Induction Chemotherapy with Docetaxel, Cisplatin and S-1 Followed by Proton Beam Therapy Concurrent with Cisplatin in Patients with T4b Nasal and Sinonasal Malignancies

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Objective: For the treatment of patients with T4b nasal and sinonasal malignancies, definitive chemoradiotherapy was contraindicated due to the risk of brain damage and blindness. However, combination chemotherapy with docetaxel, cisplatin and S-1 is well tolerated and effective. We conducted a retrospective analysis to evaluate the efficacy and feasibility of induction chemotherapy using docetaxel, cisplatin and S-1 followed by proton beam therapy concurrent with cisplatin.

Methods: Thirteen patients treated with docetaxel, cisplatin and S-1 were analyzed. Docetaxel, cisplatin and S-1 consisted of 60–70 mg/m²/day docetaxel on day 1, 70 mg/m²/day cisplatin on day 1 and 60–80 mg/m²/day S-1 on days 1–14. Treatment was repeated every 3–4 weeks with a maximum number of three treatment cycles. According to the response to docetaxel, cisplatin and S-1, patients received either proton beam therapy concurrent with cisplatin or proton beam therapy alone.

Results: Neutropenia represented the most common Grade 3/4 hematological toxicity (76.9%), while the most frequently observed non-hematological toxicity was nausea (23.0%). After the completion of docetaxel, cisplatin and S-1, the overall response rate was 38.4% (5 of 13), with 1 patient achieving complete response and 4 patients achieving partial response. Subsequently, 10 patients received proton beam therapy concurrent with cisplatin, 2 received proton beam therapy alone and 1 received palliative radiation. No severe toxicity was observed during proton beam therapy. After the completion of proton beam therapy, 11 patients (84.6%) achieved complete response and no brain damage or blindness occurred.

Conclusions: Induction chemotherapy with docetaxel, cisplatin and S-1 followed by proton beam therapy concurrent with cisplatin is well tolerated and displays promising antitumor activity that warrants further investigation.

Key words: nasal – sinonasal – induction chemotherapy – proton – head and neck
INTRODUCTION

Nasal and sinonasal malignancies are rare, representing only 3–5% of all head and neck cancers (HNC) (1,2). Although a variety of malignancies arise in this region, squamous cell carcinoma is most frequent, followed by adenocarcinoma and adenoid cystic carcinoma (3). As the nasal and sinonasal regions have limited anatomical access and permit the asymptomatic growth of malignancies, most patients first realize symptoms when tumors reach a large size or invade the surrounding normal critical organs, and are often initially diagnosed with unresectable disease (4). These patients are not candidates for gross total resection and are typically treated with either definitive radiotherapy or concurrent chemoradiotherapy. However, due to the proximity of critical organs to malignancies in the nasal and sinonasal sinuses, 15–30% of the patients develop radiation-induced serious complications, including brain necrosis, hearing loss, meningitis, unilateral or bilateral blindness, optic neuritis, cataracts, osteoradionecrosis and central nervous system damage (5–7). Despite the use of radiotherapy with or without chemotherapy, outcomes are often poor in these patients due to the high occurrence of local relapse, as reflected in the reported 5-year overall survival (OS) rate of only 15% (8).

To reduce radiation-induced toxicity and improve treatment outcomes for locally advanced nasal and sinonasal malignancies, we previously evaluated two treatment strategies involving induction chemotherapy (IC) and proton beam therapy (PBT) (9). In the first approach, we demonstrated that IC led to reduced tumor sizes and avoided brain damage and ocular/visual toxicity that often results from radiotherapy (9). We also examined IC with irinotecan plus docetaxel (ID) for olfactory neuroblastoma, but the relatively poor treatment outcomes suggested that ID was not a suitable approach (9). We subsequently performed a Phase I clinical study of IC with docetaxel, cisplatin and S-1 (TPS) and found that this treatment was well tolerated, feasible and showed a good antitumor activity with locally advanced HNC, which included several nasal and sinonasal malignancies (10). As the response rate to TPS was 70%, IC combined with TPS appears to be a superior approach than IC with ID.

In addition to IC, we have also evaluated the use of PBT for the treatment of nasal and sinonasal malignancies (11,12). PBT was anticipated to improve tumor local control probability and decrease acute and late toxicities of the surrounding normal tissue (13–15). A previous retrospective analysis of 14 patients with olfactory neuroblastoma from our institute who were treated with PBT displayed excellent local control and survival outcomes without serious adverse effects, suggesting that PBT allows the delivery of tumoricidal doses with minimal complications (11).

Here, we conducted a retrospective analysis to evaluate the efficacy and feasibility of IC with TPS followed by PBT concurrent with cisplatin for the treatment of T4b nasal and sinonasal malignancies.

PATIENTS AND METHODS

PATIENTS

We reviewed the case records of 13 patients who were treated for T4b nasal and sinonasal malignancies at the ‘Search’ between January 2006 and March 2012. Tumor staging in the present study was evaluated based on sections of the nasal cavity and sinonasal sinuses using the TNM classification of the UICC 6th edition, regardless of the histology type.

TREATMENT PLAN

INDUCTION CHEMOTHERAPY

Patients received three cycles of TPS chemotherapy followed by PBT concurrent with cisplatin. The chemotherapy regimen consisted of a 1 h infusion of docetaxel at 60–70 mg/m²/day on day 1, a 2 h infusion of cisplatin at 70 mg/m²/day on day 1 and S-1 twice daily on days 1–14 at 60–80 mg/m²/day. The treatment was repeated every 3–4 weeks with a maximum number of three treatment cycles. Ciprofloxacin was administered as a prophylactic on days 5–15.

CHEMOTHERAPY CONCURRENT WITH PBT

After the completion of TPS, patients received PBT concurrent with cisplatin, which was administered at 20 mg/m² daily for 4 days. The treatment was repeated every 3 weeks with a maximum of three treatment cycles. The total dose of PBT was 65 cobalt Gray equivalents (GyE) for 4–5 fractions per week in 2.5 GyE once-daily fractions.

PBT planning was performed using a three-dimensional computed tomography (CT) planning system. In this system, the proton beam was generated using a Cyclotron C235 with an energy of 235 MeV at the exit. Relative biologic effectiveness was defined as 1.1, based on our preclinical experiments (16). Dose distribution was optimized using the spread-out Bragg peak method and obtained using a broad-beam algorithm.

Gross tumor volume (GTV) was determined by examination using CT, magnetic resonance imaging (MRI) and/or positron emission tomography-CT. Clinical target volume (CTV) was defined as the GTV plus a 5 mm margin and the sinuses adjacent to the GTV. In cases of tumor invasion into the brain, the area of T2 prolongation on MRI was also included in the CTV. Planning target volume (PTV) was basically defined as the CTV plus a 3 mm margin, but was finely adjusted where necessary in consideration of organs at risk. Beam energies and spread-out Bragg peaks were fine-tuned such that the PTV was minimally covered by a 90% isodose volume of the prescribed dosage. The irradiated dose was minimized by the delivery of the proton beam with two or three beam arrangements.

Elected nodal irradiation was not planned because of the low incidence of lymph node metastases in these diseases.
EVALUATIONS

Pretreatment evaluation consisted of complete history and physical examinations, complete blood counts, liver function tests, chest X-rays and ECGs. All patients were imaged with CT and MRI scans of the head and neck. Bone scans and CT scans of the abdomen or chest were performed when clinically indicated. Treatment responses were assessed radiographically according to RECIST 1.0 criteria after the third cycle of chemotherapy and on the completion of chemoradiotherapy. The National Cancer Institute Common Toxicity Criteria (version 3.0) was used to describe chemotherapy- and chemoradiation-related toxicities.

STATISTICAL METHODS

The follow-up time for each patient was calculated as the time from the start of treatment to 31 March 2012. A survival curve was estimated using the Kaplan–Meier method. Safety and efficacy analyses were both conducted on an intention-to-treat population, defined as all patients enrolled in the study who received at least one dose of chemotherapy. Progression-free survival (PFS) was calculated from the date of the first administration of chemotherapy to the first documentation of disease progression, subsequent therapy or death. OS was determined from the date of the first administration of chemotherapy to the date of death or the last confirmation of survival. Statistical data were obtained using the SPSS software package (SPSS 11.0 Inc. Chicago, IL, USA).

RESULTS

PATIENT CHARACTERISTICS

The clinical and disease characteristics of the 13 patients with histologically proven tumors examined in this retrospective analysis are summarized in Table 1. The median patient age was 47 years (range, 28–60 years). The primary tumor sites involved the nasal cavity (9 of 13) and ethmoid sinus (4 of 13). The leading histology was olfactory neuroblastoma. No patients had clinical or pathologic evidence of neck disease at the time of initial treatment.

Nine patients (69%) completed the three cycles of planned IC. Three patients who were refractory to IC did not receive the third cycle of IC, while one patient received only one cycle due to disease progression. Ten patients received PBT concurrent with cisplatin and two patients received PBT alone, while the patient who experienced disease progression during IC received palliative radiotherapy.

ADVERSE EVENTS

The acute toxicities experienced during the TPS treatment are listed in Table 2. Although 10 patients (76.9%) experienced Grade 3 or 4 neutropenia and 3 patients (23.0%) experienced Grade 3 nausea, toxicity was as expected and manageable.

Acute toxicity scores of chemoradiotherapy are summarized in Table 3. Two patients (16.6%) experienced Grade 3 mucositis, which developed on the hard palate and to a lesser degree on the cheek and pharynx. Interference with
nutrition was minor, and no patients required a feeding tube. No brain damage or blindness was recorded. In addition, late toxicities were not observed at the time of March 2012.

**TREATMENT OUTCOMES**

Efficacy data for the TPS therapy are listed in Table 4. All patients enrolled in the present study were assessable for a response to TPS. Objective response rate (ORR) was documented in five patients (38.4%), including one patient with complete response (CR) and four with partial responses (PRs) after the IC of TPS (Figs 1 and 2). After the completion of chemoradiotherapy, ORR was documented in 12 patients (92.3%), including 11 with CR and 1 with PR. Each ORR to TPS according to the histology was 14.2% for patients with olfactory neuroblastoma, 33.3% for patients with squamous cell carcinoma and 100% for patients with others.

The median follow-up time was 56.5 months (range, 0.6–63.5 months), and the 5-year PFS and OS were 33.8 and 75.5%, respectively. Eight of the 13 patients were alive at the time of this report with no evidence of disease, while 2 patients were alive with disease. Two patients died due to local disease progression and one died as a result of distant metastasis.

Local relapse developed in three patients. The median time to local relapse was 14.4 months (range, 0.3–25.1 months). Relapses occurred within the irradiated region in two patients and on the margin of the irradiated region in one patient. Of the three patients with local relapses, two subsequently died of their disease, while one patient is presently alive with disease and continue to receive chemotherapy. Regional relapse developed in four patients; two of

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**Table 3.** Toxicities experienced during proton beam therapy

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>No. of patients (n = 12)</th>
<th>Percent Grade 3–4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td><strong>Hematological toxicity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukopenia</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td><strong>Non-hematological toxicity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucositis</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Anorexia</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Nausea</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Vomiting</td>
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<td>0</td>
</tr>
<tr>
<td>Infection</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

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**Table 4.** Treatment outcomes

<table>
<thead>
<tr>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
<th>RR (%)</th>
<th>95% Cl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction chemotherapy (n = 13)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>4</td>
<td>7</td>
<td>1</td>
<td>38.4</td>
<td>17.7–64.4</td>
</tr>
<tr>
<td>IC → PBT with cisplatin* or palliative RT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>92.3</td>
<td>66.6–98.6</td>
</tr>
</tbody>
</table>

CR, complete response; PR, partial response; PD, progression disease; RR, response rate; SD, stable disease.

*Two patients did not receive cisplatin due to refractory disease following TPS.

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**Figure 1.** Coronal magnetic resonance imaging (MRI) of a patient with a T4b squamous cell carcinoma in the nasal cavity, with invasion of the orbit and intracranial extension.

**Figure 2.** The MRI was repeated after three cycles of docetaxel, cisplatin and S-1, demonstrating a complete response.
these patients are presently alive with disease, while two patients who underwent elective neck dissection are alive with no relapse. Finally, one patient developed distant metastasis to meninges 9.1 months after the start of treatment and was dead with disease.

DISCUSSION

In the present retrospective study, we evaluated the efficacy of IC using TPS followed by PBT concurrent with cisplatin. Of the 10 patients who received PBT concurrent with cisplatin, 9 patients (90%) achieved CR, and the 5-year OS rate was 77.7%, with no brain damage or blindness recorded. Our study suggests that IC with TPS followed by PBT concurrent with cisplatin is well tolerated and displays reducing complication and promising antitumor activity.

The efficacy of chemotherapy for nasal and sinonasal malignancies is unclear (5), as it is generally used for palliative treatment of advanced or recurrent disease. However, favorable responses obtained with various chemotherapeutic regimens have prompted several institutions to modify standard therapeutic approaches in an attempt to improve treatment outcomes. Recently, chemotherapy has been evaluated as part of multimodality therapy delivered in either induction or concomitant settings (17,18). For example, Licitra et al. (17) reported the retrospective analysis of 49 patients with resectable sinonasal cancer who were treated with IC (cisplatin, fluorouracil and leucovorin) followed by surgery and post-operative radiotherapy. The objective response to IC and 3-year OS were 43 and 69%, respectively, suggesting that IC may play a role in surgery-sparing treatment approaches. In a similar study, Lee et al. (18) reported that a subgroup of 16 patients with Stage III or IV sinonasal carcinoma who received IC consisting of three cycles of cisplatin and fluorouracil achieved an 87% clinical response, indicating that IC could be an avenue for further improving the suboptimal results often encountered with reductions in tumors in close proximity with important structures. In the present retrospective study, after the completion of TPS, the overall response rate was 38.4% (5 of 13), with one patient achieving CR and four patients achieving PR. Neutropenia was the most common Grade 3 and 4 hematological toxicity (76.9%), while the most frequently observed non-hematological toxicity was nausea (23.0%). IC of TPS was well tolerated, feasible and showed good antitumor activity, which enabled the reduction in large tumor masses without severe toxicity.

Although squamous cell carcinoma is the most frequent pathology of HNC, olfactory neuroblastoma was most often observed in the present study. We speculate that the dominance of olfactory neuroblastoma among patients was due to referrals from institutions in the surrounding area with limited experience treating this type of carcinoma. Rosenthal et al. (19) reported that patients with olfactory neuroblastoma had excellent local and distant control rates with local therapy alone, but found higher rates of systemic failure for patients with neuroendocrine carcinoma, undifferentiated sinonasal carcinoma and small cell carcinoma. Although data concerning the response of nasal and sinonasal malignancies to IC are limited, several authors have reported the effectiveness of chemotherapy in the treatment of olfactory neuroblastoma, squamous cell carcinoma, undifferentiated carcinoma and adenocarcinoma. In the present study, about half of the patients had olfactory neuroblastoma, and the response rate after the completion of IC followed by PBT concurrent with cisplatin was high. This further emphasizes the need for accurate pathologic diagnosis of nasal and sinonasal malignancies, which may allow the use of separate IC as dictated by the histological analyses.

PBT approaches that would allow decreased irradiation doses to the surrounding critical organs while simultaneously delivering curative high-dose irradiation doses to tumors is critical for minimizing severe complications (5–7). Improvements of local control rates in treatment plans with lower doses to critical organs have been demonstrated when proton plans have been compared with photon plans in patients with nasal and sinonasal malignancies (13–15). Weber et al. (20) examined the long-term toxicity in patients with advanced sinonasal malignancies treated with proton/photon accelerated fractionated radiation and found that at a median dose of 69.6 GyE, 5.6% of the patients developed Grade 3 late visual/ocular toxicity, and no Grade 4–5 late visual/ocular toxicity, vascular glaucoma, retinal detachment or optic neuropathy were observed. Our group previously examined the clinical outcomes of 39 patients with unresectable malignancies treated with PBT at our institution between 1999 and 2006 and demonstrated that most patients experienced Grade 1–2 dermatitis in the acute phase, and 5 patients (12.8%) experienced Grade 3 or greater were observed (12). In the present study, 12 patients received PBT and no brain damage or blindness was recorded. When radiation is combined with concurrent chemotherapy, the acute and long-term side effects are occasionally more pronounced, and greater care and attention to the dose to normal surrounding organs is required for preventing complications. In the present study, 10 patients received PBT concurrent with cisplatin and no brain damage or blindness was recorded, suggesting that IC led to reduced tumor size and PBT could allow the delivery of tumoricidal doses with minimal complications.

Several limitations of the study warrant mention. First, this study includes the inherent limitations of a retrospective study. Second, only a small number of patients with biased histological types of cancer were examined. Here, sufficient doses of chemoradiotherapy without severe complications were achieved using IC and PBT; however, we cannot make definitive conclusions regarding the safety or side effect because of these limitations. Although it is difficult to conduct a prospective study as nasal and sinonasal malignancies are rare, additional patients are needed to confirm these results.
In conclusion, our retrospective analysis revealed that IC with TPS followed by PBT concurrent with cisplatin was well tolerated and effective in patients with locoregionally advanced malignancies of the nasal cavity and paranasal sinuses. This treatment approach demonstrated promising activity and minimal toxicity to warrant Phase II testing and may represent a suitable substitute for chemoradiotherapy alone for patients with T4b nasal and sinonasal malignancies.

Conflict of interest statement
None declared.

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