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SYSTEMIC TREATMENT OF NASOPHARYNGEAL CARCINOMA: LITERATURE REVIEW AND CURRENT RECOMMENDATIONS

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SUMMARY

Nasopharyngeal carcinomas, dominated by the undifferentiated subtype, are a specific entity that differs from other head and neck cancers; they present complex epidemiological characteristics, with an unusual geographical distribution and a multifactorial etiopathogeny, as well as evolutive particularities with a high rate of invasion and metastasis requiring an exhaustive staging work-up and leading to a frequent failure of our therapeutic management. This management is based on radiotherapy, which remains the mainstay of treatment for localized nasopharyngeal carcinomas. With more precise intensity modulation techniques, locoregional control has been improved. Treatments combining chemotherapy and radiotherapy according to different modalities (concomitant, induction and/or adjuvant)) have improved disease-free survival and overall survival in locally advanced stages, while further therapeutic advances are needed for better treatment of recurrent and/or metastatic disease. Immune checkpoint inhibitors represent a first step in this way despite the absence of predictive factors of response.

KEYWORDS: Nasopharyngeal carcinoma, Epstein Barr virus, Intensity-modulated radiotherapy, Chemotherapy, Immunotherapy.

INTRODUCTION

Nasopharyngeal carcinomas (NPCs) are epithelial malignant tumors, most often developing in the lateral pharyngeal space. They are characterized by an endemic distribution in certain regions of the world, a complex etiopathogenesis, and a high rate of invasion and metastases compared to other head and neck tumors, leading to frequent treatment failure, which is currently based on radiotherapy and/or chemotherapy according to the stage of the disease. In this article, we will review the literature on the efficacy and tolerance of different systemic treatments and the results of the latest therapeutic trials, and put these data in perspective with the current recommendations for the treatment of NPC.

Epidemiology and etiology

NPCs represent more than 133.354 new cases worldwide in 2020 and are responsible for 80.008 deaths, with an age-standardized incidence rate of around 1.5 per 100.000 inhabitants. Geographic distribution across the globe represents one of the most important characteristics of the disease: endemic with an incidence of ~ 4-25 per 100.000 inhabitants in South-East China, Indonesia, Malaysia and South-East Asia. The incidence rate is intermediate in the rest of Asia and North Africa and low in the rest of the world. There is also a clear male predominance with a sex ratio of 2.6.[1]

In Morocco, during the period 2013-2017, the population-standardized incidence is estimated at 1.7 per 100.000 inhabitants, comparable to that of the world population during the same period of study.[2]

This unique geographic distribution is attributed to genetic factors but also to environmental factors related to a diet containing nitrosamines.[3] Epstein-Barr virus (EBV) infection is ubiquitous in non-keratinized NPC and high-grade dysplasia, in contrast to the normal epithelium and low-grade dysplasia, and plays an important pathogenic role. Its role in the oncogenesis of keratinizing carcinomas is less clear.[4]

Staging and prognostic factors

WHO Classification

The term « nasopharyngeal carcinoma » refers to all squamous cell carcinomas of the nasopharynx, which are classified according to the 4th edition of the World Health Organization (WHO) classification in 3

histological subtypes: keratinizing (up to 25% of cases), non-keratinizing subdivided into differentiated (around 15%) and undifferentiated (up to 65%) and the very rare basaloid carcinoma subtypes.[5] The non-keratinizing subtype, due to the EBV infection, represents more than 95% of NPC in the endemic areas, while it represents 75% of cases in the United States.[6]

Undifferentiated NPC presents some specific characteristics such as invasive and distant metastatic potential, and sensitivity to radiotherapy and chemotherapy, while the differentiated form, which is not associated with EBV, has a predominantly locoregional development similar to other squamous cell carcinomas of the head and neck, and is less sensitive to chemotherapy and radiotherapy.[7]

Diagnostic work-up

Most tumors have an insidious development and are therefore diagnosed late at a locally advanced or metastatic stage.[8] In order of frequency, NPC metastasizes to bone, liver, lung, and lymph nodes.[9]

Staging work-up should include nasofibroscopy, computed tomography (CT) or magnetic resonance imaging (MRI) of the nasopharynx, skull base and neck coupled with 18-fluorodeoxyglucose positron emission tomography (18-FDG PET). MRI is more sensitive than CT in the assessment of locoregional tumor extension. FDG-PET offers a better lymph node staging than MRI and remains the reference imaging method for detecting distant metastases.[10]

Prognostic factors

Clinical staging of NPC is currently performed according to the 8th edition of the American Joint Committee on Cancer (AJCC) classification.[11] Overall survival (OS) at 5 years is 100%, 93%, 90% and 75% respectively for stages I, II, III and IVA in the IMRT era in a large study in an endemic zone.[12]

TNM classification alone remains insufficient to predict the prognosis. For example, patients with stage I-II NPC (according to the 5th edition of the AJCC classification in this study) and a low plasma EBV DNA level <4.000 copies/ml before treatment had a similar 5-year OS (91%) to that of stage I patients (92%), while the 5-year OS in patients with high plasma EBV DNA levels ≥4.000 copies/ml was lower (64%) than that observed in patients with stage III disease (73%).[13] Pre-therapeutic plasma EBV DNA level is considered a prognostic factor, with a cut-off between 1.500 and 4.000 copies/ml in endemic areas[14,15], but has no impact at present on therapeutic strategy.

Plasma EBV DNA levels are currently evaluated for screening with a sensitivity and specificity of 97.1% and 98.6% respectively in endemic areas[16], but also for staging[17,18], selection of candidates for adjuvant chemotherapy[19], and post-treatment monitoring in localized stages.[20]

Treatment

The majority of clinical trials evaluating different therapeutic strategies in the treatment of NPC have been conducted in endemic areas and therefore in EBV-related non-keratinizing carcinomas.

Due to the deep topography of the nasopharynx, local treatment of non-metastatic forms is based on radiotherapy. At present, the majority of patients with stage I-II NPC are treated by intensity-modulated radiotherapy (IMRT) with or without chemotherapy: at 5 years, estimated OS for stage I and II NPC is 98% and 92% respectively, locoregional failure-free survival (FFS) is 98% and 94%, and distant FFS is 98% and 91%.[21]

Historically, patients with stage III-IVA disease had a poor prognosis due to the high incidence of distant metastases after conventional two-dimensional (2D) radiotherapy, with 5-year OS and Progression-free survival (PFS) of 58.6% and 52.1%, respectively.[22] Since the 2000s, two major advances have improved the prognosis of these locally advanced forms: the gradual integration of IMRT techniques[23], and the addition of concomitant chemotherapy to radiotherapy[24,25], awaiting more data on the place of immunotherapy in these situations.

Chemotherapy

Concomitant chemotherapy

Concomitant radio-chemotherapy (CT-RT) with cisplatin is the standard treatment in stages III-IVA. The 0099 intergroup trial was the first phase III trial conducted in a non-endemic region to show a benefit in OS and recurrence-free survival (RFS) after the addition of concomitant then adjuvant chemotherapy to radiotherapy.[26]

And since then, several phase III trials, almost all conducted in the 2D conventional radiotherapy era, evaluating concomitant chemotherapy, with or without adjuvant treatment, have confirmed this survival benefit in endemic areas.[22,27-33]

The MAC-NPC (meta-analysis of chemotherapy in nasopharynx carcinoma) collaborative group has updated a meta-analysis of individual data on 4806 patients with locally advanced NPC (89% stage III or IV) included in 19 trials: addition of chemotherapy to radiotherapy significantly increased OS (Hazard-Ratio [HR]: 0.79, 95% confidence interval (CI):0.73– 0.86, $p < 0.0001$) at the cost of increased acute toxicity (particularly hematological), but also chronic with ototoxicity and cranial nerve damage. This benefit was seen with concomitant and adjuvant chemotherapy (HR: 0.65, 95% CI: 0.56-0.76) or concomitant alone (HR: 0.80, 95% CI: 0.70-0.93), but not with adjuvant chemotherapy alone

(HR: 0.87, 95% CI: 0.68-1.12) or induction alone (HR: 0.96, 95% CI: 0.80-1.16).[24]

For stage II, a phase III study including 230 patients cT2N0M0 or T1-2N1M0 (including 13% of patients reclassified as stage III according to the AJCC 7th edition classification) demonstrated a survival benefit in the concomitant cisplatin 30mg/m2/week arm compared with conventional 2D radiotherapy alone.[34]

The indication for IMRT in stage II is not yet fully defined. A single-center, randomized phase III trial presented at the ASCO (American Society of Clinical Oncology) meeting in 2022 gives us the first indication for these stage II (AJCC 7th edition) and T3N0 tumors with low EBV DNA <4.000 copies/ml; IMRT alone is not inferior in terms of FFS at 3 years to CT-RT with 3 cycles of cisplatin 100 mg/m2/3 weeks with better tolerability. It should be noted that the acceptable upper limit for non-inferiority was set at 4.5%.[35]

In stage II, according to the recently published joint recommendations of CSCO (Chinese Society of Clinical Oncology) and ASCO, and for T1-2 N1 tumors (AJCC 8th edition), concomitant chemotherapy may be proposed, particularly for T2 N1 tumors. For T2N0 (AJCC 8th edition), chemotherapy is not routinely recommended but may be offered in cases of poor prognostic factors such as large tumors or high plasma EBV DNA copy numbers.[36]

The two cisplatin regimens most commonly used in these studies (40 mg/m2/week and 100 mg/m2/3 weeks), were directly compared in two randomized phases II and III trials.[37,38] The largest study, using IMRT, showed no significant difference in terms of efficacy or grade 3-4 toxicity, although patients in the 100mg/m2/3 weeks arm received only 2 courses of chemotherapy vs. 6 courses in the weekly arm. Both regimens are currently recommended, and a minimum cumulative dose of at least 200 mg/m2 is required.[36]

Other platinum agents such as carboplatin[39,40], oxaliplatin[28] or nedaplatin[41] have been evaluated with interesting results in terms of efficacy and tolerability, making them a good option in cases where cisplatin is contraindicated.

Adjuvant chemotherapy

The main study evaluating the place of adjuvant chemotherapy with cisplatin and 5-fluorouracil (PF) after CT-RT in patients with stage III-IVB NPC (except T3-T4N0, according to the 6th edition of the AJCC classification) showed no benefit in terms of survival to treatment failure or OS[42], in contrast to the MAC-NPC meta-analysis suggesting a survival benefit when concomitant and/or adjuvant chemotherapy is added to radiotherapy.[25]

These contradictory results could be explained in part by the heterogeneity of inclusion criteria in these different trials in terms of prognosis, so a better selection of patients seems necessary. In this sense, the addition of adjuvant chemotherapy with 6 courses of gemcitabine-cisplatin vs. monitoring in stages IIB-IV in the case of residual circulating EBV DNA after CT-RT did not improve RFS or OS in a randomized trial, probably due to low statistical power (50 patients per arm).[43] Poor compliance with adjuvant therapy is another possible explanation for these divergent results; only 55-63% of patients complete the planned cycles.[26,42]

The role of metronomic chemotherapy in improving compliance has recently been explored in a phase III study presented at ASCO 2021 and published the same year, in which patients with stage III-IVA NPC (excluding those with T3-4N0 and T3N1) were randomized to observation or adjuvant capecitabine at a dose of 650 mg/m2 twice daily continuously for up to one year after CT-RT with possible induction chemotherapy in 78% of cases. At 3 years, FFS was significantly improved in the capecitabine arm, as well as OS, with an acceptable safety profile.[44]

The 2nd phase III study presented at the same congress showed a benefit in RFS of the addition of 8 cycles of capecitabine as adjuvant therapy after CT-RT in stage III-IVB NPC with poor prognosis criteria currently requiring induction chemotherapy using the TPF (Docetaxel-cisplatin-5-Fluorouracil) or gemcitabine-cisplatin protocol.[45]

Despite these results with capecitabine monotherapy, PF remains the recommended protocol when adjuvant chemotherapy is indicated.[36] For improved tolerability, reductions in the dose of 20% and dose density to 4 weeks between cycles may be proposed.[42]

Induction chemotherapy

Early studies, conducted in the 90s and early 2000s, compared induction chemotherapy before radiotherapy versus radiotherapy alone, showing an improvement in disease-free survival but no benefit in OS.[46-51]

Since then, randomized phase III trials have compared CT-RT to induction chemotherapy followed by CT-RT using more modern protocols. The addition of three cycles of modified TPF in induction in patients with stage III-IV NPC (except T3-4N0, according to the 7th edition of the AJCC classification) improved OS, locoregional and distant RFS at 3 and 6 years without increasing long-term toxicity.[52,53] These good tolerability results with the TPF protocol were confirmed by the GORTEC 2006-02 trial, despite being stopped early for lack of inclusions.[54]

In another study, patients with stage III-IVB NPC (except T3N0-1, according to the 6th edition of the AJCC classification) who received induction

chemotherapy with cisplatin-5-fluorouracil had better survival results than those who did not receive induction chemotherapy.[55,56] However, two other studies with less commonly used regimens such as mitomycin C - epirubicin - cisplatin - 5-fluorouracil - leucovorin[57] or paclitaxel - carboplatin - gemcitabine[58] did not find this survival benefit.

A more recent phase III study evaluated the benefit of adding three cycles of cisplatin-gemcitabine induction to CT-RT using IMRT in patients with stage III-IVB disease (AJCC 7th edition excluding those with N0 tumors). At 3 years, RFS and OS were significantly improved without any increase in late toxicity. This trial defines a new standard of care for patients with locally advanced NPC.[59]

Induction vs adjuvant chemotherapy

To define the best therapeutic strategy in stage III-IVA NPC, the MAC- NPC group presented at ASCO 2020 the updated data from a meta-analysis including 8221 patients from 28 randomized trials after a median follow-up of 7.2 years. Results in terms of OS, analyzed according to the P-score which measures the probability that one treatment is better than another, show that the best treatment is the sequence of taxane-based induction chemotherapy followed by CT-RT compared with CT-RT alone. The CT-RT followed by adjuvant chemotherapy appears to be the 2nd best sequence.[60] Four other meta-analyses, including trials conducted in endemic areas, confirm the benefit of adding induction chemotherapy compared with CT-RT alone.[61-64]

Currently, there are insufficient data directly comparing induction chemotherapy followed by CT-RT with adjuvant chemotherapy after CT-RT, and the 6-arm NPC-0501 trial showed no significant difference between the induction or adjuvant TPF regimen.[65] The only study directly comparing the 2 strategies has been presented at the ASCO meeting in 2022, with no difference in terms of efficacy between 3 courses of TPF in induction before CT-RT and 3 cycles of 5-fluorouracil-platinum after CT-RT, with slightly different toxicity profiles. The very short median follow-up of 19 months in this study does not yet allow us to define the best therapeutic strategy in this situation.[66]

The joint recommendations of the CSCO and ASCO consider induction chemotherapy followed by CT-RT as the standard of care for stage III-IVA NPCs, with the possible exception of the T3N0 subgroup (according to the 8th edition of the AJCC classification). This sequence allows better compliance to treatment, Tumor-downstaging before radiotherapy and early control of micro-metastatic disease.[36] Five regimens have been selected: cisplatin - gemcitabine[59]; cisplatin - 5-fluorouracil[56,65]; cisplatin - capecitabine[65]; cisplatin - docetaxel (phase II)[67]; and TPF.[53,54] Only one randomized trial directly compared 2 induction regimens, with comparable efficacy of TPF and PF protocols.[68]

Chemotherapy for recurrent/metastatic disease

Despite the absence of randomized trials comparing chemotherapy versus best supportive care in recurrent or metastatic NPC, platinum-based chemotherapy remains the standard treatment in this situation. Median survival in multiple phase II trials ranges from 11 to 28 months, and median time to progression from 7.3 to 10 months.[69] The only phase III trial in this situation comparing 2 platinum-based doublets showed a significant benefit in PFS and OS in favor of the gemcitabine - platinum arm compared with platinum - 5-fluorouracil, probably defining a new standard in first-line.[70]

Similarly, for a lack of randomized trials, no standard of treatment has been approved in 2nd line after a platinum-based doublet, and mono-chemotherapy remains the norm. Active drugs in this situation are gemcitabine, paclitaxel, docetaxel, 5-fluorouracil, capecitabine, vinorelbine, and doxorubicin.

Immunotherapy

EBV-induced NPC is a typical example of an "immunogenic" tumor, with a stroma heavily infiltrated by inflammatory cells. The tumor's escape from the control of the immune system can be explained by several mechanisms:

- poor tumor immunogenicity due to defective antigen presentation by alteration of major histocompatibility complex I (MHC I) genes.[71]
- Overexpression of programmed cell death receptors PD-1 on lymphocyte surface[72], as well as other costimulation-inhibiting molecules such as T-cell immunoglobulin mucin-3 (TIM-3), Lymphocyte Activating 3 (LAG3), T cell immunoreceptor with Ig and ITIM domains (TIGIT) and cytotoxic T lymphocyte-associated protein 4 (CTLA4).[73]
- Modulation of the tumor microenvironment with infiltration by regulatory T lymphocytes (Treg), tumor-associated macrophages (TAMs), and other immunosuppressive cells.[74,75]

Different approaches have been explored in the last few years, but PD-1/PD-L1 checkpoint inhibitors are the most studied.

In 2021, the first results of phase III trials in 1st line metastatic cancer were published. The JUPITER-02 trial tested the addition of toripalimab to chemotherapy with gemcitabine-cisplatin, followed by maintenance with toripalimab or placebo until progression or intolerance. The study was positive for the primary endpoint (PFS), even though the curves did not separate until 6 months after the end of the induction phase. The benefit of OS was marginally significant, requiring further follow-up.[76] The 2nd trial evaluating the addition of camrelizumab to the same chemotherapy regimen showed the same results at interim analysis.[77] These concordant results are encouraging and should lead to a change in practice when the benefit of OS has been

confirmed. Other phases III trials in 1st line with Tislelizumab (NCT03924986) and Nivolumab (NCT04458909) are underway.

In 2nd line, pretreated patients who had received platinum-based chemotherapy were randomly assigned to pembrolizumab or physician's choice chemotherapy (docetaxel, gemcitabine, or capecitabine) in KEYNOTE-122. The trial was negative on its primary endpoint (OS) and no subgroup seemed to benefit from immunotherapy, including patients with PDL1 CPS ≥1.[78]

The place of immunotherapy in NPC remains to be defined, while other phase III trials at early stages (NCT03427827 and NCT03700476) are ongoing.

Targeted therapies

Several phase II trials have evaluated molecules targeting signal transduction pathways, angiogenesis, the cell cycle, and epigenetic modifications.[79] But no targeted therapy is currently approved for the treatment of NPC despite these clinical research efforts.

The latest published results suggest a benefit in OS for the addition of Nimotuzumab, an anti-EGFR antibody, to cisplatin-based CT-RT for stage III-IVA NPC. However, the standard arm is suboptimal in this phase III trial for locally advanced tumors that are currently treated with induction and/or adjuvant chemotherapy.[80]

CONCLUSION

The management of NPC must be personalized according to the stage, performance status, patient comorbidities, available treatments, patient preference, and expected toxicity. A better individualization of treatment via the development of biomarkers is an absolute necessity. Plasma EBV DNA levels are currently under evaluation in many therapeutic trials.

At present, radiotherapy remains the mainstay of treatment for localized NPC; with more precise radiotherapy techniques, locoregional tumoral control has been improved. Combined treatments, using chemotherapy and radiotherapy in different modalities, have improved disease-free survival and overall survival rates in locally advanced stages. The gemcitabine cisplatin protocol, eventually combined with locoregional radiotherapy in de novo metastatic tumors, is the standard of care in relapsed or metastatic NPC while awaiting survival data from the immune checkpoint inhibitors trials.

Declaration of interests

We declare no potential conflicts of interest.

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