Original Article

Preliminary results of proton beam therapy combined with weekly cisplatin intra-arterial infusion via a superficial temporal artery for treatment of maxillary sinus carcinoma

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Abstract

Objective: This study aimed to evaluate the efficacy and toxicity of proton beam therapy combined with cisplatin intra-arterial infusion via a superficial temporal artery as treatment for maxillary sinus carcinoma.

Methods: Twenty-six patients with confirmed maxillary sinus carcinoma were enrolled in this study from May 2009 to April 2011. Patients underwent proton beam therapy and intra-arterial infusion chemotherapy with cisplatin.

Results: The median total dose was 70.4 GyE per 32 fractions, and the median dose of cisplatin was 300 mg/body for six cycles of intra-arterial infusion. The 3-year overall survival rate was 58% for all patients (n = 26), 58% for patients with stage T4 disease (n = 12), 57% for patients with <Stage T3 disease (n = 14), 66% for patients with squamous cell carcinoma (n = 15) and 45% for patients with non-squamous cell carcinoma (n = 11). Two patients developed non-hematologic side effects such as Grade 3 radiation dermatitis, one developed osteonecrosis and one developed brain necrosis. Ocular/visual problems occurred in three patients, which included Grade 4 retinopathy and Grade 3 cataract in one and two patients, respectively.

Conclusions: Proton beam therapy combined with cisplatin intra-arterial infusion administered via a superficial temporal artery appears to be safe and effective for maxillary sinus carcinoma.

Key words: proton beam therapy, intra-arterial infusion, maxillary sinus carcinoma, superficial artery, cisplatin

Introduction

Maxillary sinus cancer is an extremely rare disorder. It accounts for ~3% of cancers of the head and neck and ~0.5% of all malignant disease (1). Trimodal therapy, consisting of surgery, systemic chemotherapy and irradiation, is generally used in the treatment of maxillary sinus cancer. The 5-year survival rates in patients with T4
Stage tumors receiving trimodal therapy have been reported to be ~50% (2).

Superselective transarterial infusion therapy using high doses of cisplatin was introduced as a novel intra-arterial infusion chemoradiotherapy regimen (radiotherapy and concomitant intra-arterial cisplatin) by Robbins et al. (3–5). However, these previous reports on intra-arterial chemotherapy have used a standard femoral artery approach. Intra-arterial infusion via a superficial temporal artery (STA) can easily provide repeated chemotherapy for patients with maxillary sinus cancer.

Proton beams are characterized by their rapid fall-off at the distal end of the Bragg peak and sharp lateral penumbra, depending on energy, depth and delivery (6). As a result of these physical characteristics, proton beam therapy (PBT) offers better dose distribution than X-ray irradiation (6). Moreover, PBT is now considered a practical and efficient therapeutic approach in which curative dose irradiation can be used to eradicate tumors without affecting normal healthy tissue (7).

In the present Phase III study, the aim was to evaluate the efficacy of PBT as a treatment for maxillary sinus carcinoma with cisplatin intra-arterial infusion via the STA. To the best of our knowledge, this is the first report of PBT with intra-arterial chemotherapy for maxillary sinus cancer.

**Patients and methods**

**Eligibility**

Twenty-six patients with histologically confirmed maxillary sinus cancer were enrolled in this study. Written informed consent was obtained from each patient before enrollment. In the present study, there was no restriction on the age of the subjects. Specific eligibility criteria were: Eastern Cooperative Oncology Group performance status, 0–3; adequate hematological (white blood cell count >3500/µl; neutrophil level >2000/µl; platelet count >1×10^6/µl; hemoglobin level >9 g/dl), hepatic (aspartate transaminase-alanine transaminase ratio; three times the upper limit of normal; total bilirubin level <1.5 mg/dl) and renal (creatinine clearance rate >30 ml/min) functions; and life expectancy >3 months.

**Intra-arterial infusion procedure via the STA**

Three-dimensional (3D) computed tomography (CT) angiography of the carotid artery was performed to identify the main tumor-feeding arteries and determine the morphology and course of the tumor-feeding arteries from the external carotid artery prior to treatment. Catheterization from the STA was performed as previously reported (8). Briefly, the anterior ear on the affected side was incised under local anesthesia to expose the STA. During fluoroscopy, a catheter was placed into the external artery. When the lesion also involved the contralateral side beyond the median line, another catheter was inserted into the contralateral side for bilateral arterial injection.

The extent of arterial injection was confirmed by dyeing the tumor with a pigment, using angiography or magnetic resonance imaging (MRI) with an extremely low dose of contrast medium slowly infused by way of the catheter for arterial injection.

**Chemotherapy**

Cisplatin was administered by intra-arterial infusion at 50 mg/body over 5 h on Day 1 and was continued once a week for a total of six courses. During intra-arterial infusion of Cisplatin (CDDP) a CDDP-neutralizing agent, sodium thiosulfate, was also administered intravenously at 10 g/body for 8 h, starting 1 h before intra-arterial infusion of CDDP (Fig. 1). A 5HT3-receptor antagonist and steroid were administered to all patients before intra-arterial infusion to minimize nausea and vomiting.

**Proton beam therapy**

Treatment planning was performed on a 3D CT planning system. The relative biological effectiveness value was defined as 1.1 (9). The gross tumor volume (GTV) was determined by CT, MRI and positron emission tomography (PET) CT scans prior to treatment. Clinical target volume (CTV) was defined as GTV plus a 3 mm margin. Planning target volume (PTV) was basically defined as CTV plus a 3 mm margin, but could be finely adjusted where necessary to take into account organs at risk. The beam energy and spread-out Bragg peak were fine-tuned such that a 90% isodose volume of prescribed dosage encompassed PTV (Fig. 2). An irradiation schedule of 70.4 Grays equivalent (GyE) was set with 32 fractions over 6.5 weeks. The treatment plan was readjusted as required to conform to the shrinking tumor sizes. Patients with regional lymph node metastases of the neck were treated with the same dose of PBT as described above or with an additional 8.8 GyE in four fractions; the total dose was 79.2 GyE.

The treatment protocol for this study was approved by the ethics committee of our institute.

**Evaluation and follow-up**

Baseline evaluation included a complete medical history and physical examination, a blood cell count, serum chemistry analysis and PET CT scan. Blood biochemistry and symptoms/signs of toxicity were monitored on a weekly basis during treatment. Clinical response was evaluated 8 weeks after the completion of the radiotherapy and was judged according to Response Evaluation Criteria in Solid Tumors guidelines.

Overall survival was calculated from the start of treatment to the date of death or last confirmed date of survival. Local control was defined as lack of progressive disease at the primary tumor site. Patterns of treatment failure were defined by the first site of failure. Acute and late toxicities were graded according to the Common Terminology Criteria for Adverse Events, version 4.0.

The probability of overall survival, which included death from any cause, and local control rate, were calculated using the Kaplan–Meier method.

**Figure 1.** Treatment schema of intra-arterial chemotherapy. i.a., intra-arterial infusion; STS, sodium thiosulfate; i.v., intravenously.
Results

Patients’ characteristics

Twenty-six patients with maxillary sinus carcinoma were treated with PBT and intra-arterial infusion chemotherapy at our institute from May 2009 to April 2011. The patients’ detailed characteristics are listed in Table 1. The median age was 69 years, ranging from 43 to 82 years. There were 19 men and 7 women included in the study. There were 15 patients (58%) who had squamous cell carcinomas (SCC), 6 (23%) with adenoid cystic carcinomas and the remaining 5 (19%) had other types of cancers.

Tumor and node classifications are shown in Table 2. Two patients with large tumors received induction chemotherapy before radiotherapy to avoid exposing the eyeball and/or optic nerve of the unaffected side to radiation. The protocol of induction chemotherapy was a combination of CDDP and 5-fluorouracil. One patient received one course, and the other received two courses.

Compliances

All patients were treated with at least four cycles of cisplatin intra-arterial infusion chemotherapy. The median number of cycles of arterial chemotherapy per patient was six (range, 4–99). The median catheterization time was 39 (range, 15–61) days.

The total delivered dose to the primary target volume ranged between 55 and 83.6 GyE per 25–38 fractions of PBT. The reason for the wide radiation of total dose was the discretion of the treating physician. The median dose was 70.4 GyE per 32 fractions. The eight patients with lymph nodes metastases were also given additional PBT to the lymph nodes. The delivered total dose to the lymph nodes was 70.4 GyE per 32 fractions.

Toxicity

Table 3 shows the major adverse reactions to PBT and cisplatin intra-arterial infusion chemotherapy. There were no treatment-related deaths during therapy, and no patients experienced Grade 3–4 hematologic toxicities or cerebrovascular accidents. The refractory late toxicities were ocular/visual problems (n = 3), osteonecrosis (n = 1) and brain necrosis (n = 1). Of the patients who experienced ocular/visual issues, one had Grade 4 retinopathy and the other two had Grade 3 cataracts.

Overall survival and local control

The 3-year overall survival rate was 57% for all patients (n = 26), 58% for patients with Stage T4 disease (n = 12), 57% for patients with ≤Stage T3 disease (n = 14), 67% for patients with SCC (n = 15) and 45% for patients with non-SCC disease (n = 11; Fig. 3). The local progression-free survival rates at 3 years were 74, 70, 78, 70 and 82%, respectively.

Response of the primary disease

Of the 26 patients, 21 were classified as complete response (81%), and 5 were classified as partial response (PR; 19%). Three of the PR patients died, two due to regrowth of the primary disease and one due...
Table 3. Toxicity in study patients (n = 26)

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CNS, central nervous system.
*CTCAE v4.0 = common terminology criteria for adverse events version 4.0.

Figure 3. (Thick line) Overall survival curve. Three-year overall survival was 58%. (Thin line) Progression-free survival curve. Three-year progression-free survival was 74%.

to brain abscess. Of the two remaining patients, one is alive with disease, and in the other, the disease is well controlled.

Pattern of recurrence
The site of the first recurrence was identified whenever possible. Seven cases had recurrence that first occurred at the primary tumor site. Of these, two unsuccessfully underwent salvage surgery. Recurrence of regional lymph nodes was observed in one patient, and distant metastases were observed in five. Histological examination of specimens from patients with distant metastases revealed adenoid cystic carcinoma in two cases, adenocarcinoma in one, SCC in one and melanoma in one.

Discussion
Combined radical surgery and radiotherapy constitutes the standard treatment for patients with cancer of the nasal cavity and paranasal sinus, as well as most epithelial malignancies. However, the overall treatment of paranasal malignancies has resulted in 5-year survival rates in the range of 30–50%, despite refinements in imaging studies such as CT and MRI scans, surgical techniques and radiotherapy (10–13). Recently, prospective randomized trials have demonstrated improved survival rates in patients treated with chemoradiotherapy (CRT) versus radiotherapy alone for unresectable SCC of the head and neck (14–16). Harrison et al. (17) also reported a local progression-free survival rate of 94% in 20 patients with unresectable malignant tumors of the skull base who were treated with aggressive CRT, among whom 15 had SCC. Robbins, a pioneer of superselective intra-arterial infusion of CDDP, reported 5-year overall survival and locoregional control rates of 38.8 and 74.3%, respectively, in 213 patients with Stage 3–4 SCC of the head and neck (18). Moreover, Homma et al. (19) reported 5-year overall survival and locoregional control rates of 69.3 and 78.4%, respectively, in 47 patients with nasal cavity and paranasal sinus cancers. Fukumitsu et al. (20) reported 2-year and 5-year overall survival rates of T4 or recurrent nasal cavity and paranasal sinus carcinoma treated with proton beam alone of 47.1 and 15.7%.

Intra-arterial delivery of chemotherapy has the potential to increase drug concentrations at tumor sites, whereas the intra-arterial infusion of CDDP together with sodium thiosulfate lowers systemic toxicity. Paranasal sinus carcinomas tend to be encompassed mostly within the territory of terminal branches of the internal maxillary artery, which can be catheterized consistently and repeatedly. In our institution, intra-arterial infusion via an STA is the definitive treatment of choice for patients with advanced nasal cavity and nasal paranasal sinus cancer to achieve improved survival rates and to avoid surgery. This method has become feasible for daily concurrent radiotherapy and chemotherapy. The superficial temporal approach is technically simple and probably the easiest method of inserting a catheter into the target artery. In addition, due to the relatively low daily dose, this method can be used in elderly patients or patients with poor performance status. Transfemoral catheterization is also easy to perform and enables catheter insertion into the target artery but can sometimes cause serious problems such as a cranial nerve disorder (21). In the present study, major complications such as neurological complications or massive bleeding were not encountered with this treatment option, thus confirming the safety profile of this method. Recently, Homma et al. reported 5-year overall survival and locoregional control rates of 65.8 and 67.9%, respectively, in 54 patients with maxillary sinus cancers. They reported that 39 of 54 patients (72%) experienced Grade 3–4 toxicity, compared with 6 of 26 patients (23%) in the present study (22).

With regard to late toxicity, conventional radiotherapy is associated with a number of potentially severe complications, leading to radiation-induced injuries to the visual pathways, central nervous system and adjacent bone structures. With the recent widespread adoption of intensity-modulated radiation therapy, several studies have reported improvements in severe toxicity rates (23–25), without any improvement in efficacy. A study by Zenda et al. (26) demonstrated both the safety and efficacy profiles of PBT for the treatment of nasal cavity and paranasal sinus cancers. Although advances in treatment plans for PBT have led to lower doses being delivered to critical organs and decreased late toxicity (26,27), further reductions in toxicity remain possible.

In view of these reports, intra-arterial chemotherapy via the STA has the advantage of less hematological toxicity than the Seldinger technique performed through the groin. In addition, proton beam therapy can reduce radiation late toxicities because of better dose distribution compared with photons, and it also results in effective...
outcomes with the combined use of intra-arterial injection, compared with the use of the proton beam alone.

Conclusions

PBT combined with chemotherapy for maxillary sinus carcinoma using intra-arterial infusion via an STA can result in organ preservation and cure in a majority of patients. Overall, drug-related toxicities were manageable in the current study. However, late adverse reactions such as osteonecrosis, brain necrosis and ocular/visual problems should be monitored in the future.

Conflict of interest statement

None declared.

References