Nasopharyngeal carcinoma and therapeutic management: the place of chemotherapy

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introduction

Nasopharyngeal carcinoma (NPC) differs from others head and neck cancers by many points. Its incidence remains high in some parts of the globe, in southern China, Southeast Asia and North Africa. In North Africa there are two peaks of age-specific incidence, in young (between 10 and 20 years old) and adult patients (50 years old) [1, 2].

Among the three histological types, the Undifferentiated Carcinoma of Nasopharyngeal Type (UCNT) (WHO type 2 and 3) is the most frequent in endemic areas; however, squamous cell carcinoma (WHO type 1) is more common in Europe and has a worse prognosis [2].

The role of Epstein–Barr virus (EBV) infection in the NPC carcinogenesis is well documented but non-exclusive and environmental factors and genetically determined susceptibility may play a role [1].

prognostic factors

Tumor develops initially in the walls of the nasopharynx, without any symptoms, explaining a usual late diagnosis. Later, locoregional invasion may extend to the cranial nerves and the base of the skull, which increases the risk of local failure after radiotherapy [3].

Lymph node involvement is frequent. Node-positive patients (N+) have a high risk of distant metastasis (bone, lung and liver metastasis) and a decreased survival: patients with N1 and N2/N3 disease have a 33% and 70% incidence of distant metastasis at 10 years respectively [4]. TNM stage is, accordingly, the major prognostic factor, but is controversial as two classifications are currently used: Ho’s and UICC2003 classification [2].

Among biological parameters, which could be useful prognostic markers, pretreatment and post-radiotherapy EBV DNA levels have been correlated with outcome and survival [5, 6].

treatment: new approaches

Usually unresectable, NPC is more responsive to radiotherapy and chemotherapy than other head and neck cancers. Radiotherapy alone has been the first curative treatment of NPC and remains the standard treatment of the initial stages I, without node involvement, yielding a 10-year survival rate of 98% [4].

If the place of chemotherapy is not discussed in metastatic disease, its role and modality in the initial management remains controversial. In terms of efficacy, recent trials and meta-analysis highlight the need to adjunct chemotherapy to radiotherapy: concomitant radiochemotherapy appears now to be superior to radiotherapy alone and can be defined as the standard treatment in 2006 for locally advanced (T2B and more) and/or N+ patients. In this review we focus on these recent advances.

concurrent chemo-radiotherapy: a standard treatment for locoregionally advanced NPC

Until now, results of six randomized trials and two meta-analyses [7–9] had shown that concomitant chemotherapy and radiotherapy are superior to radiotherapy alone in terms of relapse-free and overall survival, but the real benefit was not clear.

The results of the last meta-analysis on behalf of the MAC-NPC collaborative group have recently been published [10]. This study used updated individual patient data from eight randomized trials comparing chemotherapy plus radiotherapy versus radiotherapy alone in locally advanced NPC. The trials included 1753 patients, and 728 deaths (42%) occurred. All trials used conventional radiotherapy and cisplatin-based chemotherapy. A small, but significant benefit was found for overall survival (6% at 5 years) and event-free survival (10% at 5 years) with the addition of chemotherapy (Figure 1). The benefit on survival was essentially observed when chemotherapy was administered concomitantly with radiotherapy (Figure 2). The only excess treatment-related deaths were observed in the induction chemotherapy trials. However, chemotherapy lowered the risk of locoregional and distant failure whatever the timing of chemotherapy.

This meta-analysis confirms the role of concurrent chemo-radiotherapy as a standard treatment for locoregionally advanced NPC. However, the higher incidences of acute and late toxicities need the development of conformal radiotherapy techniques and new cytotoxic agents [9, 11, 12].
induction chemotherapy

The high objective response rate usually observed and the good tolerance in treatment-naïve patients is in favor of induction chemotherapy compared to adjuvant chemotherapy. For instance, all randomized trials of adjuvant chemotherapy failed owing, in part, to poor tolerance [13–16]. In addition, cisplatin-based induction chemotherapy, with epirubicin, 5-fluorouracil (5-FU) or taxanes, does not compromise further radiotherapy or chemoradiotherapy [17].

However, four phase III trials comparing induction chemotherapy to radiotherapy alone [18–21] failed to show an improvement in overall survival, despite a significant reduction in local and distant failures [19, 20]. The recent meta-analysis conducted by the MAC-NPC collaborative group confirms these data [10]. However, these trials did not use chemoradiotherapy but radiotherapy alone, and did not use new cytotoxic compounds like taxanes or gemcitabine.

To date, neoadjuvant chemotherapy is only routinely recommended for patients with bulky intracranial tumors extending too close to the optic chiasm or brainstem [22]. Nevertheless, despite concomitant chemoradiotherapy, incidence of locoregional or distant metastasis remains high for locoregionally advanced NPC and remains in the order of more than 40%.

What is the way to reduce distant metastasis? Is induction chemotherapy followed by concomitant chemoradiotherapy the best strategy? Several phases II studies have shown that this strategy might obtain good results on a limited but poor prognostic population [23–25]. In order to show an advantage for such an intensified treatment, a selection of good candidates, i.e. with a high risk of distant failure (T2B, 3, 4 and/or N+) and a good performance status, is needed.

Using new drugs is another way to improve results: taxanes have shown a higher efficacy in combination with cisplatin and 5-FU as induction chemotherapy for head and neck cancer, 2and this regimen could be used in NPC [26]. A phase
III trial randomizing induction chemotherapy is necessary to answer this important question.

**treatment of metastatic disease**

To date, platinum-based regimens are the standard chemotherapy for metastatic NPC patients, and the most used in first-line remains the combination of cisplatin and 5-FU [9, 27, 28]. Platinum-based triplets or more have not demonstrated better results but significant toxicities [9, 29]. Platinum-based combinations with new agents including gemcitabine or paclitaxel have yielded good responses rates [30–35]. Anthracyclines and bleomycine are active in this peculiar epidermoid head and neck cancer. If survival is usually poor for metastatic patients, sometimes long-term disease-free survival may be obtained [35, 36].

Targeted therapies such as cetuximab are in development [37]. Multitarget vascular epidermal growth factor (VEGF) tyrosine kinase inhibitors have shown activities in phase 1 studies [38].

**conclusions**

Chemoradiotherapy is now the standard treatment of locally advanced NPC. However, some questions remain unresolved: What is the best chemotherapeutic regimen during radiotherapy? Is there a benefit of induction chemotherapy before chemoradiotherapy? What is the contribution of new cytotoxic compounds (taxanes, gemcitabine, pemetrexed and biotherapy)? Which patients are the best candidates for intensified systemic therapies? Is there a risk to increase late sequel with new combinations? New trials should focus on these points.

**references**


