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Controversies in the systemic treatment of Nasopharyngeal carcinoma

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SUMMARY

In conjunction with radiotherapy, the concurrent use of systemic chemotherapy has been proven to improve treatment outcome and thus have been incorporated into the treatment paradigm for patients with loco-regionally advanced Nasopharyngeal carcinoma. The benefits from the use of chemotherapy in stage II disease remain controversial. There is now also increasing evidence for the use of neoadjuvant chemotherapy prior to definitive concurrent chemoirradiation, which is associated with decreased risks of distant metastases, translating to improvement in overall survival. Dose intensity of chemotherapy administered during radiotherapy has been shown to have prognostic significance in NPC treatment. The role of adjuvant chemotherapy after completion of concurrent chemoirradiation is less well defined, with studies indicating an insignificant survival improvement. However, this approach may still be of value in patients with high-risk disease. Data in support of this approach shall become available in the coming years. This article will discuss and highlight these findings and controversies in systemic treatment of NPC.

Introduction

Nasopharyngeal carcinoma (NPC) is distinct from other malignancies in the head and neck with respect to its epidemiology, pathology, clinical presentation and response to treatment [1]. Studies have highlighted the prognostic significance of different stage groupings in NPC, with patients with higher tumour (T) or nodal (N) stages experiencing higher rates of local relapse and distant recurrences, and also at earlier time points.

Radiotherapy (RT) remains the cornerstone of management both in early-stage and locoregionally-advanced disease, but systemic chemotherapy has also been shown to significantly improve survival in the latter group [2–4]. The overall magnitude of benefit of concurrent chemoradiotherapy (CRT) has been previously reported in the Meta-analysis of Chemotherapy in Nasopharyngeal Carcinoma (MAC-NPC) study [5]. This analysis demonstrated a survival benefit with the use of chemotherapy in the treatment of NPC. Chemotherapy led to a small, but significant, benefit in overall survival (OS) and event-free survival (EFS). The effect was most significant for the concurrent group where the pooled hazard ratio of death was reportedly 0.60 (95% confidence interval, CI, 0.48 to 0.76). This benefit was observed irrespective of the type or schedule of concurrent chemotherapy employed, which included cisplatin alone [3,6,7], cisplatin and 5-fluorouracil in combination [8], or tegafur and uracil (UFT) – an oral fluoropyrimidine [9]. The trial encompassed in this meta-analysis that only investigated the use of adjuvant chemotherapy alone [10] failed to demonstrate a positive impact on OS or EFS. Combined modality treatment using concurrent cisplatin-based chemotherapy is thus far the only strategy supported by several large randomized studies to improve survival.

Since the publication of this meta-analysis, ten trials have been conducted representing over 2400 patients. Most of these trials compared radiotherapy to the same radiotherapy plus concurrent with or without adjuvant chemotherapy [3,11–13], with a remaining handful comparing same CRT plus neoadjuvant chemotherapy [14–16]. An update of the MACH-NPC with trials reported up to 2010 is currently underway with an aim to include new trials, update older trials that were included in the original MACH-NPC and also to try and study treatment related toxicities in order to balance them against the survival benefit. Whilst we are clear that radiotherapy is the cornerstone of management for early and locoregionally advanced disease, whether or not patients with stage II disease should also receive chemotherapy remains controversial. To a certain extent, this controversy may have been contributed by the stage migration of patients – both in the discrepancies between various staging systems as well as the changes in AJCC N-staging classifications in their updates. This has meant that

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conclusions drawn from prior investigations may now no longer necessarily apply and there is a need to meticulously review, update and incorporate the data. This further highlights the importance of the MACH-NPC update that is currently underway.

This article aims to address the current established role of chemotherapy in NPC, and several contentious issues with regard to the role of chemotherapy in early stage NPC, the optimal sequence of treatment in loco-regionally advanced disease and also the possible relevance and importance of dose intensity of concurrent chemotherapy.

The current established role of chemotherapy in NPC

With the plethora of data from prospective studies, retrospective series and meta-analysis available for potential advantages and disadvantages of neoadjuvant or adjuvant chemotherapy, it is important to note that whilst there was a significant 18% reduction in the HR of death (HR 0.82; 95% CI 0.71–0.94, $p = 0.006$) with the use of chemotherapy described in the MACH-NPC meta-analysis [5], the currently established and repeatedly validated role of chemotherapy is in the concurrent setting [17]. Cisplatin-based chemotherapy has been shown to result in higher response rates in previously untreated, recurrent or metastatic NPC with non-cisplatin regimens [18,19]. Thus cisplatin-based regimens have repeatedly been investigated and proven to be effective in the peri-radiotherapy setting. CRT trials showed a better treatment effect than neoadjuvant or adjuvant trials. Although benefit for event-free survival was seen in the subset of trial using neoadjuvant chemotherapy in the same meta-analysis, there were no evidence of OS benefit observed with neoadjuvant and adjuvant chemotherapy.

At present, concurrent chemotherapy during the course of radiotherapy should be considered the standard of care. Weekly (30–40 mg/m^2) as well as 3-weekly (100 mg/m^2) cisplatin-based regimens are accepted as standard practice. Toxic effects are considerable with the 3-weekly schedule as revealed by the Intergroup study by Al-Sarraf and colleagues [4] in which only 63% of patients having received all three 3-weekly-courses of concurrent 100 mg/m^2 cisplatin. Kim and colleagues [20] have retrospectively reviewed their experience in Korea of both weekly and 3-weekly regimens. They have found weekly scheduling practical and feasible for CRT in NPC, resulting in decreased interruptions in radiation treatment and minimal acute toxic events without compromising local control. There is a trend for centres in the endemic regions opting for the weekly regimen due to the more favorable toxicity profile and comparable efficacy.

The role of chemotherapy in stage II disease

Results of numerous randomized clinical trials have confirmed efficacy of CRT over radiotherapy alone for loco-regionally advanced NPC. Consensus guidelines, such as the National Comprehensive Cancer Network (NCCN), has recommended CRT for stage II to IVb NPC, and radiation therapy alone for earlier stage disease. However, the evidence for its efficacy in early stage disease is relatively sparse.

An earlier study [21] with retrospective data have shown that disease-free survival of patients with stage II disease with CRT is equal to that of patients with stage I disease treated with RT alone, suggesting the use of CRT counteracts the unfavourable prognosis of stage II patients and reducing their risk of failure to similar to that of patients with stage I disease.

The 2 main objectives of delivering chemotherapy in the treatment of NPC are to improve locoregional control by enhancing radiosensitivity, and to improve OS by controlling subclinical distant metastatic foci. As local recurrences is a relatively common mode of treatment failure in patients with stage II NPC, and skip metastasis from upper cervical lymph nodes (i.e. N1 disease) is rare [22,23], it has been postulated that the function of chemotherapy in the treatment of stage T1-2N1M0 NPC is limited to improving radiosensitivity for locoregional control. The wide use of intensity-modulated radiotherapy (IMRT) for NPC with its advantage of improved dose distribution and improvement in local and regional control rates both exceeding 90% in reported series have also lead to the question of necessity of concurrent chemotherapy for patients with limited primary disease and upper cervical lymphadenopathy in the IMRT-era.

Tham and colleagues have reported their retrospective review of treatment outcomes in patients with stage IIb NPC after definitive IMRT without CRT [24]. In their cohort of over 100 patients treated between August 2003 to December 2006 in two tertiary cancer centres in Singapore and China, more than half received IMRT only, with the remainder of patients having received an abbreviated neoadjuvant, adjuvant and/or concurrent chemotherapy. At a median follow-up of 39 months, there was no significant difference in survival outcomes demonstrated in patients treated with or without chemotherapy of any schedule. A significant criticism of the above study however, is that most patients were treated with neoadjuvant chemotherapy only and the use of concurrent chemotherapy or adjuvant chemotherapy was left to the physician's discretion to selected patients with bulkier disease. Only 8 patients received CRT. The neoadjuvant treatment regimen was also different in the 2 centres. Thus, whether the above findings can really be considered representative for the effects of CRT is debatable.

Chen and colleagues [25] published their randomized phase III prospective CRT study of stage II (with Chinese 1992 staging system) NPC patients. Patients were randomized to either RT alone ($n = 114$) or CRT ($n = 116$) with concurrent intravenous weekly cisplatin at 30 mg/m^2 during the course of radiation. Primary endpoint was overall survival (OS). At a median follow-up at 60 months, the addition of chemotherapy statistically improved the 5-year OS rate (94.5% vs. 85.8%; HR of death = 0.30; 95% CI 0.12 to 0.76; $P = 0.007$), progression-free survival (PFS) and distant-metastatic free survival and distant relapse rate. Surprisingly, there was no statistically significant difference in the 5-year locoregional relapse-free survival rate (93.0% vs. 91.1%; HR of locoregional relapse = 0.61; 95% CI = 0.25 to 1.51; $P = 0.29$). Multivariate analysis showed that number of chemotherapy cycles was the only independent factor associated with OS, PFS and distant control in stage II NPC. Interestingly, the importance of total dose of cisplatin in the treatment of NPC during CRT and its prognostic impact has also been reported by the Chinese University of Hong Kong group previously [26]. It is important to note, however, that all patients in this study underwent conventional RT using two-dimensional technique under a uniform RT protocol, with no planning computerized tomography (CT) scan performed.

As there are no published prospective data on the impact of CRT in stage II NPC patients treated with IMRT, a defining conclusion of CRT in the IMRT-era for early stage NPC patients cannot be drawn. The practice of CRT in stage II disease is acceptable as long as a balance is taken with the associated short and long-term toxicities of concurrent chemotherapy. It is also not unreasonable to omit the use of concurrent chemotherapy during RT in patients who maybe more elderly or with a poorer performance status.

Optimal sequencing of chemotherapy in locoregionally advanced NPC

Clinical trials [2,8] and meta-analyses [5,27] have clearly demonstrated that chemotherapy administered concurrently with