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Comparison of efficacy of neoadjuvant chemotherapy with gemcitabine plus cisplatin versus docetaxil, cisplatin, plus fluorouracil in locally advanced nasopharyngeal carcinoma

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Abstract: Induction followed by concurrent chemoradiation (CCRT) is the standard of care for locally advanced nasopharyngeal carcinoma (LANPC). This study evaluated and compared the efficacy of two regimens of neoadjuvant chemotherapy along with CCRT in LANPC. Patients with LANPC were randomly divided in Group I (receiving neoadjuvant gemcitabine and cisplatin) and Group II (receiving neoadjuvant docetaxil, cisplatin and fluorouracil). Both groups also received concurrent single agent (i.e., cisplatin) chemotherapy and radiotherapy (70Gy). Treatment response was assessed at 8 weeks after the completion of CCRT using RECIST criteria. A total of 68 LANPC patients were enrolled. Group I comprised of 32 patients, with male to female ratio of 2.2, a mean (range, median) age of 38.6±11.3 (19-58, 36) years. Group II comprised of 36 patients, with male to female ratio of 3.5, mean (range, median) age of 40.9 ±11.6 (17-63, 40) years. The complete response was higher whereas the partial response was lower in Group I as compared to Group II (23/32 versus 16/36, and 06/32 versus 18/36, respectively). LANPC patients receiving gemcitabine plus cisplatin based neoadjuvant chemotherapy showed higher response, as compared with docetaxil, cisplatin and fluorouracil based neoadjuvant chemotherapy.

Keywords: Nasophargeal carcinoma, neoadjuvant chemotherapy, response evaluation, diagnosis.

INTRODUCTION

Nasopharyngeal carcinoma (NPC) exhibit a distinctive global distribution pattern, with the highest incidence rates concentrated in regions encompassing South China, South-eastern Asia, and North Africa (Sung *et al.,* 2021). In the year 2018, NPC affected an estimated 130,000 individuals globally, where more than 70% of patients received a diagnosis of locoregionally advanced disease upon initial presentation (Sung *et al.,* 2021; Sharma 2021). Within this subset of patients characterized by an unfavourable prognosis, concurrent chemoradiotherapy featuring a platinum-based agent assumes a pivotal role in the therapeutic regimen (Xu *et al.,* 2023). It is worth noting that this chemotherapy agent has a considerable role in enhancing the sensitivity of the tumor for subsequent radiotherapy, thereby improving the treatment efficacy (Zhang *et al.,* 2019; Yan *et al.,* 2022). Moreover, distant metastasis emerges as the predominant mode of disease relapse, contributing to cancer-specific mortality in approximately 70% of afflicted individuals (Yu-Chen *et al.,* 2024; Dai *et al.,* 2024). This clinical feature underscores the formidable challenges associated with the management of NPC and highlights the imperative for ongoing research efforts aimed at optimizing treatment strategies and improving patient outcomes (Huang *et al.,* 2023).

The incorporation of chemotherapy into the treatment regimen, either as an induction or adjuvant approach alongside chemoradiotherapy, has been the subject of extensive investigation, yielding heterogeneous outcomes (Juarez-Vignon Whaley *et al.,* 2023; Li *et al.,* 2024; Huang *et al.,* 2023). The toxicity and side effects associated with the systemic therapy following the administration of chemoradiotherapy remains a major concern (Meng *et al.,* 2023; Li *et al.,* 2024). Induction chemotherapy has entered the clinics after convincing evidence stemming from a randomized, controlled trial with a long follow-up period. In this trial, the inclusion of docetaxil, cisplatin, and fluorouracil alongside chemoradiotherapy in patients presenting with locoregionally advanced NPC resulted in a demonstrable extension of overall survival (Tang *et al.,* 2023; Liu *et al.,* 2023; Chan *et al.,* 2018; Huang *et al.,* 2023). These findings substantiate the potential advantages of incorporating induction chemotherapy into the therapeutic approach for locally advance NPC (LANPC).

Nevertheless, this treatment approach is not devoid of limitations. For example, these neoadjuvant chemotherapy protocols may pose challenges in terms of

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patient tolerance and toxicity. The administration of multiple cytotoxic agents prior to definitive chemoradiotherapy increases the risk of adverse effects, potentially compromising patients' quality of life and treatment adherence. Moreover, the optimal timing and sequencing of neoadjuvant chemotherapy in LANPC still remains debatable. Consequently, careful consideration of patient-specific factors and toxicity profiles is essential in optimizing the therapeutic efficacy of this treatment regimen.

Previously, several phase 2 trials have substantiated the efficacy of gemcitabine in conjunction with cisplatin as a chemotherapy regimen for patients presenting with NPC (Nie *et al.,* 2024; Yang *et al.,* 2022). Notably, this combination has been established as the preferred first-line treatment option, surpassing cisplatin combined with fluorouracil, particularly in patients presenting with recurrent or metastatic disease (Liu *et al.,* 2024). However, within the specific context of patients newly diagnosed with non-metastatic, locoregionally advanced NPC, there are speculations regarding the therapeutic efficacy and safety profile of induction therapy involving gemcitabine and cisplatin in conjunction with chemoradiotherapy. In this context, this study was designed to assess the clinical response of gemcitabine and cisplatin (GC) versus docetaxil, cisplatin and fluorouracil (TPF) in LANPC.

MATERIALS AND METHODS

Study design

This study enrolled patients from the Department of Medical Oncology, Jinnah Medical Postgraduate Center (JMPC), Karachi from January to December, 2022. A total of 68 patients were enrolled.

Ethical considerations

The study was approved by the institutional review board of JMPC, Karachi under the reference number F.81/2022-GENL/345/JPMC. Before enrollment, all the patients signed a written informed consent. After enrollment, the patients were allowed to withdraw consent at any time and discontinue participation in this study.

Inclusion and exclusion criteria

Patient's eligibility criteria for inclusion in this study were: patients aged between 16 and 65 years without restriction on their gender, histologically proven NPC, no previous chemotherapy and/ or radiotherapy to head and neck region, no distant metastasis, locally advance stage NPC (i.e., stage III to IVA disease), an ECOG performance status ≤ 2, adequate renal, hematologic and hepatic function. The exclusion criteria comprised of: tumor with intra-orbital extension, involvement of cranial nerves, recurrent NPC, and ECOG performance status >2, receipt of treatment with palliative intent; a history of cancer treatment (chemotherapy, radiotherapy, or surgery), severe multiple comorbidities.

Randomization and procedure

All enrolled patients were divided in two groups using simple randomization technique. Specifically, each patient had an equal chance of being assigned to any treatment group through computer-generated random numbers. This approach not only ensured unbiased treatment allocation and safeguarded against systematic biases but also improved the statistical robustness.

All patients included in this study underwent essential clinical assessment prior to treatment initiation; this included complete history and clinical examination, hematologic and biochemical analyses and nasopharyngoscopy. The diagnosis of NPC was confirmed with histopathology and immunohistochemistry studies. To assess in staging the disease, radiological studies (i.e., contrast enhanced computed tomography (CT) and/ or magnetic resonance imaging (MRI) of the nasopharynx and neck) were performed. Moreover, all patients underwent CT examination of the chest and abdomen for evaluation of distant metastasis. Bone scintigraphy was performed to evaluate skeletal metastasis.

Treatment protocol

The selected patients were divided in two groups using simple randomization technique. Patients in Group I were given gemcitabine and cisplatin (GC) while patients in Group II received docetaxil, cisplatin, and fluorouracil (TPF) as neoadjuvant chemotherapy, followed by cisplatin in concurrent setting.

The neoadjuvant chemotherapy dosage were as follows: for Group I, gemcitabine 1g/m^2 given intravenously (IV) once daily on days 1 and 8 and cisplatin 80mg/m^2 IV once daily on day 1, 3 weekly); for Group II, the patients received weekly docetaxil 30mg/m^2, cisplatin 40mg/m^2 and fluorouracil (5FU) 750mg/m^2 (all three agents were given in IV infusion on day 1) and cisplatin 40mg/m^2 weekly in both protocol as a concurrent chemotherapy. Patients in both groups received a radiation dose of 70 Gy (02 Gy per fraction) with the use of 3D conformation radiotherapy (3DCRT) technique.

Follow-up and treatment assessment

Disease was assessed at 8 weeks after the completion of chemoradiotherapy with the use of CT and/or MRI examination of the nasopharyngeal and neck areas. The primary end point of the study was the treatment response, as assessed with the RECIST 1.1 criteria (Ruchalski *et al.,* 2021). Specifically, the treatment outcome was categorized as complete response (CR: disappearance of all target lesions on CT/MRI examination), partial response (PR: at least a 30%

decrease in the sum of diameters of target lesions), progressive disease (PD: At least a 20% increase in the sum of diameters of target lesions or appearance of one or more new lesions) and stable disease (SD: neither qualifying for PR nor PD).

STATISTICAL ANALYSIS

The sample size was estimated using Open-epi online sample size calculator. The input parameters were selected as per the standard practice. Data analysis was carried out using the statistical tool of SPSS version 23 (IBM Corp., Armonk, NY). Quantitative data variables were expressed as mean and standard deviation (SD), while qualitative data variables were expressed in terms of frequency and percentage. Chi square test was used to evaluate the statistical differences.

RESULTS

This study enrolled 68 LANPC patients. Group I comprised of 32 patients, while Group II comprised 36 patients. The demographic characteristics of the patients are given in table 1. For Group I, there were 22 males (male to female ratio of 2.2), with a mean ± standard deviation (SD) (range, median) age of 38.6±11.3 (19-58, 36) years. For Group II, the male to female ratio was 3.5 (28 males, 08 females) having a mean ± SD (range, median) age of 40.9±11.6 (17-63, 40) years. There were 15 (47%) smokers in Group I and 16 (44%) smokers in Group II.

Table 2 presents details of chemotherapy regimens and the number of chemotherapy cycles administered to the LANPC patients in the two groups. For the neoadjuvant chemotherapy in Group I, the patients received induction chemotherapy with 3 cycles of GC (18 (56%) cases, 07 (22%) cases of 02 cycles, 05 (16%) cases of 04 cycles. For the concurrent chemotherapy in Group I, majority of patients received 06 (15: 47% cases) and 05 (11: 34%) cycles of cisplatin. Patients in Group II received relatively higher number of neoadjuvant (i.e., docetaxil, cisplatin, and fluorouracil: TPF) due to weekly protocol and concurrent (i.e., cisplatin) chemotherapy cycles. Specifically, 10 (28%) and 05 (14%) cases were given 09 and 08 cycles of neoadjuvant, while 16 (44%) cases were given 06 cycles of concurrent chemotherapy, respectively.

The distribution of tumor–node–metastasis (TNM) stage of all LANPC patients included in this study is shown in fig. 1. The solid (gray pseudo color) and open bars represent pre- and post-treatment data, while the plain bars and bars with tilted-line pattern depicts Group I and II, respectively. It may be noted that the data is presented in the form of normalized number of patients so as to facilitate one-to-one comparison between the two groups. The normalized number of patients was defined as the ratio of the number of patients in a given TNM stage to the total number of patients in the group. For example, the normalized number of patients presented with TNM stage III (pre-treatment) in Group I and II was 0.625 (=20/32) and 0.556 (=20/36), respectively. Comparing the TNM stage based treatment response, the normalized number of disease-free patients in Group I was higher compared to Group II (i.e., 0.688 vs. 0.472), as shown in fig. 2b.

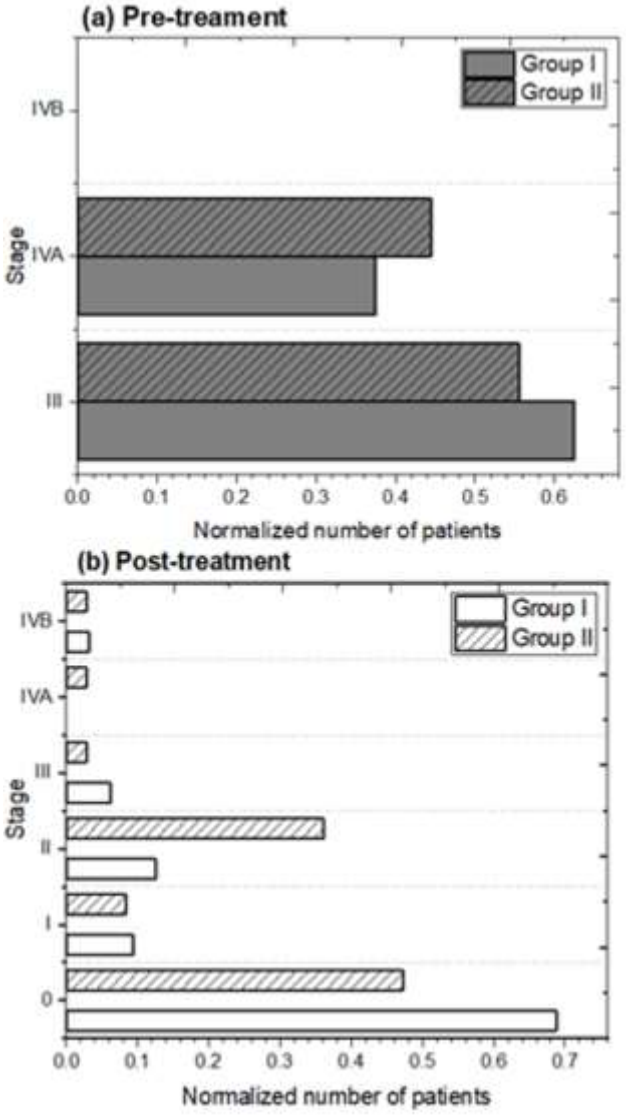

Fig. 1: Tumor-node-metastasis (TNM) stage distribution of the LANPC patients in the two groups (a) before and (b) after treatment. Normalized number of patients was defined as the ratio of the number of patients in a given TNM stage to the total number of patients in that group.

A comparison of pre- and post-treatment TNM stage of all LANPC patients for Group I and Group II is shown in fig. 2a and 2b, respectively. It is evident that both groups contained patients presenting (i.e., pre-treatment) with stage III and IVA disease. Moreover, treatment regimen in both groups either eliminated the disease (i.e., stage 0) or down-staged the disease to stage I and II. However,

few cases of advance stage disease were also observed in both Group I and II.

Results of the treatment response, as assessed with the RECIST 1.1 criteria, are presented in fig. 3. The treatment response was categorized as complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). It is evident that the CR in Group I was higher as compared to Group II, with normalized number of patients at 0.72 (23/32) versus 0.44 (16/36), respectively. On the other hand, the PR in Group II was higher as compared to Group I, with normalized number of patients at 0.19 (06/32) versus 0.50 (18/36), respectively. For a few cases in each group, the treatment response was categorized as SD and PD. Overall, these results indicate that the treatment outcomes for patients in Group I (administered with neoadjuvant GC) are superior to that of Group II (administered with neoadjuvant TPF).

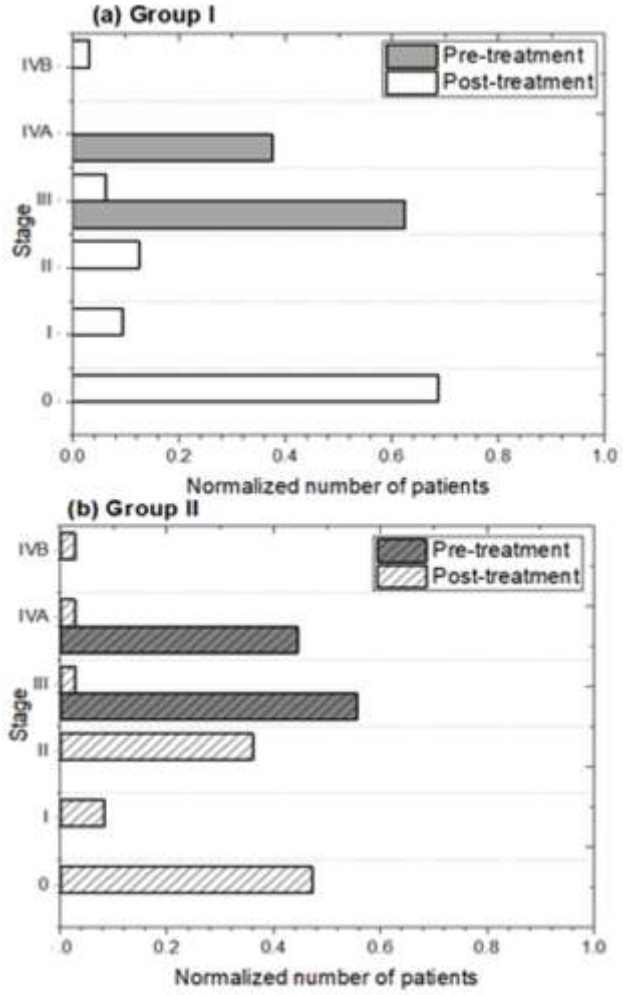

Fig. 2: Comparison of the treatment response in terms of tumor-node-metastasis (TNM) stage of the LANPC patients in (a) Group I and (b) Group II. Normalized number of patient was defined as the ratio of the number of patients in a given TNM stage to the total number of patients in that group.

We also evaluated the hematological toxicity profiles of chemotherapy across both Group I and Group II patients. Predominantly, low-grade anaemia and lymphopenia were prevalent, affecting a significant proportion of patients in both groups. Specifically, Grade I anaemia and lymphopenia were evident in 47.2% and 44.4% of Group I patients, respectively, with similar trends observed in Group II. Moreover, the severity of neutropenia was notable. Specifically, 80.6% and 65.6% of Group I and Group II patients, respectively, encountered severe neutropenia. Grade I and II thrombocytopenia affected 58.4% of Group I patients, alongside a consistent trend observed in Group II. These findings highlight the need for careful management strategies to mitigate potential complications.

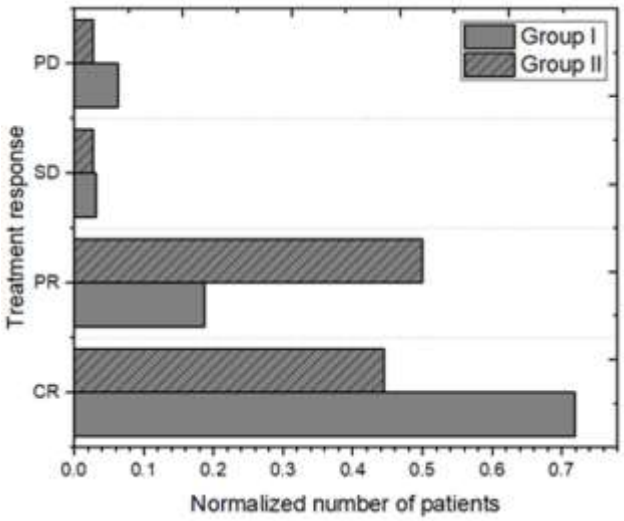

Fig. 3: Comparison of the treatment response of the LANPC patients in the two groups. Normalized number of patient was defined as the ratio of the number of patients in a given treatment response category to the total number of patients in that group. CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease

DISCUSSION

This study reports the results of comparing two different neoadjuvant chemotherapy regimens (i.e., GC vs. TPF) in the management of LANPC. The results demonstrated superior tumor control with GC-based (compared to TPF-based) neoadjuvant chemotherapy in selected patients presenting with high-risk LANPC. Although majority of the selected patients had unfavorable prognostic factors (e.g., T3 or T4 tumors and N2 or N3 disease), the higher efficacy of GC-based neoadjuvant chemotherapy was because of the lower incidence of locoregional recurrences in Group I than in Group II. This may also explain the superior treatment response in patients treated in the GC-based neoadjuvant chemotherapy group.

Table 1: Demographic details of the LANPC patients in the two groups

Demographics		Group I (GC)	Group II (TPF)
Number of patients		32	36
Gender	Male	22	28
	Female	10	8
	Male: Female	2.2:1	3.5:1
Age (Years)	Minimum	19	17
	Maximum	58	63
	Mean ± SD	38.6 ± 11.3	40.9 ± 11.6
	Median	36	40
Smoking	Yes	15	16
	No	17	20

SD: standard deviation, G: Gemcitabine, C: Cisplatin, T: Taxane (i.e., Docetaxil), F: Fluorouracil,

Table 2: Details of chemotherapeutic agents and the number of chemotherapy cycles administered to the LANPC patients in the two groups

Number of CT cycles	Group I (GC)			Group II (TPF)		
	Population with Neoadjuvant	Population with Concurrent	Total	Neoadjuvant	Concurrent	Total
2	7	0	7			
3	18	0	18	1	3	4
4	5	2	7	2	2	4
5	0	11	11	3	7	10
6	0	15	16	7	16	23
7		3	3	6	7	13
8				5	1	6
9				10		10
10				1		1
11				0		0
12				1		1

LANPC: locally advance nasopharyngeal carcinoma, CT: Chemotherapy, G: Gemcitabine, C: Cisplatin, T: Taxane (i.e., Docetaxil), F: Fluorouracil

This study noted an overall higher treatment response rates (complete plus partial response) of 91% and 94% with neoadjuvant gemcitabine plus cisplatin (Group I) and docetaxil, cisplatin, plus fluorouracil (Group II), respectively. These results are consistent with previous studies. To exemplify, gemcitabine plus cisplatin alone and together with camrelizumab have demonstrated response rates (CR plus PR) of 64% and 91%, respectively *(Fang et al.,* 2018). A recent randomized controlled trial illustrated that neoadjuvant chemotherapy with gemcitabine plus cisplatin, in combination with concurrent cisplatin-based chemoradiotherapy improve recurrence-free survival in LANPC patients (Zhang *et al.*, 2019). Moreover, induction therapy with the same chemotherapy regimen (i.e., gemcitabine plus cisplatin) enabled high treatment responses (>90%) among patients with locoregionally advanced disease (Yau *et al.*, 2006).

It is speculated that the acute adverse effects among patients treated with induction chemotherapy are higher than among those treated with chemoradiotherapy alone. Such adverse effects include severe neutropenia, leucopenia, thrombocytopenia, anemia, lymphocytopenia, nausea, and vomiting, among others. These adverse events in varying degree of severity have been reported in several studies. The present study, however, did not analyzed the adverse effects of neoadjuvant chemotherapy with the use of both GC and TFC regimens. Nevertheless, analyzing the incidence of acute grade adverse effects (particularly hematological toxicities) are the focus of an extension of the present study and will be published in future. This study will hopefully clarify the difference with regard to toxicity (in addition to efficacy evaluated in this study) in the two induction chemotherapy regimens.

STUDY LIMITATIONS

The primary limitation of this study was the single-center design, which may constrain the generalizability of findings. The sample size, albeit appropriately calculated, remains relatively modest, potentially limiting the robustness of statistical analyses and the extrapolation of results to broader patient populations. Additionally, the exclusion criteria, while necessary for maintaining homogeneity, might inadvertently exclude subsets of patients with distinct clinical characteristics, thereby affecting the study's external validity. Also, the adverse

effects, being the subject of a separate future study, were not comprehensively presented here.

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CONCLUSION

Neoadjuvant chemotherapy with gemcitabine plus cisplatin in tandem with concurrent chemoradiotherapy demonstrated higher complete response in patients with LANPC, compared to neoadjuvant chemotherapy with docetaxil, cisplatin, plus fluorouracil. To generalize the findings of this study to a broader patient population, it is recommended to conduct a multi-center randomized controlled trial with a larger patient cohort, thus providing more comprehensive insights into the efficacy and safety of the chemotherapy regimens evaluated in naso-pharyngeal carcinoma management.

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