Received: 16 May 2022 | Revised: 23 June 2022 | Accepted: 27 July 2022

DOI: 10.1002/cac2.12347

CANCER COMMUNICATIONS Open Access

EDITORIAL

Low-dose metronomic chemotherapy improves tumor control in nasopharyngeal carcinoma

1 | BACKGROUND

Nasopharyngeal carcinoma (NPC) is a unique head and neck malignancy prevalent in East Asia [1]. It is highly malignant, with the non-keratinizing pathological subtype constituting approximately 95% of NPC cases in endemic areas. Chemotherapy in combination with radiotherapy is recommended for locoregionally advanced NPC (LA-NPC), especially in subgroups at higher risk of distant metastasis (e.g., N2-3 *vs*. N0-1 diseases, high *vs*. low plasma Epstein-Barr virus [EBV] DNA copy number) [2, 3]. Concurrent chemoradiotherapy with or without induction chemotherapy is considered the backbone of the current chemoradiotherapy strategies for NPC [2, 3]. Nevertheless, although complete clinical remission could be achieved in more than 90% of patients after definitive chemoradiotherapy, about 20%-30% of patients will have disease recurrence subsequently [4, 5], which might be caused minimal residual disease (MRD), either at locoregional or distant sites [6, 7]. Thus, adjuvant therapy is needed to improve tumor control. Unfortunately, whether additional adjuvant chemotherapy following chemoradiotherapy could bring survival benefit for NPC patients remains controversial. Probably because of the high toxicity and unfavorable tolerance of conventional adjuvant agents using cisplatin and fluorouracil or cisplatin and gemcitabine, poor efficacy was observed for adjuvant chemotherapy in patients with NPC [8, 9]. It is of urgent need to seek for suitable adjuvant therapies.

Abbreviations: NPC, nasopharyngeal carcinoma; LA-NPC, locoregionally advanced nasopharyngeal carcinoma; EBV, Epstein-Barr Virus; MRD, minimal residual disease; MTD, maximum tolerated dose; LDM, low-dose metronomic; CSC, cancer stem cell; FFS, failure-free survival; OS, overall survival; D-FFS, distant failure-free survival; LR-FFS, locoregional failure-free survival; HRQOL, health-related quality of life; HR, hazard ratio; CI, confidence interval; PD-1, programmed death 1.

2 | MECHANISMS OF METRONOMIC CHEMOTHERAPY

Unlike conventional chemotherapy with drugs administered at a maximum tolerated dose (MTD), low-dose metronomic (LDM) therapy administers chemotherapeutic agents frequently and regularly at substantially lower, less toxic doses over prolonged periods, which shows superior tolerability [10]. Convenient orally administered fluorouracil analogs, such as capecitabine and tegafur-uracil, are commonly used LDM regimens [11, 12]. Besides, it is proposed that MRD is highly enriched for cancer stem cells (CSCs) [13, 14], and that metronomic chemotherapy appears to facilitate better inhibition of CSCs compared with conventional chemotherapy [15, 16]. Using 3-dimensional (3D) soft fibrin gels, which could select stem-cell-like cancer cells according to previously published studies [17, 18], we found a significantly greater reduction of stem-cell-like NPC cells using the LDM-fluorouracil regimen than the MTD-fluorouracil regimen (Figure 1). Furthermore, metronomic chemotherapy is also believed to exert antitumor activity by targeting angiogenesis and activating an immune response [10]. Therefore, it might be promising to use metronomic chemotherapy as the adjuvant treatment in NPC.

3 | METRONOMIC ADJUVANT CAPECITABINE IMPROVES DISEASE CONTROL IN LA-NPC

Based on the above rationale, we initiated a multicenter, open-label, randomized, phase 3 trial to assess the efficacy and safety of metronomic adjuvant capecitabine in patients with high-risk LA-NPC (NCT02958111), which has recently been published in the Lancet, entitled "Metronomic capecitabine as adjuvant therapy in locoregionally advanced nasopharyngeal carcinoma: a multicenter,

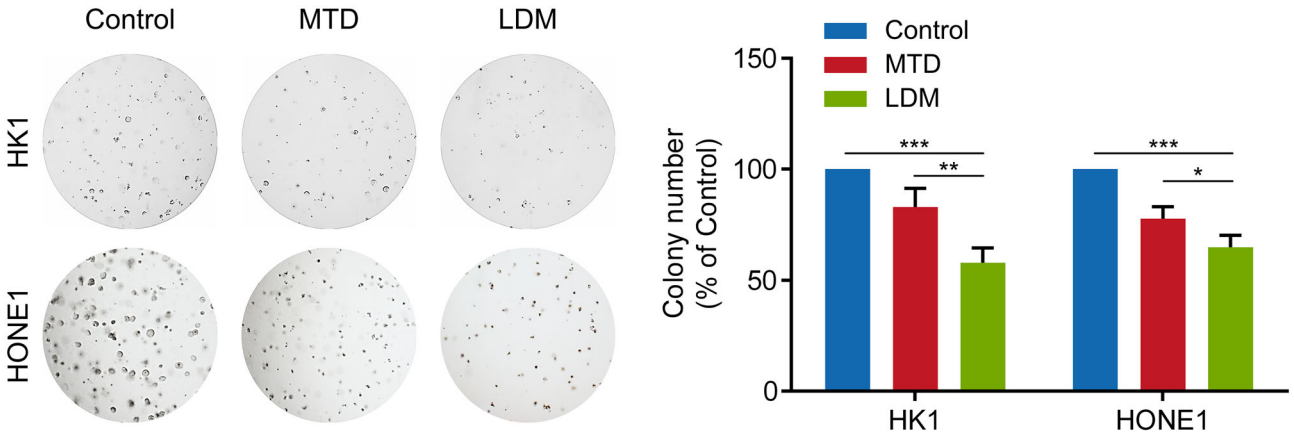

FIGURE 1 Killing assay of stem-cell-like NPC cells. Representative images (left panel) and colony number (right panel) of stem-cell-like HK1 and HONE1 cells exposed to PBS (control group), the maximum tolerated dose (MTD)-fluorouracil regimen (MTD group), or the low-dose metronomic (LDM)-fluorouracil regimen (LDM group). On day 0, HK1 and HONE1 cells (20,000 cells per well) were seeded into 3-dimensional (3D) soft fibrin gels that could select stem-cell-like cancer cells and then cultured in 24-well plates. On day 2, the already transformed stem-cell-like HK1 and HONE1 cells were treated with PBS, MTD-fluorouracil regimen (20 μm × 24 h), or LDM-fluorouracil regimen (5 μm daily for 4 consecutive days), and tumor colonies were counted on day 6. The MTD and LDM dosages were based on the 50% and 25% inhibitory concentrations measured using a Cell Counting Kit-8 assay, respectively. Data are presented as mean ± SD from three independent experiments; *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ (one-way ANOVA). Detailed description of methods are provided in Supplementary Materials and Methods

open-label, parallel-group, randomized, controlled, phase 3 trial" [19].

In this trial, patients (aged 18-65 years) who have high-risk LA-NPC (T4N1M0 and T1-4N2-3M0), and had no locoregional or distant recurrence after definitive chemoradiotherapy (receiving the final radiotherapy dose within 12 to 16 weeks before randomization) were deemed eligible. Patients were randomly assigned in a 1:1 ratio to the metronomic capecitabine group (receiving metronomic capecitabine at a dose of 650 mg/m^2 bid for 1 year) or the standard therapy group (receiving observation only). Failure-free survival (FFS) in the intention-to-treat population was the primary end point, which was defined as the freedom from disease failure or death from any cause. The secondary end points included overall survival (OS), distant FFS (D-FFS), locoregional FFS (LR-FFS), safety, and health-related quality of life (HRQOL).

A total of 406 patients were enrolled between Jan 2017 and Oct 2018, in which 204 and 202 patients were randomly assigned to the metronomic capecitabine and the standard-therapy groups, respectively. Among 201 patients who received metronomic capecitabine (3 patients withdrew consent and received clinical observation only), 149 (74%) finished the 1-year treatment. As for capecitabine, median relative dose intensity was 98.1% (interquartile range = 72.0%-100%). After a median follow-up of 38 months, 29 (14%) events were in the metronomic capecitabine group and 53 (26%) were in standard-therapy group. Patients in the metronomic capecitabine group had significantly higher 3-year FFS compared to those in the standard-therapy group (85.3% *vs*. 75.7%; stratified hazard ratio [HR] = 0.50, 95% confidence interval [CI] = 0.32-0.79; $P = 0.002$). The metronomic capecitabine group had a better 3-year OS than the standard-therapy group (93.3% *vs*. 88.6%; stratified HR = 0.44; 95% CI = 0.22-0.88; $P = 0.018$). Besides, in the metronomic capecitabine group, patients had both a better 3-year D-FFS (89.4% *vs*. 82.1%; stratified HR = 0.52; 95% CI = 0.30-0.88; $P = 0.014$) and 3-year LR-FFS (92.6% vs. 87.8%; stratified HR = 0.50; 95% CI = 0.25-0.98; $P = 0.041$) than those in the standard-therapy group. Metronomic capecitabine has a consistent benefit over all patient subgroups with respect to FFS, including different T and N categories, and clinical stages. Of note, consistent benefits favoring metronomic capecitabine were observed irrespective of the use of induction chemotherapy (yes *vs*. no), and the regimens (docetaxel + cisplatin *vs*. docetaxel + cisplatin + fluorouracil *vs*. gemcitabine + cisplatin) or cycles (2 *vs*. 3) of induction chemotherapy if used.

A total of 201 and 200 patients from the metronomic capecitabine and standard-therapy groups were included in the safety analysis, respectively. There were 73% (147/201) patients in the metronomic capecitabine and 51% (101/200) patients in the standard-therapy group experienced grade 1 or 2 adverse events. Grade 3 adverse events were observed in17% (35/201) and 6% (11/200) patients in the metronomic capecitabine and standard-therapy groups, respectively; one (<1%) grade 4 neutropenia was observed in the metronomic capecitabine group. The most

common event related to capecitabine was hand-foot syndrome (18 [9%]). Neither group suffered from treatment-related deaths. Besides, no meaningful HRQOL deterioration relevant to metronomic adjuvant capecitabine was observed. Thus, metronomic adjuvant capecitabine added to definitive chemoradiotherapy was well-tolerated with improved disease control.

4 | CONCLUSIONS AND PERSPECTIVES

In summary, among patients with high-risk LA-NPC, adjuvant metronomic capecitabine significantly improved patient survival, the toxicity of which was manageable with no reduction to quality of life. Future considerations for the adjuvant use of metronomic capecitabine include the combined use of metronomic chemotherapy and immunotherapy. A preclinical study reported that metronomic chemotherapy can have an immunomodulatory impact that could be synergistic with immunotherapy using anti-programmed death 1 (anti-PD-1) [20]. The efficacy and safety of the addition of immune checkpoint inhibitors to metronomic adjuvant chemotherapy merits further exploration, and an ongoing phase 3 trial (NCT05342792) investigating metronomic capecitabine, with or without anti-PD-1, as adjuvant therapy in high-risk NPC might provide more evidence. Besides, the optimal duration for the adjuvant use of metronomic capecitabine should be further explored. It is not clear whether one year of treatment is sufficient for NPC patients because recurrence commonly occurs within the first two years after radiotherapy. Finally, as plasma EBV DNA serves as a biomarker of MRD in NPC, whether patients with detectable plasma EBV DNA after radiotherapy could benefit more from adjuvant metronomic capecitabine warrants further studies.

DECLARATIONS

ACKNOWLEDGEMENT
We thank the patients who participated in the trial and their families.

COMPETING INTERESTS
The authors declared that no conflicts of interest exist.

FUNDING INFORMATION
This work was supported by grants from the National Natural Science Foundation of China (82172749), the Natural Science Foundation of Guangdong Province (2021B1515020010), and the Fundamental Research Funds for the Central Universities, Sun Yat-sen University (22ykqb14).

AUTHOR CONTRIBUTIONS
Yu-Pei Chen and Jun Ma designed the research. Yu-Pei Chen and Jia-Yi Shen conducted the experiments. Yu-Pei Chen and Xiao-Yu Liang acquired and analyzed the data. Yu-Pei Chen wrote the manuscript. Jia-Wei Lv, Zhen-Ji Deng, and Ying Sun revised the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE
Not applicable.

CONSENT FOR PUBLICATION
Not applicable.

AVAILABILITY OF DATA AND MATERIALS
The authenticity of this manuscript has been validated by uploading the key raw data to the Research Data Deposit public platform (www.researchdata.org.cn) under approval RDD number RDDB2022123608.

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