Nasopharyngeal carcinoma—some closing remarks

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Submitted Feb 17, 2016. Accepted for publication Mar 01, 2016.
doi: 10.21037/cco.2016.03.23
View this article at: http://dx.doi.org/10.21037/cco.2016.03.23

Introduction

We thought it would be appropriate for us as editors to close this issue with some personal reflections on certain areas with respect to nasopharyngeal carcinoma (NPC).

Nasopharyngeal carcinoma (NPC) carcinogenesis

Poh and colleagues (1) recently published an article in the *Chinese Journal of Cancer*; suggesting an alternative hypothetical mechanism for NPC carcinogenesis. In it, the authors postulate that a bottleneck occurring in the ancient migration of East Asians from central Asia into east Asia has resulted in genetic polymorphisms in Toll-like receptor 8 (*TLR8*) that predisposed the East Asian population with early neonatal Epstein Barr virus (EBV) infection. This, in the presence of a transformation zone in the fossa of Rosenmüller, made this population susceptible to developing NPC in a process perhaps not too dissimilar to human papilloma virus (HPV)-induced carcinogenesis.

The second genetic polymorphism common in East Asians is the ectodysplasin A receptor gene (*EDAR*), which is responsible for thick hair, salivary gland morphogenesis, breast development, and the development of teeth. Some common East Asian tooth characteristics that may be due to this gene include dens evaginatus, incisor shovelling, and crown size (2). A study from the University of California San Francisco (UCSF) (3) revealed that East Asians had shorter tooth root morphology and a thin gingival biotype, which may place these patients at a greater risk of periodontal breakdown. Another paper showed that Asian-Americans (4) were more prone to harbour *A actinomycetemcomitans* and *P gingivalis* (organisms thought to be responsible for periodontitis). All these might explain why East Asians appear more susceptible to periodontitis. Previous epidemiological surveys have also associated NPC with prior chronic ear nose throat (ENT) conditions like sinusitis and otitis media (5). One may thus postulate that chronic infections produce inflammatory cytokines that have unwittingly induced a systemic bystander effect, inhibiting the protective inflammatory response of the body against the precursor lesion, leading to the development of NPC (6). In support, subsequent restoration of this protective inhibition through adoptive T-cell transfer in the metastatic setting has translated into better outcomes for these patients (7).

Adjuvant chemotherapy in curative nasopharyngeal carcinoma (NPC)

The role of adjuvant chemotherapy in the curative setting remains controversial, despite the number of trials and meta-analysis that had been reported.

Instead of the TNM system for classifying NPC, Traditional Chinese Medicine (TCM) (8,9) classifies NPC into upward progressing, downward progressing, mixed progressing, early and metastases stages. Perhaps this is a more pragmatic classification, as a Stage 4 in the TNM system may well have a high risk of local recurrence (T4) or a high risk of distant metastasis (N3)—risks which probably warrant different treatment strategies. The twin Hong Kong NPC-9901 and NPC-9902 trials were perhaps an attempt to use the correct strategy for the correct patient. Thus, differences in results of the various trials, which essentially used the same radiotherapy (RT) technique and differed mainly in the number of drugs used, could perhaps be attributed to the proportion of cases with different failure patterns (i.e., local or distant) included.

For example, in Tan's induction GCP (gemcitabine, carboplatin, paclitaxel) trial (NCT00997906) (10)—although the overall trial result was "negative", a subsequent sub-set analysis did suggest that induction triplets was perhaps beneficial in those with high initial pre-treatment titres of EBV DNA (11).

In the same vein, HK NPC-9901(HARECCTR0500023) took a "long time" before it turned "positive", which was 'contrary" to several other trials all using similar designs and drugs (12,13). This could perhaps be explained by the fact that HK NPC-9901 had specifically excluded T3–4 N0–1 patients who were accrued to HK NPC-9902 instead; and thus, the former was left with a cohort that was biased towards a much higher distant burden risk, and that could have seemingly reduced the effect of the regimen in purportedly stage 3 and 4 NPC patients.

Ma and colleagues from Guangzhou have performed two consecutive trials examining the role of adjuvant PF (cisplatin, 5-fluorouracil), and then neo-adjuvant TPF (docetaxel, cisplatin, 5-fluorouracil) chemotherapy with concurrent cisplatin-RT—both trials having specifically excluded T3–4 N0 disease. It is therefore not surprising to see the adjuvant PF trial being negative (14), possibly because the remaining cohort had too high a distant burden for just two drugs—cisplatin and 5FU; but positive for progression free survival (PFS) in early reports of the TPF trial (15) because now they had correctly selected for a cohort with a higher risk of distant tumour burden that would benefit from the extra drugs (i.e., 5-fluorouracil and docetaxel).

Similarly comparing the TPF versus the GCP induction trials—the GCP trial might have diluted the effect of GCP by including too many patients for whom induction triplets might have been considered an "overkill"; whereas the TPF trial, which selected for patients with a higher distant burden risk, probably "appropriately" used the correct number of drugs to do the job.

The efficacy of the number of drugs (with cisplatin as base) used appears to correlate well with the distant tumour burden that it had to tackle.

Thus, single agent cisplatin:

- Was useful for stage 2 disease (16);
- And only borderline useful after Cox regression analysis, when in addition to stage 2 disease; stages 3 and 4 disease were also included as in the PWHQEH-94 trial (17);
- Alternatively, one could propose an alternative single-agent chemotherapy such as 5-fluorouracil and its analogues to cisplatin in the adjuvant phase (18,19), targeted at patients with advanced disease, but perhaps harbouring an 'intermediate-risk' of systemic micro-metastasis (e.g., high pre-treatment EBV DNA titre, but undetectable post-radiotherapy). This could serve to improve tolerability of adjuvant treatment, and simultaneously allow the targeting of 'cisplatin-resistant' tumour clones.

Two drugs (cisplatin, 5-fluorouracil):

- Was useful in general for most stage 3, 4 disease (20);
- In Lin's subsequent analysis, he found that cisplatin—5-fluorouracil (PF) concurrent with RT only benefitted patients with low risk disease (21);
- HK NPC-9901 taking a "longer time to turn positive" possibly because it ended up selecting for a cohort with higher risks of distant failure. It is also not surprising then that the Guangzhou adjuvant PF trial—which has a similar "experimental arm" to HK NPC-9901 would be negative since the standard in this arm is now cisplatin-RT as opposed to RT alone in the Hong Kong trial, both trials having excluded T3–4N0[1] patients.

Three drugs (either GCP or TPF):

- Useful for those with higher risk disease as in Tan's GCP trial (11);
- And early results of Ma's TPF trial show improved PFS (15).

This philosophy broadly concurs with the scientific rationales underlying the current NRG Oncology trial (NRG HN001) design, which is accruing globally for locally advanced NPC.

Spatially fractionated (GRID) radiotherapy for N3 nasopharyngeal carcinoma (NPC)

In ancient Chinese writings, NPC was referred to as "lo li" meaning neck gland enlargement (22). Today in some endemic low- and middle-income countries (LMICs), about 40% still present with N3 disease and only a small number achieve a complete response. The lack of sufficient facilities as well as the inability of patients to tolerate the rigors of concurrent chemo-radiation, begs for an alternative option for these patients with very advanced neck nodal disease (23).

GRID radiotherapy has been around for nearly a hundred years, and was initially used to treat deep seated tumours using an orthovoltage machine. It fell out of favour with the advent of the mega-voltage era because of the skin sparing effect of the Linacs. There has been a recent resurgence of interest and excellent responses have been reported

in advanced large tumours, including head and neck cancers (24-26).

Essentially 15 Gy in a single fraction is administered to the gross tumour region using a "slot-into Linac" applicator (27,28). This essentially applies very high doses of pencil beam irradiation to parts of the tumour, while the intervening regions are spared. This sparing of normal tissue allows a very high dose (15 Gy) to be applied and it relies on the bystander effect to kill the cancer cells (29) which are not within the irradiation field, but allows the skin in the non-irradiated areas to regenerate. This makes the treatment very tolerable and with minimal toxicity that one might expect from such a high dose of radiation. When 50 Gy (to 70 Gy) by conventional radiation is added, the responses appear to be durable (24).

The simplicity of the treatment (30,31), and the potential ability to achieve major responses without the concomitant use of chemotherapy (by leveraging the immune and other bodily systems) to our minds, makes this modality a very viable option to be investigated in the LMICs setting. This may also represent how RT can be delivered with lower morbidity (i.e., induction 15 Gy GRID followed by 50–70 Gy conventional RT). This should reduce considerably the morbidity of radiotherapy and perhaps allow for full doses of adjuvant chemotherapy to be delivered to tackle any microscopic distant disease.

Conceivably a randomised phase I/II trial might be performed as proof of principle—comparing the Al-sarraf regimen as standard and an experimental arm treating with 15 Gy parallel opposed GRID followed by 50–70 Gy RT alone (26,30) followed by one year of adjuvant oral 5-fluorouracil analogue (18) with the end point being 3-year PFS (32,33). The success of this regimen will result in better tolerance by patients; a reduction in up to potentially nine fractions of precious radiotherapy treatment slots and no necessity for an infusional chemotherapy facility. All this should make this proposal attractive to patients and centres in a LMIC setting.

It should be cautioned that GRID has not been used to treat areas over the brain, spinal cord, the eye or the kidneys because the tolerance of these organs to GRID is unknown, and animal studies would be warranted.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Wee JT, Soong YL, Poh SS, Chua ML. Nasopharyngeal carcinoma—some closing remarks. Chin Clin Oncol 2016;5(2):29. doi: 10.21037/cco.2016.03.23

