Update on the Management and Therapeutic Monitoring of Advanced Nasopharyngeal Cancer

Herbert H. Loong, MBBS, MRCP[a], Brigette B. Ma, MBBS, FRACP[a,b,*], AnthonyT. Chan, MD, FRCP[a,b]

KEYWORDS

• Nasopharyngeal cancer • Chemotherapy
• Chemoradiotherapy • IMRT • Plasma EBV-DNA

Nonkeratinizing nasopharyngeal carcinoma (NPC) is distinguished from the other malignancies of the head and neck with respect to its epidemiology, pathology, clinical presentation, and response to treatment. NPC is endemic to Southeast Asia, North Africa, and parts of the Mediterranean basin, with the highest prevalence in Southern China, where an average of 80 cases per 100,000 population are reported each year.[1] It is the seventh most common cancer in Hong Kong and accounts for more than 50% of newly diagnosed cases of head and neck cancers. Nonkeratinizing NPC is uniquely sensitive to chemotherapy and is almost universally associated with the Epstein-Barr virus (EBV).[1] Plasma-derived EBV DNA has been shown to be an important biomarker of prognosis and response to treatment in large cohort studies conducted in endemic regions.[2,3]

Although patients with American Joint Committee on Cancer (AJCC, 6th edition) stages I and II NPC have a high rate of cure with radiotherapy (RT) alone, those

[a] Department of Clinical Oncology, Prince of Wales Hospital, Shatin, New Territories, Hong Kong SAR
[b] Department of Clinical Oncology, Sir Y K Pao Center for Cancer, Hong Kong Cancer Institute, Li Ka Shing Institute for Health Sciences, State Key Laboratory in Oncology in South China, Chinese University of Hong Kong, Hong Kong
* Corresponding author. Department of Clinical Oncology, Prince of Wales Hospital, Shatin, New Territories, Hong Kong SAR.
E-mail address: brigette@clo.cuhk.edu.hk (B.B. Ma).

Hematol Oncol Clin N Am 22 (2008) 1267–1278
doi:10.1016/j.hoc.2008.08.012 **hemonc.theclinics.com**
0889-8588/08/$ – see front matter

who present with nonmetastatic stages III and IV (or locoregionally advanced) disease have a 5-year overall survival rate of only 50% to 60% after RT alone.[4,5] This is because approximately 30% and 20% of these patients will develop distant and local recurrences after RT, respectively.[5,6] The median overall survival of patients who develop distant metastases is at best 12 to 15 months after treatment with platinum-based chemotherapy in phase II clinical trials.[7] Researchers have focused their efforts on evaluating new treatment strategies, and as a result, the treatment outcome for patients who have NPC has improved substantially in recent years. This article examines some of these therapeutic advances that could have contributed to this improvement.

INTEGRATING CHEMOTHERAPY WITH RADIOTHERAPY IN THE MANAGEMENT OF LOCOREGIONALLY ADVANCED NASOPHARYNGEAL CARCINOMA

Since the early 1990s, more than 15 randomized clinical trials and 3 meta-analyses have been reported on the use of induction and concurrent and adjuvant chemotherapy in the treatment of locoregionally advanced NPC. The predominant finding of these studies is a survival advantage associated with the use of concurrent chemoradiotherapy over RT alone.[4,5,8–11] The magnitude of this benefit was reported in a meta-analysis by the MAC-NPC Collaborative Group,[12] in which the pooled hazard ratio of death was 0.60 (95% confidence interval, 0.48–0.76). This benefit was observed regardless of the type or schedule of concurrent chemotherapy used, which included cisplatin alone,[4,8,9] cisplatin and 5-fluorouracil in combination,[5] or Tegafur and uracil.[11]

The pivotal study is the US Intergroup (0099) trial,[10] in which 147 patients were randomized to either RT alone (70 Gy in 35 fractions) or RT with three cycles of concurrent cisplatin (100 mg/m^2) followed by three cycles of adjuvant cisplatin (80 mg/m^2, day 1) and fluorouracil (100 mg/m^2, days 1–4) repeated every 3 weeks. The 5-year overall survival rate was 37% in the RT alone arm compared with 67% in the combined arm ($P = .001$). Statistically significant advantages in disease-free survival and locoregional and distant failure rates also were reported with the combined arm. The applicability of this result to Asian patients in whom nonkeratinizing NPC is more prevalent had been questioned, however. Consequently, at least five other phase III studies have been completed in Asian populations,[4,5,8,9,11] which confirmed the benefit of concurrent chemoradiotherapy.

To date, little evidence suggests that adjuvant chemotherapy alone without concurrent chemotherapy adds to the benefits of RT in advanced NPC.[11,13,14] In comparison, the contribution of induction chemotherapy to the treatment outcome of patients with advanced NPC has been conflicting in the literature. None of the phase III studies completed to date has identified a clear survival benefit of adding chemotherapy before RT.[15–19] This negative result should be interpreted with caution because some of the studies were underpowered,[4,19] and the toxicities of some of the chemotherapy regimens were significant.[16] A recent updated and pooled analysis of two phase III studies reported a 5% absolute improvement in disease-specific survival with the use of induction chemotherapy.[20] A randomized phase II study that evaluated the role of adding two cycles of cisplatin-docetaxel before chemoradiotherapy recently was completed at our center. Preliminary results suggested that induction chemotherapy was associated with an improved overall survival and a hazard ratio of death of 0.17 (confidence interval 0.04–0.82, $P = .013$).[21] Further evaluation of this approach in a well-powered phase III study is warranted.