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EDITORIAL

Nasopharyngeal carcinoma treatment paradigm after HK0501 – a potential way forward

The Hong Kong Nasopharyngeal Carcinoma (NPC) Study Group 0501 trial (HK0501) is the first trial that directly compares induction (IC) versus adjuvant chemotherapy (AC) both given together with concurrent chemoradiation (CCRT) treatment, which long has been a contentious issue [1]. Its most salient finding is that when adjusted for platinum doses and other significant factors, the timing of the chemotherapy sequence is not important. In the era where chemotherapy is administered at maximum tolerated doses (MTD), the induction strategy has the advantage because of better tolerability. On the other hand, with the realization that there may be more ways to skin a cat, adjuvant metronomic chemotherapy has gained traction at the 2021 American Society of Clinical Oncology (ASCO) meeting [2] and provides an alternative to the decades' old dogma of MTD. Metronomic chemotherapy works by exerting an anti-angiogenic effect [3-6] and also has immune effects like removing regulatory T cells (Tregs) [7] and myeloid-derived suppressor cells (MDSCs) from the tumour microenvironment [8] and causing dendritic cell maturation, which upregulates and primes the anti-tumor T cell immune response [9,10]. Pediatricians are probably the first to successfully incorporate 2 years of maintenance metronomic chemotherapy in their childhood acute lymphoblastic leukaemia protocols [11] which now boast cure rates of over 90% [12].

Locally advanced NPCs may relapse locally or distantly. In terms of local recurrence, the overall treatment time (measured from the start of chemotherapy or radiation therapy [RT]) to the end of RT is critical. To reduce the risk of distant disease relapse, this requires the patient to have received sufficient chemotherapeutic drugs. Prior to 2021, induction chemotherapy was favored over adjuvant chemotherapy, as treatment with the commonly used adjuvant cytotoxic chemotherapy drugs was poorly tolerated, especially after CCRT. However, the ASCO Xeloda presentations [2, 13] introduce a new treatment route for adjuvant chemotherapy post CCRT which is well tolerated and effective.

The Sun Yat-sen trials of concurrent chemotherapy with or without induction chemotherapy for locally advanced NPC conclusively point towards the superiority of the induction arm over CCRT alone, with a 3 year recurrence-free survival improvement of almost 10 percent and a 3 year overall survival improvement of 4.3 percent [14–16]. However, we should not forget that the control cisplatin-RT alone arms already managed to achieve a very remarkable cure rate of at least 75% without the addition of either induction or adjuvant chemotherapy. While the addition of induction chemotherapy did bring about a survival advantage for 10% of the treatment cohort, the increased cumulative doses of cisplatin can result in further hematological [14–16], auditory [17] and neurological morbidities [18], especially from the standpoint of the 75% of patients who would have been cured with cisplatin-RT alone.

In order to avoid this potential overtreatment of NPC patients who would have been cured with cisplatin-RT alone, many groups have attempted to identify the subset of patients most likely to have a survival advantage from adding on induction chemotherapy. Parameters such as pre-treatment Epstein-Barr virus (EBV) DNA levels [19], positron emission tomography maximum standardized uptake value (PET SUV_{max}) [20], radiomic features [21] and various combinations of these factors [22] have all been investigated. However there has been no conclusive outcomes for any of these studies at the present time. On the other hand, the use of the kinetics of EBV DNA clearance during and after radiotherapy appears to be highly prognostic; and coupled with the realisation that there are now tolerable adjuvant regimens, has given the adjuvant option a new lease of life. One could envisage a future

List of abbreviations: NPC, nasopharyngeal carcinoma; IC, induction chemotherapy; AC, adjuvant chemotherapy; CCRT, concurrent chemoradiation; MTD, maximum tolerated doses; ASCO, American Society of Clinical Oncology; Treg, regulatory T cell; MDSC, myeloid-derived suppressor cell; RT, radiation therapy; EBV, Epstein-Barr virus; 5-FU, fluorouracil; SCLC, small cell lung cancer; SYSUCC, Sun Yat-sen University Cancer Center; PET SUV_{max}, positron emission tomography maximum standardized uptake value; PD-1, programmed cell death protein 1.

TABLE 1 Potential clinical trial design of adjuvant metronomic chemotherapy using an adaptive EBV DNA kinetics profile*

EBV DNA level			Expected percentage of patients with the corresponding EBV DNA kinetics profile (%)	Regimen
Pre-treatment	Mid RT	Post RT		
+ve	-ve	-ve	35-50	Observe
+ve	+ve	-ve	20-35	1 year of metronomic capecitabine [2, 51, 52]
+ve	+ve	+ve	15-30	1 year of metronomic capecitabine and IO [2, 28, 51, 52, 53, 54]

*Cut-off values dependent on individual lab-specific values.

Abbreviations: +ve, EBV DNA levels detectable; -ve, EBV DNA levels undetectable; IO, immuno-oncologic agents.

clinical trial looking at EBV DNA at mid-point [23-25] and after the end of RT [26-27] to select an appropriate adjuvant regimen (Table 1). A recent phase III trial in metastatic squamous cell head and neck cancers showed significant improved responses and overall survival when a programmed cell death protein 1 (PD-1) inhibitor (nivolumab) at low fixed doses was added to metronomic chemotherapy [28]. Such a strategy would be of immense relevance to NPC and should be thoroughly investigated.

The HK0501 study observed that the optimal platinum dose was ≥160 mg/m^2 in the concurrent phase and ≥260 mg/m^2 in the induction/adjuvant phase. We suggest that the "cisplatin in the induction/adjuvant settings" may simply be a surrogate for the fluorouracil (5-FU)/capecitabine doses needed, and thus perhaps the total amount of cisplatin given during the concurrent chemoradiotherapy treatment phase is sufficient [29]. This might then explain the observations in the adjuvant single agent capecitabine trials alluded to as well as the observations by others on the cumulative doses of cisplatin needed. If anything, the fact that the induction capecitabine arm was superior to the induction intravenous 5-FU arm supports the idea that metronomic chemotherapy is a very viable option [30].

Another less discussed potential advantage of offering adjuvant chemotherapy over induction chemotherapy is the better local control it affords compared to the induction route, in view of the shorter overall treatment time. Peters *et al.* [31] first introduced the hypothesis that the overall combined duration of treatment is an important determinant of outcome, and Milas *et al.* [32] proved the concept in mice. Bourhis *et al.* [33] finally showed that accelerated repopulation occurred after induction chemotherapy in patients with oropharyngeal cancers.

In squamous cell head and neck cancers, Brockstein *et al.* [34] reported on the outcomes of concurrent chemotherapy versus induction chemotherapy strategies. The induction group had superior distant control but worse local control and the concurrent group showed the reverse. The latest MACH-NC meta-analysis [35] similarly reports on the poorer local control rates associated with induction strategies (see Web-Figure 6 and Web-Figure 8 of Reference 35 Supplementary Material). A more recent publication from the MD Anderson group also highlights the risks of accelerated repopulation after induction chemotherapy [36]. In anal canal cancers [37], the pooled RTOG trial's conclusion was that "Total treatment time, but not duration of radiation therapy, seems to have a detrimental effect on local failure and colostomy rate in anal cancer. Induction chemotherapy may contribute to local failure by increasing total treatment time". In small cell lung cancers (SCLC), De Ruysscher *et al.* [38] proposed a new metric "SER", which was derived from the start of any treatment (chemotherapy or radiotherapy) until the end of radiotherapy. The authors concluded that the time between the first day of chemotherapy and the last day of chest radiation is the most important predictor of survival in limited-stage SCLC. In both anal cancers and SCLC current management guidelines recommend upfront radiotherapy [39,40]. In non-small cell lung cancers, the CALGB trial of CCRT versus induction plus CCRT [41] failed to show any survival benefits with the induction route. Interestingly, it was durvalumab [42] given in the adjuvant setting after CCRT that has resulted in a survival advantage in more recent times. Another report by Chen *et al.* [43] documented actual accelerated regrowth of tumours after induction chemotherapy. In limited-stage extranodal NK/T cell lymphoma (ENKTL), a recent meta-analysis [44] showed that compared with induction chemotherapy followed by RT, upfront RT significantly improved overall survival. There is no reason to think that radiotherapy for NPC would behave any differently. The MAC-NPC meta-analysis presented at ASCO 2020 [45], showed that IC-CCRT was superior for distant control whereas CCRT-AC was superior for loco-regional control.

In a Sun Yat-sen University Cancer Center (SYSUCC) article looking at a propensity score-matched analysis of induction versus adjuvant chemotherapy combined with concurrent chemoradiotherapy in locoregionally advanced nasopharyngeal carcinoma by Tang *et al.* [46] "Figure 1" in the paper clearly shows the "inverse" nature of local vs. distant control of AC vs. IC. Other retrospective

studies from Thailand [47] and South Korea [48] give similar reports.

However, despite all the evidence above, it may be pointed out that the 4 trials of induction chemotherapy with CCRT compared with CCRT alone from SYSUCC [14–16] currently do not show any difference in local control. Experience from the Singapore GCP trial [49, 50] (and in the SCLC De Ruysscher report [38]) suggests that local failure might be a late event – becoming obvious only after a long follow up. Whether the use of "SER" and a longer follow up of the SYSUCC trials will uncover an eventual difference in local control outcomes remain to be seen.

While local failure alone may be thought of as salvageable, its occurrence still necessitates nasopharyngectomy or re-irradiation, both of which may cause significant morbidity. More pertinently, there are several cases where local salvage therapy is not suitable (such as that due to anatomical concerns or concerns regarding dose tolerances from initial RT), leaving palliative systemic treatment as the only feasible option remaining.

In conclusion, if adjuvant metronomic chemotherapy fulfils its promise of improving on distant relapses without the risks of potential accelerated repopulation as with induction treatment, all while reducing the toxicities from added platinum chemotherapy, it would represent a new standard for locally advanced NPC treatment. Clinical trials of adjuvant metronomic chemotherapy in patients with locally advanced NPC are thus of utmost and urgent importance.

DECLARATIONS

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

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