Head and neck cancer: treatment of nasopharyngeal cancer

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Introduction

Nasopharyngeal carcinoma (NPC) is a rare disease in most parts of the world, with an age-standardised annual incidence of less than 1 per 100,000. However, in Southern China, parts of Southeast Asia and the Mediterranean basin, NPC is an endemic disease with an incidence of 10–30 per 100,000 [1]. The three major well-defined aetiological factors for NPC include genetically determined susceptibility, early-age exposure to chemical carcinogens particularly of Southern Chinese salted fish, and association with a latent Epstein–Barr virus (EBV) infection [2]. Three histopathological types are recognised in the WHO classification [3]. Type I is squamous cell carcinoma with varying degrees of differentiation, type II is non-keratinising carcinoma and type III is undifferentiated carcinoma. WHO types II and III can be considered together as undifferentiated carcinoma of the nasopharyngeal type (UCNT), which accounts for >95% of cases in endemic areas and ~50% of cases in non-endemic areas. The histological subtype may be of prognostic significance, with UCNT having a higher local control rate after treatment with radiotherapy and a higher propensity for development of distant metastases [4].

EBV DNA monitoring

Tumour-derived cell-free EBV DNA was first detected by Lo et al. [5] in NPC patients, with a sensitivity of 96% and specificity of 93% using a real-time quantitative PCR technique. Subsequent studies have found that pretreatment EBV DNA levels correlated with disease stage [6] and that it was a highly significant prognosticator for treatment outcome and survival [7]. EBV DNA is a useful tool for monitoring patients during radiotherapy and chemotherapy [8], as well as for early detection of tumour recurrence [9]. In a prospective study of 170 NPC patients, a EBV DNA level of >500 copies/ml at 6–8 weeks after radiotherapy completion was significantly associated with poorer overall survival (hazard ratio 8.6) compared with patients with low or undetectable EBV DNA levels [10]. Further studies are required to investigate the use of this marker in risk-stratification of patients for treatment.

Treatment

Radiotherapy has been the standard treatment for NPC and achieves high 5-year overall and disease-free survival rates in early-stage disease. However, >60% of NPC patients present with advanced-stage disease, for which there are significant rates of local failure and distant metastases subsequent to radiotherapy. The disease is highly chemosensitive and hence efforts have been made to improve treatment results by integrating chemotherapy with radiotherapy in the primary treatment [11–22]. At the same time, improvements in radiation treatment, including altered fractionation and more precise delivery of a high dose to the tumour target by intensity-modulated radiotherapy (IMRT), have been reported to improve local control rates [23, 24]. The clinical trial results on the various chemotherapy–radiotherapy sequencing approaches are summarised in the following sections.

Adjuvant chemotherapy

Neither of the two randomised studies of adjuvant chemotherapy given after radiotherapy demonstrated any overall survival advantage compared with radiotherapy alone [11, 12]. Both of these studies have major limitations. The failure of the study by Rossi et al. [11] to demonstrate any advantage for adjuvant chemotherapy could be due to the relatively low efficacy of the combination (vincristine, cyclophosphamide and adriamycin) in comparison with a cisplatin combination, the high percentage of patients failing to receive the assigned treatment and the long time interval after completion of loco-regional radiotherapy before randomisation was undertaken and adjuvant chemotherapy initiated. The failure of the Taiwan study [12] to show a reduction in distant metastasis, or a survival benefit, could be due to the high patient drop-out rate from the chemotherapy arm and the high non-tumour-related mortality rate after chemotherapy. Both studies reported a significant rate of patient-refusal to complete planned adjuvant chemotherapy, and this is consistent with our own experience [13]. In our randomised study comparing radiotherapy with neo-adjuvant and adjuvant chemotherapy against radiotherapy alone, only 55% of patients completed the planned adjuvant chemotherapy owing to poor tolerance. Similarly, in the Intergroup 0099 study, only 55% of patients completed the planned adjuvant chemotherapy [17]. The main limiting toxicity was oral and oropharyngeal mucositis with exacerbations during chemotherapy, causing difficulty in feeding and swallowing. It therefore appears that after radical radiotherapy for NPC, which delivers a significant dose to the oral and oropharyngeal mucosa, patients’ tolerance to chemotherapy is poor.
Neo-adjuvant chemotherapy

Two of the four randomised studies on the use of neo-adjuvant chemotherapy showed positive results (Table 1) [12–14, 17]. The VUMCA I study [14] showed significant reduction of both local and distant failures after chemotherapy. Ma et al. [16] also showed significant improvement in local control after neo-adjuvant chemotherapy. The negative study by Chan et al. [13] is limited by its low power, since it included only 77 evaluable patients. In the overall negative AOCOA study [15], an unplanned subgroup analysis showed significant improvement in local control among 53 patients with very large nodes. Nevertheless, none of the studies demonstrated a significant overall survival benefit. Hence neo-adjuvant chemotherapy at this time is only routinely recommended for patients with very bulky intracranial NPC extending to such close proximity to the optic chiasma and/or the brainstem that even with IMRT adequate dose-sparing to within radiation tolerance of these important neural organs is not possible. In such cases, neo-adjuvant chemotherapy may help to shrink the tumour away from the critical structures and provide a wider safety margin around the gross tumour volume.

Concurrent chemo-radiation

In non-NPC head and neck cancers, meta-analysis of randomised studies (MACH-NC) [25] concluded that the addition of chemotherapy to locoregional treatment yielded a pooled hazard ratio of death of 0.9, with significant benefit from concurrent chemo-radiation but no significant benefit from adjuvant or neo-adjuvant chemotherapy. Concurrent chemotherapy and radiotherapy appears to be the most optimal way of sequencing the two modalities that consistently improves survival in head and neck cancers.

The first evidence that concurrent chemo-radiation with adjuvant chemotherapy produces survival advantage over radiotherapy alone in NPC was provided by the Intergroup study 0099 [17, 18] (Table 2). Cisplatin 100 mg/m² 3 weekly ×3 given concurrently with radiotherapy, followed by

Table 1. Randomised studies on neo-adjuvant chemotherapy in nasopharyngeal carcinoma

<table>
<thead>
<tr>
<th>Study</th>
<th>Neo-adjuvant chemotherapy</th>
<th>5-year OS</th>
<th>5-year PFS</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>CT</td>
<td>RT</td>
</tr>
<tr>
<td>Chan et al. [13] (n=77), median follow-up 28.5 months</td>
<td>2 cycles neo-adjuvant (every 3 weeks) and 4 cycles adjuvant (every 3 weeks); cisplatin 100 mg/m² day 1; 5-FU 1000 mg/m² continuous iv infusion days 2–4</td>
<td>80% (2 year figures, NS)</td>
<td>80.5% (2 year figures, NS)</td>
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<tr>
<td>VUMCA I [14] (n=339), median follow-up 49 months</td>
<td>3 cycles (every 3 weeks); cisplatin 100 mg/m² day 1; bleomycin 15 mg day 1 then 12 mg/m²/day days 1–5; epirubicin 70 mg/m² day 1</td>
<td>60% (3 year figures, NS)</td>
<td>52% (3 year figures, P&lt;0.01)</td>
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<td>AOCOA [15] (n=334), median follow-up 30 months</td>
<td>2–3 cycles (every 3 weeks); cisplatin 60 mg/m² day 1; epirubicin 110 mg/m² day 1</td>
<td>78% (3 year figures, NS)</td>
<td>71% (3 year figures, NS)</td>
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<tr>
<td>Ma et al. [16] (n=456), median follow-up 62 months</td>
<td>2–3 cycles (every 3 weeks); cisplatin 100 mg/m² day 1; bleomycin 10 mg/m² days 1 and 5; 5-FU 800 mg/m²/2 continuous iv infusion days 1–5</td>
<td>63% (NS)</td>
<td>56% (P = 0.05)</td>
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</table>

OS, overall survival; PFS, progression-free survival; CT, chemotherapy treated group; RT, radiotherapy alone group; 5-FU, 5-fluorouracil; iv, intravenous; NS, not significant.

Table 2. Randomised studies on concurrent chemo-radiation in nasopharyngeal carcinoma

<table>
<thead>
<tr>
<th>Study</th>
<th>Concurrent schema</th>
<th>5-year OS</th>
<th>5-year PFS</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>CT</td>
<td>RT</td>
</tr>
<tr>
<td>Intergroup 0099 [17, 18] (n = 193), median follow-up &gt;5 years</td>
<td>Cisplatin 100 mg/m² day 1 every 3 weeks for 3 cycles + adjuvant cisplatin 80 mg/m² day 1, 5-FU 1 g/m² days 1–4 every 3 weeks for 3 cycles</td>
<td>67% (P &lt;0.001)</td>
<td>37%</td>
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<tr>
<td>Chan et al. [19, 20] (n = 350), median follow-up 5.5 years</td>
<td>Cisplatin 40 mg/m² weekly</td>
<td>70.3% (P = 0.049)</td>
<td>58.6%</td>
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<td>Lin et al. [21] (n = 284), median follow-up 65 months</td>
<td>Cisplatin 20 mg/m²/day and 5-FU 400 mg/m²/day, 96-h infusion 2 cycles weeks 1 and 5</td>
<td>72.3% (P = 0.0022)</td>
<td>54.3%</td>
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<tr>
<td>Kwong et al. [22] (n = 219), median follow-up 37 months</td>
<td>UFT 200 mg 3 times per day ± adjuvant 6 cycles alternating PF/VBM (cisplatin 100 mg/m² day 1, 5-FU 1 g/m² days 1–3; vincristine 2 mg day 1, bleomycin 30 mg day 1, methotrexate 250 mg/m² day 1)</td>
<td>86.5% (3 year figures, P = 0.06)</td>
<td>76.8%</td>
</tr>
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</table>

OS, overall survival; PFS, progression-free survival; CT, chemotherapy treated group; RT, radiotherapy alone group; 5-FU, 5-fluorouracil; UFT, uracil and tegafur; NS, not significant.
adjuvant cisplatin 80 mg/m² day 1 and 5-fluorouracil (5-FU) 1 g/m² days 1–4 × 3 has been considered standard treatment for advanced-stage NPC in the USA.

Although the radiotherapy control arm of the Intergroup study [17, 18] has been criticised for its poor results in a heterogenous histological mix of WHO type I, II and III NPC patients, raising questions of the applicability of the results for WHO type II and III NPC patients in endemic areas, a confirmatory study from Taiwan by Lin et al. [21] demonstrated progression-free and overall survival advantage using two cycles of concurrent chemotherapy with cisplatin 20 mg/m²/day plus 5-FU 400 mg/m²/day by 96-h continuous infusion during weeks 1 and 5 of radiotherapy.

Two further studies in Hong Kong have been undertaken at the Prince of Wales Hospital in collaboration with Queen Elizabeth Hospital [19, 20], and at the Queen Mary Hospital [22], in patients with nodally advanced NPC (Table 2). The overall survival analysis of the first study demonstrated significant benefit in favour of chemo-radiation using cisplatin 40 mg/m² weekly during radiotherapy [20]. In the second factorial study with patients sequentially randomised to receive uracil and tegafur (UFT) or not concurrently with radiotherapy, and then further randomised to receive adjuvant chemotherapy or not using PF/VBM (cisplatin, 5-FU, vincristine, bleomycin and methotrexate); a borderline overall survival benefit was shown for UFT concurrent with radiotherapy arms and no survival advantage was shown for the arms with adjuvant chemotherapy [22].

It thus appears that one can confidently apply concurrent cisplatin–radiation with or without adjuvant chemotherapy using cisplatin and 5-FU as standard treatment for the locoregionally advanced NPC. The optimal cisplatin schedule has not been defined.

Neo-adjuvant chemotherapy followed by concurrent chemo-radiation

Since the use of both neo-adjuvant chemotherapy and concurrent chemo-radiation has been shown consistently to improve progression free and/or overall survival in advanced NPC, the development of sequential neo-adjuvant chemotherapy and concurrent chemo-radiation would seem a logical strategy in an attempt to summate the benefit from both approaches. In addition, when concurrent chemo-radiation, rather than radiotherapy alone, is used as the mainstay treatment, patients tolerate neo-adjuvant chemotherapy better than adjuvant chemotherapy for reasons discussed earlier. This strategy has been tested in two phase II studies at Peter Macallum Institute in Australia [26] and Prince of Wales Hospital in Hong Kong [8]. Both studies demonstrated that neo-adjuvant chemotherapy followed by concurrent chemo-radiotherapy was well tolerated, with encouraging survival rates. The strategy of neo-adjuvant chemotherapy followed by concurrent chemo-radiation should be further studied in a prospective randomised fashion against concurrent chemo-radiation.

Metastatic disease

Combination chemotherapy using cisplatin (100 mg/m²) administered together with a 3- to 5-day infusion of 5-FU (1 g/m²) consistently yields a response rate of 66–78% with a median survival of 11 months [27, 28], and is regarded as the standard therapy for metastatic NPC. Newer agents including paclitaxel and gemcitabine have demonstrated high response rates and favorable toxicity profile given in combination with cisplatin or carboplatin [29–33]. However, patient survival remains poor after initial response to chemotherapy and hence novel therapy is very much needed. Ongoing research is focusing on biological agents that target epidermal growth factor receptor, with a phase II study demonstrating that the addition of cetuximab to carboplatin in patients with platinum-refractory metastatic NPC has clinical benefit [34].

References


