International Journal of Pediatric Otorhinolaryngology (2007) 71, 447–455

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International Journal of Pediatric Otorhinolaryngology

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Immunohistochemical expression of epidermal growth factor receptor and cyclooxygenase-2 in pediatric nasopharyngeal carcinomas: No significant correlations with clinicopathological variables and treatment outcomes

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Received 9 October 2006; received in revised form 16 November 2006; accepted 17 November 2006

KEYWORDS
Nasopharyngeal carcinoma;
EGFR;
COX-2;
Children

Summary Epidermal growth factor receptor (EGFR) and cyclooxygenase-2 (COX-2) were separately found associated with prognosis in adult patients with nasopharyngeal carcinoma (NPC). To date, their expression patterns and prognostic utility have never been specifically addressed in children and adolescents. Thirty consecutive NPC patients aged $\leqq$20 years and treated by radiotherapy (RT) with (n = 14) or without (n = 16) systemic chemotherapy (CT) were accrued between 1988 and 2001 in a single institute. The clinical outcomes were correlated with clinicopathological features in 30 patients and with immunostains of EGFR and COX-2 in 20 patients with available blocks. The 5-year rates of overall survival (OS) and disease-free survival (DFS) were both 76.4%. Overexpression of EGFR and COX-2 was identified in 13 (65%) and 14 (70%) cases, respectively. The expression levels of these two oncoproteins did not significantly correlate with each other, DFS, OS, and any of clinicopathological factors,

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0165-5876/$ – see front matter
doi:10.1016/j.ijporl.2006.11.019

including histological subtype, AJCC stage, T stage, and N stage. The only significant prognosticator predictive of adverse outcomes was AJCC stage IV at presentation, which, compared with lower-staged diseases, decreased the rates from 85.2% to 55.6% at 5 years for both DFS ($p = 0.05$) and OS ($p = 0.05$). Despite lacking significant prognostic values, EGFR and COX-2 were overexpressed in approximately two-thirds of pediatric NPC. Such high frequencies provide the basis of combined targeted therapy by specific pharmacological inhibitors to enhance the effects of RT and CT. However, it requires further investigation on the difference between pediatric and adult NPC patients in clinical and biological implications of EGFR and COX-2.

1. Introduction

Nasopharyngeal carcinoma (NPC) represents an endemic disease strongly associated with Epstein-Barr virus (EBV) infection in Southern China and Taiwan, where it generally affects adults over 40 years of age but only 1—2% of pediatric patients. Furthermore, the prognostic implication of age in NPC appears discrepant among populations with different susceptibility. For instance, younger age at presentation is associated with better prognosis in endemic areas [1,2]. However, childhood NPC in lower incidence regions frequently presents with advanced locoregional disease and greater metastatic propensity, although it is not significantly different from the adult counterpart in final survival outcomes [1—3]. This may be ascribed to the frequent undifferentiated histology in pediatric NPC that renders it highly sensitive to radiotherapy (RT) and chemotherapy (CT) [2]. In this context, the therapeutic strategy for childhood NPC has generally followed the guidelines for adults, consisting of high-dose RT with or without combined systemic CT. With recent advances in RT and CT, the cure rates in childhood NPC have improved. However, approximately 20—50% of patients still suffer from relapses or metastases, with the majority of these patients dead of their disease [2—5]. It is therefore highly desirable to search molecular markers to correlate with actual clinical outcomes in these pediatric NPC patients for potential molecular targeted therapy.

Epidermal growth factor receptor (EGFR), a 170 kD surface receptor with intrinsic tyrosine kinase activity, belongs to the erbB growth factor receptor family [6]. Cyclooxygenase-1 (COX-1) and COX-2 catalyze prostanoid synthesis from arachidonic acid [7]. In contrast to the constitutive expression of COX-1, COX-2 is barely detectable in normal tissues and rapidly induced in response to inflammatory and mitogenic stimuli. EGFR and COX-2 have been separately shown to mediate pleiotropic carcinogenic processes, including cell survival, proliferation, angiogenesis, and invasiveness, etc. In addition, both proteins are overexpressed and associated with poorer prognosis in a variety of human carcinomas, including head and neck cancer and NPC [6—12]. An expanding body of evidence further shows tight interaction between these two signaling pathways [6,8], which upholds the rationale for combining lower doses of COX-2 and EGFR tyrosine kinase inhibitors as a novel therapeutic approach to minimize drug toxicity and resistance [6].

To our knowledge, the expression and prognostic utility of molecular biomarkers have never been specifically addressed in pediatric NPC. We aimed at examining EGFR and COX-2 oncoproteins by immunohistochemistry and analyzing their correlations with clinical outcomes for consecutive childhood NPC patients treated at a single institute in Southern Taiwan.

2. Materials and methods

2.1. Study population

From June 1988 to May 2001, 1931 consecutive patients with previously untreated and histologically confirmed NPC received RT at a tertiary medical center in Taiwan. Among them, there were only 34 patients (1.8%) aged $\leq$20 years (Fig. 1). Four patients were excluded because of distant metastasis at diagnosis (stage IVc) or incomplete radiotherapy course. The characteristics of 30 patients eligible for analysis are summarized in Table 1. There were 23 males and 7 females with the median age being 17 years (range, 13—20). The histological subtypes were reappraised according to the World Health Organization (WHO) classification [2]. In all, differentiated and undifferentiated non-keratinizing carcinomas were identified in 13 (43.3%) and 17 (56.7%) patients, respectively. By using the 1997 American Joint of Cancer Committee (AJCC) system, 11 (33.3%) cases were classified as stage II, 11 (33.3%) cases as Stage III, and 9 (30.0%) cases as either Stage IVa or IVb. The immunostaining of EGFR and COX-2 could be performed in 20 patients with