Nasopharyngeal carcinoma – EML

The application sought the addition of cisplatin and oxaliplatin to the core list of the Essential Medicines List for the treatment of nasopharyngeal carcinoma. The application also sought endorsement of carboplatin, fluorouracil and paclitaxel (currently included on the complementary list) specifically for use in this indication.

The application, amended to include details of the Expert Committee's consideration and decision, is presented in this section.

Introduction

Globally, nasopharyngeal carcinoma (NPC) is an uncommon cancer; approximately 80 000 new cases are reported per year and NPC accounts for 0.7% of all cancers. In North America and Europe, the incidence rate is less than 1 case per 100 000 population, but in endemic areas such as southern China (e.g. Hong Kong Special Administrative Region) and south-east Asia, the annual age-standardized incidence rates in men and women are as high as 20–30 and 8–15 cases per 100 000 population respectively *(1)*.

Historically, NPC has been classified into different histological subtypes: type 1 (I) squamous cell carcinoma; type 2a (II) keratinizing undifferentiated carcinoma; and type 2b (III) non-keratinizing undifferentiated carcinoma. The WHO III subtype is the commonest form of NPC in endemic areas and differs from the squamous cell subtype in its association with the Epstein–Barr virus and sensitivity to chemotherapy and radiotherapy. Staging of NPC is based on the depth of invasion of the soft tissue, cranial nerves and bony structures at and near the nasopharynx by the primary tumour, the involvement of local and regional lymph nodes of the head and neck, and the presence of distant metastases. In Hong Kong SAR, the stage distribution at presentation is: stage I, 7%; stage IIA–B, 41%; stage III, 25%; stage IVA–C, 28%. The age-adjusted mortality rate of NPC is 3.9 per 100 000 persons; 5-year overall survival (OS) in stage I and II NPC is now approaching 90%, and in non-metastatic stage III and IV it is around 60%.

The standard of care for the treatment of stage I NPC is radiotherapy (RT); non-metastatic stage II–IV NPC is treated with concurrent chemoradiotherapy, with or without adjuvant chemotherapy. A total RT dose of 70 Gy is needed for eradication of gross tumour and either 50–60 Gy or 46–60 Gy for elective treatment of sites at potential risk. Three-dimensional RT is the minimum requirement, while intensity-modulated radiation therapy is the preferred approach in expert centres. Neoadjuvant chemotherapy is sometimes used to down-stage those locally advanced NPCs that cannot be encompassed readily within the radiation field without incurring significant risks to adjacent normal tissues. For metastatic NPC, the standard first-line therapy is a platinum-based doublet that commonly consists of cisplatin or carboplatin in combination with one of the following drugs: fluorouracil (5-FU), gemcitabine, paclitaxel, docetaxel. Other drugs such as capecitabine, irinotecan, doxorubicin, vinorelbine and oxaliplatin can also be used, alone or in combination. For locally recurrent NPC, the options are individualized on the basis of the patient's condition, prior oncological

treatment and disease stage at recurrence; these may include re-irradiation, surgery or palliative chemotherapy.

Public health relevance

Although NPC is the most common malignant tumour of the nasopharynx, it constitutes only 0.7% of cancers worldwide. According to GLOBOCAN, the age-standardized incidence for both sexes in many countries is 1 per 100 000 people per year. Globally, there are 80 000 new cases per year, making NPC the 23rd most common of all new cancers worldwide. GLOBOCAN estimates that men are 2–3 times more likely than women to develop NPC. Geographically, south-east Asia, southern China and north African countries have the highest prevalence of NPC *(1)*. The stark difference in geographical distribution suggests that genetic factors play a large role in NPC susceptibility.

Requirements for diagnosis, treatment, and monitoring

Diagnostics

Diagnosis is based on histological examination. Immunohistochemical detection for Epstein–Barr virus-encoded small RNA expression may be useful for distinguishing inflammatory atypia from non-keratinizing NPC.

Testing

Staging of NPC is based on the staging system of the Union for International Cancer Control and the American Joint Committee on Cancer. Routine staging procedures include history, physical examination (including cranial nerve examination), complete blood cell count, serum biochemistry (including liver function test), chest X-ray, nasopharyngoscopy, computerized tomography (CT) scan or magnetic resonance imaging (MRI) of nasopharynx and base of skull and neck. Although MRI is generally preferred if available, each centre will choose the best imaging technique according to its usual clinical practice and experience. Imaging for distant metastases, including isotope bone scan and CT scan of chest and upper abdomen, could be considered for at-risk subsets (node-positive, especially N3 stage) and for those patients in whom clinical or biochemical abnormalities have been detected. The use of positron emission tomography-computerized tomography(PET-CT) and plasma/serum load of Epstein–Barr viral DNA are optional *(2)*.

Administration and care of patients

Planning and delivery of RT should be done by a team of qualified personnel at an experienced oncology centre. As a minimum, the team should comprise radiation oncologists, radiologists, oncology nurses, physicists and radiographers. During RT, patients should be carefully and regularly monitored by clinicians and nurses for any treatment-related toxicities. Supportive measures such as nutritional supplementation, skin care,

antiemetics, pain control and, if applicable, treatment for chemotherapy-related marrow toxicities should be readily provided. Assessment of post-treatment response in the nasopharynx and neck should be made via clinical and endoscopic examination and/or imaging studies. MRI is often used to evaluate the response to RT or chemoradiotherapy, especially for stage T3 and T4 tumours, although distinguishing between post-irradiation changes and recurrent tumours may be difficult. Follow-up for patients includes periodic examination of the nasopharynx and neck, cranial nerve function and evaluation of systemic complaints to identify distant metastasis. For stage T3 and T4 tumours, MRI might be used on a 6- to 12-month basis to evaluate the nasopharynx and the base of the skull, at least for the first few years after treatment. Evaluation of thyroid function in patients with irradiation to the neck is recommended at 1, 2 and 5 years *(2)*.

Overview of regimens

The following include basic information on administration and dosing of chemotherapy during concurrent chemoradiotherapy, and palliative chemotherapy; no details are given of ancillary medications pertaining to the management of adverse events.

Standard regimens for concurrent chemotherapy during RT for non-metastatic stage II–IV NPC

- **Low-dose cisplatin at weekly intervals, starting at day 1 of RT (6–8 cycles)**
  - cisplatin 40 mg/m^2 IV infusion[1] weekly

- **High-dose cisplatin at 3-weekly intervals during RT**
  - cisplatin 100 mg/m^2 IV infusion on days 1, 22 and 43

The Expert Committee noted that the EML currently includes carboplatin with a square box symbol as representative of the therapeutic class of platinum chemotherapy agents. However, the Committee highlighted that, in the treatment of NPC, cisplatin is the recommended standard and it was therefore appropriate that cisplatin be specifically included in the EML for this indication.

Oxaliplatin, another platinum agent, has also been shown to improve outcomes when combined with RT; however, it has not been shown to be superior to cisplatin and is more expensive. An alternative regimen of oxaliplatin is an option for patients who have contraindications or who cannot tolerate cisplatin.

- **Oxaliplatin for patients who cannot tolerate cisplatin or have contraindications**
  - oxaliplatin 70 mg/m^2 IV infusion weekly during radiation for 6 weeks

[1] Infusion time of cisplatin depends on the volume of normal saline in which cisplatin has been diluted and on the hydration scheme, which may vary across institutions. Prolonged infusion may need inpatient administration.

The Committee considered that carboplatin (already listed) was an alternative platinum-based treatment option to cisplatin for NPC and there was no clear justification for oxaliplatin being added to the EML for this indication.

Importantly, the Committee noted that the addition of adjuvant chemotherapy after concurrent treatment has not been shown to improve overall survival and is not recommended for all patients but has been included in some guidelines in Europe and USA. In the absence of a demonstrated survival advantage, the Committee considered that inclusion of adjuvant chemotherapy treatment options on the EML (for use after standard chemoradiation) was not supported.

Standard regimens for palliative or neoadjuvant chemotherapy

- **Fluorouracil and cisplatin (or carboplatin), 3-weekly schedule (6 cycles if palliative, 2–3 cycles if neoadjuvant)**
  - cisplatin 80–100mg/m^2 IV infusion[2] on day 1
    (*or* carboplatin AUC 5 or 6 IV infusion on day 1)
  - 5-FU 1000 mg/m^2 per 24 hours IV infusion on days 1–4 or 1–5

- **Paclitaxel and carboplatin (or cisplatin), 3-weekly schedule (6 cycles if palliative, 2–3 cycles if neoadjuvant)**
  - carboplatin AUC 5 or 6 IV infusion on day 1
    (*or* cisplatin 80–100 mg/m^2 IV infusion on day 1)
  - paclitaxel 135 mg/m^2 IV infusion on day 1

Several other agents have been tested in this setting and would be considered appropriate alternatives. The application proposed listing only of these regimens on the basis of their common use and widespread availability.

Review of benefits and harms

Benefits

At least eight randomized studies have confirmed the survival benefit of adding concurrent platinum-based chemotherapy to RT in patients with non-metastatic stage II–IVB NPC *(3-10)*. Two meta-analyses have reported an 18% reduction in the risk of death and an absolute survival benefit of 4–6% at 5 years with the use of chemotherapy in addition to radiation *(11, 12)*. The largest effect in terms of overall survival– from approximately 65% to 85% – was found for concomitant chemotherapy, with a pooled HR for death of 0.48 (95% CI: 0.32–0.72), which corresponds to an absolute survival benefit of 20% after 3 years *(12)*. Metastatic or recurrent NPC is highly chemosensitive, and first-line doublet chemotherapy has been

[2] Infusion time of cisplatin depends on the volume of normal saline in which cisplatin has been diluted and on the hydration scheme, which may vary across institutions. Prolonged infusion may need inpatient administration.

shown to achieve response rates of 50–80% in multiple phase II trials, with a median time to progression of 5–11 months and median overall survival of 12–20 months *(13-20)*.

Few prospective randomized trials have been conducted in this setting. The impact on survival of palliative chemotherapy in the second and subsequent lines of treatment of metastatic or recurrent NPC is unclear.

Harms and toxicity considerations

Common

In patients receiving concurrent cisplatin-containing regimens during RT, the addition of chemotherapy commonly results in increased nausea and vomiting, myelosuppression, anaemia, renal impairment and RT-related oropharyngeal mucositis (which may result in odynophagia and weight loss). Carboplatin has a similar adverse effect profile in the above regimens *(21)*. These acute toxicities can usually be successfully managed and palliated with good supportive care *(4, 6, 7, 9)*.

The impact of concurrent cisplatin on the incidence of late RT-related toxicities is still being defined. Some institutional reports suggest that cisplatin may exacerbate the risk of hearing impairment following RT, but not the risk of late neurological and endocrine toxicities. Low-grade peripheral neuropathy is common in patients treated with oxaliplatin but is typically mild and reversible *(10)*.

Serious

The use of chemotherapy increases the risk of myelosuppression and thus the risk of febrile neutropenia and infections; however, the risk of severe infection with the above regimens in this population is low (1%) *(4, 6, 7, 9)*.

Recommendations

On the basis of the evidence presented in the application, the Expert Committee recommended that cisplatin be added to the complementary list of the EML for the treatment of nasopharyngeal cancer.

The Committee also endorsed the listing of carboplatin, fluorouracil and paclitaxel (already included in the complementary list) for this indication.

In the absence of evidence demonstrating a survival advantage of oxaliplatin over other platinum-based chemotherapy options, and the availability of both cisplatin and carboplatin on the EML, the Committee did not recommend the addition of oxaliplatin to the EML for treatment of nasopharyngeal cancer.

1. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013 [Available from: http://globocan.iarc.fr.
2. Chan AT, Gregoire V, Lefebvre JL, Licitra L, Hui EP, Leung SF, et al. Nasopharyngeal cancer: EHNS-ESMO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2012;23(Suppl 7):vii83-5.
3. Al-Sarraf M, LeBlanc M, Giri PG, Fu KK, Cooper J, Vuong T, et al. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized Intergroup study 0099. J Clin Oncol. 1998;16(4):1310-7.
4. Chan AT, Teo PM, Ngan RK, Leung TW, Lau WH, Zee B, et al. Concurrent chemotherapy-radiotherapy compared with radiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: progression-free survival analysis of a phase III randomized trial. J Clin Oncol. 2002;20(8):2038-44.
5. Chen QY, Wen YF, Guo L, Liu H, Huang PY, Mo HY, et al. Concurrent chemoradiotherapy vs radiotherapy alone in stage II nasopharyngeal carcinoma: phase III randomized trial. J Natl Cancer Inst. 2011;103(23):1761-70.
6. Lee AW, Lau WH, Tung SY, Chua DT, Chappell R, Xu L, et al. Preliminary results of a randomized study on therapeutic gain by concurrent chemotherapy for regionally-advanced nasopharyngeal carcinoma: NPC-9901 Trial by the Hong Kong Nasopharyngeal Cancer Study Group. J Clin Oncol. 2005;23(28):6966-75.
7. Lin JC, Jan JS, Hsu CY, Liang WM, Jiang RS, Wang WY. Phase III study of concurrent chemoradiotherapy versus radiotherapy alone for advanced nasopharyngeal carcinoma: positive effect on overall and progression-free survival. J Clin Oncol. 2003;21(4):631-7.
8. Ma BB, Hui EP, Chan AT. Systemic approach to improving treatment outcome in nasopharyngeal carcinoma: current and future directions. Cancer Sci. 2008;99(7):1311-8.
9. Wee J, Tan EH, Tai BC, Wong HB, Leong SS, Tan T, et al. Randomized trial of radiotherapy versus concurrent chemoradiotherapy followed by adjuvant chemotherapy in patients with American Joint Committee on Cancer/International Union against cancer stage III and IV nasopharyngeal cancer of the endemic variety. J Clin Oncol. 2005;23(27):6730-8.
10. Zhang L, Zhao C, Peng PJ, Lu LX, Huang PY, Han F, et al. Phase III study comparing standard radiotherapy with or without weekly oxaliplatin in treatment of locoregionally advanced nasopharyngeal carcinoma: preliminary results. J Clin Oncol. 2005;23(33):8461-8.
11. Baujat B, Audry H, Bourhis J, Chan AT, Onat H, Chua DT, et al. Chemotherapy in locally advanced nasopharyngeal carcinoma: an individual patient data meta-analysis of eight randomized trials and 1753 patients. Int J Radiat Oncol Biol Phys. 2006;64(1):47-56.
12. Langendijk JA, Leemans CR, Buter J, Berkhof J, Slotman BJ. The additional value of chemotherapy to radiotherapy in locally advanced nasopharyngeal carcinoma: a meta-analysis of the published literature. J Clin Oncol. 2004;22(22):4604-12.
13. Au E, Ang PT. A phase II trial of 5-fluorouracil and cisplatinum in recurrent or metastatic nasopharyngeal carcinoma. Ann Oncol. 1994;5(1):87-9.
14. Boussen H, Cvitkovic E, Wendling JL, Azli N, Bachouchi M, Mahjoubi R, et al. Chemotherapy of metastatic and/or recurrent undifferentiated nasopharyngeal carcinoma with cisplatin, bleomycin, and fluorouracil. J Clin Oncol. 1991;9(9):1675-81.
15. Chua DT, Sham JS, Au GK. A phase II study of docetaxel and cisplatin as first-line chemotherapy in patients with metastatic nasopharyngeal carcinoma. Oral Oncol. 2005;41(6):589-95.

16. Li YH, Wang FH, Jiang WQ, Xiang XJ, Deng YM, Hu GQ, et al. Phase II study of capecitabine and cisplatin combination as first-line chemotherapy in Chinese patients with metastatic nasopharyngeal carcinoma. Cancer Chemother Pharmacol. 2008;62(3):539-44.
17. Ma BB, Hui EP, Wong SC, Tung SY, Yuen KK, King A, et al. Multicenter phase II study of gemcitabine and oxaliplatin in advanced nasopharyngeal carcinoma--correlation with excision repair cross-complementing-1 polymorphisms. Ann Oncol. 2009;20(11):1854-9.
18. Ngan RK, Yiu HH, Lau WH, Yau S, Cheung FY, Chan TM, et al. Combination gemcitabine and cisplatin chemotherapy for metastatic or recurrent nasopharyngeal carcinoma: report of a phase II study. Ann Oncol. 2002;13(8):1252-8.
19. Taamma A, Fandi A, Azli N, Wibault P, Chouaki N, Hasbini A, et al. Phase II trial of chemotherapy with 5-fluorouracil, bleomycin, epirubicin, and cisplatin for patients with locally advanced, metastatic, or recurrent undifferentiated carcinoma of the nasopharyngeal type. Cancer. 1999;86(7):1101-8.
20. Yeo W, Leung TW, Chan AT, Chiu SK, Yu P, Mok TS, et al. A phase II study of combination paclitaxel and carboplatin in advanced nasopharyngeal carcinoma. Eur J Cancer. 1998;34(13):2027-31.
21. Hui EP, Chan ATC, Le QT. Treatment of early and locoregionally advanced nasopharyngeal carcinoma. In: UpToDate [website]. Waltham, MA: UpToDate; 2014.