short review

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Nasopharyngeal carcinoma

Essential news regarding current guidelines

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Summary The incidence of nasopharyngeal carcinoma (NPC) shows geographically differences between certain parts of Asia and the rest of the world. While NPC is an orphan disease in Western Europe/United States of America, it is endemic to southern China, southeast Asia and northern Africa. NPC is a radio- and chemotherapy sensitive malignancy. Although it is essential to follow the evidence-based treatment recommendations outlined in the international guidelines, it has to be emphasized that the field is rapidly involving and relevant data gaps such as the optimal treatment strategy for stage II disease, non-Epstein Barr Virus associated NPC or the role of immunotherapy in low incidence areas exist. These topics will be addressed in this article. Most importantly, interdisciplinary management of NPC patients is key for the optimal management at all disease stages.

Keywords Ebstein-Barr Virus · Immunotherapy · Locally advanced NPC · Recurrent/metastatic NPC · Induction chemotherapy

Introduction

Incidence rates of nasopharyngeal carcinoma (NPC) show geographically differences between certain parts of Asia and the rest of the world. While NPC is an orphan disease in Western Europe/United States of America with an incidence of 0.5 and 2 cases per 100,000 people, it is endemic to southern China, southeast Asia, and northern Africa [1]. In endemic regions the incidence lies between 4 and 25 cases per 100,000 individuals [2, 3]. In the USA and Europe, alcohol and tobacco use are the major risk factors for the development of NPC, while NPC is mainly associated with Epstein–Barr virus (EBV) infection in endemic regions [1]. NPC more commonly affects male patients than female patients (ratio 2.75) [2]. According to the World Health Organization (WHO), three histological NPC subtypes can be distinguished: keratinizing squamous cell carcinoma (type I), nonkeratinizing carcinoma, which is further divided into differentiated (type II) and the EBV-associated undifferentiated (type III) NPC, and the rare type of basaloid squamous cell carcinoma [3]. In southern China the majority of patients are diagnosed with type III (95%) NPC followed by type II (3%) and type I (2%), whereas in Northern America type III NPC accounts for 63%, type I for 25% and type II for 12% of the cases [4].

From this background it is not surprising that most clinical NPC trials were performed in endemic regions including mainly NPC type III patients and a data gap regarding the optimal treatment strategy for non-EBV-associated NPC exists. In the absence of clinical trials in this subgroup, the treatment recommendations for non-EBV-associated NPC patients are identical to the ones given for NPC type III patients.

However, it is essential for the optimal management of NPC patients that a multidisciplinary team is involved including radiation oncologists and medical oncologists. In addition, it is advised to refer NPC patients to specialized centres, since it has been shown that treatment of NPC patients in high-volume facilities improves the survival of these patients [5].

NPC is sensitive to both radiotherapy (RT) and chemotherapy. Thus, standard treatment options include (chemo)radiation for localised disease and chemotherapy (plus/minus immunotherapy) for re-

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current/metastatic (R/M) NPC. Surgery has no role in the treatment of newly diagnosed or metastatic NPC.

The recent National Comprehensive Cancer Network (NCCN), European Society for Medical Oncology (ESMO) and American Association of Clinical Oncology (ASCO) guidelines provide comprehensive recommendations regarding the diagnosis, therapy and follow-up of NPC [6–9].

The treatment landscape of NPC is rapidly evolving and a couple of practice changing studies have been reported in recent years, although the therapy of R/M NPC remains challenging.

It is the aim of this brief report to address the most relevant and controversial recommendations made by the aforementioned guidelines for the management of NPC taking into account the most recent developments from a medical oncologist's point of view.

Since early stage I is commonly treated with single-modality treatment (i.e. radiotherapy) accompanied by a good prognosis, the focus will be laid on stage II–IV NPC.

Intermediate stage II NPC

The prognosis for patients with stage II (i.e. T1 to T2, N1 or T2N0) is generally favourable. There has been an ongoing debate regarding the optimal therapy—radiotherapy alone vs. chemoradiation—in this setting. While the international guidelines state that both options are valid, a closer look at the data seems to be necessary:

A phase III randomised study performed in the two-dimensional conventional radiotherapy era compared RT (68 to 70 Gy) to RT in combination with cisplatin weekly given at 30 mg/m^2 in 230 stage II NPC patients. CRT was superior to RT alone in terms of overall survival (OS) at 10 years (OS 83.6 vs 65.8%, $p = 0.001$). Besides the caveat of the RT technique, it has to be stated that the OS benefit was mainly driven by the T2N1 population, while the Chinese 1992 staging system was used and a fraction of patients would be classified as stage III patients according to the current Union Against Cancer/American Joint Committee on Cancer (UICC/AJCC) TNM classification criteria [10].

Employing intensity-modulated radiotherapy (IMRT) the benefit of adding chemotherapy to RT in stage II patients becomes less clear. While meta-analyses mainly from retrospective trials showed comparable outcomes accompanied by less toxicity for IMRT alone [11], more recent prospective studies confirmed this finding:

A phase III study, which included 341 low-risk (defined as all lymph node size < 3 cm, no level IV/VB lymph nodes, no extra-nodal extension and EBV DNA < 4000 copies/mL) stage II and T3,N0,M0 (stage III) patients, comparing IMRT to IMRT plus cisplatin 100 mg/m^2 given on days 1, 22, and 43 demonstrated that IMRT is non-inferior to chemoradiation in terms of OS (3-year OS 98 vs. 99%, hazard ratio [HR] = 3.22; 95% confidence interval [CI] 0.65–15.98). Grade ≥ 3 toxicities were more frequent with chemoradiation versus IMRT alone [12].

Likewise, a randomized phase II trial conducted in 84 stage II patients showed that the OS in individuals treated with IMRT alone was similar to those treated with chemoradiation (100 vs. 94%, $p = 0.25$) [13].

From this background it seems reasonable to omit chemotherapy in low-risk stage II NPC patients and opt for chemoradiation in stage II patients with adverse features (such as bulky disease or high plasma EBV-DNA, T2,N1 patients), although an individualised treatment decision has to be made taking into account the heterogeneity of this subgroup [7, 9].

Stage III–IVA NPC

During the last few decades a constant improvement in survival in stage III–IV NPC has been observed due to the introduction of chemotherapy plus IMRT into clinical practice.

The current standard of care is induction chemotherapy followed by chemoradiation (± adjuvant metronomic capecitabine) rather than chemoradiation followed by adjuvant chemotherapy [6, 7, 9].

This recommendation is based on several clinical phase III studies:

In a randomized phase III study conducted in China 480 patients with node-positive stage III to IVB (AJCC seventh edition staging classification) NPC were treated with either induction chemotherapy (ICT) followed by concurrent chemoradiation (CRT) or concurrent chemoradiation alone. ICT consisted of three cycles of docetaxel (60 mg/m^2 d1), cisplatin (60 mg/m^2 d1), and fluorouracil (daily 600 mg/m^2 at d1–5) (=TPF) every 3 weeks. Of note the dosing of this regimen is lower compared to the European version of TPF. In an updated analysis the authors reported the results with a median follow-up of 71.5 months confirming the initial report. ICT plus CRT was superior to CRT alone yielding in a better failure-free survival (77.4 vs. 66.4%, $p = 0.019$), OS (85.6 vs. 77.7%, $p = 0.042$), distant failure-free survival (88 vs. 79.8%, $p = 0.030$), and locoregional failure-free survival (90.7 vs. 83.8%, $p = 0.044$) [14].

These results were confirmed in the phase III GORTEC 2006–02 trial employing full-dose TPF as an ICT regimen and a similar design to study outlined above. The 3-year PFS and OS rates were 73.9% in the TPF arm versus 57.2% in the CRT arm (HR = 0.44; 95% CI 0.20–0.97, $p = 0.042$) and 86.3% in the TPF arm versus 68.9% in the reference arm (HR = 0.40; 95% CI 0.15–1.04, $p = 0.05$), respectively [15]. The trial, however, was prematurely stopped due to accrual issues.

The most widely used ICT regimen is cisplatin 80 mg/m^2 administered on day 1 plus gemcitabine 1000 mg/m^2 on days 1 and 8 given every 3 weeks for 3 cycles (GP), which was established in a phase III

trial including 480 node-positive stage III to IVB (AJCC seventh edition staging classification) NPC patients, which were randomly assigned to ICT followed by CRT vs. CRT alone. ICT group showed a significantly higher 5-year OS compared to CRT alone (87.9 vs. 78.8%, HR = 0.51; 95% CI 0.34–0.78; $p = 0.001$), failure-free survival (81.3 vs. 67.2%, HR = 0.51, 95% CI 0.36–0.73) and distant metastasis-free survival (90 vs. 77.9%, HR 0.42, 95% CI 0.27–0.67). Of note, a subgroup analysis indicated that there was no OS benefit for patients, whose pretherapy cell-free EBV DNA was < 4000 copies/mL (90.6 vs. 91.4%, $p = 0.77$), although this result has to be interpreted with caution, since pretreatment EBV DNA was only available for 65% of the study population. Toxicities were well manageable [16].

The recent update of the network meta-analysis chemotherapy for nasopharynx carcinoma (MAC-NPC) collaborative group analysing 28 trials with 8214 NPC patients confirmed that ICT with taxanes followed by CRT (HR = 0.75; 95% CI 0.59–0.96; *p* score 92%) and ICT without taxanes followed by CRT (HR= 0.81; 0.69–0.95; *p* score 87%) have a higher benefit for OS compared to CRT alone [17].

Since the above-mentioned studies excluded T3N0M0 patients, the evidence for ICT in this group is lower and CRT alone a reasonable option in this population [7].

In an attempt to further improve the outcomes in node-positive stage III–IVA patients treatment intensification studies were performed.

At the ASCO 2023 annual meeting the phase III Continuum trial was presented, which randomly assigned 417 stage III/IV (excluding T3–T4,N0 and T3,N1) patients to ICT with GP plus the immune checkpoint inhibitor sintilimab followed by CRT and sintilimab maintenance for 12 cycles or to standard of care GP followed by CRT. The primary endpoint was event-free survival (EFS) and significantly improved by GP plus sintilimab compared to the standard of care arm (3-year EFS: 86.1 vs. 76.0%, HR = 0.59, 95% CI 0.38–0.92; $p = 0.019$). OS was not different and a longer follow-up is needed. As expected and despite being well manageable, there were higher rates of grade 3–5 adverse events compared to the standard arm (75.15 vs. 70.4%) [18].

This trial defined a potential new standard of care in this setting, although sintilimab is mainly available in Asia and not globally approved for the treatment of NPC.

Another "intensification" study investigated the role of adjuvant metronomic capecitabine given orally at 650 mg/m^2 twice daily for 1 year vs. observation in 406 stage III/IV (excluding T3–T4,N0 and T3,N1) patients previously treated with CRT or ICT followed by CRT. Metronomic capecitabine improved 3-year failure-free survival (85.3 vs. 75.7%, HR = 0.50; 95% CI 0.32–0.79) and 3-year OS (93.3 vs. 88.6%, HR = 0.44; 95% CI 0.22–0.88). Adverse event rate was higher in the experimental arm compared to the observation group [19].

Since the majority of the patients (77%) were pretreated with ICT plus CRT, the results of this study are applicable to the current practice and metronomic capecitabine is stated as an option for high-risk patients according to the ESMO guidelines [6].

R/M NPC

Patients with small local recurrences should be evaluated for salvage surgery. Re-irradiation is an option as well in this setting and should be discussed in a multidisciplinary team [7].

For patients not amenable to local therapy and for newly metastatic patients systemic therapy is the standard of care.

The regimen of choice is GP, since a randomised phase III study comparing GP to cisplatin plus fluorouracil (CF) in 362 R/M NPC showed an improved PFS for GP vs. CF (7 vs. 5.6 months; HR = 0.55; 95% CI 0.44–0.68) [20]. At a median follow-up of 70 months, GP also improved OS (22.1 vs. 18.6 months, HR = 0.72, 95% CI 0.58–0.90) [21]. GP was well tolerated, although it was associated with more hematologic toxicity than CF [20].

Patients with newly diagnosed metastatic NPC should undergo consolidation RT upon response to chemotherapy rather than chemotherapy alone [7].

This recommendation is based on the results of a randomized phase III trial investigating chemotherapy with CF vs. chemotherapy with CF plus RT in 126 metastatic NPC patients, who achieved a complete or partials response after three cycles of CF. The authors reported a 24-month OS of 76.4% (95% CI 64.4–88.4%) in the CF plus RT group, compared to 54.5% (95% CI 41.0–68.0%) in the chemotherapy alone group [22].

There are currently three published randomized phase III trials (Jupiter-02, Captain 1st and Rational 309) [23–25] demonstrating that the addition of immunotherapy to GP improves PFS compared to GP alone in R/M NPC patients.

The Jupiter-02 study conducted in 289 R/M NPC patients, for instance, showed that GP in combination with the immune checkpoint inhibitor toripalimab results in an PFS benefit compared to GP alone (11.7 versus 8.0 months; HR = 0.52; 95% CI 0.36–0.74, $p = 0.0003$) [23]. The study results were recently updated and a significant OS benefit for the toripalimab group reported over the GP arm (median OS not reached vs. 33.7 months; HR = 0.63; 95% CI 0.45–0.89, $p = 0.0083$) [26].

Thus, it is evident that immunotherapy with toripalimab plus GP is the new standard of care in this setting, although it remains controversial if toripalimab can be substituted by other checkpoint inhibitors in regions where toripalimab is not available. This controversy will be ongoing given the negative results of the phase III Keynote 122 trial, which failed to show

superiority of pembrolizumab compared to investigator's choice chemotherapy in the second-line platinum pretreated setting [27].

Conclusion

Nasopharyngeal carcinoma (NPC) is a rare malignancy outside of southern Asia/China and significant data gaps regarding the optimal treatment strategy for non-Epstein–Barr virus (EBV)-associated NPC exist. NPC is a radio- and chemotherapy sensitive disease: For locally advanced NPC induction chemotherapy followed by chemoradiotherapy is regarded as the standard of care, while in the metastatic setting systemic therapy is the treatment of choice. A growing number of trials have shown that the course of the disease can be modified by implementing immunotherapy into the current treatment regimens. Interdisciplinary management is key for the optimal management of NPC patients at all disease stages.

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