Original Article

A Prospective Protocol for Nasopharyngeal Carcinoma in Children and Adolescents

The Italian Rare Tumors in Pediatric Age (TREP) Project

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BACKGROUND: Nasopharyngeal carcinoma (NPC) is very rare in childhood. It differs from its adult counterpart in the prevalence of the nonkeratinizing, undifferentiated subtype and by an advanced clinical stage at onset and better chances of survival. The risk of long-term treatment-related toxicity also may be a more important issue in younger individuals. **METHODS:** A prospective chemoradiotherapy protocol for pediatric NPC was started in Italy in 2000 within the framework of the Rare Tumors in Pediatric Age (TREP) project. Three courses of cisplatin/5-fluorouracil induction chemotherapy were followed by radiotherapy (doses up to 65 grays) with concomitant cisplatin. **RESULTS:** Forty-six patients (ages 9-17 years) were considered eligible for the study over a 10-year period. The ratio of observed to expected cases based on epidemiological data was approximately 1 for both children and adolescents. All but 1 patient had lymph node involvement, and 5 patients had distant metastases. The rate of response to primary chemotherapy was 90%. The 5-year overall and progression-free survival rates were 80.9% and 79.3%, respectively (median follow-up, 62 months). The only statistically significant prognostic variable was the presence or absence of distant metastases. A 65% incidence of late sequelae was reported. **CONCLUSIONS:** This study demonstrates the feasibility and efficacy of a prospective protocol even for such rare tumors as pediatric NPC. The use of lower radiotherapy doses than those used in adults did not affect locoregional failure rates. Long-term follow-up will be needed to obtain more information on both survival and treatment sequelae. The next objective will be to establish broader, international prospective cooperation schemes. ***Cancer*** **2011;000:000–000.** © *2011 American Cancer Society.*

KEYWORDS: nasopharyngeal carcinoma, rare pediatric tumors, children and adolescents, Rare Tumors in Pediatric Age (TREP) project, chemotherapy, radiotherapy, sequelae.

INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a very rare disease in childhood. Its incidence varies widely in different regions, reflecting interactions between genetic and environmental factors, such as exposure to Epstein-Barr virus (EBV).[1] Italy is a low-incidence area: The annual incidence of NPC has been estimated at 0.73 per million children (ages 10-14 years) and at 1.08 per million adolescents (ages 15-17 years), with an incidence of nil among children aged <10 years.[2] Similar data emerged from a recently published series in the North American population-based Surveillance, Epidemiology, and End Results (SEER) database: From 1988 to 2006, 129 children/adolescents (ages 0-19 years) were registered, for an incidence of 0.5 per million person-years. Six thousand adult cases were collected in the SEER database during the same period.[3]

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We thank Ms. Elisa Mancini for data management.

DOI: 10.1002/cncr.26528, **Received:** June 23, 2011; **Revised:** August 2, 2011; **Accepted:** August 2, 2011, **Published online** in Wiley Online Library (wileyonlinelibrary.com)

The treatment for pediatric patients generally is extrapolated from guidelines tailored for adult patients, but children are usually excluded from adult clinical trials because of strict age cutoffs.[4] The development of prospective trials for children has been hindered by the rarity of the disease and accrual difficulties, even for multi-institutional collaborative trials. The North-American Pediatric Oncology Group (POG) study enrolled 17 patients from 15 different centers in the POG 9486 trial, which ran from 1996 to 1998.[5] The German Pediatric Oncology and Hematology Group (GPOH) trial included 59 patients from 1992 and 2003.[6] The need to establish cooperative prospective studies on children is of paramount importance in the light of evidence that NPC has certain distinctive characteristics when it occurs in children/adolescents as opposed to adults. The majority of tumors in young patients are of the nonkeratinizing, undifferentiated subtype (previously called type 3); children and adolescents are more likely to have advanced disease at onset (and lymph node metastases in particular), but they generally have a significantly better chance of survival.[3,7] Moreover, the risks of long-term, treatment-related toxicity (growth retardation, dental problems, life-long xerostomia, endocrine problems, ototoxicity) and of second malignancies (relating particularly to high-dose radiotherapy) may be more severe in younger individuals.[8-12] A recent report from the St. Jude Children's Research Hospital (Memphis, Tenn) reported a 15-year cumulative incidence of any morbidity of 84% (53% for hearing loss, 43% for hypothyroidism, and 14% for growth hormone deficiency), with a correlation between radiotherapy dosage and many of these sequelae. The risk of a second malignancy was 8.5%.[13]

The Rare Tumors in Pediatric Age (TREP) project—a national-scale, cooperative initiative launched in Italy in 2000 to improve the clinical management of very rare pediatric cancers and to conduct further basic research on these diseases[14]—consequently developed a prospective chemoradiotherapy protocol for pediatric NPC based on the prior single-institutional experience of the Italian National Cancer Institute in Milan[15] and on findings in the adult literature.[16,17] The treatment program consisted of a preradiation phase with induction chemotherapy in the form of cisplatin and 5-fluorouracil (5-FU) followed by radiotherapy with concomitant cisplatin. Lower doses of radiotherapy than in adult schemes were used with a view to limiting the severity of long-term toxicity. In this article, we present the results from the TREP NPC protocol.

MATERIALS AND METHODS

All patients aged <18 years with a diagnosis of NPC were registered centrally as of January 1, 2000 at the data center (Clinical Trials and Biostatistics Unit, Veneto Oncology Institute, Padova, Italy) and enrolled in the protocol. Specific printed forms (clinical findings, histopathology, diagnostic workup, therapy, follow-up) were used for data collection.

Study Objectives

The first objectives of the study were to create a nationwide cooperative network for the management of pediatric patients with NPC, to standardize their treatment for all Italian centers, and to improve the survival rates for these patients. Specific objectives were to assess: the feasibility of a treatment plan involving primary chemotherapy followed by radiotherapy with concomitant chemotherapy, the response to primary chemotherapy, and the acute and long-term sequelae related to the treatment.

Eligibility Criteria

Eligibility criteria included age ≤18 years; histologically proven, hitherto untreated NPC; measurable disease assessed on magnetic resonance imaging (MRI) scans; and normal renal and hepatic function. Written informed consent was obtained from all patients and/or their parents or guardians before starting the therapy. The availability of histologic specimens for central review was mandatory. The histologic diagnosis of NPC was based on morphology plus immunocytochemistry (cytokeratin expression) in all patients. In situ hybridization to detect EBV-encoded small RNA (EBER) in tumor cells was performed in more recent cases and, even more recently, NUT antibody (1:000 dilution; Cell Signaling Technology, Beverly, Mass; DAKO autostainer; Dako, Carpinteria, Calif) also was applied.

Pretreatment and Follow-Up Assessments

Pretreatment evaluation included a complete clinical history and physical examination, endoscopic examination of the nasopharynx, blood tests with serum titers of EBV infection, MRI scans with gadolinium contrast of the head and neck region, technetium bone scan, computed tomography (CT) or x-ray studies of the chest, CT or ultrasound studies of the abdomen, and an audiogram. Patients also underwent endocrine and dental assessment. From 2006 onward, positron emission tomography (PET) was included in the protocol as the sole staging

Table 1. The 5th Edition of the American Joint Committee on Cancer Staging System

Variable	Definition
Tumor classification	
TI	Tumor confined to the nasopharynx
T2	Tumor extends to soft tissue of nasopharynx and/or nasal fossa
T2a	Without parapharyngeal extension
T2b	With parapharyngeal extension
T3	Tumor invades bony structures and/or paranasal sinuses
T4	Tumor with intracranial extension and/or involvement of cranial nerves, infratemporal fossa, hypopharynx, or orbit
Lymph node status	
N0	No regional lymph node metastases
NI	Unilateral metastasis lymph node(s) measuring <6 cm in greatest dimension above the supraclavicular fossa
N2	Bilateral metastases in lymph node(s) measuring <6 cm in greatest dimension above the supraclavicular fossa
N3	Metastasis in a lymph node(s)
N3a	Metastasis >6 cm in greatest dimension:
N3b	Extension to the supraclavicular fossa.
Metastasis classification	
M0	No distant metastases
MI	Distant metastases
AJCC disease stage	
I	TIN0M0
IIA	T2aN0M0
IIB	TI-T2aN1M0
	T2bN0-N1M0
III	T1-T2N2M0
	T3N0-N2M0
IVA	T4N0-N2M0
IVB	TanyN3M0
IVC	TanyNanyM1

Abbreviations: AJCC, American Joint Committee on Cancer.

procedure (instead of bone scan, chest CT scan/x-ray, abdominal CT scan/ultrasound),[18] and an evaluation of EBV-DNA levels at diagnosis was added.[19] The fifth edition of the American Joint Committee on Cancer (AJCC) *AJCC Cancer Staging Manual*, which was released in 1997, was adopted in this study (Table 1).[20]

During primary chemotherapy, patients were assessed clinically with weekly examinations and laboratory tests (including renal function tests). An audiogram was suggested before each chemotherapy course. No standardized guidelines for dose modifications because of hearing loss or renal toxicity were included in the protocol.

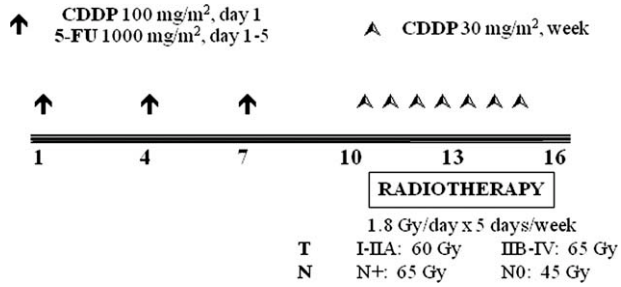

Figure 1. The treatment program for nasopharyngeal carcinoma in the Italian Rare Tumors in Pediatric Age project is illustrated. CDDP indicates cisplatin; 5-FU, 5-fluorouracil; T, tumor classification; N, lymph node status.

Tumor response was assessed by means of a clinical examination after each course; MRI scans with gadolinium contrast of the head and neck region and appropriate imaging studies in patients with metastatic disease were performed after completing the induction chemotherapy phase (before starting radiotherapy) and at the end of the course of radiotherapy. After 2006, EBV-DNA levels were evaluated after Cycle 1, before radiotherapy and 6 to 8 weeks after its completion.

Response to chemotherapy was evaluated after 3 cycles and was defined according to Response Evaluation Criteria in Solid Tumors.[21] During follow-up, MRI scans with gadolinium contrast of the head and neck region were obtained every 3 months during the first 2 years after completing the treatment and every 6 months thereafter. Endocrine assessment was recommended every 6 months.

Treatment Protocol

All patients received initial chemotherapy, consisting of cisplatin 100 mg/m^2 on day 1 followed by 5-FU 1000 mg/m^2 daily as a continuous infusion on days 1 through 5. This course was repeated 3 times, once every 3 weeks, before starting chemoradiotherapy (Fig. 1).

Before each cycle, patients had to have an absolute neutrophil count $\geq$1000 cells/mm^3, a platelet count $\geq$100 cells/mm^3, and a serum creatinine level $\leq$1.5 the upper normal limit; if not, then chemotherapy was delayed for 1 week. Chemotherapy toxicity was graded using the National Cancer Institute's Common Toxicity Criteria (version 2.0; National Cancer Institute, Bethesda, Md).

Three weeks after the third cycle, patients received radiotherapy concomitantly with cisplatin 30 mg/m^2 every week for a total of 7 weeks. The total cumulative dose of cisplatin was 510 mg/m^2.

The use of 3-dimensional, conformal radiotherapy was considered mandatory. Intensity-modulated radiotherapy (IMRT) was strongly suggested when available. Megavoltage (6-12 MV photon) radiotherapy was delivered once daily in single doses of 1.8 grays (Gy) to the primary tumor and regional lymph nodes. The gross tumor volume included the extent of disease in the primary lesion and cervical lymph nodes, as observed on MRI studies with gadolinium contrast (T1 and T2 sequences). The clinical target volume included the gross tumor volume and all sites of potential subclinical disease with 1-cm margins. An additional margin of 0.3 to 0.5 mm, depending on local policy, was added to define the planning target volume. The primary tumor received a total dose of 60 Gy for patients with stage I to IIA disease and 65 Gy for those with stage IIB, III, or IV disease. All involved lymph nodes received a total dose of 65 Gy, whereas uninvolved regional lymphoid areas were irradiated with a total dose of 45 Gy. Masticatory physiotherapy to prevent trismus and fluoride application to prevent caries were recommended during radiation treatment.

Expected Cases

The number of cases of NPC (in patients aged <18 years) expected to be diagnosed in Italy each year was calculated from the incidence data in the well established Italian network of population-based cancer registries, The Italian Tumor Registry Association (AIRTum) comprises 22 general registries and 3 specialist registries that cover 32.9% of the Italian resident population in the group ages 0 to 14 years and 26.9% of the population in the group ages 15 to 19 years. The number of patients actually enrolled in the TREP protocol (observed cases [O]) was compared with the expected number (E).[2]

Statistical Analysis

Progression-free survival (PFS) and overall survival (OS) were estimated according to the Kaplan-Meier method. Patients were evaluated from the date of diagnosis to the time of disease progression or relapse for PFS and until they died for OS. The time scale extended up to the latest follow-up if none of these events were observed.[22] In July 2011, the patient follow-up ranged from 12 to 133 months (median, 62 months).

RESULTS

From January 1, 2000 to December 31, 2009, 521 patients aged <18 years were registered prospectively in the TREP database by 36 Italian pediatric oncology and pediatric surgery units. NPC was the fifth most common tumor, with 48 patients registered by 12 different centers. Two patients registered in the TREP database subsequently received treatment at adult centers, and no data were available on their treatment modalities and outcome. Thus, 46 patients were included in the TREP protocol and formed the object of the current analysis.

The expected number of cases of NPC calculated on the basis of the AIRTum data was 3.8 per year (2 cases in the group ages 0-14 years and 1.8 cases in the group ages 15-17 years).[2] In the current series of 46 patients, 44 patients were born in Italy, although 5 of them had origins in Eastern Europe, 3 were from North Africa, and 1 was from India. No difference in geographic distribution across Italy emerged in our series (18 patients were from Southern regions, 8 were from central regions and 18 were from northern Italy). Two additional patients from Eastern Europe came to Italy for their treatment. Overall, 44 patients were Caucasian. The observed/expected (O/E) ratio, which was calculated for the 44 patients who were born in Italy, was approximately 1 for both children and adolescents. The patients ranged in age from 9 years to 17 years (median, 13 years): Twenty-seven patients were aged <15 years, and 19 patients were between ages 15 and 17 years. Twenty-nine patients were males, and 17 were females.

A histologic diagnosis was obtained by nasopharyngeal biopsy in 29 patients, by nasopharyngeal plus lymph node biopsy in 8 patients, and by lymph node biopsy alone in 9 patients. All patients were diagnosed with the nonkeratinizing, undifferentiated subtype, and cytokeratins were positive in all patients. EBER was positive and NUT antibody was negative in all 12 patients who were tested.

Table 2 provides the outcome of tumor staging: All but 1 patient had lymph node involvement, 5 patients had distant metastases at presentation (involving the bone in all patients, with a single metastasis in 4 patients each and multiple metastases in 1 patient). Eighty-seven percent of patients had advanced stages (AJCC stage III or greater).

Treatment and Outcome

All patients received treatment as required by the protocol; 16 patients received IMRT, and 30 patients received 3-dimensional conformal radiotherapy. Response to primary chemotherapy was reported as follows: Forty patients had a partial response, 4 patients had no response,

Table 2. Staging of the 46 Patients

Variable	No. of Patients (%)
Tumor classification	
T1	8 (17.4)
T2	12 (26.1)
T3	8 (17.4)
T4	18 (39.1)
Lymph node status	
N0	1 (2.2)
N1	11 (23.9)
N2	24 (52.2)
N3	10 (21.7)
Metastasis classification	
M0	41 (89.1)
M1	5 (10.9)
AJCC stage	
IIB	6 (13)
III	15 (32.6)
IVA	11 (23.9)
IVB	9 (19.60
IVC	5 (10.9)

Abbreviations: AJCC indicates American Joint Committee on Cancer.

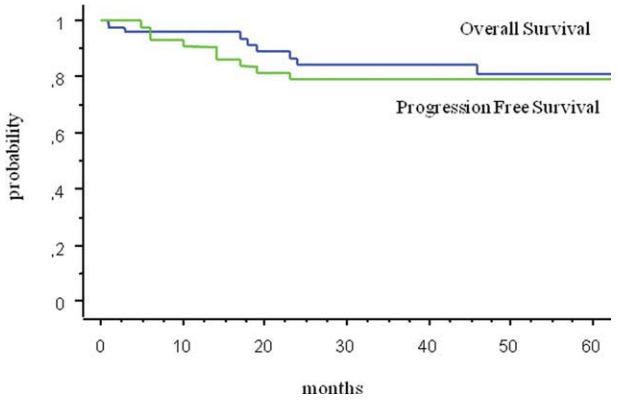

Figure 2. Kaplan-Meier estimates of overall survival and progression-free survival are shown for the whole series.

and 2 patients were not evaluable (early deaths). Overall, the rate of response to cisplatin/5-FU chemotherapy was 91%. Two early deaths were registered during induction chemotherapy: One patient died of respiratory failure because of pneumonia (potentially related to treatment toxicity), and 1 patient died of other causes (rupture of cerebral aneurysm and hemorrhage).

At the first evaluation at the end of the treatment program, 41 patients were in complete remission, and 3 patients (who had metastatic disease at the time of their diagnosis) had metastatic progression. In 6 patients who achieved tumor remission, the disease relapsed 10 to 23 months after diagnosis at distant metastatic sites in 5 patients and in a regional lymph node in 1 patient. Overall, 9 treatment failures were registered: Six patients died of their disease, 2 patients were still receiving second-line therapy at the time of this analysis, and 1 patient achieved a second remission with second-line chemotherapy (ifosfamide and doxorubicin) plus radiotherapy to a single site of bone metastasis.

Table 3. Five-Year Progression-Free Survival According to Clinical Variables: Univariate Analysis

Variable	No. of Patients	5-Year PFS, %	*P*
Whole series	46	79.3	
Sex			
Male	29	73.6	
Female	17	88.2	.2360
Age, y			
≤14	27	88	
≥15	19	67.4	.0821
Tumor classification			
T1-T3	28	74.1	
T4	18	87.8	.3152
Lymph node status			
N0-N1	12	83.3	
N2-N3	34	77.7	.7053
Metastasis classification			
M0	41	87	
M1	5	20	<.0001
AJCC stage			
II	6	100	
III	15	85.7	
IV	25	70	NE

Abbreviations: NE, not evaluable; PFS, progression-free survival.

For the whole series, the 5-year OS and PFS rates were 80.9% (standard error, 6.2%) and 79.3% (standard error, 6.2%), respectively (Fig. 2). On univariate analysis, the only statistically significant prognostic variable was the presence or absence of distant metastases (only 1 of the 5 patients with M1 disease was alive in first remission at the time of our analysis). Neither tumor (T) classification nor lymph node (N) status was correlated with survival rates. There was evidence of a (statistically insignificant) trend toward better survival in younger patients (Table 3).

Toxicity

One patient died of respiratory failure because of pneumonia (unassociated with neutropenia) after the first cycle of chemotherapy: Although it could not be demonstrated, this event may have been related to the treatment's

Table 4. Incidence of Late Sequelae in 26 Surviving Patients With a Follow-Up of at Least 24 Months[a]

Sequelae	Percentage of Patients
Any morbidity	65
Hypothyroidism	54
Xerostomia	50
Neck fibrosis	38
Trismus	35
Hearing loss	27
GH deficiency	23
Caries	23
Chronic/recurrent sinusitis and otitis	19
Pulmonary fibrosis	15
Recurrent pneumothorax	7
LH/FSH deficiency	4
Renal dysfunction	4

Abbreviations: FSH, follicle-stimulating hormone; GH, growth hormone; LH, luteinizing hormone.
[a] Data were unavailable for 4 patients.

toxicity. No major acute toxicities were registered among the other patients. No grade 3/4 hematologic toxicity was reported. No granulocyte-colony–stimulating factors were administered, and none of the patients received blood transfusions. Similarly, no grade 3/4 renal toxicity was reported (ie, evaluated with serum concentrations of creatinine, sodium, potassium, magnesium, calcium, phosphate, or bicarbonates and urine examinations for pH and glucose and protein loss), and no hepatic or neurologic toxicities were observed. Grade 2/3 dermatologic toxicity associated with mucositis was observed in most patients during the radiotherapy phase.

The incidence of sequelae was evaluated in surviving patients with a follow-up of at least 24 months. No data were provided for 4 patients; whereas, in a subset of 26 available patients, some type of morbidity was reported in 65%. Hypothyroidism, xerostomia, neck fibrosis, and trismus were the most common late effects observed, but hearing loss and growth hormone deficiencies also were common (Table 4). One patient had an adrenal gland ganglioneuroma 1 year after NPC was diagnosed. Three female patients gave birth to a child 2 to 5 years after the end of treatment.

EBV-DNA Evaluation

Pretreatment quantitative EBV-DNA levels were available for only 10 patients: The level was 0 for 2 patients, $<10^3$ for 4 patients, between 10^3 and 10^4 for 1 patient, between 10^4 and 10^5 for 2 patients, and $>10^5$ in 1 patient. The small number of patients hindered any correlation with stage or prognosis. In all but 1 patient with high levels at diagnosis, EBV-DNA levels dropped below the detection threshold after the first cycle of chemotherapy. In the 1 patient who had a detectable titer after 1 course of chemotherapy, this became negative after the second course; this patient's tumor progressed shortly after completing the treatment accompanied by an increase in EBV-DNA levels. One other relapse was observed in a patient whose initially high EBV-DNA levels dropped to nil after the first cycle of chemotherapy; however, in that patient, the EBV-DNA titer did not rise again at the time of the recurrence.

DISCUSSION

This report describes the clinical results from the prospective chemoradiotherapy protocol for pediatric NPC that was developed within the frame of the Italian TREP project on rare pediatric tumors. First, this experience demonstrates that prospective trials are feasible even for such rare tumors. The comparison between the numbers of observed and expected cases indicated that the accrual of patients with NPC for the TREP protocol was excellent. For other rare tumors considered in the TREP project, patient accrual was only satisfactory for children aged <15 years, whereas there were signs of significant under reporting of adolescents.[2] For NPC, we were able to register and, thus, to treat homogeneously virtually the same number of patients that would be expected on the basis of epidemiological data. It is noteworthy that a single center (the Italian National Cancer Institute), which is a referral center not only for pediatric cancer but also for adult tumors and for head and neck cancers in particular, was able to treat half of the patients. Although patient accrual was satisfactory vis-a-vis the number of cases expected in the Italian pediatric population, our experience demonstrated that, for NPC, as in the case of other rare pediatric neoplastic diseases, the number of patients that could be enrolled within a reasonable time period in a national-scale protocol will never be enough for randomized clinical trails to be conducted to answer certain questions, for instance, on the efficacy of alternative chemotherapy regimens.

The main purpose of our protocol was to standardize the treatment of children and adolescents with NPC in Italy, adopting a dedicated program. In the past, patients with this very rare disease were treated very differently at different pediatric centers. Our intention was not to test an innovative therapy but to ensure a good level of care at all Italian pediatric oncology centers. The approach proposed in the TREP protocol proved feasible (with acceptable acute toxicity), and compliance was high at all centers

involved. The results were similar to those reported in the recent literature,[3,5-7,13,15,23-27] supporting the practice of combining radiation and chemotherapy for the optimal treatment of NPC. Response to initial chemotherapy was in the range of 90%. The use of lower radiotherapy doses than those used for adults (eg, 70 Gy) did not affect the local or locoregional failure rates (only 1 locoregional relapse was observed). This is an important finding, because the high incidence of severe sequelae in survivors[8-13] suggests that outcomes should be measured by combining overall survival with the "cost" of survival in terms of treatment sequelae rather than considering survival alone. Clearly, long-term follow-up is needed to obtain more mature results regarding survival and the late effects of treatment. In our series, there was a 65% incidence of overall morbidity, from fibrosis and trismus to hormone deficiencies. The incidence of sequelae reported by the different centers varied, however, particularly when centers that enrolled large numbers of patients with dedicated follow-up programs were compared with smaller centers (data not shown). This suggests the need to investigate particular potential side effects, such as endocrine dysfunctions. A document containing detailed guidelines on follow-up will be prepared and circulated to the TREP centers.

An interesting approach aiming to limit the radiotherapy dose to the cervical lymph nodes (and, thus, contain the related toxicity) has recently been reported by the Curie Institute in Paris, where children who responded well to neoadjuvant chemotherapy (tumor volume reduction $\geq$90%) received lower doses of radiotherapy ($<$50 Gy): Half of those patients had reduced lymph node irradiation with a satisfactory regional failure rate.[27] The increasing availability of IMRT techniques, including tomotherapy and volumetric modulated arc therapy, also will lead to a substantial reduction in the long-term sequelae in the pediatric patient population, as already reported in several adult series.[28-33]

Conversely, it is important to explore new therapeutic options with a view to improving the results of treatment, particularly for patients who present initially with metastases, whose prognosis remains largely unsatisfactory. Adult experiences have indicated that docetaxel is active against NPC, and promising pediatric data also are now available.[34] The results of a phase 2 international trial that randomized pediatric patients to a conventional 5-FU/cisplatin regimen with or without docetaxel currently are pending. A better understanding of the biology of NPC,[35,36] particularly concerning the pathogenic role of EBV, has led to investigations on the efficacy of treatments other than radiotherapy and chemotherapy. In the GPOH study, a 6-month maintenance therapy with interferon was administered to children and adolescents with NPC after standard chemoradiotherapy[6] with a view to boosting their immune systems' capacity to capture cells harboring the EBV genome and eliminate any minimal residual disease resistant to chemotherapy and radiotherapy. In fact, the German series achieved the best reported OS rate (91% at 108 months). Another promising approach consists in using EBV-specific cytotoxic T-lymphocytes (in patients with recurrent disease).[37,38] Finally, pediatric oncologists also may be able to exploit other advances made in the management of adult NPC, such as the use of PET scanning[18] or quantitative EBV-PCR,[19,39] which can improve staging and prognostication, and enable a better, risk-based tailoring of therapy to individual patients. In the next-generation TREP study, PET scanning and evaluating EBV-DNA levels will be mandatory, and a centralized review of radiologic images (and consequent staging) will be required. The lack of any radiological review is a limit of the current study and may partially explain why T classification and N status did not correlate with survival rates.

In conclusion, this study demonstrates the feasibility and efficacy of a prospective chemoradiotherapy protocol for pediatric NPC that was developed within the Italian TREP network. At the same time, this experience reinforces the need to establish larger, international, prospective cooperative trials. The Italian TREP group recently joined forces with national groups focusing on rare pediatric tumors in France, the United Kingdom, Poland, and Germany, leading to the foundation of a new international cooperative group called the European Cooperative Study Group for Pediatric Rare Tumors (ExPeRT). Among other tumor types, NPC is considered 1 of the priorities for the new group, which aims to exchange experience and data, develop a prospective international registry, and promote tailored research and treatment protocols.

FUNDING SOURCES

The TREP Project was supported by grants from the "Fondazione Citta della Speranza," Padova, and the "Fondazione Cassa di Risparmio di Padova e Rovigo."

CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

REFERENCES

1. Bray F, Haugen M, Moger TA, et al. Age-incidence curves of nasopharyngeal carcinoma worldwide: bimodality in low-

risk populations and aetiologic implications. *Cancer Epidemiol Biomarkers Prev.* 2008;17:2356-2365.
2. Pastore G, De Salvo GL, Bisogno G, et al. Evaluating the access to pediatric cancer care centers of children and adolescents with rare tumors in Italy: the TREP project. *Pediatr Blood Cancer.* 2009;53:152-155.
3. Sultan I, Casanova M, Ferrari A, et al. Differential features of nasopharyngeal carcinoma in children and adults: a SEER study. *Pediatr Blood Cancer.* 2010;55:279-284.
4. Ferrari A, Casanova M, Massimino M, Sultan I. Peculiar features and tailored management of adult cancers occurring in pediatric age. *Expert Rev Anticancer Ther.* 2010;10:1837-1851.
5. Rodriguez-Galindo C, Wofford M, Castleberry RP, et al. Preradiation chemotherapy with methotrexate, cisplatin, 5-fluorouracil, and leucovorin for pediatric nasopharyngeal carcinoma. *Cancer.* 2005;103:850-857.
6. Mertens R, Granzen B, Lassay L, et al. Treatment of nasopharyngeal carcinoma in children and adolescents: definitive results of a multicenter study (NPC-91-GPOH). *Cancer.* 2005;104:1083-1089.
7. Ozyar E, Selek U, Laskar S, et al. Treatment results of 165 pediatric patients with non-metastatic nasopharyngeal carcinoma: a Rare Cancer Network study. *Radiother Oncol.* 2006;81:39-46.
8. Pao WJ, Hustu HO, Douglass EC, et al. Pediatric nasopharyngeal carcinoma: long term follow-up of 29 patients. *Int J Radiat Oncol Biol Phys.* 1989;17:299-305.
9. Wei WI, Sham JS. Nasopharyngeal carcinoma. *Lancet.* 2005;365:2041-2054.
10. Chan SH, Ng WT, Kam KL, et al. Sensorineural hearing loss after treatment of nasopharyngeal carcinoma: a longitudinal analysis. *Int J Radiat Oncol Biol Phys.* 2009;73:1335-1342.
11. Chen MC, Feng IJ, Lu CH, et al. The incidence and risk of second primary cancers in patients with nasopharyngeal carcinoma: a population-based study in Taiwan over a 25-year period (1979-2003). *Ann Oncol.* 2008;19:1180-1186.
12. Ulger S, Ulger Z, Yildiz F, Ozyar E. Incidence of hypothyroidism after radiotherapy for nasopharyngeal carcinoma. *Med Oncol.* 2007;24:91-94.
13. Ka Leung Cheuk D, Billups CA, Martin MG, et al. Prognostic factors and long-term outcomes of childhood nasopharyngeal carcinoma. *Cancer.* 2011;117:197-206.
14. Ferrari A, Bisogno G, De Salvo GL, et al. The challenge of very rare tumours in childhood: the Italian TREP project. *Eur J Cancer.* 2007;43:654-659.
15. Casanova M, Ferrari A, Gandola G, et al. Undifferentiated nasopharyngeal carcinoma in children and adolescents: comparison between staging systems. *Ann Oncol.* 2001;12:1157-1162.
16. Al-Sarraf M, Leblanc M, Giri PGS, et al. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized intergroup study 0099. *J Clin Oncol.* 1998;16:1310-1317.
17. Langendijk JA, Leemans CR, Buter J, et al. The additional value of chemotherapy to radiotherapy in locally advanced nasopharyngeal carcinoma: a meta-analysis of the published literature. *J Clin Oncol.* 2004;22:4604-4612.
18. Ng SH, Chan SC, Yen TC, et al. Staging of untreated nasopharyngeal carcinoma with PET/CT: comparison with conventional imaging work-up. *Eur J Nucl Med Mol Imaging.* 2009;36:12-22.
19. Lin JC, Wang WY, Chen KY, et al. Quantification of plasma Epstein-Barr virus DNA in patients with advanced nasopharyngeal carcinoma. *N Engl J Med.* 2004;350:2461-2470.
20. Fleming ID, Cooper JS, Henson DE, et al, eds. AJCC Cancer Staging Manual. 5th ed. Philadelphia, PA: Lippincott-Raven; 1997.
21. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst.* 2000;92:205-216.
22. Kaplan EL, Meier P. Non-parametric estimation from incomplete observation. *J Am Stat Assoc.* 1958;53:457-481.
23. Frikha M, Toumi N, Ghorbel L, et al. Pediatric nasopharyngeal carcinoma: anatomoclinic aspects, therapeutic results and evolutive particularities. *Cancer Radiother.* 2010;14:169-175.
24. Kupeli S, Varan A, Ozyar E, et al. Treatment results of 84 patients with nasopharyngeal carcinoma in childhood. *Pediatr Blood Cancer.* 2006;46:454-458.
25. Afqir S, Ismaili N, Alaoui K, et al. Nasopharyngeal carcinoma in adolescents: a retrospective review of 42 patients. *Eur Arch Otorhinolaryngol.* 2009;266:1767-1773.
26. Saeed H, Zaidi A, Adhi M, et al. Pediatric nasopharyngeal carcinoma: a review of 27 cases over 10 years at Shaukat Khanum Memorial Cancer Hospital and Research Center, *Pakistan Asian Pac J Cancer Prev.* 2009;10:917-920.
27. Orbach D, Brisse H, Helfre S, et al. Radiation and chemotherapy combination for nasopharyngeal carcinoma in children: radiotherapy dose adaptation after chemotherapy response to minimize late effects. *Pediatr Blood Cancer.* 2008;50:849-853.
28. Laskar S, Bahl G, Muckaden M, et al. Nasopharyngeal carcinoma in children: comparison of conventional and intensity-modulated radiotherapy. *Int J Radiat Oncol Biol Phys.* 2008;72:728-736.
29. Sterzing F, Stoiber EM, Nill S, et al. Intensity-modulated radiotherapy (IMRT) in the treatment of children and adolescents—a single institution's experience and a review of the literature [serial online]. *Radiat Oncol.* 2009;4:37.
30. Chen YY, Zhao C, Wang J, et al. Intensity-modulated radiation therapy reduces radiation-induced trismus in patients with nasopharyngeal carcinoma: a prospective study with >5 years of follow-up. *Cancer.* 2011;117:2910-2916.
31. Xiao WW, Huang SM, Han F, et al. Local control, survival, and late toxicities of locally advanced nasopharyngeal carcinoma treated by simultaneous modulated accelerated radiotherapy combined with cisplatin concurrent chemotherapy: long-term results of a phase 2 study. *Cancer.* 2011;117:1874-1883.
32. Hsin CH, Chen TH, Young YH, et al. Comparison of otologic complications between intensity-modulated and 2-dimensional radiotherapies in nasopharyngeal carcinoma patients. *Otolaryngol Head Neck Surg.* 2010;143:662-668.
33. Louis CU, Paulino AC, Gottschalk S, et al. A single institution experience with pediatric nasopharyngeal carcinoma: high incidence of toxicity associated with platinum-based chemotherapy plus IMRT. *J Pediatr Hematol Oncol.* 2007;29:500-505.
34. Varan A, Ozyar E, Corapcioglu F, et al. Pediatric and young adult nasopharyngeal carcinoma patients treated with preradiation cisplatin and docetaxel chemotherapy. *Int J Radiat Oncol Biol Phys.* 2009;73:1116-1120.

35. Ayan I, Kaytan E, Ayan N. Childhood nasopharyngeal carcinoma: from biology to treatment. *Lancet Oncol.* 2003;4:13-21.
36. Pathmanathan R, Prasad U, Sadler R, et al. Clonal proliferations of cells infected with Epstein-Barr virus in preinvasive lesions related to nasopharyngeal carcinoma. *N Engl J Med.* 1995;333:693-698.
37. Comoli P, De Palma R, Siena S, et al. Adoptive transfer of allogeneic Epstein-Barr virus (EBV)-specific cytotoxic T cells with in vitro antitumor activity boosts LMP2-specific immune response in a patient with EBV-related nasopharyngeal carcinoma. *Ann Oncol.* 2004;15:113-117.
38. Straathof KC, Bollard CM, Popat U, et al. Treatment of nasopharyngeal carcinoma with Epstein-Barr virus-specific T lymphocytes. *Blood.* 2005;105:1898-1904.
39. Ji MF, Wang DK, Yu YL, et al. Sustained elevation of Epstein-Barr virus antibody levels preceding clinical onset of nasopharyngeal carcinoma. *Br J Cancer.* 2007;96:623-630.