Phase II study of sorafenib in combination with cisplatin and 5-fluorouracil to treat recurrent or metastatic nasopharyngeal carcinoma†

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Background: We aimed to investigate the efficacy and tolerability of sorafenib combined with cisplatin and 5-fluorouracil (5-FU) in patients with recurrent or metastatic nasopharyngeal carcinoma (NPC).

Patients and methods: It was a Simon two-stage designed trial. Chemotherapy-naive patients with recurrent or metastatic disease were enrolled. The regimen was sorafenib 400 mg orally b.i.d., cisplatin 80 mg/m² i.v. day 1, and 5-FU 1000 mg/m²/day CIIV for 4 days, repeated every 21 days. After a maximum of six cycles of chemotherapy, patients received maintenance of sorafenib.

Results: In total, 54 patients were enrolled. The objective response rate reached 77.8%, including 1 complete response and 41 partial responses. The median progression-free survival was 7.2 months (95% CI 6.8–8.4 months), and the median overall survival was 11.8 months (95% CI 10.6–18.7 months). Major toxic effects included hand-foot skin reaction, myelosuppression, and gastrointestinal (GI) reaction. The incidence of hemorrhage was 22.2%, and one patient with liver metastases died of GI bleeding. Contrast-enhanced ultrasonography was carried out in a subset of patients with liver metastases.

Conclusion: Combination of sorafenib, cisplatin (80 mg/m²) and 5-FU (3000 mg/m²) was tolerable and feasible in recurrent or metastatic NPC. Further randomized trials to compare sorafenib plus cisplatin and 5-FU with standard dose of cisplatin plus 5-FU in NPC are warranted.

Key words: angiogenesis, chemotherapy, nasopharyngeal carcinoma, sorafenib

Introduction

Nasopharyngeal carcinoma (NPC) is characterized by its unique geographic distribution [1]. Southern China has one of the highest incidence rates in the world (20–30 per 100,000), and the incidence remained stable in the last 30 years [2]. Intense-modulated radiotherapy (RT)/RT alone or with chemotherapy are the standard of care for nonmetastatic disease [3]. Owing to the advances in tumor imaging and RT technique, the 5-year local control rate rose to 94.9%, and the 5-year disease-free survival rate reached 76.7%. Treatment failures are mainly distant metastasis, which develop in ~20% of patients with locally advanced disease [4].

Many cytotoxic agents are active against metastatic NPC. Cisplatin-containing regimens remain the cornerstone of palliative chemotherapy. The response rates (RRs) achieved of cisplatin and 5-fluorouracil (5-FU) were ~60% [5, 6], so they represent the treatment of choice for most patients with recurrent or metastatic NPC. Other active agents, including taxanes, gemcitabine, oxaliplatin, vinorelbine, irinotecan, and capecitabine, yield the objective RR (ORR) from 14% to 73% after failure of platinum-based chemotherapy, but their efficacy in first-line therapy still needs to be validated in randomized phase III trials [7–17].

In spite of the relatively high RRs and emerging new drugs, survival in advanced disease is not significantly improved, with the progression-free survival (PFS) ranged from 5.6 to 10.6 months and overall survival (OS) from 7.6 to 19.6 months.
Molecularly targeted drugs have been added to cytotoxic chemotherapy regimens in order to improve the survival of patients with other advanced tumors [18, 19]. Therefore, it is imperative to explore novel targeted therapies for patients with advanced NPC.

VEGF/VEGFR is a potential target, as angiogenesis constitutes an important pathway for tumor growth and metastases. Overexpression of VEGF was seen in 60%–67% of patients with NPC and the higher expression was related to lower OS [20, 21]. These evidences provided a rationale for investigating anti-angiogenesis agent for this tumor. Sorafenib is a multi-kinase inhibitor [22]. Previous trial revealed that sorafenib monotherapy had modest antitumor activity in patients with relapsed advanced or metastatic squamous cell carcinoma of the head and neck (SCCHN), including NPC [23, 24]. We conducted the current study to determine the efficacy and toxicity profile of sorafenib combined with cisplatin and 5-FU in advanced NPC. Sorafenib was chosen because its combination with single cytotoxic agents and platinum-based doublet chemotherapy did not severely increase side-effects in several cancer models [25–27]. The hypothesis is that sorafenib might increase the ORR and improve PFS without adding substantial toxicity.

patients and methods

patients

Patients enrolled in this study had histologically confirmed NPC that was metastatic or locally recurrent at diagnosis or after previous curative treatment. Disease was measurable as defined by RECIST [28]. Patients must not have received prior treatments for recurrent or newly diagnosed metastatic disease; however, chemotherapy or radiation as part of the initial curative therapy was permitted.

Patients were excluded if they had significant cardiac disease; were pregnant or breast-feeding; or showed evidence of bleeding diathesis and were unable to take oral medications. All patients provided informed consent, and the institutional ethics review board of each participating center approved the study.

study medications

Sorafenib was administered orally 400 mg twice a day for 21 days. Cisplatin (80 mg/m2) was administered intravenously on day 1, and 5-FU (1000 mg/m2/day) was administered via continuous infusion on day 1 through 4 of a 21-day cycle during the chemotherapy phase. In the cases of tumor stabilization or response after a maximum of six cycles of chemotherapy, patients received maintenance treatment with sorafenib until there was objective evidence of tumor progression or intolerable drug-related toxic effects. We chose this dose of cisplatin and 5-FU because of the following reasons. First, there were a lot of studies using sorafenib plus cisplatin and other cytotoxic agents in malignant cancers, and the dose of cisplatin ranged from 75 to 80 mg/m2 [27, 29, 30]. Second, this study aimed to assess the efficacy and safety of sorafenib combined with cisplatin and 5-FU. We carried out this trial in a two-stage design. In the first stage, 19 patients were enrolled to check the efficacy as well as the tolerability of the initial dose. If the trial moved on to the second stage with feasible and tolerable set dose, we enrolled the rest of patients at this dose. Otherwise, the initial dose should be reduced.

Dose reduction levels of sorafenib were based on interval adverse events (AEs): level 1 was 400 mg once daily, and level 2 was 400 mg once every other day. No dose escalations were allowed after a dose reduction. The chemotherapy dosage modifications were allowed when patients experienced grade 4 hematologic or grade 3 non-hematologic AEs.

study procedures

Tumor size was evaluated by carrying out computed tomography or magnetic resonance imaging at baseline (within 21 days before starting treatment). Target lesions were evaluated every two cycles during the chemotherapy phase and every 2 months during the maintenance period. Objective responses were confirmed 4 weeks after documentation. After withdrawal, patients were followed up once every 3 months until death. AEs were defined according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0 (http://ctep.cancer.gov/reporting/ctc_v30.html).

contrast-enhanced ultrasonography

Contrast-enhanced ultrasonography (CEUS) was carried out in consented patients with liver metastasis at baseline and after two cycles by using standard methodology as described previously [31]. The contrast uptake rate of liver metastases was evaluated by a specialized radiologist using specific image processing software (Image-Pro Plus 6.0, Media Cybernetics). Receiver operating characteristic curve (ROC) analysis was done using the nonparametric assumption to compare contrast uptake rates by means of ultrasonography measurements. The optimal cut-offs point was defined by ensuring best sensitivity and specificity.

statistical analysis and sample size calculation

Simon’s optimal two-stage design was used for sample size calculation [32]. We used the baseline RR of 60% seen with cisplatin and 5-FU in the first-line setting as our null hypothesis. To detect a 30% improvement in RR (60% versus 78%) with the proposed regimen, at a significance level of 3% and a statistical power of 90%, we estimated accrual to be 53 patients in a two-stage design. It was determined that 19 assessable patients had to be included at the first stage. If at least 12 objective responses were observed, then an additional 34 patients would be recruited to the second stage. Sorafenib would be considered active if at least 37 responses were observed among the 53 patients.

The primary end point of this study was ORR, including the percentage of complete response (CR) and partial response (PR). The secondary end points were toxicity (particularly hand–foot skin reaction, HFSR), disease control rate (DCR, the proportion of CR, PR, and SD), PFS, and OS. The analysis was done on an intention-to-treat (ITT) basis. ORR was evaluated in patients who received at least one cycle of treatment and then was re-evaluated (both at baseline and after treatment). Patients who received at least one cycle of treatment were included in the safety analysis. OS was defined as the duration from the date of consent to the date of death from any cause or the date of last follow-up. PFS was defined as the duration from the date of consent to the date of disease progression or the date of last follow-up. PFS and OS were estimated using Kaplan–Meier methods.

Analyses were carried out using the statistical software package SPSS 16.0 (SPSS, Chicago, IL). All statistical tests were two-sided, and a P-value <0.05 was considered as statistically significant.

results

patients characteristics

Fifty-four patients were enrolled from January 2009 to May 2011. All patients were included in the ITT analysis of efficacy and AEs. Their characteristics are listed in Table 1. Most patients were men (79.6%); the median age was 45.6 years.
### Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
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<tr>
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<td>1</td>
<td>51</td>
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<td>2</td>
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<tr>
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<td>Number of metastatic organs (n = 52)</td>
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<td>Others</td>
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*Including patients with metastatic disease at diagnosis and after previous curative treatment.

bOne patient had both surgery and radiochemotherapy.

ECOG, Eastern Cooperative Oncology Group.

Most patients had lung metastases (53.9%), followed by liver (48.1%) and bone metastases (40.4%), and 27 patients had multiple sites of metastases (51.9%). Among those with recurrent/metastatic disease after previous therapy (n = 38), five patients received prior curative-intent RT alone, and 33 had also received chemotherapy with RT.

**treatments**

In the ITT population, the median duration of chemotherapy was 12.1 weeks (range 6.0–18.5 weeks). Dose intensity was 0.86 in cisplatin and 0.81 in 5-FU. During the first stage of the study, 63.2% patients (12 out of 19) required 5-FU dose reduction because of mucositis (CTCAE grades 2–3); therefore, the protocol was amended so that the initial dose of 5-FU was 3000 mg/m² in the second stage. 25.7% patients (9 out of 35) required 5-FU dose reduction at the second stage. Totally, 5-FU dose reduction was carried out on 21 patients (38.9%); among them, 6 patients underwent dose reduction twice. No dose reduction of cisplatin was required.

The median sorafenib treatment time was 24.4 weeks (range 5.1–91.4 weeks). Dose intensity was 0.64 in sorafenib due to the dose interruption. Dose reduction of sorafenib was required in 22 patients (40.7%) for the following reasons: HFSR (14, 63.6%), mucositis (4, 18.2%), hypertension (2, 9.1%), diarrhea (1, 4.5%), and arrhythmia (1, 4.5%). Two of them underwent further dose reduction to 400 mg once every other day because of HFSR. Fourteen patients (25.9%) required dose interruption (HFSR 11, 78.6%; poor memory 3, 21.4%).

Treatment discontinuation was mainly due to disease progression (30 of 46, 65.2%). Other reasons were death [3, 6.5%, 1 serious AE (SAE), 2 due to progression of disease], complication (1, 2.2%), dose interruption of more than 30 days (5, 10.9%), patient request (2, 4.3%), non-adherence (5, 10.9%).

**responses and survival**

In the ITT analysis, the ORR reached 77.8%: 1 patient (1.9%) experienced CR; 41 (75.9%), PR. Seven (13.0%) patients had stable disease, and five (9.2%) patients had progressive disease. DCR was 90.8%. Waterfall plot of the maximum reduction in target tumor lesions on at least one post-treatment measurement is listed in Figure 1.

The median PFS was 7.2 months (95% CI 6.8–8.4 months). Of the 54 patients, 8 (14.8%) continued to receive sorafenib after the data cut-off date for this study (14 December 2011). The duration of treatment is listed in supplementary Figure S1, available at *Annals of Oncology* online. At a median follow-up of 19.0 months, 33 patients were alive. The median OS was 11.8 months (95% CI 10.6–18.7 months).

Of those 28 patients with lung metastasis, 9 patients (9 out of 28, 32.1%) experienced tumor cavitation during the course of treatment (Figure 2). There were no tumor cavitations at baseline.

**contrast-enhanced ultrasonography**

CEUS was carried out in 16 consented patients with liver metastases before and after two cycles of treatment in one center (SYSUCC). In an ROC analysis, the area under the ROC predicting response by tumor contrast uptake rate at baseline was 0.906. Using the optimal cut-off point identified in the ROC analysis, patients with ≥85.87% of tumor contrast uptake rate have a better response. Actually, eight of the nine patients with higher uptake rate showed PR, versus none of the seven patients with lower uptake rate (88.9% versus 0%, P = 0.00042). The response was specifically related to the lesions in the liver.

The median values of the contrast uptake of responders (eight cases) and non-responders (eight cases) are summarized in supplementary Table S1, available at *Annals of Oncology* online. Pre-treatment tumor contrast uptake rate was significantly higher in responders than in non-responders.
93.6% (mean percentage of contrast uptake) versus 56.6% ($P = 0.005$). After two cycles of treatment, the mean percentage of tumor contrast uptake decreased to 38.0% in responders and remained at 46.1% in non-responders. The changes in contrast uptake before and after treatments were statistically significant in responders (93.6% versus 38.0%, $P = 0.002$) but not in non-responders (56.6% versus 46.1%, $P = 0.211$). The CEUS of patients who experienced PR is shown in Figure 3.

adverse events

The most common AEs are listed in Table 2. Most of these were consistent with the known toxic effects of the chemotherapy agents and sorafenib. The most commonly reported AEs include HFSR (83.3%), leucopenia (77.8%), anemia (74.1%), anorexia (74.1%) and nausea (64.8%). Most of these events were mild to moderate. The most common grade 3 or worse toxicity was mucositis with 11 patients (20.3%). Other grade 3 and worse toxicity included HFSR (18.5%), thrombocytopenia (13%), neutropenia (13%), and leukopenia (7.4%).

Hemorrhagic events (all grades) occurred in 12 patients (22.2%): epistaxis in 8 patients, gingival bleeding in 2 patients, hemoptysis in 1 patient, and fatal hematemesis in 1 patient. One patient with liver metastasis died of gastrointestinal (GI) bleeding during the sorafenib maintenance treatment period.

Figure 1. Waterfall plot of the maximum decrease in the sum of the longest diameters of target lesions observed. Patients are listed in order of increasing percentage response. The dashed line indicates a tumor reduction of 30% from baseline—the lower limit of partial response, according to Response Evaluation Criteria in Solid Tumors.

Figure 2. Baseline and post-treatment computed tomography scans of one patient with nasopharyngeal carcinoma lung metastases.
The patient, aged 45 years, was diagnosed with locally advanced NPC and received CCRT in 2009. He was enrolled into this study in April 2010 after multiple liver metastases were found. In the study, the patient received four cycles of chemotherapy and the efficacy was PR. After that, sorafenib was given for maintenance treatment. However, the patient had fatal GI bleeding during light manual labor in the first maintenance phase. Autopsy was refused.

Serious AE (SAEs) occurred in five patients (9.3%): electrolyte disturbance including hyponatremia and/or hypopotassaemia (two), vomiting (one), hemorrhage (one), and active pulmonary tuberculosis (one). All were considered to be drug-related except active pulmonary tuberculosis.

**discussion**

As yet, five anti-angiogenesis agents had been investigated in NPC, including sorafenib, sunitinib, pazopanib, axitinib, and bevacizumab [24, 33–36]. Monotherapy of sorafenib, sunitinib, and pazopanib had demonstrated clinical efficacy in advanced NPC. The clinical benefit rates ranged from 28.6% to 54.5%, most of which were SD, revealing that VEGFR inhibitors might...
induce better ORR when combined with chemotherapy or radiation rather than monotherapy [24, 33, 35, 37]. Recently, a phase II study of bevacizumab combined with chemoradiation also revealed promising efficacy in treating Locally advanced NPC [34]. In our study, evidence for the efficacy of sorafenib plus cisplatin–5-FU regimen seems favorable in metastatic NPC with an RR of 77.8%, a DCR of 90.8%, and PFS of 7.2 months. OS was not significantly prolonged in this patient population compared with previous studies [5-8, 10-12, 14, 15, 17]. Several reasons may contribute to this finding. First, nearly half of the patients (48.1%) enrolled had liver metastasis, which is a poor survival prognostic factor. In fact, OS of patients with liver metastasis was significantly shorter than those without liver metastasis (11.2 months versus 17.0 months, P = 0.048). We also found that patients with lung metastases lived longer than those with other organ metastases (20.9 months versus 11.7 months, P = 0.050), which was consistent with previous literature [38]. Second, only a limited proportion of patients received salvage therapy when diseases progressed (26 out of 46, 56.5%). In our subgroup analysis, patients with second-line therapy (chemotherapy or radiation) were associated with a significant longer OS compared with those with best supportive care only [median 13.8 months (95% CI 11.2–20.9) versus 7.6 months (95% CI 7.2–11.7), P = 0.0014]. Third, the modification of dosage might compromise the maximal benefit from systemic chemotherapy combined with a targeted agent. To our knowledge, this is the first clinical trial to evaluate VEGFR TKIs combined with active cytotoxic agents in recurrent or metastatic NPC.

Previous data had showed the potential of CEUS in monitoring the response of anti-angiogenetic agents, and initial contrast uptake was a predictive factor of the response of imatinib in GI stromal tumors [31, 39]. In our current study, we explored the usage of CEUS as a non-invasive assessment tool for predicting tumor response of liver metastasis in NPC. The ROC analysis was able to identify a threshold of contrast uptake rate at baseline. The correlation between contrast uptake rate and response indicated the potential of using this parameter as a predictive biomarker in future. We also found different patterns of contrast uptake rate changing in CEUS between responders and non-responders, similar to what Lassau et al. [31] found previously. The change of contrast uptake rate pre- and post-treatment may be valuable as a sensitive parameter to monitor response.

Whether or not sorafenib aggravated the known toxic effects of chemotherapy is unknown [27, 40]. In our study, we did observe higher incidences of hematologic and non-hematologic toxic effects with combination therapy than previously reported with chemotherapy alone [41], but all events were consistent with the known safety profile of sorafenib, cisplatin, and 5-FU. The overall grade 3 or greater toxic effects showed that we should be more careful when carrying out this combined regimen, although most of them were reversible. Regarding our result, we assumed that the combination of sorafenib with 5-FU might have synergetic effect on onset of mucositis, although a recent study revealed no evidence of sorafenib–5-FU interactions [42]. The regimen was feasible when the initial dose of 5-FU reduced to 3000 mg/m2 at the second stage. So, we recommend having 5-FU dosage reduced in further study.

Patients with recurrent or metastatic SCCHN/NPC are prone to bleeding events [33, 37, 43]. In a phase II trial of sunitinib and pazopanib, Hui et al. [33] and Lim et al. [35], respectively, reported fatal hemorrhage in previously treated NPC patients. Bleeding events in our study were mostly low grade, and the overall incidence risk (22.2%) was similar to that found in the meta-analysis of patients being treated with sorafenib or sunitinib (16.7%) [44]. However, there was still one death due to hemorrhage in our study; clinicians should monitor for potentially serious bleeding events in future clinical trials with significant caution.

There are some limitations in our study. First, as this was a single-arm study, all patients received sorafenib combined with chemotherapy. The true effect of sorafenib in this combination cannot be defined without control group. Second, the small number of patients meant the results should be interpreted with caution. Third, the dose reduction might not reveal the maximal effect of these drugs. These limitations all argue for a randomized study to further investigate the incorporation of sorafenib with commonly used regimens in the first-line treatment of patients with advanced NPC.

In conclusion, our study results revealed that the combination of sorafenib, cisplatin (80 mg/m2), and 5-FU (3000 mg/m2) was a tolerable and feasible regimen in recurrent or metastatic NPC. Further randomized trials to compare sorafenib plus cisplatin and FU with standard dose of cisplatin plus FU in NPC are warranted.

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disclosure
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references


