Treatment Results of Capecitabine Metronomic Chemotherapy in Locally Advanced Nasopharyngeal Carcinoma after Standard Chemoradiotherapy– A Single- Arm Phase II Study

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Abstract:

Background: High recurrence risk exists for patients with locoregionally advanced nasopharyngeal carcinoma (NPC) thus adjuvant therapies are required to lower the risk of recurrence and mortality. This phase II trial was designed for evaluating the effectiveness and safety of adding metronomic capecitabine as an adjuvant therapy to chemoradiation in patients with locally advanced NPC.

Methods: This prospective single-arm phase II single trial involved 41 patients aged from 18 to 75 years, with locally advanced NPC (Stage III - Stage IVA) with no previous treatment or distant metastases at diagnosis. Oral metronomic capecitabine (Xeloda; 650 mg/m² body surface area was administered twice daily for 1 year. Clinical or imaging exams were conducted. Individuals were assessed to have had a full response when they showed no recorded signs of the disease following the completion of therapy and were free from disease for three months at least. The duration of follow-up was for 24 months.

Results: Locoregional recurrence was developed in 6 (14.63%). Rates of two-year overall survival (OS) for all patients (n = 41) in this trial was 92.68%, the 2-year disease free survival (DFS) rate for them was 85.37% and progression free survival (PFS) was 78.05%.

Conclusions: Metronomic chemotherapy with capecitabine was a promising treatment for patients with locally advanced NPC. The 2-year OS and PFS were improved, and the acute and late toxicities were tolerated.

Keywords: Capecitabine Metronomic; Locally Advanced Nasopharyngeal Carcinoma; Standard Chemoradiotherapy

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Introduction:

The origin of nasopharyngeal carcinoma (NPC) is the lining of the nasopharynx, the tubular channel behind the nasal cavity. Although, there was a remarkable difference in the ethnic and geographic distribution in 2020, over 130,000 new cases and 80,000 deaths were reported [1]. Due to the radiosensitive nature of NPC and its deep-seated location, radiotherapy (RT) is the only effective treatment for this condition [2]. However, locally advanced cancer is inadequately treated with radiation alone, resulting in a modest 5-year survival rate [3].

The mainstay of treatment is concurrent platinum-based chemoradiation (CCRT) with or without induction chemotherapy. In order to decrease the likelihood of recurrence and mortality, adjuvant therapy is essential [4]. In NPC, the value of adjuvant chemotherapy addition to chemoradiation remains controversial [5].

The low effectiveness of adjuvant treatment may be attributable to the potential toxicity and poor tolerability of usual chemotherapy regimens following definitive chemoradiation [6].

Metronomic chemotherapy involves the delivery of chemotherapeutic medications at much lower dosages than generally provided during specified time periods without extended drug-free intervals. This might result in low toxicity and high adherence [7]. On a biological level, it is believed that metronomic chemotherapy primarily inhibits angiogenesis to produce its anticancer effects. Other pathways include direct cytotoxic effects and immunological activation [8]. Multiple clinical studies have shown the effectiveness of metronomic chemotherapy in the management of different malignancies, involving breast cancer and colorectal cancer [7, 9].

In patients with recurrent or metastatic NPC, capecitabine, an accessible, orally taken fluorouracil

medication, was characterized to have therapeutic advantages [10], as it can replace intravenous (IV) fluorouracil with lower toxicity in patients with advanced locoregionally NPC [11]. Consequently, a good option for usage in adjuvant metronomic situations is capecitabine.

The 2021 guideline of the Chinese Society of Clinical Oncology recommends metronomic adjuvant capecitabine for locoregionally advanced NPC patients at high risk [12]. Therefore, this phase II trial was designed for evaluating the effectiveness and safety of adding metronomic capecitabine as an adjuvant therapy to chemoradiation in patients with locally advanced NPC.

Patients and Methods:

This prospective single-arm phase II trial involved 41 patients aged from 18 to 75 years, Karnofsky status of performance ≥70, with locally advanced NPC (Stage III - Stage IVA) as regard the American Joint Committee on Cancer classification system, eighth edition with no previous treatment or distant metastases at diagnosis. This study was performed after approval of ethical committee in Clinical Oncology Department, Faculty of Medicine, Tanta University Hospital, Egypt from January 2017 and December 2019. Before initiating any treatment, all patients were given their written informed consent.

Exclusion criteria were incomplete planned treatment, double primary cancers or non-epithelial cell cancers, dementia of pregnancy, disturbed mental status, or any psychological disorder

Treatment Protocol

Eligible patients received induction chemotherapy (DCF regimen) for 2-3 cycles followed by standard RT using intensity modulated radiation therapy (IMRT) technique and RT has been administered concurrently with chemotherapy. The DCF regimen was administered as a sort of chemotherapy which consisted of docetaxel (75 mg/m2 IV infusion (I) on day 1), cisplatin (75 mg/m2 IVI on day 1), and 5-fluorouracil (750 mg/m2 IVI on days 1 to 5). Cisplatin was provided as a 6-hour infusion with sufficient pre- and post-hydration to avoid nephrotoxicity. Dexamethasone 20 mg was administered orally before docetaxel as a standard premedication. Diphenhydramine 50 mg IV and cimetidine 300 mg IV (or ranitidine 50 mg IV) were administered 24 hours prior of chemotherapy and administered six hours and thirty minutes prior to chemotherapy and for 2 days after regimen. Antiemetics were used at the oncologist's decision. WBC > 3 x 103/mm3 and platelets > 100 x103/mm3 were prerequisites for initiating cycles and were repeated after 21 days. The dosage was modified to account for non-hematologic effects, such as mucositis. If a patient's cycle was delayed for more than four weeks, he or she was excluded from the research.

Upon confirmation of full response, patients administered one year of oral metronomic capecitabine (Xeloda) medication (650 mg/m2, twice daily). Metronomic therapy with oral capecitabine (Xeloda) is discontinued if disease recurrence or serious adverse effects occur. The last patient has completed capecitabine metronomic treatment. No dose reductions were noted, and only two individuals experienced a one-week dose delay due to diarrhea Grade 3 (one patient) and hand-foot syndrome grade 3/4 (one patient) (one patient). On an outpatient basis, chemotherapy is administered. Every month, adequate hematological and organ functions were monitored. Throughout the trial, adverse effects were monitored. Except for alopecia and weariness, all hematologic and non-hematologic effects must resolve completely. If toxicities persisted, a 1–2-week delay was permitted.

As appropriate, Supportive care included blood transfusions, growth hormones, and the prescription of antiemetics. In this study, preventative usage of growth factors was not indicated.

Patient assessment

Monitoring included full history, local and physical examination, flexible nasopharyngoscopy; CT images of the chest, nasopharynx and neck MRI or CT scan; biopsy or fine-needle aspiration from suspected lesion, ultrasonography and/or CT images of the abdomen and pelvis, and reserved bone marrow, liver function, and renal function measurement was done before and during treatment. Patients suspected of having persistent locoregional illness or distant metastases underwent PET/CT scan.

Criteria for Response, Follow-Up, and Late Toxicity

Blood counts and serum chemistries were done every week. Creatinine clearance was measured before chemotherapy during treatment. Weight was evaluated weekly and prior to each cycle to determine performance status. Three to four weeks following the end of the RCT, the response quality was evaluated in accordance with WHO guidelines. Complete response, partial response, stagnant disease, and advancing disease constituted the types of therapeutic response. A partial response was recognized when tumors or lymph nodes shrank by at least 50 percentage points. Clinical or imaging exams were conducted. Individuals were assessed to have had a full response when they showed no recorded signs of the disease following the completion of therapy and were free from disease for three months at least. In the event of CR, patients were eligible for a one-year course of oral capecitabine (Xeloda) therapy. Patients were monitored every three months for the first two years, and thereafter every six months. Assessments included physical examination, relevant medical history, full blood counts and blood chemistry and imaging tests with biopsies of any suspected sites. In the event of a chronic or recurring tumor, treatment was indicated and began as soon as possible. Using the grading method for late effects on normal tissue (LENT), the evaluation of late treatment-related toxicity was undertaken. In accordance with the normal WHO toxicity standards, acute toxicity was rated.

Overall survival (OS) (Time interval from the date of diagnosis to the date of death by whatever means or the most recent follow-date up's), and disease- free survival (DFS) (from the conclusion of treatment till the date of local recurrence or distant metastasis of the tumor), and distant metastasis-free survival rate(the duration between the date of diagnosis and the date of distant metastases or the date of censorship, if later.), the progression-free survival (PFS) (time from randomization or introduction of treatment to the occurrence of disease progression or death).

Our outcomes

This prospective study's primary outcome was to evaluate the OS for 2 years of all studied patients. Secondary outcome was the DFS for 2 years and toxicity.

Statistical analysis

SPSS v26 was used to perform statistical analysis (IBM Inc., Armonk, NY, USA). Mean and standard deviation were used to express numerical parameters (SD). Frequency and percentage were used to express categorical variables (%). The Kaplan-Meier technique was applied to assess OS, DFS and PFS. P-values below 0.05 were considered statistically significant.

Results:

Radiotherapy combined with chemotherapy were used in all patients in the form of cisplatin, fluorouracil and docetaxel drug combinations. The eligibility to this study was for patients who achieved complete response after standard therapy.

Table 1 lists patient and tumour baseline characteristics. This study involved 41 patients 25 (60.98%) men and 16 (39.02%) women, with age ranging from 23 to 75 years with a mean of 50.17 years. The accepted clinical stage scheme was the AJCC (1). The AJCC stage was Stage III in 26 (63.41%) cases and Stage IVA in 15 (36.59%) patients. 28 (36.58 %) patients demonstrated weight loss. The majority of patients (63.41%) were smokers. Pulmonary disease was the most common comorbidity 14 (34.14 %), then cardiac disease in 7 (17.07%). Enlarged neck lymph nodes were the most common symptom (29 cases [70.73%]) followed by dysphagia (12 [29.26%]).

Karnofsky performance status was ≥70-<80 in 24 (58.54%) patients and 80-90 in 17 (41.46%) patients. Tumor size was ≥10cm3 in 20 (48.78%) patients and was <10 cm3 in 21(51.22%) patients. Pathological tumor type was squamous cell carcinoma in 30 (73.17%) patients and was anaplastic carcinoma in 11(26.83%) patients. Tumor grading was grade I/II in 19 (46.34%) patients and was III/IV in 22(53.66%) patients. Stage before treatment was III in 26 (63.41%) patients and was IVA in 15(36.59%). Number of cycles of induction chemotherapy was 2 in 14(34.15%) patients and was 3 in 27(65.85%) patients.

Table 1. Pretreatment patient and tumor characteristics (n = 41)

	No.	%
Age in years ≤ 50	18	43.90%
>50	23	56.10%
Gender Male	25	60.98%
Female	16	39.02%
Smoking Smokers	26	63.41%
Non-smokers	15	36.59%
Karnofsky performance status ≥70-<80	24	58.54%
80-90	17	41.46%
Tumor size ≥10cm^3	20	48.78%
<10 cm^3	21	51.22%
Tumor type Squamous cell carcinoma	30	73.17%
Anaplastic carcinoma	11	26.83%
Tumor grading Grade I/II	19	46.34%
Grade III/VI	22	53.66%
Stage before treatment		
III	26	63.41%
IVA	15	36.59%
Number of cycles of induction chemotherapy		
2	14	34.15%
3	27	65.85%
Tumor category		
T1	3	7.32%
T2	8	19.51%
T3	13	31.71%
T4	17	41.46%
Node category		
N1	3	7.32%
N2	17	41.46%
N3	21	51.22%

Table 2 Hematologic and non-hematologic toxicities of capecitabine metronomic therapy

Toxicity	Grade 1/2 No. (%)	Grade 3/4 No. (%)
Non-hematologic toxicity		
Hand-foot syndrome	14 (34.15%)	5 (12.20%)
Diarrhea	4 (9.76%)	1 (2.44%)
Nausea/vomiting	6 (14.63%)	0.0
Fatigue	4 (9.7%)	0.0
Weight loss	3 (7.32%)	0.0
Hematologic toxicity		
Anemia	17 (41.46%)	0.0
Leukopenia	2 (4.88%)	0.0
Neutropenia	1 (2.44%)	0.0

Table 3: OS rate, DFS and PFS

	Mean (months)	SE	95% CI for the mean	
OS	22.585	0.788	21.041 -24.130	92.68%
DFS	21.390	1.022	19.387 - 23.393	85.37%
PFS	21.390	1.084	19.266-23.515	78.05%

Toxicity

Table 2 lists the most common adverse effects. The majority of hematologic and non-hematologic effects were tolerable and modest. No Grade 3/4 hematologic toxicities were documented. Hand-foot syndrome was the most common treatment-related adverse event occurring in 23 (51.21%) of patients. 14 (34.15%) of them were grade 1/2, and only 5 (12.20%) were grade 3/4, which recovered promptly to grade 0/1 with rest and symptomatic therapy. Five (12.20%) patients developed diarrhoea. 4 (9.76%) of them suffered from Grade 1/2 toxicity and 1 (2.44%) experienced from grade 3/4 toxicity. Other non-hematologic grade 1/2 toxicities noted were nausea and vomiting in 6 (14.63%) patients, fatigue in 4 (9.7%), weight loss in 3 (7.32%). Regarding hematologic toxicity, 17 (41.46%) of patients had Grade 1/2 anemia, 2 (4.88%) had Grade 1/2 Leukopenia and 1 (2.44%) had Grade 1/2 neutropenia. Capecitabine was administered in full doses to each patient. Throughout the study, none of our patients required a dose reduction.

Survival rate

The duration of follow-up was 24 months. Locoregional recurrence was developed in 6 patients (14.63%). Rates of two-year OS for all patients (n = 41) in this trial was 38 (92.68%) (Fig. 1), the 2-year DFS rate for them was 35 (85.37%) (Fig. 2) and PFS was 32(78.05%) (Fig. 3) (Table 3).

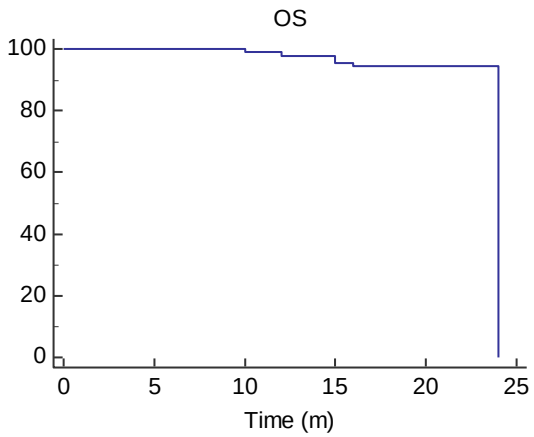

Figure 1: Kaplan-Meier analysis of 2 years overall survival rate

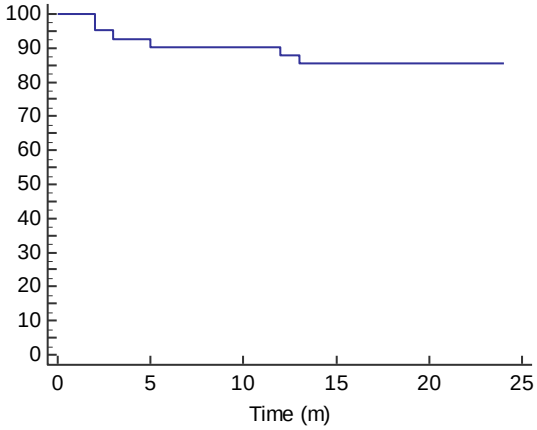

Figure 2: Kaplan-Meier analysis of 2 years disease-free survival rate

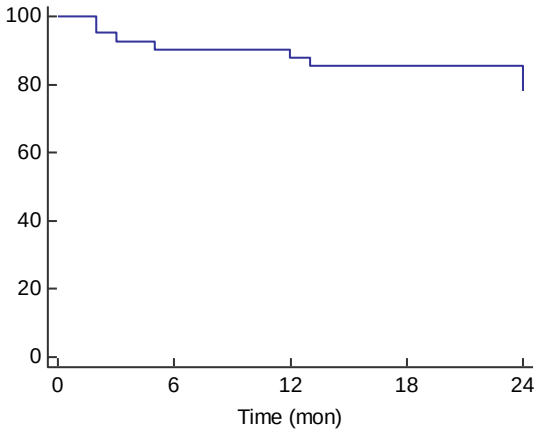

Figure 3: Kaplan-Meier analysis of 2 years progression-free survival rate

Discussion:

CCRT followed by adjuvant chemotherapy increased the 5-year OS rate by 30 % to RT alone in locally advanced NPC [13]. Several phase III clinical studies in endemic locations demonstrated the superiority of CCRT followed by adjuvant chemotherapy over RT alone [14-16]. Simultaneously, concomitant and adjuvant chemotherapy were investigated; hence, it remained unclear whether type of chemotherapy provides the greatest benefit.

CCRT could enhance PFS [17]. Consequently, four Phase III clinical studies were launched to investigate the precise role of CCRT, [18-20] which demonstrated that CCRT was superior to RT alone regarding of OS and PFS. Based on the results of these clinical trials, several guidelines suggest CCRT followed by adjuvant chemotherapy or not for locoregionally advanced NPC.

Therefore, there is an urgent need for adjuvant therapy to lower the risk of recurrence and mortality.

This phase II experiment was designed to examine the effectiveness and safety of adding metronomic capecitabine to chemoradiation as an adjuvant treatment in NPC patients.

Our results revealed that, survival rate was 92.68%, DFS was 85.37% and PFS was 78.05% and recurrence rate was14.63% of all patients.

This came in line with Feng et al. [21] who investigated sixty-seven patients with stage III-IV (UICC 8th) locally progressed NSC treated with concomitant chemoradiotherapy and metronomic capecitabine chemotherapy and found that the 2-year OS was 96 % and the 2-year DFS was 94.9%.

Also, Chen et al [22] conducted phase 3 study of metronomic capecitabine as adjuvant treatment for 406 individuals with locoregionally progressed NPC and found that OS at 3 years was 93.3% and distant failure-free survival was 82.1% with 14% recurrence rate.

The majority of hematologic and non-hematologic toxicities were manageable and mild. Hand-foot syndrome was the most prevalent adverse effect of treatment occurring in 51.21% patients, 34.15% of them were grade 1/2, Diarrhea was experienced in 12.20% of patients 4 (9.76%) of them were grade 1/2 toxicity and 2.44% were grade 3/4 toxicity. Regarding hematologic toxicity, 41.46% of patients had grade 1/2 anemia.

Similarly with Chen et al. [22] the occurrence of grade 3 or higher adverse events of hematological and non-hematological were lower in metronomic capecitabine [17%]. Also, Hand-foot syndrome grade 1/2 (49%) was the most frequent side effect with metronomic chemotherapy

In addition, we identified no major side effects in the group receiving capecitabine administered at a metronomic rate. All of these unwanted effects were largely controllable and had little clinical impact.

Previous studies have demonstrated that metronomic chemotherapy offers the benefits of excellent tolerance and minimal toxicity [23, 24]. Furthermore, this low-cost and readily available regimen is seen as an attractive method for improving patient survival, particularly in nations with limited resources. (e.g. in locations where NPC is prevalent) [25].

Therefore, metronomic chemotherapy may be the optimal adjuvant approach for NPC patients.

Our study has certain limitations that must be noted. Firstly, relatively small sample size with short follow-up duration only 2 years. Our research did not have a control group.

Further studies are required for at least 5 years follow -up for the determination of OS and DFS of advanced-stage adverse events and to investigate toxicities of capecitabine.

Conclusion:

Metronomic chemotherapy with capecitabine was a promising treatment for patients with locally advanced NPC. The 2-year OS and PFS were enhanced, and the acute and late toxicities were tolerated.

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Conflict of Interest: Nil

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