Nasopharyngeal Carcinoma in Children and Adolescents: Single Institution Study

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Background: Nasopharyngeal carcinoma (NPC) is very rare in children and adolescents. The aim of this study was to evaluate clinical characteristics and treatment outcomes of pediatric NPC.

Methods: Medical records of 9 patients treated for NPC at the Seoul National University Children’s Hospital between 1988 and 2012 were analyzed retrospectively.

Results: The median age at diagnosis was 11 years (range, 9–13 years). One patient had stage II disease, 3 had stage III disease, and 5 had stage IV disease. The histologic subtypes were undifferentiated carcinoma and squamous cell carcinoma in 7 and 2 patients, respectively. All patients were initially treated with cisplatin (100 mg/m² intravenous [IV] every 4 weeks for 4–6 months), bleomycin (15 unit/m² IV every 1 week×7), and fluorouracil (1,000 mg/m² IV every 4 weeks for 1 year). Eight patients received radiotherapy with doses of 45–59.4 Gy at the primary site and neck nodes. Seven patients (77.8%) achieved complete remission, 1 (11.1%) achieved partial remission, and 1 (11.1%) showed disease progression. Six patients developed fluorouracil-related neurotoxicity; the regimen was changed to cisplatin, epirubicin, and bleomycin in five of the 6 patients. One patient died of progressive disease without responding to treatment. Treatment-related mortality occurred in 1 patient owing to septic shock. Secondary osteosarcoma developed in 1 patient 6 years after treatment. The overall survival was 77.8%, with a median follow-up of 40.8 months (range, 4.5–287.6 months).

Conclusion: Children and adolescents with advanced NPC treated with combined chemotherapy and radiotherapy have a good survival rate.

Key Words: Nasopharyngeal neoplasms, Pediatrics, Chemoradiotherapy, Korea
Introduction

Nasopharyngeal carcinoma (NPC) is a very rare malignancy in children and adolescents. The incidence of NPC of the age range 1-19 years in Korea was as follows: the total number of cases was 58, and age standardized rate was 0.4 per million between 1999 and 2007 [1]. The World Health Organization (WHO) classification categorizes NPC into the following groups: keratinizing squamous cell carcinoma (type I), non-keratinizing squamous carcinoma (type II), and undifferentiated carcinoma (type III). Type II and III are well known to be related to latent Epstein-Barr virus (EBV) infection [2,3]. Undifferentiated carcinoma, which is associated with advanced locoregional disease and high incidence of distant metastasis, is the most common type of NPC in pediatric patients [4].

Treatment of adult NPC has evolved over the past two decades. Radiotherapy (RT) is usually successful in controlling early stage NPC, but survival rates decrease in patients with advanced locoregional disease. Recently, various combinations of concurrent, neo-adjuvant, and adjuvant chemotherapy were evaluated [5]. However, there are no definite optimal treatment strategies for pediatric patients with NPC owing to the rarity of this cancer.

Single institution data of pediatric patients with advanced stage NPC treated with RT and chemotherapy are presented. The results expand our understanding of the clinical characteristics, treatment outcomes, and toxicities in pediatric NPC.

Materials and Methods

1) Patients and study design

The medical records of newly diagnosed NPC patients treated at the Seoul National University Children’s Hospital between 1988 and 2012 were reviewed. The study included 9 patients (6 boys and 3 girls), with a median age of 11 years at diagnosis (range, 9-13 years). The histologic type was categorized based on the WHO classification. Clinical stage was determined according to the TNM staging system given in the 7th edition of American Joint Committee of

Pediatric Nasopharyngeal Carcinoma

Cancer and updated in 2010. Pathology was confirmed via nasopharyngeal biopsy. Epstein-Barr encoded RNA (EBER) in situ hybridization (ISH) was performed to evaluate latent EBV infection at the time of diagnosis. Staging evaluations included head and neck computed tomography (CT) or magnetic resonance imaging (MRI) to assess locoregional disease status, as well as chest and abdominal CT, bone scintigraphy, and bone marrow examination to assess distant metastasis.

2) Radiation therapy

RT was initiated at weeks 16-20 of the treatment schedule, and it was administered concurrently with chemotherapy. Eight patients (88.9%) received RT with a median dose of 53 (range, 45-59.4 Gy) at the primary site and neck nodes. Seven of the 8 patients received curative RT, and 1 patient received palliative RT. Seven patients received intensity-modulated RT, and one patient received 3-dimensional conformal RT.

3) Chemotherapy

All patients were administered first-line chemotherapy comprising cisplatin, bleomycin, and fluorouracil (5-FU). Cisplatin was intravenously (IV) administered at a dose of 100 mg/m² IV every 4 weeks for 4-6 months, bleomycin at a dose of 15 unit/m² IV every 1 week×7, and 5-FU at a dose of 1,000 mg/m² IV for 5 days every 4 weeks. The total duration of chemotherapy was 52 weeks (Fig. 1).

Dose modifications were based on toxic effects during chemotherapy, such as severe mucositis or febrile neutropenia. If the patient was suspected to have 5-FU-related neurotoxicity, they were considered to switch to the second-line regimen or reduce the dose of 5-FU. The second-line regimen consisted of cisplatin, epirubicin (60 mg/m² IV every 4 weeks), and bleomycin (15 mg/m² IV every 4 weeks). Cisplatin was not administered after patients received RT. Three of the 9 patients finished the 52-week schedule, and 5 patients who developed neurotoxicity were switched to the second-line regimen after 2-5 cycles of first-line chemotherapy.
4) Response and toxicity evaluation

Response was evaluated at the following time points in the treatment protocol: after the third cycle of chemotherapy (neoadjuvant chemotherapy), after concurrent chemoradiotherapy (CCRT), and after completion of treatment. Toxicities were evaluated according to the Common Terminology Criteria for Adverse Events v4.0.

5) Statistical analysis

The overall survival (OS) was calculated from the date of diagnosis to death or the date of last follow-up. The event-free survival (EFS) was calculated from the date of diagnosis to the date of the event or the date of last follow-up if the patient did not have events. Events were defined as death owing to disease progression, relapse, secondary malignancy, or treatment-related mortality (TRM). Kaplan-Meier analysis was used to estimate the OS and EFS.

6) Ethics statement

This study was approved by the institutional review boards of the Seoul National University Hospital, Seoul, Korea (IRB number: 1407-008-591). Informed consent was waived by the board.

Results

1) Baseline characteristics

Seven patients had type III cancer, and 2 patients had type I. Five of the 9 patients had stage IV disease, 3 had stage III disease, and 1 had stage II disease. No patients had evidence of distant metastasis (M0). The first presenting symptoms were hearing problems including tinnitus and otalgia (66.7%), neck mass (66.7%), headache (44.4%), epistaxis (33.3%), fatigue (22.2%), and diplopia (11.1%). EBER ISH of nasopharyngeal biopsy tissue conducted in 5 patients was positive. The remaining 4 patients were not evaluated for the EBV status (Table 1).

2) Response to treatment (Overall survival and Event free survival)

After 3 cycles of chemotherapy, 5 of the 9 patients had a complete response (CR) and 3 patients experienced a partial response (PR). One patient discontinued treatment temporarily owing to encephalomyelitis after 2 cycles of chemotherapy and eventually died of disease progression despite palliative chemotherapy and RT. After completing CCRT, 2 of the 3 patients with a PR in the previous evaluation achieved a CR, and 1 patient died of septic shock during chemotherapy. Seven (77.8%) of the 9 patients are alive without regional recurrence or distant metastasis at the last follow-up, with a median follow-up duration of 40.8 months (range, 4.5-287.6 months) from the time of diagnosis. Causes of death were disease progression in 1 patient and sepsis in 1 patient (Table 1). The OS was 77.8%, and the EFS was 38.9% (Fig. 2).

3) Toxicity and treatment-related mortalities

The most common acute toxicities were oropharyngeal mucositis and febrile neutropenia for all patients. Treatment-related mortality was one. He died of sepsis due to Klebsiella pneumoniae. 5-FU-induced neurotoxicity was suspected in 6 patients. The symptoms were dysarthria,
### Table 1. Summary of the patients

<table>
<thead>
<tr>
<th>No.</th>
<th>Sex/ Age at diagnosis</th>
<th>Histologic type</th>
<th>TNM</th>
<th>Stage</th>
<th>EBER ISH(^a)</th>
<th>Chemotherapy regimen</th>
<th>RT(^b) Response to neoadjuvant chemotherapy</th>
<th>Response to CCRT(^c)</th>
<th>Event/Cause of death</th>
<th>Status</th>
<th>Follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M/9</td>
<td>Squamous cell carcinoma (type I)</td>
<td>T2N2M0</td>
<td>IVa</td>
<td>Not evaluated</td>
<td>CDDP+Bleo5FU(^d)×14</td>
<td>Yes CR(^e) CR</td>
<td>Secondary malignancy (osteosarcoma)</td>
<td>Alive</td>
<td>287.6</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>M/12</td>
<td>Undifferentiated carcinoma (type III)</td>
<td>T4N2M0</td>
<td>IVa</td>
<td>Not evaluated</td>
<td>CDDP+Bleo5FU(^d)×4</td>
<td>No PR(^f) Not available</td>
<td>TRM(^g) (septic shock)</td>
<td>Dead</td>
<td>4.5</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>F/12</td>
<td>Undifferentiated carcinoma (type III)</td>
<td>T1N2M0</td>
<td>III</td>
<td>+</td>
<td>CDDP+Bleo5FU(^d)×14</td>
<td>Yes CR CR</td>
<td>Alive</td>
<td>97.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>M/10</td>
<td>Undifferentiated carcinoma (type III)</td>
<td>T2N2M0</td>
<td>III</td>
<td>+</td>
<td>CDDP+Bleo5FU(^d)×14</td>
<td>Yes CR CR</td>
<td>Alive</td>
<td>86.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>M/13</td>
<td>Undifferentiated carcinoma (type III)</td>
<td>T2N1M0</td>
<td>II</td>
<td>+</td>
<td>CDDP+Bleo5FU(^d)×4+CDDP+Epirubicin(^h)×1+Bleo+Epirubicin(^h)×7</td>
<td>Yes PR CR</td>
<td>Alive</td>
<td>50.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>M/12</td>
<td>Undifferentiated carcinoma (type III)</td>
<td>T2N2M0</td>
<td>III</td>
<td>+</td>
<td>CDDP+Bleo5FU(^d)×5+Bleo+Epirubicin(^h)×9</td>
<td>Yes CR CR</td>
<td>Alive</td>
<td>40.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>F/8</td>
<td>Squamous cell carcinoma (type I)</td>
<td>T2N2M0</td>
<td>IVa</td>
<td>Not evaluated</td>
<td>CDDP+Bleo5FU(^d)×2+CDDP+Epirubicin(^h)×5</td>
<td>Yes Progression Not available</td>
<td>Died of disease</td>
<td>Dead</td>
<td>14.7</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>M/11</td>
<td>Undifferentiated carcinoma (type III)</td>
<td>T4N2M0</td>
<td>IVa</td>
<td>Not evaluated</td>
<td>CDDP+Bleo5FU(^d)×5+Bleo+Epirubicin(^h)×8</td>
<td>Yes CR CR</td>
<td>Alive</td>
<td>29.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>F/9</td>
<td>Undifferentiated carcinoma (type III)</td>
<td>T4N2M0</td>
<td>IVa</td>
<td>+</td>
<td>CDDP+Bleo5FU(^d)×3+CDDP+Epirubicin(^h)×1+Bleo+Epirubicin(^h)×8</td>
<td>Yes PR CR</td>
<td>Alive</td>
<td>39.2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)EBER ISH, Epstein Barr encoded RNA In situ hybridization; \(^b\)RT, radiotherapy; \(^c\)CCRT, concurrent chemoradiotherapy; \(^d\)CDDP+Bleo5FU, Cisplatin+Bleomycin+Fluorouracil; \(^e\)CR, complete response; \(^f\)PR, partial response; \(^g\)TRM, treatment related mortality; \(^h\)CDDP+Epirubicin, Cisplatin+Bleomycin+Epirubicin.
memory impairment, gait abnormality, decreased sensory and/or motor power, and decreased consciousness, with a median time of 3.6 months (range, 2.0-4.4 months) to develop neurotoxicity. Five of the 6 patients was changed to the second-line regimen, and one patient was reduced the dose of 5-FU by 50%. Neurotoxicity of 5 patients recovered after discontinuing or reducing 5-FU, but 1 patient who was in a coma, with extensive white matter alterations observed on brain MRI scans, did not improve despite methyl-prednisolone pulse therapy. Her disease progressed, and neurological recovery was not observed. One patient developed secondary osteosarcoma of the mandible 6 years after completion of treatment, but he is alive with no evidence of primary or secondary cancer.

Discussion

In accordance with previous reports, undifferentiated carcinoma comprising 77.8% of the cases was the most frequent histologic type of NPC observed in our study [6,7]. Downing et al, reported that more advanced diseases are more frequently seen in young patients (under 25 years) than in adults [8]. In our study, most patients (88.9%) had advanced stage disease (stage III or IV). EBER ISH was positive in all patients evaluated, all of whom had type III histology. On the basis of the positivity of EBER ISH, it is likely that type III NPC is associated with EBV infection, Although the high incidence of advanced stage NPC in pediatric patients could be explained by the high prevalence of type III histology, other factors may also contribute to this. The initial symptoms of NPC such as otalgia, cervical lymph node enlargement, and epistaxis may also be present in healthy children. Because the incidence of NPC is low, these initial symptoms may often be ignored.

It is well known that NPC is a radiosensitive cancer, but RT alone resulted in poor overall survival in pediatric patients with advanced NPC [9,10]. In recent years, chemoradiotherapy demonstrated a survival benefit compared with RT alone in several adult studies [11-14]. Bachouchi et al, reported therapeutic effects of three drug regimen consisting of cisplatin, bleomycin, and 5-FU with RT for metastatic and locoregional NPC [15]. Subsequently, they modified their combination, substituting epirubicin for 5-FU, and treatment results showed high complete response [16]. We applied these regimens with modifying the dose and duration of treatment. Compared with the GPOH-NPC-91 study, our regimen comprised much more cycles of chemotherapy, even though there was no significant difference of total treatment duration [17]. There were several trials with various combinations of chemotherapy and RT, but only our study used all 3 combinations of CCRT, neoadjuvant and adjuvant chemotherapy. Furthermore, researchers have not shown better outcomes by adding neoadjuvant or adjuvant chemotherapy than CCRT alone until now [18,19]. In our study, the overall response rates after neoadjuvant chemotherapy and after CCRT were 55.6% and

Fig. 2. Survival of patients with nasopharyngeal carcinoma. (A) Overall survival was 75.0%. (B) Event free survival was 37.5%.
77.8%, respectively. No patients experienced disease recurrence after completion of treatment, with a median follow-up duration of 40.8 months. Distant metastasis is the major cause of treatment failure in many studies, but the patients included in this study did not develop distant metastasis during the follow-up period. Our experiments showed that it may reduce distant metastasis to apply more cycles of chemotherapy than others.

Several studies have reported the association of RT dose and local tumor control [4,20]. However, patients who received high dose RT experienced significant morbidity. Hu et al. reported that RT doses >70 Gy may increase sensorineural hearing loss and growth hormone deficiency [6]. Lower radiation doses with chemotherapy were applied to pediatric patients owing to the late effects of RT. In a prospective study, Mertens et al. [17] demonstrated that combined chemotherapy allows the RT dose to be reduced to <60 Gy. We reduced the total RT dose to <60 Gy in all patients. Our data suggest that the combination of RT and chemotherapy could be effective to control advanced NPC and reduce RT-related late toxicities in pediatric patients.

Unfortunately, severe toxicities associated with chemotherapeutic agents occurred in 2 patients. In this study, toxicities were the main cause of treatment failure and death. However, most treatment complications were temporary and reversible. Cerebellar dysfunction and encephalopathy have been relatively well known as neurotoxicity of 5-FU, but peripheral neuropathy could also be associated with 5-FU therapy [21]. Whereas the most common neurotoxicity of cisplatin is peripheral neurotoxicity, and the onset of toxicity is delayed until a cumulative dose higher than 300 mg/m² [22]. Cerebellar dysfunction, encephalopathy or peripheral neuropathy was presented in 6 of the 9 patients. In this regard neurologic side effects of the patients may be induced by 5-FU rather than cisplatin, and we decided to discontinue or reduce 5-FU. Although 5-FU-related neurotoxicity was common, it resolved in all but 1 patient after discontinuing 5-FU. It seems that longer treatment duration did not affect the occurrence of neurotoxicity, because all neurologic side effects developed in early phase of total treatment. One case of secondary malignancy has been reported as a long-term complication, There has been no definite evidence of increasing toxicities by applying more cycles of chemotherapy until now, but further follow-up is needed.

Our study has several limitations. It is a retrospective study with a small sample size. However, there are limited studies of the outcomes in pediatric NPC patients in Korea after combined treatment. A positive point of this study is the application of a uniform treatment regimen for pediatric NPC patients.

Our data demonstrated good survival rates in pediatric NPC patients after treatment with a combination of systemic chemotherapy and RT. We expect that reduction of the RT dose combined with the addition of neoadjuvant and concomitant chemotherapy will aid long-term survival. To improve outcomes, new strategies to decrease toxicities are needed. Prospective randomized studies in pediatric groups will lead to treatments that are more effective.

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References


