang SY, Zhang HY, Chen ZB : Safety and efficacy of S-1 chemotherapy in recurrent and metastatic nasopharyngeal carcinoma patients after failure of platinum-based chemotherapy : multi-institutional retrospective analysis. Drug Des Devel Ther. doi : 10.2147/DDDT.S67592. eCollection 2014
12) Elting LS, Cooksley C, Chambers M, Cantor SB, Manzullo E, Rubenstein EB : The Burdens of Cancer Therapy. Clinical and Economic Outcomes of Chemotherapy-Induced Mucositis. Cancer **98** : 1531-1539, 2003
13) Pallis AG, Fortpied C, Wedding U, Van Nes MC, Penninckx B, Ring A, Lacombe D, Monfardini S, Scalliet P, Wildiers H : EORTC elderly task force position paper : approach to the older cancer patient. Eur J Cancer **46** : 1502-1513, 2010

75 歳以上の頭頸部癌根治治療後症例に対する S–1 による補助化学療法の安全性に関する検討

勝部泰彰　岡本伊作　佐藤宏樹
近藤貴仁　岡田拓朗　塚原清彰

東京医科大学耳鼻咽喉科・頭頸部外科学分野

【要旨】 S-1 の大規模臨床試験はいずれも 75 歳未満が対象である。本稿の目的は「75 歳以上の頭頸部癌根治治療後症例に対する S-1 を用いた補助化学療法の安全性と有効性後ろ向きに検討すること」である。75 歳以上の頭頸部癌根治治療後症例 20 例を対象とし、後ろ向き研究を行った。男性 18 例、女性例 2、年齢平均は 77 歳であった。1 年間投与完遂できたのは 8 例（40%）であった。Grade 3/4 の有害事象を 6 例（30%）に認めた。3 年全生存率は 55% であった。高齢者でも根治治療後補助化学療法としての S-1 投与は治療選択肢の一つとなりえることが示唆された。

〈キーワード〉 頭頸部癌、S-1、高齢者、テガフール、補助化学療法