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Phase II trial of concurrent chemoradiotherapy with S-1 versus weekly cisplatin for locoregionally advanced nasopharyngeal carcinoma

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Abstract. This is a prospective randomized trial performed to compare the efficacy of concurrent chemoradiotherapy (CCRT) + S-1 (oral fluoropyrimidine) with that of CCRT + cisplatin in patients with locoregionally advanced nasopharyngeal carcinoma. A total of 105 eligible patients were randomly assigned to receive CCRT with S-1 (S-1 arm, n=50) or cisplatin weekly (control arm, n=55). Patients in the S-1 arm received CCRT plus S-1 (40-60 mg, twice daily for 4 consecutive weeks. Patients in the control arm received standard CCRT with weekly cisplatin. All the patients were included in an intention-to-treat survival analysis. Our results demonstrated that the S-1 and control arms did not differ significantly in terms of complete response, partial response, progression-free survival or overall survival (all P-values >0.05). However, the two arms varied significantly regarding certain grade 3-4 toxicities, including leukopenia, 5.5 vs. 22.0% (P=0.013); mucositis, 20.0 vs. 46.0% (P=0.004); dermatitis, 15.5 vs. 32.7% (P=0.011); and nausea, 9.1 vs. 41.6% (P<0.001) for the S-1 and control arms, respectively. In conclusion, CCRT with S-1 was found to be similar in efficacy but superior in terms of toxicity compared to the standard CCRT with weekly cisplatin.

Introduction

Nasopharyngeal carcinoma (NPC) is widespread in Southern China and Southeastern Asia, although it is less common in North America and Western Europe. Among head and neck carcinomas, NPC is characterized by clinical, pathological, phenotypic and biological heterogeneity (1). Radical external radiotherapy (RT) has always been the mainstay of treatment for all-stage NPC (2). Currently, although patients with early-stage NPC may be cured by RT alone, the majority of NPC patients present with stage III or IV disease and have a poor prognosis (3). Numerous attempts have been made to improve the outcome of locoregionally advanced NPC (4).

As NPC has been found to be radiosensitive as well as chemosensitive and responds well to various chemotherapeutic agents, such as cisplatin, fluorouracil and paclitaxel (5-9), combined chemotherapy and RT have become the standard treatment strategy for locoregionally advanced NPC (10,11), particularly concurrent chemoradiotherapy (CCRT), on the basis of the INT 0099 trial (12). Randomized trials of induction chemotherapy followed by RT alone have resulted in encouraging response rates and improvement in disease-free survival (DFS), but not overall survival (OS) (13). The development of a sequential schedule of induction chemotherapy followed by chemoradiotherapy is a logical strategy to maximize the benefit from the two approaches, which has been widely used in Southern China. However, the high incidence of severe toxicity with this approach is the biggest obstacle to its wider application in the treatment of Asian patients with advanced NPC. The majority of the trials consistently demonstrated that CCRT increased acute toxicity by ~30%. Although most of these toxicities were recovered uneventfully, they were associated with 1% increased mortality in all Asian trials (14). New drugs and regimens have been combined with RT in an attempt to maximize efficacy and minimize toxicity. S-1 (TS-1; Taiho Pharmaceutical, Co., Ltd., Tokyo, Japan) is an orally active combination of tegafur, gimeracil and oteracil; its efficacy and safety have been investigated in gastric cancer, non-small-cell lung cancer and head and neck squamous cell carcinoma (15-18). Therefore, we designed a new strategy of CCRT with S-1. The objective of the present study was to determine the efficacy and tolerance of this strategy in locoregionally advanced NPC.

Patients and methods

Eligibility criteria. The patients were evaluated using the American Joint Committee on Cancer 2002 staging system. Patients with stage III-IV (M0) histologically proven NPC were eligible for this trial. The patients were required to have no prior history of cancer, apart from carcinoma *in situ* of the

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cervix or non-melanoma cancers of the skin. The inclusion criteria were as follows: Karnofsky performance status ≥60%; WBC count ≥4,000/mm^3; platelet count ≥100,000/mm^3; serum creatinine level ≤1.6 mg/dl; normal liver function with total bilirubin ≤2.5 mg/dl; and no evidence of systemic metastasis. This study was performed following approval from the Institutional Ethics Committee. All the patients were randomly assigned to the treatment groups and each patient provided written informed consent prior to treatment.

Pretreatment evaluation. All the patients underwent endoscopy and biopsy to obtain specimens for pathological diagnosis. Additional pretreatment evaluation included a complete history and physical examination; chest X-ray; nasopharyngoscopy; computed tomography scan of the nasopharynx, neck and thorax; ultrasound of the abdomen; hematology; biochemistry, including 24-h creatinine clearance; and urinalysis. Magnetic resonance imaging examination was not mandatory. Bone scan was performed only when bone metastasis was suspected.

Trial design. A total of 105 patients were enrolled in this trial. The randomization code was developed using a computerized random number generator. The patients were randomly assigned into the groups receiving CCRT with S-1 (S-1 arm) or weekly cisplatin (control arm), using blocks of 4 based on 1:1 treatment allocation. The design was not stratified, as the participant characteristics were well balanced by the large patient sample in this trial. The clinicians who assessed the treatment outcomes were blinded to the patients' group assignments.

Chemotherapy. For the S-1 arm, oral S-1, 400 mg twice per day, 7 days a week, was administered for 4 weeks concurrent with RT. For the control arm, the patients received RT concurrent with cisplatin 40 mg/m^2, administered for 7 weeks. All the patients received antiemetic prophylaxis of 5-hydroxytryptamine-3 receptor antagonists and were encouraged to ingest large amounts of water during chemotherapy infusion. The second chemotherapy cycle was delayed in case of any persistent leucopenia or severe mucositis and was promptly resumed after recovery.

Radiotherapy. All the patients were treated in a uniform manner, with intention-to-treat RT in both study arms. A 6-MV linear accelerator was used for treatment, using the split-field technique consisting of two lateral opposed faciocervical fields to the primary tumor and upper neck, supplemented by a single anterior field to the lower neck with a central block. The nasopharynx and the adjacent muscles and bones were treated by a shrinking-field technique to avoid further irradiation of the spinal cord. An anterior facial electron field was added for cases with nasal and ethmoidal tumor extensions. The bulky nodal area was boosted with a posteroanterior neck field of an electron beam of appropriate energy. The total planned dose was 66-76 Gy/7-8 weeks to the primary tumor, 60-66 Gy/6-7 weeks to the positive neck region and 50-55 Gy/5-6 weeks to the negative neck region.

Patient assessment. After completing the combined treatments, the patients were followed up every 2 months over the first year, every 3 months for the second and third years and every 6 months thereafter. Patients who developed local or distant recurrence were subjected to any treatment considered appropriate in the opinion of the attending physician, including surgery, chemotherapy, or RT.

Two months after completing all the treatment schemes, the response to the combined modalities was assessed by MRI and clinically by flexible nasopharyngoscopy. The response to combined treatment was evaluated according to the World Health Organization response criteria. Treatment-related toxicities were recorded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) classification, version 2.0. Hematological assessments were performed weekly to determine the worst toxicity points. For the toxicity analysis, the worst data for each patient in all the cycles of chemotherapy and RT were used.

Endpoints and analysis. The primary endpoints of this study were progression-free survival (PFS) and OS at 2 years in both arms. Distant metastasis DFS was also evaluated. PFS was defined as the time from randomization to the time of disease progression; and OS was defined as the time from the first day of treatment to the date of death from any cause, or the date of the last follow-up visit. The analyses assumed the intention-to-treat approach. Kaplan-Meier survival curves

Table I. Characteristics of the eligible patients.

Characteristics	S-1 arm, no. (%) (n=55)	Control arm, no. (%) (n=50)
Age, years		
Median	48	46
Range	25-68	20-69
Gender		
Male	36 (65.5)	30 (60.0)
Female	19 (34.5)	20 (40.0)
Karnofsky PS		
>80	31 (56.4)	31 (62.0)
≤80	24 (43.6)	19 (38.0)
Stage[a]		
III	38 (69.1)	32 (64.0)
IV	17 (30.9)	18 (36.0)
Pathology[b]		
Type I	2 (3.6)	2 (4.0)
Type II	40 (72.7)	39 (78.0)
Type III	13 (23.7)	9 (18.0)
T stage[a]		
T1-T2	22 (40.0)	22 (44.0)
T3-T4	33 (60.0)	28 (56.0)
N stage[a]		
N0-N1	28 (50.9)	25 (50.0)
N2-N3	27 (49.1)	25 (50.0)

[a]2002 American Joint Committee on Cancer. [b]World Health Organization. PS, performance status.

Table II. Response to combined chemotherapy and radiotherapy.

Response	S-1 arm, no. (%) (n=55)	Control arm, no. (%) (n=50)
Not assessable	2 (3.0)	
Assessable	53 (47.0)	
CR	37 (67.3)	28 (54.0)
PR	13 (23.6)	13 (26.0)
No change	2 (3.6)	4 (8.0)
Progression	1 (1.8)	2 (4.0)

CR, complete response; PR, partial response.

were used to analyze time-to-event endpoints. Toxicity and response were analyzed with χ^2 tests. All the reported significance levels were based on two-sided tests.

Results

Patient characteristics. Between January, 2007 and December, 2010, a total of 105 patients were randomly assigned to the S-1 or control arms; 2 patients (1 from the S-1 and 1 from the control arm) did not complete the entire course of treatment due to the treatment cost, but were included in the analysis according to the intention-to-treat principle. No other patients refused or discontinued their treatment due to toxicities, coexisting illness, or other causes. The baseline characteristics, including age, gender, Karnofsky performance status, pathology, T stage and N stage, did not significantly differ between the two arms (Table I).

Tumor response. Response was evaluated by MRI at 2 months after completion of treatment (Table II). We considered 2 patients in the S-1 arm and 3 in the control arm to be unevaluable due to lack of treatment, incomplete treatment, or major protocol violations. In the S-1 arm, the complete response (CR) rate was 67.3% (37/55) and the partial response (PR) rate 23.6% (13/55), with an overall response rate (ORR) of 90.9%. In the control arm, CR and PR were 54.0% (28/50) and 26.0% (13/50), respectively, with an ORR of 80.0%. The two arms did not significantly differ in ORR (χ^2=1.551, P=0.299). Additionally, as there was residual primary tumor and the neck nodes usually regress slowly or may become fibrotic after several months, no planned neck dissection was performed for 6 months.

Survival. The median follow-up time was 28.4 months (range, 9-50 months). The rates for 2-year PFS (S-1 arm, 81.3%; control arm, 65.8%; P=0.090; Fig. 1) and 2-year OS (S-1 arm, 86.2%; control arm, 82.5%; P=0.103; Fig. 2) did not differ significantly between the two arms.

Toxicity and compliance. Grade 3-4 toxicities according to the NCI CTC 2.0 classification are listed in Table III. No fatal treatment-related toxicities occurred in either arm. No patient developed grade 3-4 liver or renal function impairment in

Table III. Summary of grade 3-4 adverse events during treatment according to the National Cancer Institute Common Toxicity Criteria classification, version 2.0.

Toxicity	S-1 arm, no. (%) (n=55)	Control arm, no. (%) (n=50)
Hematological		
Leukopenia	3 (5.5)	11 (22.0)
Anemia	1 (6.2)	7 (14.0)
Thrombocytopenia	0 (0.0)	2 (4.0)
Non-hematological		
Mucositis	11 (20.0)	23 (46.0)
Dermatitis	8 (14.5)	18 (36.0)
Nausea/vomiting	5 (9.1)	20 (40.0)
Mouth dryness	5 (9.1)	7 (14.0)
Fatigue	2 (3.6)	7 (14.0)
Otitis externa	1 (1.8)	1 (2.0)

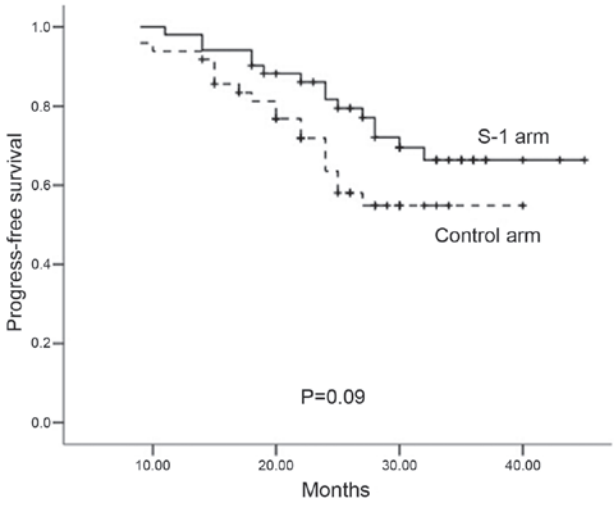

Figure 1. Comparison of progression-free survival curves between patients treated by concurrent chemoradiotherapy (CCRT) + S-1 and those treated with CCRT + cisplatin.

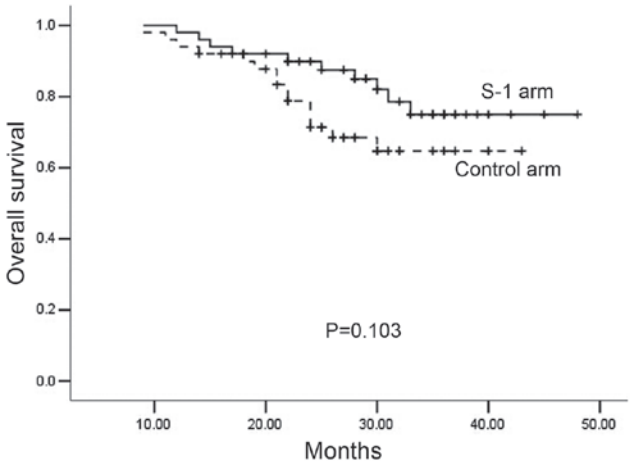

Figure 2. Comparison of overall survival curves between patients treated by concurrent chemoradiotherapy (CCRT) + S-1 and those treated with CCRT + cisplatin.

either arm. The main toxicities were leukopenia, mucositis, dermatitis and nausea/vomiting in both arms; the secondary hematological toxicities were anemia and thrombocytopenia and the secondary non-hematological toxicities were mouth dryness, fatigue and otitis externa.

Of note, the main non-hematological grade 3-4 toxicities were significantly less frequent in the S-1 arm compared to the control arm (mucositis, 20.0 vs. 46.0%, P=0.004; dermatitis, 14.5 vs. 36.0%, P=0.011; and nausea/vomiting, 9.1 vs. 40.0%, P=0.000). In the S-1 arm, leukopenia (the main hematological toxicity) was also less frequent compared to the control arm (5.5 vs. 22.0%, P=0.013). Additionally, the incidence rate of grade 1-2 nausea was 23.6% (13/55) in the S-1 arm and 52.0% (26/50) in the control arm (P=0.03). Clearly, nausea was a significantly less important issue, in terms of degree and extent, in the S-1 arm compared to the control arm (P<0.05).

Discussion

Over the last few years, numerous trials have investigated optimal strategies of combined chemoradiotherapy (19). Induction chemotherapy appears to be a logical and attractive method to control subclinical metastatic foci and may help reduce distant metastasis, thus improving OS. CCRT has been established as standard treatment for locoregionally advanced NPC on the basis of the Intergroup Trial 00-99 (12) in 1998, the first randomized trial to demonstrate a survival benefit for NPC with combined treatment modalities. However, the suitability of CCRT for patients in China remains controversial due to its significant toxicity. Therefore, drug selection and dosage are crucial, as overly toxic schedules may impair RT delivery. In China, various chemotherapeutic agents have been combined with RT to establish less toxic regimens for locoregionally advanced NPC.

Recently, S-1, as a novel oral chemotherapeutic agent, has been investigated for use in gastric cancer, non-small-cell lung cancer and head and neck squamous cell carcinoma. The development of anticancer drugs has favored oral over intravenous regimens, due to their relative ease of administration and lower hospital resource demands. Oral fluoropyrimidines, in particular, appear to possess at least equivalent efficacy and potentially lower toxicity compared to intravenous therapies. Using rational drug design, several oral fluoropyrimidines have been developed, including capecitabine, UFT (tegafur and uracil), eniluracil plus oral 5-fluorouracil and S-1. Numerous studies have shown S-1 with CCRT to exhibit significant antitumor activity and safety in cancers of the rectum, pancreas, esophagus and oral cavity. Interestingly, S-1 has exhibited higher efficacy and less toxicity in squamous cell carcinoma of the head and neck (SCCHN). However, NPC has a natural history distinct from that of other SCCHNs and, to date, no studies have determined whether S-1 with RT yields the same benefit in NPC as in other SCCHNs.

To the best of our knowledge, the present study was the first to introduce oral S-1 with concurrent RT for locoregionally advanced NPC. In China, CCRT with weekly cisplatin is widely popular in clinical practice. However, several patients experienced severe toxicities when administered CCRT with cisplatin. With the aim to maximize efficacy and minimize toxicity, we designed a CCRT + S-1 regimen and then compared this strategy with standard CCRT + cisplatin for locoregionally advanced NPC. Our results demonstrated that CR and PR were similar in the S-1 and control arms (67.3 vs. 54.0%, respectively, P=0.235; and 23.6 vs. 26.0%, respectively, P=0.779), which is consistent with the literature (20). The 2-year PFS and OS were also similar in the S-1 and control arms (81.3 vs. 65.8%, respectively, P=0.090; and 86.2 vs. 82.5%, respectively, P=0.103). Therefore, our results demonstrated that CCRT + S-1 exhibited similar efficacy to that of CCRT + cisplatin in this population.

The aim of the present study was to determine the optimal strategy for CCRT, with a focus on improved tolerance to combined modalities. We observed that the main non-hematological toxicities in the S-1 arm were significantly less frequent compared to the control arm (mucositis, 20.0 vs. 46.0%, P=0.004; dermatitis, 14.5 vs. 36.0%, P=0.011; and nausea/vomiting, 9.1 vs. 40.0%, P=0.000) and were also significantly less frequent compared to the majority of the trials of CCRT in NPC (5,9,21). Our results suggest that S-1 increased tolerance to the regimen in this study. Chemotherapy as well as RT may lead to gastrointestinal reactions (i.e., anorexia, nausea, nausea, constipation and skin or mucosal injury). Therefore, CCRT + S-1 is associated with a high incidence of non-hematological toxicities. As oral S-1 exhibits relatively low toxicity, its use in CCRT lowers the risk of toxicity. Leukopenia was the most common hematological adverse effect in our study. Grade 3-4 leukopenia was significantly less frequent in the S-1 compared to the control arm (5.5 vs. 22.0%, P=0.013). Moreover, cases of severe leukopenia during induction chemotherapy and the concurrent S-1 phase were all uncomplicated and manageable. Hematological toxicity may be further ameliorated with the use of growth factor support and prophylactic antibiotics. Additionally, as a linkage effect, fewer severe toxicities encourage patients to complete their treatment course, thus improving the PFS and OS of patients with locoregionally advanced NPC.

In conclusion, this novel strategy may be considered as an alternative approach to treat locoregionally advanced NPC in a population in whom NPC is particularly common. We found the combination of CCRT and S-1 to be efficacious, feasible and well tolerated; therefore, an optimal regimen and schedule should be established, with more randomized trials on larger patient samples with longer follow-up. Moreover, as molecular-targeted agents become increasingly available and refined, their use should also be investigated in this context.

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