Preradiation Chemotherapy with Methotrexate, Cisplatin, 5-Fluorouracil, and Leucovorin for Pediatric Nasopharyngeal Carcinoma

Results of Pediatric Oncology Group (Now Children's Oncology Group) Study 9486

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BACKGROUND. Nasopharyngeal carcinoma (NPC) is rare in children, accounting for < 1% of all cases. Treatment most commonly includes radiotherapy but long-term side effects of such treatment can produce devastating cosmetic and functional sequelae in children. Chemotherapy may help to decrease the radiotherapy dose and limit the side effects of local therapies. However, little is known regarding the chemosensitivity of NPC tumors in pediatric patients.

METHODS. Patients with American Joint Committee on Cancer (AJCC) Stage I/II disease (Stratum 01) received irradiation only. Patients with AJCC Stage III/IV disease (Stratum 02) received 4 courses of preradiation chemotherapy comprising methotrexate (120 mg/m²) on Day 1, with cisplatin (100 mg/m²) 24 hours later, 5-fluorouracil 1000 mg/m² per day as a continuous infusion for 3 days, and leucovorin 25 mg/m² every 6 hours for 6 doses. Irradiation was given after chemotherapy and consisted of 50.4 gray (Gy) to the upper neck and 45.0 Gy to the lower neck, with a boost to the primary tumor and positive lymph nodes for a total dose of 61.2 Gy.

RESULTS. One patient was enrolled in Stratum 01 and 16 evaluable patients were enrolled in Stratum 02. The median age of the patients was 13 years and 65% of the patients were black. All patients tested had evidence of Epstein–Barr virus infection. Two-thirds of the patients developed Grade 3–4 mucositis during chemotherapy. The overall response rate to induction chemotherapy was 93.7%. The overall 4-year event-free and overall survival rates (± the standard error) were 77±12% and 75±12%, respectively.

CONCLUSIONS. The current study demonstrated that childhood NPC was sensitive to chemotherapy and that chemotherapy before irradiation was feasible. Future trials should investigate equivalent efficacy with a reduced radiotherapy dose.


KEYWORDS: radiotherapy, chemotherapy, nasopharyngeal carcinoma, pediatric patients.

Nasopharyngeal carcinoma (NPC) differs from other head and neck carcinomas by its very distinct histologic, epidemiologic, and biologic characteristics, which determine its clinical behavior and treatment approach. It is very rare in children (1% of all pediatric cancers). Only 1% of NPC occurs in patients < 19 years old.1,2 In the United States, childhood NPC is more prevalent among blacks and its geographic distribution favors southern states.3 Virtually all patients with childhood NPC have World Health Organization (WHO) type III histology and present with advanced-stage disease.3–14
NPC is very radiosensitive, and radiotherapy is the primary treatment modality. However, with radiotherapy alone, high doses (> 65 gray [Gy]) are usually required to ensure good locoregional control. In adults, disease control rates with radiotherapy are stage dependent, with survival rates > 75% for patients with localized disease and < 50% for those with advanced-stage disease. Unlike other head and neck carcinomas, NPC is very chemosensitive, and the chemotherapy may help to reduce tumor burden, improve local control, and eliminate systemic micrometastases. This approach is particularly important in children, in whom late somatic and endocrine effects to head and neck structures from radiotherapy can have disastrous consequences. Many chemotherapeutic agents have proven effective against NPC. Those with the best single-agent activity include methotrexate, bleomycin, 5-fluorouracil (5-FU), cisplatin, and carboptin. The response rates in studies of combination regimens ranged from 38% to 91%, with cisplatin-containing regimens showing a clear advantage over regimens without cisplatin.

Between 1990 and 1994, investigators at St. Jude Children’s Research Hospital developed the NPC-1 protocol for children with NPC. It included an induction phase with four courses of moderate-dose methotrexate, cisplatin, and continuous infusion 5-FU with leucovorin, followed by radiotherapy. The NPC-1 protocol subsequently was used in a collaborative unfunded study, and long-term disease remission was achieved in 21 of 22 patients. These encouraging results led to a proposed Phase II study in the Pediatric Oncology Group (POG) using the same regimen to further define the regimen’s efficacy. We report the results of the Phase II study.

### MATERIALS AND METHODS

#### Eligibility

Eligibility criteria included age < 22 years, new diagnosis (enrolled within 28 days of diagnosis), untreated histologically proven NPC (WHO types II and III, and undifferentiated carcinomas—not adenocarcinoma—of unknown etiology), disease measurable in 2 dimensions using computed tomography (CT) or magnetic resonance imaging (MRI) scans, and normal renal and hepatic functions, as defined by serum creatinine levels 2 × normal, and liver function tests < 3 normal. The American Joint Committee on Cancer (AJCC) staging system was used for the current study (Table 1). It should be noted that the AJCC staging system for NPC underwent significant changes in the subsequent version, released in 1997. The protocol was approved by the institutional review boards (IRB) of all the participating institutions, and written informed consent was obtained from all patients before the initiation of therapy.

### Pretreatment and Follow-up Evaluations

Pretreatment evaluation included a complete history and physical examination, a complete blood count, serum biochemistry tests (including evaluation of electrolyte levels and hepatic and renal function tests), serum Epstein–Barr virus (EBV) infection titers, an audiogram, CT or MRI scans of the head and neck region, a CT scan of the chest and abdomen, a bone scan, and a chest X-ray. Patients were referred for endocrine and dental evaluation before therapy. Patients receiving chemotherapy were assessed clinically with weekly examinations and laboratory evaluations. Tumor response was assessed by clinical examination after each course, and with appropriate imaging studies (e.g., CT or MRI scans of the head and neck region and CT scans and X-rays of the chest) after completion of prechemoradiotherapy and at the end of radiotherapy. Endocrine evaluations were recommended at 1–2-year intervals.

### TABLE 1

<table>
<thead>
<tr>
<th>Classification</th>
<th>Definition</th>
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</thead>
<tbody>
<tr>
<td>T1</td>
<td>Tumor confined to one subsite of the nasopharynx</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor invades more than one subsite of the nasopharynx</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor invades the oropharynx and/or nasal cavity</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor invades the skull and/or cranial nerves</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Single ipsilateral lymph node measuring ≤ 6 cm in greatest dimension</td>
</tr>
<tr>
<td>N2</td>
<td>Single ipsilateral lymph node measuring &gt; 3 cm but not &gt; 6 cm in greatest dimension; or multiple ipsilateral lymph nodes, none measuring &gt; 6 cm; or in bilateral or contralateral lymph nodes, none measuring &gt; 6 cm in greatest dimension</td>
</tr>
<tr>
<td>N2a</td>
<td>Metastasis in single ipsilateral lymph node measuring 3-6 cm in greatest dimension</td>
</tr>
<tr>
<td>N2b</td>
<td>Metastasis in multiple ipsilateral lymph nodes, none measuring &gt; 6 cm in greatest dimension</td>
</tr>
<tr>
<td>N2c</td>
<td>Metastasis in bilateral or contralateral lymph nodes, none measuring &gt; 6 cm in greatest dimension</td>
</tr>
<tr>
<td>N3</td>
<td>Massive ipsilateral lymph node(s), bilateral or contralateral lymph node(s)</td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
<tr>
<td>Stage I</td>
<td>T1N0M0</td>
</tr>
<tr>
<td>Stage II</td>
<td>T2N0M0</td>
</tr>
<tr>
<td>Stage III</td>
<td>T3N0M0</td>
</tr>
<tr>
<td>Stage IV</td>
<td>T4 (any N) N2-3 (any T) M1 (any T, any N)</td>
</tr>
</tbody>
</table>

**AJCC American Joint Committee on Cancer.**
Treatment Plan
The protocol included two treatment strata. Stratum 01 included patients with T1–T2N0M0 disease, and Stratum 02 included patients with T3–T4 and/or N1–N3, and/or M1 disease. Patients in Stratum 01 were treated with radiotherapy alone, whereas patients in Stratum 02 were treated with four courses of chemotherapy, followed by radiotherapy.

Chemotherapy
Chemotherapy consisted of 4 courses of chemotherapy at 3-week intervals. On Day 1 of each cycle, patients received methotrexate 120 mg/m² by intravenous bolus. On Day 2, patients received cisplatin hydration with 5% dextrose in 1/2 normal saline (D5 1/2 NS) 500 mL/m² with mannitol 10 g/m² over 2 hours. Cisplatin (100 mg/m²) was then administered intravenously over 6 hours in 1000 mL/m² of NS with mannitol 10 g/m². Twenty-four hours after methotrexate, patients received an intravenous bolus of leucovorin, 25 mg/m², every 6 hours for 6 doses. Immediately after the first dose of leucovorin, continuous infusion of 5-FU was started at 1000 mg/m² per day for 3 days. Chemotherapy toxicity was graded using the National Cancer Institute Common Toxicity Criteria system.

Before each course, patients were required to have an absolute neutrophil count ≥ 750 cells/mm³, a platelet count ≥ 100,000 cells/mm³, a serum creatinine level ≤ 1.5, and an alanine aminotransferase level ≤ 3 × normal. Chemotherapy was not initiated until these parameters were attained. For patients with severe (Grade 4) mucositis, the infusion time of 5-FU in subsequent courses was decreased by 12 hours (without reducing the drug concentration).

Radiotherapy
Equipment
For the initial wide fields, cobalt-60 gamma or accelerator X-ray beams with a nominal energy of ≥ 4 MV or ≥ 6 MV were used. Higher-energy photons were permitted for boosts, providing dose uniformity was met. Electron beams (5–15 MeV) could be used to treat the boost to the posterior cervical triangle and other superficial areas, providing the dose uniformity requirement was met.

Target volume and dose
The target volume was the pretreatment volume as defined by any combination of CT/MRI scans or nasopharyngeal examination. The usual treatment consisted of opposed lateral fields with anterior supraclavicular fields when required. The initial primary and upper neck target volume consisted of the pretreatment volume with a 2-cm margin. The target volume to the lower neck extended laterally to the mid point of the clavicles and inferiorly 1 cm below the lower edge of the clavicles. After 3960 cGy (22 fractions), the spinal cord was blocked out of the primary field, and treatment to the posterior neck was continued with bilateral posterior electron fields. After 5040 cGy (28 fractions), the primary tumor and involved lymph nodes were treated with coned-down fields to a total dose of 6120 cGy (except the posterior neck, which received 5580 cGy).

Response Criteria
Response was evaluated after four courses of chemotherapy and radiotherapy completion. A complete response (CR) was defined as no evidence of disease. A partial response (PR) was defined as a ≥ 50% decrease in the sum of the product of the maximum perpendicular dimensions of all measurable lesions, and no evidence of progression in any lesion or development of new lesions. A minor response was defined as a ≥ 25% to a < 50% decrease in the sum of the product of the maximum perpendicular dimensions of all measurable lesions, and no evidence of progression in any lesion or development of new lesions. No response or stable disease was defined as a < 25% increase in the sum of the product of the maximum perpendicular dimensions of all measurable lesions, and no evidence of progression in any lesion or development of new lesions. Progressive disease (PD) was defined as a ≥ 25% increase in the sum of the product of the maximum perpendicular dimensions of all measurable lesions and/or the appearance of new lesions.

Statistical Methods
The end point used to assess the study’s primary objective was the patient’s best response after four courses of therapy. A responder was defined as achieving a CR or PR. A 2-stage rule was used within Stratum 02 (T3 and/or T4N1–N3 and/or M1).

Stage 1
Of the first 14 evaluable patients, the therapy would be considered ineffective if ≤ 4 patients responded to chemotherapy; the protocol would continue to Stage 2 if 5–8 patients responded, with the accrual of 11 more evaluable patients; or it would be concluded that the therapy was effective if ≥ 9 patients responded. This rule would test the null hypothesis that the response rate was 30% against the alternative hypothesis that the response rate was 55% with 81% power and a type I error of 0.045.
Table 2
Characteristics of 17 Patients with NPC on POG Study 9486

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>13 (76)</td>
</tr>
<tr>
<td>Female</td>
<td>4 (24)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>5 (29)</td>
</tr>
<tr>
<td>Black</td>
<td>11 (65)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Stratum</td>
<td></td>
</tr>
<tr>
<td>01: T1–T2N0M0 (Stage II)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>02: T3–T4 and/or N1–N3 and/or M1</td>
<td>16 (94)</td>
</tr>
<tr>
<td>Stage III</td>
<td>1</td>
</tr>
<tr>
<td>Stage IV</td>
<td>13</td>
</tr>
<tr>
<td>Not available</td>
<td>2</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
</tr>
<tr>
<td>WHO type II</td>
<td>1 (6)</td>
</tr>
<tr>
<td>WHO type III</td>
<td>16 (94)</td>
</tr>
<tr>
<td>EBV serology</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>11 (65)</td>
</tr>
<tr>
<td>Not available</td>
<td>6 (35)</td>
</tr>
</tbody>
</table>

NPC: nasopharyngeal carcinoma; POG: Pediatric Oncology Group; WHO: World Health Organization; EBV: Epstein-Barr virus infection.

Stage 2

Of the 25 evaluable patients, the protocol would be considered ineffective if 5–11 patients responded, whereas the therapy would be considered effective if ≥ 12 patients responded.

The Fisher exact test was used to compare the proportion of patients enrolled by geographic location. Event-free (EFS) and overall survival (OS) rates were calculated using the Kaplan–Meier method and expressed as the rate ± the Peto standard error (SE).

For EFS, the time to event was calculated from the time of enrollment to the occurrence of the earliest disease recurrence, disease progression, secondary malignancy, or death. If no event occurred, then the ending time was considered the date of last patient contact. The OS time was calculated from enrollment to the death date or to last contact date if the patient did not die.

Results

Patient Characteristics

Of 18 patients enrolled, only 1 was in Stratum 01, so that Stratum 01 was closed eventually for lack of patient accrual. Of 17 patients in Stratum 02, 1 was ineligible because of a wrong diagnosis. Therefore, 16 Stratum 02 patients were analyzed for a response rate. Patient characteristics are depicted in Table 2. The median age at diagnosis was 13 years (range, 11–21 years). There was predominance of males (76%) and blacks (65%). Fifty-nine POG institutions had IRB approval for patient enrollment, although only 15 institutions enrolled ≥ 1 patient. In a count of patients by geographic location of the institution, 16 patients enrolled at institutions in the southeastern or southern-midwestern United States (Alabama, n = 1; Kansas, n = 1; Texas, n = 2; Oklahoma, n = 2; South Carolina, n = 4; North Carolina, n = 1; Virginia, n = 3; Florida, n = 2; Mississippi, n = 1), whereas only 2 patients enrolled at institutions located elsewhere (province of Ontario (Canada), n = 1; Wisconsin, n = 1). The geographic distribution of institutions with zero patients enrolled was 21 in the southeastern or southern-midwestern United States and 23 elsewhere. The proportion of patients at southeastern/southern-midwestern institutions was statistically and significantly greater than the proportion of patients enrolled elsewhere (P = 0.0023).

Eight patients had base-of-skull erosion, and cranial nerve deficits were documented in three patients. EBV serology was documented in 11 patients, and in all patients there was evidence of past EBV infection. In two patients, situ hybridization for EBV-encoded RNA was performed, and was positive in both.

Response Rate

The primary objective of the study was to estimate response to preradiation chemotherapy. The responses of 16 evaluable Stratum 02 patients were 5 CR (31.25%), 10 PR (62.5%), and 1 PD (6.25%), for an overall response rate of 93.75%. Evaluation by imaging after radiotherapy revealed 11 patients in CR (68.75%), 4 in PR (25%), and 1 patient who had PD (6.25%). The patient treated in Stratum 01 achieved a CR after radiotherapy only.

Event-Free and Overall Survival Rates

The 4-year EFS and OS rates ± SE were 77% ± 12% and 75% ± 12% (n = 17), respectively (Fig. 1). Due to the small sample size, the fewer patients at risk when the final OS rate is calculated (n = 11) compared with the number of patients at risk when the final EFS rates is calculated (n = 13), and the finding that all 4 patients who had events subsequently died, the OS rate was slightly less than the EFS rate (which was a rare circumstance). Although no disease progression or recurrence occurred > 13 months from enrollment, 2 subsequent deaths occurred as late as 3.3 and 3.7 years after registration, respectively.

Patterns of Disease Recurrence

One patient had progressive disease at primary and lymph node sites at the end of chemotherapy and radiotherapy. Of the three additional patients who
experienced disease recurrence, all had achieved a CR after radiotherapy. Disease recurrence in these 3 patients occurred a median of 12 months from enrollment (range, 6–13 months). All disease recurrences occurred in metastatic sites (bones in three patients and mediastinum in one patient) and no disease recurrences occurred in the primary or lymph node sites. The 3 patients with recurrent disease subsequently responded to salvage regimens, but died a median of 39 months from enrollment (range, 21–45 months).

Toxicity
Toxicity data during chemotherapy were reported for all 16 patients. As expected, most severe toxicities were myelosuppression and stomatitis. Eleven (69%) patients had Grade 3 or 4 neutropenia, although no patient had major infectious complications. Ten (63%) patients had Grade 3 or 4 stomatitis, and nutritional support during chemotherapy, with either gastric feedings or parenteral nutrition, was reported in 7 patients. Because of the Phase II nature of the study, data regarding late toxicities (e.g., hearing loss, xerostomia, and endocrine deficits) were not available for analysis.

DISCUSSION
Our results were comparable to those of the best adult series, and suggest that a regimen of induction chemotherapy followed by radiotherapy is feasible and can provide excellent antitumor effect in childhood NPC.

In children, given the rarity of this neoplasm, very few studies have explored treatment strategies. Most published studies used cisplatin and/or doxorubicin-based neoadjuvant and adjuvant chemotherapy.4-12 With this combined approach, the survival rates of patients with advanced-stage disease range from 60% to 70%. Our results confirmed preliminary data generated by the St. Jude NPC-1 protocol with a group of 21 patients who had advanced-stage nonkeratinizing NPC.25 In the NPC-1 protocol, patients received four courses of induction therapy with the same four-drug regimen. After chemotherapy, patients received a total irradiation dose of 60–74 Gy to the primary site. Involved regions received 60–70 Gy, and 4 patients received a brachytherapy boost to their primary sites. All achieved a CR. Twenty patients remained disease free with a median follow-up of 41 months. In the German GPOH NPC-91 study, Mertens et al.26 used the same 4-drug regimen in a group of 20 children with advanced-stage NPC. In their study, patients received three courses of induction chemotherapy followed by radiotherapy. Similar to our study, responses to chemotherapy were observed in 18 of 20 evaluable patients. Based on data that show a suppressed immunologic response in patients with NPC at diagnosis, and given the strong role of EBV infection in the pathogenesis of the disease, a noteworthy modification of the German NPC-91 protocol was the addition of interferon-beta (IFN-β) as maintenance therapy for 6 months after completing radiotherapy. In fact, responses to IFN-β as a single agent have been observed in 10–15% of patients with recurrent NPC.29,31 Using that approach, outcome was excellent, with an EFS rate at 62 months of 91%. The role of IFN-β in the treatment of NPC is being investigated by the same group.

Our results showed that NPC is a very chemosensitive neoplasm. The response rate to this induction regimen was 94%. However, despite chemosensitivity, the beneficial effect of chemotherapy in the treatment of NPC is still not clear. Multiple randomized32-35 and nonrandomized studies36 have investigated this issue. In these comparative studies, patients received two to three courses of induction chemotherapy with cisplatin-containing regimens.32-36 Some studies also explored adjuvant chemotherapy after radiotherapy.32 The response rates for patients treated with chemotherapy ranged from 79% to 94%.32,35,36 The disease-free survival rates in these studies ranged from 50% to 80%; However, no randomized studies demonstrated a significant benefit for patients who received chemotherapy.32-35

Recent studies that incorporated concomitant chemoradiotherapy have shown improved results in patients with advanced-stage disease. Cisplatin enhances radiotherapy toxicity by inhibiting repair of sublethal damage, reoxygenation, and recruitment of cells into a proliferative state, and by radiosensitizing hypoxic cells.37 The results of two nonran-
domized\textsuperscript{38-40} and two randomized studies\textsuperscript{41,42} were reported recently. Three of them used two\textsuperscript{36,39} or three\textsuperscript{41} cycles of cisplatin during radiotherapy, followed by adjuvant cisplatin and 5-FU. The North American Intergroup randomized study 0099 showed significant advantage with concomitant chemoradiotherapy.\textsuperscript{41} Many more patients achieved a CR after radiotherapy chemotherapy in the arm (49% vs. 36%), and fewer had local and distant disease recurrences (14.1% vs. 40.6% and 12.8% vs. 34.8%, respectively). Overall, the 3-year progression-free survival (PFS) and OS rates were better with chemoradiotherapy (69% vs. 24% and 78% vs. 47%, respectively). The results of Intergroup 0099 were confirmed by other nonrandomized studies.\textsuperscript{38,39}

The practicality of concurrent chemoradiotherapy followed by adjuvant chemotherapy as in Intergroup 0099 has been questioned because concomitant chemoradiotherapy may have more severe toxicity. Only 63% of patients in Intergroup 0099 received all 3 cycles of concurrent chemoradiotherapy, and the 3 additional adjuvant cycles were given to only 55% of patients.\textsuperscript{41} An alternative is chemotherapy before radiotherapy. Rischin et al.\textsuperscript{40} reported excellent results in a nonrandomized trial that used induction therapy with 3 cycles of epirubicin and cisplatin and 8-week continuous infusion 5-FU, followed by concurrent chemoradiotherapy using 2 courses of cisplatin. This regimen had acceptable toxicity. Patients received three induction cycles and two cycles of concurrent chemoradiotherapy. The 4-year PFS and OS rates were 81% and 90%, respectively. Therefore, regimens with preradiation chemotherapy may be advantageous over those with adjuvant therapy.

Although our results were comparable to the most effective regimens for advanced-stage NPC, there were some unfavorable aspects. The drug combination and administration sequence are disadvantageous compared with the simpler cisplatin/5-FU combination. The addition of methotrexate and leucovorin to the regimen is significantly more toxic to patients. Two-thirds of our patients had moderate to severe stomatitis and most required nutritional support. Mucositis severity was greater than expected before radiotherapy compared with other induction regimens.\textsuperscript{45} Rationale is strong for combining 5-FU with leucovorin in cancer therapy. Formation of the ternary complex of fluoro-deoxyuridine-monophosphate (FdUMP), thymidylate synthase, and folate coenzymes necessary for 5-FU activity may be limited by the availability of reduced folates in some cell lines and tumors.\textsuperscript{46} Leucovorin optimizes formation of this covalent complex in vitro.\textsuperscript{44} Therefore, many 5-FU-based regimens include leucovorin. Studies showed that the response rate in colorectal carcinoma was greater when 5-FU was supplemented by leucovorin.\textsuperscript{45,46}

However, the impact on overall outcome was not clear.\textsuperscript{46}

An important consideration in the design of childhood NPC therapy is late effects. When treating patients with NPC, high doses of radiotherapy are typical, regional lymph nodes in the entire head and neck area are irradiated, and the structures surrounding the nasopharynx and entire neck are included. Such high radiotherapy doses to children are associated with severe acute and long-term toxicities. Of particular concern are the long-term effects of xerostomia and the high incidence of hearing loss and neck fibrosis. Therefore, every effort must be made to minimize late complications and maintain good disease control. Induction chemotherapy appears to be beneficial, so lower radiotherapy doses may be possible. Our study and the German NPC-91 study show that dose reduction to 60 Gy to primary sites and to 45-50 Gy to the neck is possible in chemoresponsive patients. Neither series had local disease recurrences.\textsuperscript{29} Similar to these pediatric data, Rischin et al.\textsuperscript{40} had excellent local control with 60 Gy. It is uncertain whether a higher dose of radiotherapy would have converted the four patients with a PR and the one patient with PD to a CR. In the German study, children received 59.4 Gy, and 20 of 22 had achieved a CR. The two patients who had PD after induction therapy did not respond to radiotherapy.\textsuperscript{29} In the Intergroup study 0099, the CR rate was >50% using 70 Gy with or without concomitant chemotherapy.\textsuperscript{41} In the randomized trial performed in Hong Kong, patients received 66 Gy as the initial dose, but a boost was allowed for patients with less responsive tumors, and the CR rate was >97% in both arms.\textsuperscript{42}

Additional means to decrease acute and long-term toxicity include radioprotectants and imaging-based radiotherapy techniques. Amifostine is beneficial to patients receiving head and neck radiotherapy. Brizel et al.\textsuperscript{47} reported that adults with head and neck carcinoma who received radiotherapy were assigned randomly to receive amifostine (200 mg/m\textsuperscript{2}) daily before radiotherapy. Moderate to severe chronic xerostomia was significantly less prevalent with amifostine, and the saliva volume produced was significantly greater in patients given amifostine. Long-term outcome was similar between groups, demonstrating that amifostine does not influence antitumor efficacy. With imaging-based radiotherapy techniques, particularly intensity-modulated radiotherapy, intensity can be modulated so that the dose to the surrounding tissue is decreased significantly, but the dose to the tumor remains high. Single-institution studies recently showed that this technique is comparable to other radiotherapy modalities in NPC, with marked incidence and severity decreases of acute and long-term toxicities, particularly xerostomia.\textsuperscript{48} Imaging-
based radiotherapy planning and amifostine are important to xerostomia prevention in head and neck radiotherapy, and they should be considered when managing NPC in children.

Childhood NPC may not compare with adult NPC in Western countries. In the United States, most NPCs are the keratinizing type (WHO type I), whereas children have predominantly WHO types II and III. We found a predominance of black patients, and most of the patients came from southern states, an epidemiologic association that confirmed one earlier report. Also, patients who underwent EBV studies had evidence of past EBV infections. Together, these data suggest that in Western countries, childhood NPC, unlike adult NPC, may be similar to endemic NPC. In that regard, some evidence in recent years indicates that circulating EBV DNA may be a reliable prognostic indicator. EBV DNA levels are detected in most patients with nonkeratinizing NPC in endemic areas. Using real-time quantitative polymerase chain reaction with primers for the EBNA-1 and the BamHI-W regions, Lo et al. showed that EBV DNA was detectable in the plasma samples of 96% of patients with nonkeratinizing NPC, compared with only 7% of controls. More importantly, EBV DNA levels appeared to correlate with response, and they may predict disease recurrence, suggesting that it may independently indicate prognosis. Therefore, determination of the plasma EBV DNA level may be a useful marker for risk-adapted approaches, which is particularly important in children, because regimens attempting to decrease toxicity could be applied.

Prospective studies focused on the pathogenesis and treatment of childhood NPC are necessary. The continuing initiative in the Children's Oncology Group will explore the use of induction chemotherapy with cisplatin and 5-FU, followed by concurrent chemoradiotherapy, and has incorporated measurement of circulating EBV DNA levels at diagnosis and during therapy (ARAR 0331 study). We anticipate that children with NPC will have detectable circulating levels of EBV DNA, and that these levels will correlate with clinical events. Should the EBV DNA levels prove to indicate prognosis, risk-adapted therapies could be designed that would minimize treatment.

REFERENCES


