Current treatment of nasopharyngeal carcinoma

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Due to its anatomical location and high radiosensitivity, the mainstay treatment for primary nasopharyngeal carcinoma (NPC) is radiotherapy (RT). For patients presenting with early UICC stages I and IIA disease, RT alone achieves overall survival figures of 90% and 84% respectively [1]. With the use of intensity-modulated radiotherapy (IMRT) the local control rates have further improved and rates of xerostomia reduced through sparing of the parotid glands [2,3]. Over 60% of patients with NPC present with locoregionally intermediate to advanced UICC stages IIB–IV disease. With local control increasingly achievable using IMRT, the predominant site of failure is distant metastases. Since NPC is also highly chemosensitive, combining chemotherapy with primary RT has been extensively studied in the past two decades.

While the number of stage IIB patients included in prospective clinical trials have been limited [4,5], this group of patients are at increased risk of developing distant metastases and are therefore recommended to be treated with concurrent chemotherapy radiotherapy (CRT), which is the standard treatment for stages III and IV NPC [6].

Meta-analysis of prospective randomised trials demonstrated that concurrent CRT improved both progression-free survival (HR 0.63) and overall survival (HR 0.60) [7]. In North America, the standard CRT regimen is cisplatin 100 mg/m^2 on days 1, 22, and 43, concurrent with RT followed by adjuvant cisplatin 80 mg/m^2 D1 and 5-fluorouracil 1000 mg/m^2 D1–4 for three cycles [8]. In Asia, weekly cisplatin 40 mg/m^2 for 6–8 weeks concurrent with RT has been reported to improve five-year overall survival with good tolerability [9]. Randomised studies of adjuvant chemotherapy after RT alone have all been negative and tolerance of adjuvant chemotherapy after CRT is difficult, especially in patients whose nutritional status is not optimal [10].

Randomised trials of neoadjuvant chemotherapy followed by RT alone have demonstrated improvement in disease-free survival but not overall survival [11,12]. Single-arm phase 2 studies have demonstrated encouraging results using sequential neoadjuvant and CRT [13,14] and a randomised phase 2 trial of neoadjuvant docetaxel/cisplatin followed by cisplatin/RT versus cisplatin/RT reported good tolerability and survival improvement [15]. At least five ongoing international and national studies are studying this strategy and the role of neoadjuvant chemotherapy will be better defined in the near future.

In distant metastatic disease, the best outcome has been achieved with an aggressive multi-disciplinary approach in patients with lung metastases only [16]. Doublet platinum-based chemotherapy is the standard first-line systemic treatment achieving high response rates of 60–80%; however, the median survival remains around 12–20 months.

Clinical benefit has been demonstrated using cetuximab, the monoclonal antibody against epidermal growth factor receptor in combination with carboplatin in platinum-refractory metastatic NPC [17]. Trials are ongoing combining cetuximab with CRT in locoregionally advanced NPC. Other targeted therapies being investigated include bevacizumab, multi-targeted anti-angiogenic agents, AKT inhibitors as well as epigenetic therapies [18].

Epstein–Barr virus (EBV) is universally associated with endemic undifferentiated NPC. Quantitative plasma EBV DNA using real-time polymerase chain reaction technique has a sensitivity and specificity of 96% and 93% respectively [19]. Pre- and post-treatment EBV DNA are highly prognostic and may be useful for guiding therapy [20–22].

Immunotherapeutic approaches targeting EBV antigens in NPC cells are under investigation. Adoptive transfer of cytotoxic lymphocytes, pulsing dendritic cells with LMP-2 peptides and recombinant Modified Vaccinia Ankara vaccine encoding EBV antigens have been reported with promising results [23].

In conclusion, IMRT has been established as the standard technique for NPC, and concurrent cisplatin RT with or without adjuvant chemotherapy is the current standard of care for locoregionally immediate

and advanced NPC. Intensive research efforts in the use of neoadjuvant therapies, targeted therapies, EBV DNA risk stratification and immunotherapeutic approaches are ongoing.

Conflict of interest statement

The author has received grant support from Research Grants Council of Hong Kong, US National Cancer Institute, Cancer Research UK, Sanofi-Aventis, Merck-Serono, Pfizer and Eli Lilly.

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