

Clinical trials in nasopharyngeal carcinoma—past, present and future

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Abstract: Nasopharyngeal carcinoma (NPC) has an age-adjusted incidence for both sexes with greater frequency in some endemic regions, especially the southern China. Genetic, ethnic, environmental factors and Epstein-Barr virus (EBV) infection might take part in the cause of the disease. Based on the understanding and research progresses, we have had a further step among the diagnosis and prognosis of the disease. Meanwhile, a numerous clinical trials aiming to pick out the most suitable therapeutic choice are carried on from past till now. The purpose of this review is to summarize therapeutic approaches from past RCTs, introduce hot topics at present, and explore the development trend in the future. Applying appropriate combining procedures of radiotherapy and chemotherapy with developments in gene therapy and immunotherapy, the outcomes in the future might be widely improved.

Keywords: Nasopharyngeal carcinoma (NPC); radiotherapy; chemotherapy; clinical trials

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Introduction

Nasopharyngeal carcinoma (NPC) is a sort of squamous original head and neck cancer intermixed with lymphoid cells pathologically. It is located at nasopharyngeal epithelium and featured with a unique pattern of geographical distribution. The age-standardized incidence of NPC ranges distinctly from 20–30 per 100,000 males and 15–20 per 100,000 females respectively in Hong Kong to 0.5 per 100,000 in mainly white populations and less than 1 per 100,000 in Japan (1). Besides geographical factor, some ethnic groups may have a predisposition for NPC, such as the Cantonese of southern China. Worldwide, around 86,500 new cases of NPC are diagnosed annually which account for 0.6% of all cancer diagnosed in the same year (2,3).

With the tide of improved techniques, the intensity modulated radiotherapy (IMRT) has substituted gradually the 3-dimensional conformal radiotherapy (3-DCRT) with

advantages of refined local control and accurate delineation of the target volume (4,5). So, radiotherapy, especially the IMRT, absolutely becomes the principle and first rank choice for non-disseminated NPC because of its anatomical location and radiosensitivity. Meanwhile, chemotherapy also takes a vital role in the realm of treatment which is depended to a large scale on the chemosensitive character of NPC. With those understandings, researchers tried to investigate whether the combination of chemotherapy and radiotherapy would devote a valuable efficacy. Therefore, a lot of relevant randomized trials have been burst out in the past two decades (6). Nowadays, researchers generally hold the opinion that concurrent chemoradiotherapy, with or without adjuvant chemotherapy, is the most efficacious choice (7–9), and is now the standard treatment for stage IIB and advanced types of NPC. In addition, the applying of neoadjuvant chemotherapy also performs a promising

future. Though its phase III trials and results are still not around the corner, our attentions should be focused on persistently (10). Actually, the combined approaches have been a hot topic till now with its rapid development. This review is going to talk about those classical and up to date clinical trials.

Concomitant chemotherapy

The strategy of combining chemotherapy with radiotherapy is a critical advancement in the treatment of locally advanced NPC, which evokes a lot of clinical trials. Six randomized controlled trials have reported on concomitant chemotherapy before 2004 (11-16). In 2002, Chan AT and colleagues (11) from Hong Kong reported a non-significantly different progression-free survival (PFS) between concomitant chemotherapy and radiotherapy alone. However, PFS was significantly prolonged in patients with advanced tumor and node stages. Meanwhile, concomitant chemotherapy was well tolerated in patients with advanced NPC in an endemic area. Then, an article of Lin JC and colleagues (12) from Taiwan in 2003 reported that concomitant chemotherapy could improve both overall survival and PFS, with the values of 72% *vs.* 54% and 72% *vs.* 53%, respectively. By the way, this study is the first one to demonstrate a positive effect of the combination of concomitant chemotherapy and radiotherapy in terms of NPC patients in an endemic area.

An updated edition clinical trial of Chan AT and colleagues (13) claimed an increasing overall survival of the concomitant chemotherapy excluding relapse-free survival. And three more studies about concurrent chemotherapy have been reported from Hong Kong and Singapore (14-16). Two of them reported an improvement in overall survival alone (14,15), and the rest one by Lee and colleagues (16) reported a tendency to reduce local relapse and drug toxicity without improvement of relapse-free survival or overall survival. Those results strongly promoted the concomitant chemotherapy as a preferable treatment for patients of NPC. However, only one of them (12) directed benefits of both overall survival and PFS virtually.

Chen QY and colleagues (17) showed out improvement of overall survival (95% *vs.* 86%) in stage II patients via concomitant chemotherapy compared with radiotherapy alone, mainly due to the improvement in distant metastasis-free survival (95% *vs.* 84%). Wu and colleagues (18) reported that Oxaliplatin also can be considered as an alternative optional regimen in concomitant chemotherapy

for locoregionally advanced NPC patients. What's expected in the future is to pick out more efficient therapeutic agents. Though cisplatin is the most widely used drug in concomitant chemotherapy, some clinical trials (18,19) has commenced a journey to find out new agents such as uracil plus tegafur and oxaliplatin. And a relevant dosage schedule also required more researches and reports in the future.

Whether the additional adjuvant chemotherapy to concomitant chemotherapy could bring more benefit compared with concomitant chemotherapy alone should be estimated. The most classical publication is the seminal INT-0099 trial (20) which is published in 1998. This clinical trial firstly concluded the improved overall survival and PFS of concomitant chemotherapy followed by adjuvant chemotherapy when compared with radiotherapy alone. However, it still existed a further question because this study enrolled relatively more cases of well-differentiated type which might not compatible among natural endemic areas. Three more clinical trials (21-23) concluded advancement of overall survival and relapse-free survival by the same adjuvant regimen of cisplatin plus fluorouracil. Chua DT and colleagues (24) chose concomitant chemotherapy with cisplatin followed by adjuvant agents like ifosfamide, 5-fluorouracil and leucovorin for patients with locoregionally advanced NPC, and positive outcomes were observed. That means this regimen could improve the efficacy under the condition of advanced cases. Though adjuvant chemotherapy used alone still has a controversy on its benefits, the combination of adjuvant chemotherapy and concomitant chemotherapy already performs pretty well. So, there is a kind of opinion that the best choice for NPC should be the combining approach of concomitant chemotherapy and adjuvant chemotherapy. Nonetheless, the toxicity of chemical agents should also be taken into account.

In order to assess the contribution of adjuvant chemotherapy to concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone directly, we conducted a trial and found that adjuvant chemotherapy may not change outcomes positively and significantly since all of those failure-free survival, distant metastasis-free survival and overall survival were merely and slightly gained a 2% benefits in the experimental group (25). In 2015, Blanchard P and colleagues (26) conducted a meta-analysis using individual patient data, including nineteen relevant clinical trials among 4,806 patients. Their outcome also supports the similar benefits and advantages of both concomitant chemotherapy followed by adjuvant chemotherapy and

concomitant chemotherapy alone. Given the lack of studies evaluating the efficacies of these two regimens directly, recently we perform a Bayesian network meta-analysis (9) aiming to determine the comparative efficacy of these two regimens. No significant differences were found between concomitant chemotherapy followed by adjuvant chemotherapy and concomitant chemotherapy alone for all outcomes [overall survival: HR =0.86, 95% credible interval (CI) 0.60–1.16; locoregional recurrence-free survival: HR =0.72, 95% CI 0.43–1.15; distant metastasis-free survival: HR =0.86, 95% CI 0.62–1.16]. Currently, the National Comprehensive Cancer Network (NCCN) recommends concomitant chemotherapy followed by adjuvant chemotherapy for locoregionally advanced NPC, concomitant chemotherapy alone is also an option. The European Society for Medical Oncology (ESMO) recommends concomitant chemotherapy alone for locoregionally advanced NPC, and indicates that the benefit of three cycles of adjuvant cisplatin-fluorouracil is uncertain exclude obviously substantial toxic effects (27).

In summary, viewpoints about the combination of concomitant chemotherapy and adjuvant chemotherapy are not clear enough. Whether the omission of additional adjuvant chemotherapy can reduce toxic effects without adversely affecting survival outcomes for patients with locoregionally advanced NPC should be further explored.

Adjuvant chemotherapy

Despite the achievement of concomitant chemotherapy in the past decades, some clinical trials had explored another filed, that is adjuvant chemotherapy. Nevertheless, no improvements of results were showed out either in overall survival or relapse-free survival (28,29). Considering that those two studies were published relatively out of date, some other clinical trials provide new evidences. Whose results (17,21,22,30) suggested that an additional chemotherapy after radiotherapy, no matter what kind of agents were used such as cisplatin or fluorouracil, actually performs a poorly tolerated compliance (55–57%). Lee and colleagues (31) found out that those negative outcomes might be created by lack of cycles of chemotherapy agents after radiotherapy.

Nonetheless, it is of less value to evaluate adjuvant chemotherapy alone, especially based on the fact that we have already made a progress on the combination of concomitant chemotherapy and adjuvant chemotherapy. Actually, a lot of updated clinical trials focused on the additional adjuvant chemotherapy among special

populations. Considering its toxicity and local controlled efficacy, the stratification of suitable patients is quite necessary. Those patients are usually featured with the high relapse rate and detective EBV DNA after standard treatment. A clinical trial from Taiwan (32) suggested that the concomitant chemotherapy could gain more advantages among those patients with relatively early advanced NPC such as N3 or T4N2 etc. And the additional adjuvant chemotherapy also requires a suitable population of NPC patients with the purpose to achieve survival rate. Besides, concomitant chemotherapy combined with adjuvant chemotherapy appears to benefit patients who meet certain selection criteria, and further studies are emphasized to define the patient population. Recently, it was reported that unfavorable EBV DNA response during midpoint of radiotherapy was an adverse prognosticator for treatment outcome in advanced stage NPC (33), and it may serve as an indicator for the addition of adjuvant therapy to the initial treatment. As for the development in this field, the reachable future is how to find out those patients who belongs to the premier beneficiaries of additional adjuvant chemotherapy.

Neoadjuvant chemotherapy

Studies trying to make an improvement on the usage of adjuvant chemotherapy have been reported with objectives varying from poor tolerance and severe side effects. The poor compliance with adjuvant chemotherapy after radiotherapy can be overcome by replacement of neoadjuvant chemotherapy. Therefore, neoadjuvant chemotherapy was thought to be a potentially more feasible and effective strategy of treatment intensification than adjuvant chemotherapy.

In 1996, an International Nasopharynx Cancer Study Group trial (34) showed that an improvement in relapse-free survival but not overall survival was found for neoadjuvant chemotherapy. Another trial (35) demonstrated the same conclusion. However, two studies (36,37) reported null improvement not only in relapse-free survival but overall survival. While we await further clinical trials, more evidences regarding the effectiveness of neoadjuvant chemotherapy can be inferred from published meta-analyses. A meta-analysis (38) in 2004 inferred an improvement in both relapse-free survival and disease specific survival for neoadjuvant chemotherapy. The incidence of locoregional failure and distant metastasis was reduced by 18.3% and 13.3% at 5 years, respectively. No improvement in overall

survival was observed. Oh JL and colleagues (39) held the opinion that a neoadjuvant chemotherapy followed by concomitant chemotherapy might have an excellent overall survival and pretty well compliance. In a randomized phase II trial comparing neoadjuvant chemotherapy (cisplatin and docetaxel) with or without concomitant chemotherapy (cisplatin) reported by Hui and colleagues (40) in 2009, a positive outcome was observed. The three-year overall survival was 94% in the experimental group compared with 68% in the control group ($P=0.066$). Recently, a bayesian meta-analysis conducted by us (41) included nine clinical trials evaluating neoadjuvant chemotherapy (alone or addition), and showed a significant benefit of the combination of neoadjuvant chemotherapy and concomitant chemotherapy when compared with concomitant chemotherapy alone for distant metastasis rate. Besides, the additional neoadjuvant chemotherapy had a tendency to improve overall survival. As the locoregional control has been improved significantly with the advent of IMRT, distant failure remains a major reason for treatment failure in NPC. Considering the efficacy of reducing distant metastasis rates by neoadjuvant chemotherapy, defining patients at high risk of distant failure may maximize benefits of additional neoadjuvant chemotherapy. Thus, those patients with an advanced N stage who have a high probability to suffer from distant metastasis are the targeted people. Of note, the ESMO recommends that cisplatin based neoadjuvant chemotherapy could be considered in locally advanced patients, and in no case should it negatively affect the optimal administration of concomitant chemotherapy (27).

Preliminary results of two phase III trials which were published recently showed that the additional neoadjuvant chemotherapy could not improve survival in locally advanced NPC (42,43). Meanwhile, we are conducting two phase III trials (NCT01245959 and NCT01872962) to confirm the efficacies of different induction regimens (docetaxel plus cisplatin and fluorouracil, and gemcitabine plus cisplatin) for locoregionally advanced NPC. And the final results are awaiting to be reported.

In summary, when it comes to the management of advanced NPC, the role of neoadjuvant chemotherapy has a prospective future. And current evidences promote its applying in patients planned for concomitant chemotherapy. The hottest trend warrants additional investigation with the purpose to find the most efficient combining neoadjuvant chemotherapy agent and define the target population of additional neoadjuvant chemotherapy.

Future

Based on the clinical trials which have been referred above, we could notice the hottest tendency at present even the probable breakthrough in the future. Just name a few, the most effective combining treatment strategies, explorations on chemotherapy agent which could take part in the combining treatment in order to create the most effective effect, patient stratification and so on.

Besides, some other techniques give further opportunities for novel treatment. Such as gene therapy and immune therapy. Li JH and colleagues (44) released an article about tumor-targeted gene therapy for NPC which focuses on constructing a novel replication-deficient adenovirus vector (ad5.oriP) in which transgene expression is under the transcriptional regulation of the family of repeats domain of the origin of replication (oriP) of EBV. The result demonstrates that the oriP sequence can achieve high levels of gene expression targeted specifically to EBV-positive NPC cells in the context of the adv. vector. As for immune therapy, those therapeutic augmentations tried to apply cytotoxic T-lymphocyte responses (45) and adoptive transfer of LMP2-specific cytotoxic T lymphocytes and dendritic cell-based vaccines to LMP2 epitopes (46-48) to make achievements.

Some newly researches have accentuated among those patients with metastatic NPC in order to prolong their survival. Molecular targeted agents are good choices, which were not only potentially more effective, but also reduced toxicity reactions. Several molecular targets have been identified in NPC. Such as expression or over expression of epidermal growth factor receptor (EGFR) (49,50), vascular endothelial growth factor (VEGF), c-KIT, and c-erbB-2 (HER2) (51) and so on. A phase II study of an intravenous immunoglobulin G1 monoclonal antibody (cetuximab) that specifically targets the EGFR with high affinity and competitively inhibits endogenous ligand binding was undertaken (52). Another phase II study of an orally active EGFR tyrosine kinase inhibitor (gefitinib) has also been presented recently (53). It is absolutely believed that this field will be a front line thesis in the future.

Conclusions

In summary, NPC is a highly radiosensitive disease so that the radiotherapy alone is the mainstream approach for early stage patients. Meanwhile, IMRT may improve the locoregional control to a certain scale. As for the patients

of stage II diseases, concomitant chemotherapy may be a choice. The standard treatment for locoregionally advanced NPC is concomitant chemotherapy with or without adjuvant chemotherapy. Also, the confirmation of the efficacy of concomitant chemotherapy combined with neoadjuvant chemotherapy is a hot spot. The next decade of research in the realm of NPC has a large opportunity to break out new successes with those developments which are discussed above, and that would also benefit mankind well.

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Footnote

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