Nasopharyngeal Carcinoma in Childhood and Adolescence

Concept and Preliminary Results of the Cooperative GPOH Study NPC-91

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BACKGROUND. The increasing use of chemotherapy has improved the prognosis of patients with nasopharyngeal carcinoma (NPC), and the authors demonstrated the beneficial effect of adjuvant interferon (IFN)-β in a previous pilot study of children with advanced stage NPC. The current multi-institutional, cooperative GPOH (Gesellschaft für Padiatrische Onkologie und Hämatologie) study NPC-91 was begun in 1992 to determine the efficacy of preradiation chemoradiotherapy and adjuvant IFN-β in the treatment of advanced stage NPC.

METHODS. Of a total of 22 patients, 21 had American Joint Committee on Cancer Stage III or IV disease, and 1 had Stage II disease. The median age was 12 years (range, 8–16 years). Twenty of 22 received 3 courses of preradiation chemotherapy consisting of methotrexate 120 mg/m² on Day 1, cisplatin 100 mg/m² on Day 1, and 5-fluorouracil 1000 mg/m² for five days as well as 6 doses of leucovorin 25 mg/m² every six hours beginning on Day 2. The Stage II patient received no chemotherapy, and chemotherapy was terminated for another during the first course. All patients had radiation therapy, stratified by stage. The cumulative dose to the primary sites was 59.4 gray (Gy), with single doses of 1.8 Gy. A total of 45 Gy was delivered to the neck area. Finally, all patients were treated with recombinant IFN-β (10⁵ U per kg of body weight) 3 times a week for 6 months.

RESULTS. The response rate was 91%. These patients stayed in first remission during a median follow-up of 32 months. With the exception of one reversible cardiotoxicity, moderate chemotherapy-related toxicity was observed.

CONCLUSIONS. In this study, patients with advanced stage NPC had a good prognosis with treatment consisting of neoadjuvant cisplatin and 5-fluorouracil, radiotherapy, and adjuvant IFN-β. It is particularly noteworthy that distant metastases did not develop. Cancer 1997;80:951–9. © 1997 American Cancer Society.

KEYWORDS: nasopharyngeal carcinoma, childhood, chemotherapy, radiation therapy, interferon-β.

Nasopharyngeal carcinomas (NPCs) are malignant tumors whose incidence varies widely depending on patients’ ages and geo-

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graphic and racial backgrounds. In certain areas of Africa, 10–20% of childhood malignancies are NPCs. In the U.S. and Europe, NPC is an uncommon tumor, comprising only 1–2% of pediatric malignancies. In Europe the incidence is only 0.2% of all malignancies, showing a bimodal age distribution with an early maximum age between 10 and 20 years and a second maximum age between 40 and 60 years. The high incidence of NPC in China indicates that genetic, virologic, and environmental factors may contribute to the development of NPC. NPC is one of the few malignant tumors in childhood that emerge from the epithelium. The detection of nuclear antigen associated with Epstein-Barr virus (EBNA) and viral DNA in nasopharyngeal carcinoma (NPC) have revealed that Epstein-Barr virus (EBV) can infect epithelial cells and is associated with their transformation. The detection of viral antigens, including EBNA, capsid antigen (VCA), and viral DNA in epithelial cells, shows that epithelial cells of the oropharynx are the sites of virus replication. Males are twice as likely as females to develop NPC. Children and adolescents with NPC usually present with advanced tumor stages, and prognosis with radiation therapy alone is poor. As has been noted in the literature, a benefit of survival after combined therapy has not been consistently demonstrated. Due to the poor prognosis of NPC patients, particularly those with advanced stages of disease, and due to the rarity of the disease, we designed the controlled multi-institutional trial NPC-91 for children and adolescents with NPC. This is the first report from this study, after a median follow-up of 32 months.

PATIENTS AND METHODS

Classification

Table 1 illustrates the grading of NPCs with a comparison between the Cologne modification of the World Health Organization (WHO) scheme by Krueger and Wustrow and the classical scheme. The Cologne scheme includes the degree of lymphoid infiltration. The undifferentiated NPC with lymphoid infiltration is equivalent to the lymphoepithelioma described by Schmincke in 1921. The tumor characterized by Regaud in the same year was a nonkeratinizing squamous cell carcinoma with lymphoid infiltration. The NPC observed in pediatric patients is exclusively undifferentiated and nonkeratinizing and therefore of Types IIb, IIIa, and IIIb of the Cologne (modified WHO) classification. These histologic variants are strongly associated with increased antibody titers against EBV antigens. Highly differentiated squamous cell carcinomas and nonkeratinizing carcinomas without lymphoidal stroma do not show any particular titer increase against the various EBV antigens. It is therefore doubtful that they have any pathogenetic relation to EBV infection.

The virus genome and its associated nuclear antigen (EBNA) can only be found in NPC tumor cells, not in other carcinoma cells or lymphoid cells. The immunoglobulin (Ig)A antibody against the VCA is specific to NPC, and elevated antibody titers are found at diagnosis. The titer also correlates with the tumor's response to therapy, and consistently high titers indicate a poor prognosis. A reincrease in titer, after therapy is completed, can be taken as an early indication of relapse, so this makes it suitable as a tumor marker.

TNM Staging

Tumor stage at diagnosis was determined with the TNM system of the American Joint Committee on Cancer. This is the reference used most often for staging NPC in young patients, and it is suitable for comparisons with other NPC treatment results. Figure 1 shows how our patients were categorized as either low risk or high risk in accordance with the published risk definition. The description of tumor spread by Ho (Fig. 2) places more emphasis on the localization of cervical lymph node metastases than tumor size. The literature states that enlarged cervical lymph nodes or lymph nodes that are palpable in the supraclavicular fossa are lymph node metastases, which result in a poor prognosis.

Treatment

Since 1992, 24 children and adolescents with advanced nasopharyngeal carcinoma (15 males and 9 females; ages 8–16 years; median age, 12 years) from 20 clinics have been treated and monitored as part of the NPC-91 study. Overall, 11 patients were in Stage III, 10 in Stage IV, and one in Stage II; two patients already had metastases at the time of diagnosis and were not eligible for the study. The surgical procedures for histologic diagnosis were limited to biopsy of the primary tumor or biopsy of a representative neck lymph node; in all instances the tumor type was undifferentiated carcinoma. The pathology slides of 8 patients (provided by Professor Harms, Institute for Pathology, University of Kiel) were available for review.

The tumors of the nasopharynx were evaluated by computed tomography (CT) or magnetic resonance imaging (MRI) at diagnosis and follow-up. All patients had a chest CT and a bone scan as part of their staging workup. The overall treatment schedule (Fig. 3) consisted of three courses of neoadjuvant chemotherapy, irradiation, and adjuvant interferon (IFN)-β treatment. All 21 of the previously untreated high risk patients received chemotherapy consisting of methotrex-
TABLE 1
Classification of Nasopharyngeal Carcinoma: Comparison of Different Schemes

<table>
<thead>
<tr>
<th>Classical scheme</th>
<th>WHO scheme (Cologne modification)</th>
<th>WHO scheme</th>
<th>Michaeu scheme</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCC, keratinizing</td>
<td>Type I</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCC, nonkeratinizing</td>
<td>Type IIa (NKC without lymphoid infiltration)</td>
<td>NKC</td>
<td>SCC</td>
</tr>
<tr>
<td>Transitional cell carcinoma</td>
<td>Type IIb (NKC with lymphoid infiltration)</td>
<td>NKC</td>
<td></td>
</tr>
<tr>
<td>Intermediary cell carcinoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphoepithelial carcinoma (Regaud type)</td>
<td>Type IIIa (undifferentiated carcinoma without lymphoid infiltration)</td>
<td>UC</td>
<td>UNCT</td>
</tr>
<tr>
<td>Undifferentiated (anaplastic) carcinoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clear cell carcinoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphoepithelial carcinoma (Schmincke type)</td>
<td>Type IIIb (undifferentiated carcinoma with lymphoid infiltration)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


*As modified by Krueger and Wernicke in 1983.*

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Stage I
- T1, N0, M0

Stage II
- T2, N0, M0

Stage III
- T3, N0, M0
- T1-3, N1, M0

Stage IV
- T4, any N, M0
- any T, N2 or N3, M0
- any T, any N, M1

FIGURE 1. American Joint Committee on Cancer staging for nasopharyngeal carcinoma and definitions of risk groups are shown.

FIGURE 2. N-regions of the neck are shown, according to nasopharyngeal carcinoma classification described by Ho in 1978.

1.8 Gy. The pituitary gland was excluded. A tumor boost irradiation of 14.4 Gy followed. In high risk patients, the supraclavicular region was also irradiated, receiving a dose of 45 Gy. The base of skull was included in the target. All primarily tumor-bearing areas were irradiated with an additional dose of 14.4 Gy, for a total dose of 59.4 Gy. The dose to the spinal cord was limited to 40 Gy. After completion of radiation therapy, all patients underwent 6 months of IFN-β.
treatment (with recombinant IFN-β from the CHO-β provided by Dr. Rentschler at Biotechnology GmbH, Laupheim, Germany), receiving a dose of $10^5$ U per kg of body weight 3 times per week. The IFN therapy was administered to all patients in accordance with the study protocol. The study was approved by the Ethics Committee of the University Rheinisch-Westfälische Technische Hochschule Aachen. Before the initiation of therapy, written informed consent was provided by the patients’ parents and also by the patients themselves if they were adolescents. Disease free survival was computed using the Kaplan-Meier product limit estimator, and statistical analysis was performed using cross-classification.

**RESULTS**

Twenty-two patients were enrolled in this study. In all eight available samples, EBV-encoded, nonpolyadenylated RNAs (EBERs) were detected by in situ hybridization. With immunohistochemical staining, latent membrane protein (LMP 1) was also found in these eight samples.

Twenty-one patients were treated with neoadjuvant chemotherapy in accordance with the study protocol. One Stage III patient received only one cycle of chemotherapy because of acute cardiotoxicity. Twenty of the 22 patients were in continuous first complete remission during an observation period of 5–62 months (median, 32 months). Event free survival was 91% at 62 months.

Two patients showed a poor response to chemo-
therapy; the first suffered a primary tumor progression under chemotherapy, and the other showed only a minor response. Both patients died in spite of radiation therapy because of tumor progression 5 and 9 months after diagnosis, respectively. All of the other 20 patients had a good clinical tumor response to preradiation chemotherapy (Fig. 5). After completion of radiation therapy, all patients achieved a complete clinical and radiologic remission.

Side Effects
WHO Grade 2 mucositis was observed in 19 patients, and Grade 3 was observed in 3 patients. Myelosuppression and/or nausea and vomiting were moderate and tolerable. Septicemia occurred in two patients. Nephrotoxicity was not observed. During a follow-up period of approximately 34 months, 70% of patients experienced mild-to-moderate xerostomia. No patient developed a neck atrophy, but the median follow-up time was too short for a final statement on late effects. One patient developed severe but reversible cardiotoxicity during the first cytostatic course. On the third day of 5-fluorouracil infusion, tachycardia and hypotension were observed, and the echocardiogram showed severe dilatation of the myocardium and severe reduction of the shortening fraction to 4%. However, after 2 days the cardiac function recovered, with a shortening fraction of 29%, as a result of treatment with catecholamines and diuretics. A continuation of chemotherapy was considered inadvisable in this patient's case. The patient was given radiation therapy followed by IFN-β at the dosage cited earlier in this article. He is currently in complete remission, and his cardiac parameters continue to be normal.

The side effects of IFN-β, such as fever, influenza-like symptoms, and very occasional headaches, were tolerable and manageable on an outpatient basis in all cases. The slight temperature increase to 38.5°C could be repressed by administration of paracetamol before the IFN-β infusion.

DISCUSSION
NPCs in children are largely undifferentiated and frequently diagnosed when the tumor is already in an advanced stage. Time from the onset of the NPC symptoms to the beginning of treatment varies, from a few months to half a year. Radiation therapy is an obligatory element in the treatment of NPC. A marked correlation exists between radiation dose and tumor response. With a radiation dose of >60 Gy, a relapse-free survival time of 5 years was achieved in 70% of patients with lower disease classifications (T1 and T2), compared with only 20% of patients whose disease was classified as T3 or T4. In a study by Quin et al., the high-risk patient group treated with irradiation of the primary tumor had a 35% rate of 5-year relapse-free survival with doses of 50–59 Gy and a rate of 54% with a dose of 70 Gy. The data also showed that 18.4% of patients who received more than 60 Gy developed radiation encephalopathy, and the incidence of encephalopathy increased with the dose delivered to the primary tumor. Other authors have reported endocrine abnormalities, impairment of growth, trismus, neck fibrosis, and otitis media in 15–50% of their patients. Data in the literature demonstrate that the incidence of long-term side effects of irradiation is very high in survivors of childhood NPC. Despite good local tumor control after high dose radiation therapy, many patients have distant metastases. A study by Sham et al. found a poor prognosis with radiation alone, due to the early appearance of metastases. Almost 57% of relapse patients in the high-risk group developed distant metastases. In Table 2, which shows the treatment results given by various authors, the proportion of local relapses and distant metastases and the time between diagnosis and the appearance of metastases are given. NPC metastases emerge in the first 2 years after diagnosis. In patients with advanced tumors (up to 80% of young patients), occult metastases are often present at diagnosis, so that, although the radiation sensitive primary tumor can generally be effectively controlled by local therapy, distant metastases can present independently. Therefore, systemic therapy for NPC is essential if the clinically nonapparent micrometastases are to be treated effectively.
Reports on chemotherapy for young NPC patients have been rare and controversial.26–32 Often there are case reports of young patients receiving various chemotherapeutic agents. Larger chemotherapy trials (involving monotherapy or combination chemotherapy) have been conducted with adult NPC patients. A randomized study by Rossi et al., in which 162 patients given adjuvant chemotherapy were compared with an observation group that did not receive maintenance therapy, revealed that the long term prognosis of those who received adjuvant chemotherapy was less favorable than that of those not treated.33

Jenkin et al. reported on 119 children and adolescents with NPC, including those classified favorably as T1 or T2, and demonstrated that the event free survival rate of 40% after 5 years was not influenced by adjuvant chemotherapy.34 In previous studies, adjuvant monochemo-therapy has not demonstrated any prognostic improvement. There are even signs that mild adjuvant chemotherapy given after radiation therapy may prove disadvantageous to the patient due to its drug-induced immunosuppression.

For the first time, Gasparini et al. obtained a good result, a 75% relapse free survival rate after 2 years, with preradiation chemotherapy.35 Pao et al. reported on 6 high risk patients who were successfully treated with methotrexate, 5-fluorouracil, and cisplatin both before and after radiation therapy.36 All 6 patients are currently in complete remission after a 3-year observation period. In a study by Martin and Shah involving 48 children and adolescents diagnosed with advanced stage NPC, 9 were given adjuvant chemotherapy.37 The survival rates were 63% and 54% at 5 and 10 years, respectively. In summary, these treatment results with pediatric NPCs show that chemotherapy has a very important place in NPC treatment. Among high risk patients, who make up the majority of NPC patients, chemotherapy based on cisplatin and 5-fluorouracil, if administered before local radiation therapy, can improve prognosis and in particular reduce the development of distant metastases.36,37 Douglass et al. obtained good results for young patients with NPC treated with 4 courses of preradiation chemotherapy. Only one patient developed metastases, in lung and bone marrow.38 However, in our study, two patients were unresponsive to chemotherapy and died of tumor progression. None of our patients developed distant metastases. In contrast to the treatment regime of Douglass et al., our patients received 3 instead of 4 cycles, and the radiation doses were lower for the primary site and the lymph node regions. The treatment results concerning event free survival, therapy complications, and long term damage caused by radiation therapy should also be matters of interest to pediatric oncologists. Although in our study the number of patients was small, the fact that no patient developed

<table>
<thead>
<tr>
<th>Study/Yr of publication</th>
<th>Age of patients (yrs)</th>
<th>DM at diagnosis</th>
<th>DM/No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nishiyama/1967</td>
<td>7–15</td>
<td>—</td>
<td>2/8</td>
</tr>
<tr>
<td>Snow/1975</td>
<td>9–15</td>
<td>—</td>
<td>1/4</td>
</tr>
<tr>
<td>Papavassiliou/1977</td>
<td>6–30</td>
<td>—</td>
<td>11/26</td>
</tr>
<tr>
<td>Deutsch/1978</td>
<td>11–17</td>
<td>—</td>
<td>5/7</td>
</tr>
<tr>
<td>Jenkin/1979</td>
<td>12–16</td>
<td>2</td>
<td>9/13</td>
</tr>
<tr>
<td>Jenkin/1981</td>
<td>&lt;30</td>
<td>3</td>
<td>35/66*</td>
</tr>
<tr>
<td>Fichler/1982</td>
<td>1–12</td>
<td>—</td>
<td>3/3</td>
</tr>
<tr>
<td>Lombardi/1982</td>
<td>&lt;15</td>
<td>2</td>
<td>12/27</td>
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<td>Naegle/1982</td>
<td>10–15</td>
<td>—</td>
<td>5/7</td>
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<td>Vita/1983</td>
<td>11–20</td>
<td>2</td>
<td>11/27</td>
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<tr>
<td>Sarraino/1985</td>
<td>7–15</td>
<td>—</td>
<td>12/21</td>
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<tr>
<td>Lobos-Sanahuja/1986</td>
<td>8–13</td>
<td>—</td>
<td>5/22</td>
</tr>
<tr>
<td>Gasparini/1988</td>
<td>8–15</td>
<td>—</td>
<td>4/12</td>
</tr>
<tr>
<td>Pao/1988</td>
<td>6–19</td>
<td>1</td>
<td>15/29</td>
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<tr>
<td>Ingersoll/1990</td>
<td>4–21</td>
<td>—</td>
<td>21/43</td>
</tr>
<tr>
<td>Bartiss/1993</td>
<td>&lt;25</td>
<td>—</td>
<td>30/40</td>
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<tr>
<td>Zaghloul/1993</td>
<td>&lt;18</td>
<td>—</td>
<td>15/17</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>200/383 (52%)</td>
</tr>
</tbody>
</table>

DM, distant metastases.
*Only high risk patients are included in this row.
distant metastases supports the necessity of systemic treatment.

In 1988, De-en et al. reported finding a suppressed immunologic response in NPC patients at diagnosis and even more after irradiation. The lymphocyte count was depressed after radiation therapy. T-cell immunity to EBV is considered to play an important role in the suppression proliferating EBV-infected B-cells and the outgrowth of NPC. Patients with EBV-positive NPC were found to have a profound impairment of tumor-infiltrating lymphocytes' defense against EBV. There was a correlation between low levels of lymphocytes and a higher incidence of recurrence or metastases. Cellular immunity returned to normal approximately 8 months after radiation therapy had been terminated. Other authors have also reported suppression of T-cell-mediated immunologic response in NPC patients during and after radiation therapy. CD4/CD8 ratios, interleukin (IL)-2 production, and IL-2 receptors were significantly depressed, and CD8-positive cells were elevated in peripheral blood lymphocytes (PBL) and in the tumors of NPC patients. The disturbed immunoregulation could explain the poor treatment results for those patients who received adjuvant chemotherapy, and it may also provide a clue to the effectiveness of immunostimulative IFN therapy. IFN-β exerts potent antitumor effects through a variety of mechanisms. They involve both the direct and indirect actions of IFN on tumor cells. The direct antitumor actions include antiproliferative effects, cytotoxic effects, and enhancement of cell surface antigen expression on tumor cells. The indirect antitumor actions of IFN include activation of macrophages/monocytes, activation of T cells, activation of natural killer (NK) cells, and modulation of antibody production. IFN-β inhibits suppressor T lymphocytes induced by the tumor and activates cytotoxic T lymphocytes and NK cells, in addition to having known antiproliferative effects. Numerous studies have been published on the antitumor effects of IFN-β, and it has been shown that IFN-β can be useful in immunotherapy for EBV-associated NPC. IFN-γ has no effect on NPC.

Table 3 gives a compilation of the results of various studies in which patients were treated with IFN-α and IFN-β for either advanced tumor stage or the occurrence of a relapse or metastasis. In patients who have already been treated with radiation therapy and/or chemotherapy and whose prognosis is definitely poor, IFN-α therapy can still lead to a response rate of 15–25%. Treuner et al. reported on the complete remission of a patient age 12 years who, after radiation therapy and chemotherapy, suffered a local relapse and attained complete remission solely through the administration of IFN. Four NPC patients with recurrent disease received IFN-β in doses of 0.1–0.5 × 10^6 U per kg of body weight daily, resulting in one 90% remission and one case of stable disease (Table 3). Due to the high risk of local relapse and distant metastases for patients with tumors in advanced stages, and because of previously known acceptable response rates of NPCs to IFN treatment, 7 young NPC patients from the high risk group were treated with adjuvant IFN-β 10^7 U per kg of body weight 3 times a week intravenously after completion of radiation therapy in our pilot study. Five patients are still in complete remission. Because of these results and because of the low level of side effects, adjuvant IFN therapy seems to be a promising element in the treatment of nasopharyngeal carcinoma.

NPC in childhood and adolescence demands the administration of chemotherapy prior to irradiation, because of the high incidence of early distant metastases and the possibility of the presence of micrometastases at the time of diagnosis. The results of treatment of recurrences and the positive experience gathered during the pilot treatment of 7 patients justify a therapy protocol based on neoadjuvant cisplatin, 5-fluorouracil, and adjuvant IFN-β.

In low risk patients, good local tumor control is achieved by radiation therapy. Doses of up to 60 Gy
to the primary tumor, 40–45 Gy to the neck area, and a boost for the affected lymph nodes may be considered sufficient for local treatment, even for high risk patients. In the event that a combination of chemotherapy and radiation therapy leads to a significant prognostic improvement in high risk patients, a reduction of the radiation dose or a change of modalities (e.g., to hyperfractionated irradiation) should be considered in the future.

The preliminary results of this study show that the prognosis of children and adolescents with NPC can be markedly improved with a combination therapy protocol. The proportion of local relapses, and particularly the tendency of tumors to metastasize, can be diminished. Our good results for young NPC patients encourage us to continue this form of treatment.

REFERENCES


