ORIGINAL ARTICLE

HAEMATOLOGICAL TOXICITIES OF GEMCITABINE PLUS CISPLATIN VERSUS FLUOROURACIL, CISPLATIN, PLUS DOCETAXEL FOLLOWED BY CONCURRENT CHEMORADIOTHERAPY IN LOCOREGIONALLY ADVANCED NASOPHARYNGEAL CARCINOMA

Abdul Rehman[1], Ghulam Haider[1], Aakash Ramchand[1], Shumaila Nawaz Khan[1], Sana Sehar[1], Raheela Mahmood[2], Yasir Rehman Khattak[3], Anaum, Aisha Siddiqa[2], Muhammad Arsalan Aqeel[1]

Jinnah Postgraduate Medical Centre (JPMC) Karachi-Pakistan, [2]Atomic Energy Medical Centre, JPMC Karachi Pakistan
[3]Hayatabad Medical Complex, Peshawar-Pakistan

Background: Nasopharyngeal carcinoma is endowed with unique epidemiological characteristics, treatment modalities, and prognostic considerations. Patients with bulky primary tumours and extensive nodal involvement are categorized as locoregionally advanced NPC. These patients present a high-risk cohort in terms of the unfavourable prognostic features. In this patient cohort, the 5-year local control rates have been observed to fluctuate within the range of 69–79%. The objective was the assessment of the local control and adverse haematological toxicity profiles of neoadjuvant chemotherapy (NACT) (i.e., docetaxel, cisplatin, plus fluorouracil (TCF) and gemcitabine plus cisplatin (GC)) followed by concurrent chemoradiotherapy (CCRT) in patients with locoregionally advanced nasopharyngeal carcinoma (LANPC) was the primary objective of this work. **Methods**: Patients aged 16–65 years, confirmed NPC, stage III-IVA disease and ECOG performance score ≤2 were enrolled in this prospective study. Besides the common CCRT regimen, the patients received NACT with docetaxel 30 mg/m^2, cisplatin 40 mg/m^2 plus fluorouracil 750 mg/m^2 (Group I) or gemcitabine 1 g/m^2 plus cisplatin 80 mg/m^2 (Group II). At 6 weeks after completion of CCRT, treatment response was assessed with the RECIST criteria. Adverse haematological events were evaluated with peripheral white blood cells, neutrophils, haemoglobin, and platelets after each cycle of NACT. **Results**: Of the total 68 enrolled patients with locoregionally advanced NPC (LANPC), 50 (73.5%) were male patients. Group I consisted of 36, while Group II comprised 32 patients. The mean (interquartile range) age of the patients in Group I was 40.9±11.6 (30.3–51.8) years, while in Group II was 38.6±11.3 (29.5–51.0) years. Complete response (CR) of the treatment was higher and partial response (PR) was lower in Group II compared to Group I (71.9% vs. 44.4% and 18.6% vs. 50%, respectively). Haematological toxicity profiles were consistent in Groups I and II, illustrating mild anaemia and lymphopenia, severe neutropenia and a mixed pattern of thrombocytopenia. **Conclusion**: Among patients with LANPC, GC-based NACT showed superior CR compared with TCF-based NACT. However, the haematological toxicity profiles in the two groups were comparable.

Keywords: Imaging; Haematological toxicity; Neoadjuvant chemotherapy; Diagnosis

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INTRODUCTION

Nasopharyngeal carcinoma (NPC) is endowed with unique epidemiological characteristics, treatment modalities, and prognostic considerations.[1–3] Patients with bulky primary tumours (i.e., T3 or T4) and extensive nodal involvement (i.e., N2 or N3 disease) are categorized as locoregionally advanced NPC (LANPC).[4] These patients present a high-risk cohort in terms of unfavourable prognostic features.[5,6] In this patient cohort, the 5-year local control rates have been observed to fluctuate within the range of 69–79%.[7,8]

Oncological intervention (i.e., chemotherapy and radiotherapy) in patients presenting with LANPC inevitably triggers adverse side effects, such as severe mucositis, impaired kidney and liver functions, hypernatremia and hematologic toxicities.[9,10] For example, cisplatin-based chemotherapy has adverse effects, on gastrointestinal reactions, neuro-, nephron- and oto-toxicity.[11,12] A phase II trial comparing the

toxicities of three concurrent chemotherapy protocols that consisted of cisplatin (P), docetaxel (D), and PD demonstrated the development of significantly ($p = .015$) higher grade 3 or 4 acute toxicities in PD group compared to D group and the P group (88% vs. 63% vs 52%, respectively).[11] Docetaxel endows a lower toxicity profile than cisplatin and can be used in the management of patients with LANPC.[13,14] Moreover, although a double- or triple-agent chemotherapy regimen offers the potential to achieve superior outcomes in patients with LANPC, the toxicity profiles may be unacceptable, particularly old-age patients with compromised renal function.[11,15–17] Two cycles of three-agent concurrent chemoradiotherapy (CCRT) (i.e., cisplatin, paclitaxel, and fluorouracil) caused such severe adverse effects that only 17/24 (70.8%) patients completed the planned treatment, with myelosuppression being the dominant cause.[18] A similar completion rate of 2 cycles of concurrent chemotherapy (17/25, 68.0%) has been reported for cisplatin plus docetaxel in LANPC patients, with grade 3 or 4 mucositis occurring in 60%) of patients.[11] On the contrary, 06 cycles of low dose docetaxel and cisplatin for patients with LANPC were completed in all enrolled patients, with grade 3 and above mucositis occurring in 52% of patients.[19,20] In this context, it is important to identify characteristics associated with toxicity to optimize treatment regimens for patients with LANPC.[21,22]

In addition to the conventional adverse effects, treatment-associated haematological toxicities also remain notorious for their high incidence rates. Haematological toxicities include neutropenia, anaemia, lymphopenia and thrombocytopenia[23], and are typically associated with increased chemotherapy-related toxicity in NPC patients[24,25]. Substantial differences in haematological adverse effects have been reported among different CCRT regimens utilized in LAPNC.[26] Such acute adverse effects related to haematological variables may potentially cause a delay, reduction or even termination of the therapeutic dose, all negatively impacting the treatment outcomes and quality of the patient's life.[27] As several studies have proven the efficacy of gemcitabine in conjunction with cisplatin as a chemotherapy regimen for patients presenting with NPC[28–30], here, we present a comparison of the local control and hematologic toxicities of gemcitabine plus cisplatin (GC) and docetaxel, cisplatin, plus fluorouracil (TCF) combined with CCRT in the treatment of patients with LANPC.

MATERIAL AND METHODS

This prospective observational study was conducted at Jinnah Postgraduate Medical Centre (JMPC), Karachi. LANPC patients treated sequentially with NACT and CCRT from January 2022 to December 2022 were included. The sample size was calculated with the open-source, web-based software, OpenEpi (www.OpenEpi.com). All enrolled patients underwent complete history and clinical examination, radiological evaluation, biochemical profiling and analysis of complete blood. The institutional review board of JMPC, Karachi formally approved this study.

Patients who satisfied all of the following were selected for enrolment: age 16-65 years, NPC confirmed through histopathology, locoregionally advance NPC with tumour-node-metastasis (TNM) stage III and IVA[31], ECOG performance score ≤2, clinically acceptable haematological function (assessed via white blood cell, platelets and haemoglobin), adequate hepatic function (i.e., physiological levels of serum bilirubin, aspartate aminotransferase and alanine amino transferase) and adequate renal function (ensured through confirmation of normal serum creatinine levels and creatinine clearance rate). The exclusion criteria for this study consisted of: NPC tumours with infiltration into the orbit, previously treated cases of head and neck cancers, history of any other malignancy, ECOG performance score beyond 2 and any uncontrolled medical comorbidity.

All enrolled subjects were placed in either of the two groups using simple randomization. All patients underwent complete medical history, clinical examination, nasopharyngoscopy, routine blood and biochemical analysis and radiological studies of the head and neck region - either magnetic resonance imaging (MRI) studies or computed tomography (CT) examination. To assess distant metastasis, either positron emission tomography (PET)-CT or bone scintigraphy, CT of the chest or abdomen regions were performed.

All patients received NACT and CCRT. The CCRT protocol was identical in both groups, with cisplatin and 70 Gy of radiation. However, different NACT regimens were used in Group I and II. Specifically, patients in Group I received docetaxel, cisplatin, plus fluorouracil (TPF), while patients in Group I were given gemcitabine plus cisplatin (GC) as neoadjuvant chemotherapy (NACT). The dosage of NACT regimens where: for Group I, weekly docetaxel 30 mg/m^2, cisplatin 40 mg/m^2 plus fluorouracil (5FU) 750 mg/m^2 (all drugs given intravenously on the day (D) 1); for Group II, gemcitabine 1 g/m^2 administered intravenously once daily on D1 and D8 and cisplatin 80 mg/m^2 once daily on D1. All patients received single-agent cisplatin 40mg/m^2 in a concurrent setting with radiotherapy.

To evaluate profiles of adverse haematological events of the two NACT regimens, white blood cell (WBC), haemoglobin (Hb), neutrophil, and platelet were analysed after administering each cycle. Only the highest observed haematological toxicity is reported here. The clinical severity of the haematological adverse effects was categorized, where the severity of the adverse effects increased from Grades 1 through 5. Details of the Grades for the haematological adverse effects are given in Table

1. Radiological studies comprising of CT MRI examination were carried out to characterize the disease response. RECIST guidelines were used to classify the disease response as CR: complete response, PR: partial response, PD: progressive disease or SD: stable disease.

IBM's statistical tool SPSS (IBM Corp., Armonk, NY) was utilized to analyse the data. Origin Pro (Origin Lab Corporation, USA) was employed for data visualization. Quantitative data points (e.g., age, tumour size, TNM stage, etc.) were expressed in terms of mean and standard deviation (SD). Alternatively, qualitative data points (e.g., gender, smoking, HPV, etc.) were represented as frequencies and percentages.

RESULTS

The distribution of male and female patients is shown in Figure 1. Patients in Group I (n=36) were given TPF and those in Group II (n=32) were given GC. For Group I, the patient's mean ± standard deviation (SD) age was 40.9±11.6 years, while the median age was 40 (IQR: interquartile range = 30.3–51.8) years. For Group II, the patient's mean±SD age was 38.6±11.3 years, and the median age was 40 (IQR = 29.5–51.0) years. The baseline characteristics of the patients in the two groups are summarized in Figure 2. The open bars represent Group I while the solid bars depict Group II; this symbolic convention has been adopted for all subsequent plots.

The pre- and post-treatment TNM stage of all selected patients with LANPC was assessed; the results of such assessment are displayed in Figure 2. The pre-treatment TNM stage of all patients with LANPC was either III or IVA (Figure 2a), which adheres to the eligibility criteria for patient inclusion in this study. After receiving the treatment (i.e., NACT followed by CCRT), the TNM stage of all patients was reassessed. It was found that the disease was eliminated (i.e., stage 0) in most of the patients (i.e., 17 (47%) cases in Group I and 22 (69%) cases in Group II) or partially responded to treatment, indicating the efficacy of the treatment. However, a few cases of advanced-stage disease were also observed in both Group I and II.

Details regarding the number of chemotherapy cycles received by the patients within the neoadjuvant and concurrent settings are shown in Figure 3. For interclass comparison, chemotherapy data for Group I and Group II are shown in Figure 3(a) and Figure 3(b), respectively. Moreover, the number of NACT and CCRT cycles are depicted with plain bar and lined bar, respectively. For Group I, the patients received a higher number of NACT cycles, with 10 (28%) patients were given 09 cycles and 01 (2.8%) patients each was administered with 10 and 12 cycles. In the concurrent settings, the majority of the patients (i.e., 16, 44.4%) received 06 cycles. For Group II, although the majority of the patients (18, 56.3%) were given 03 cycles of NACT, only 01 (3.1%) each received a maximum of 06 and 05 cycles. For the CCRT regimen of Group II, the majority of patients (21: 81%) received either 05 or 06 cycles.

The treatment outcomes, categorized by the RECIST 1.1 criteria, are shown in Table 2. Results demonstrated that the complete response in Group II was higher as compared to Group I (71.9% versus 44.4%). However, the partial response to treatment was higher in Group I compared to (50% versus 18.6%). Moreover, only a few cases of stable and progressive disease in both groups were also observed.

Haematological toxicity profiles for all enrolled patients were measured and presented in Figure 4(a) for Group I and Figure 4(b) for Group II. For patients in Group I, low-grade anaemia and lymphopenia was developed in the majority of the patients, accounting for 47.2% and 44.4% (Grade I) and 47.2% and 30.5% (Grade II), respectively. The incidence of anaemia and lymphopenia in patients of Group II followed a similar trend. The trend of severity in neutropenia illustrated higher grades (i.e., acute adverse events) in both Group I and Group II. Specifically, the combined Grade III and Grade IV neutropenia occurred in 80.6% and 65.6% of patients of Group I and Group II, respectively. The incidence pattern of thrombocytopenia differed from other haematological toxicities, as both mild and severe adverse effects were observed. In particular, Grade I and II (mild) and Grade III and IV (severe) thrombocytopenia occurred in 58.4% and 41.6% of patients of Group I. A consistent trend of thrombocytopenia occurred in Group II.

Table-1: Grading of haematological adverse effects as per the Common Terminology Criteria for Adverse Events[32]

	Grade				Grade 5
Toxicity type	**1**	**2**	**3**	**4**	
Neutropenia	<LLN–1500 per mm^3	<15,00–1,000 per mm^3	<10,00–5,00 per mm^3	<5,00 per mm^3	Death
Anaemia	Hgb <LLN–10.0 g/dL	Hgb <10.0–8.0 g/dL	Hgb <8.0 g/dL; transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death
Lymphopenia	<LLN–800 per mm^3	<800–500 per mm^3	<500–200 per mm^3	<200 per mm^3	Death
Thrombocytopenia	<LLN–75,000 per mm^3	- <75,000–50,000 per mm^3	<50,000–25,000 per mm^3	<25,000 per mm^3	Death

Table-2: Demographic details of the LANPC patients in the two groups

Treatment response	Group I (n = 36)	Group II (n = 32)
Complete response	22 (61.11%)	23 (71.9%)
Partial response	12 (33.33%)	6 (18.6%)
Stable disease	1 (2.8%)	1 (3.1%)
Progressive disease	1 (2.8%)	2 (6.3%)

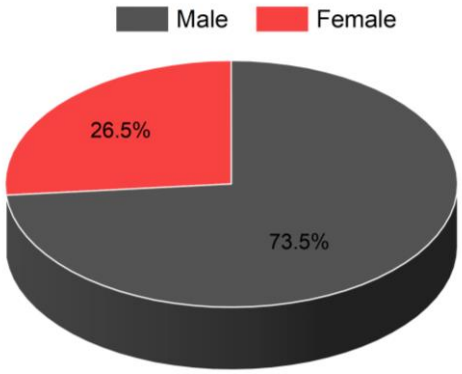

Figure-1: Gender-wise distribution of the patients included in this study

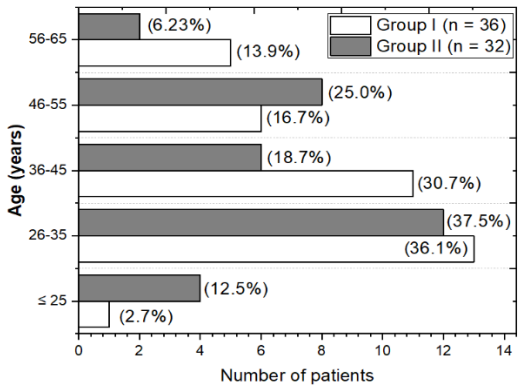

Figure-2: Summary of the baseline characteristics of the patients in the two groups

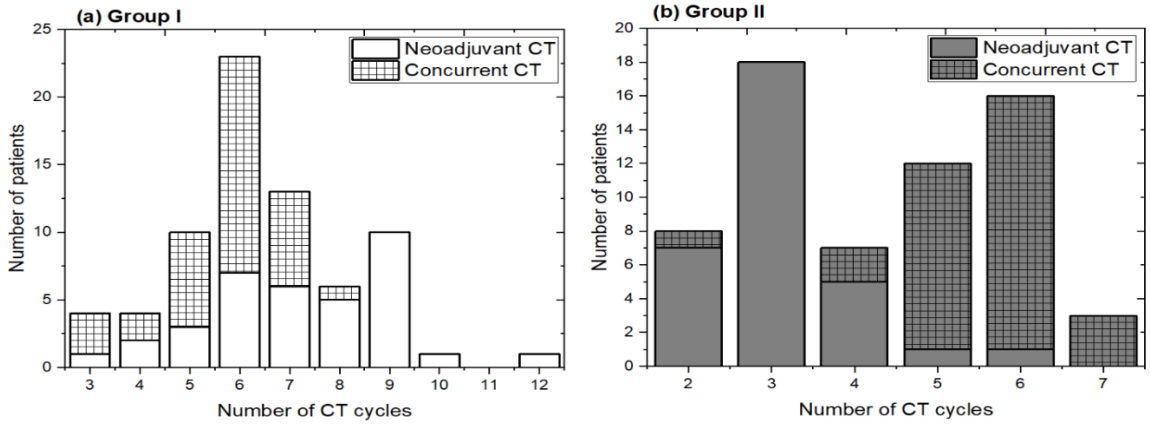

Figure-3: Number of chemotherapy (CT) cycles received by the patients in Group I (a) and Group II (b) in the neoadjuvant (plain bar) and concurrent (lined bar) settings

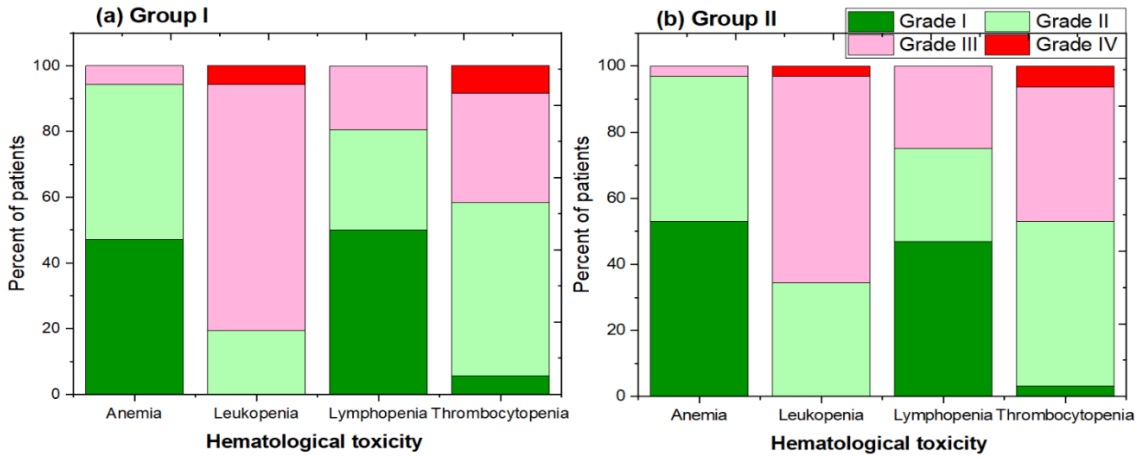

Figure-4: Haematological toxicity profiles for Group I (a) and Group II (b).

DISCUSSION

This study investigated the haematological toxicities of two different chemotherapy regimens used in the management of patients with LANPC. Multi-agent chemotherapy has a proven survival benefit in the management of NPC patients, particularly those presenting with advanced-stage diseases where the presence of micrometastases before treatment initiation is very likely.[33] Nevertheless, these multi-agent chemotherapy regimens are not free of adverse effects, as documented by several studies[34,35] and investigated herein. Despite the haematological toxicities experienced by the LANPC patients during the present study, the planned chemotherapy protocol was completed in all enrolled patients.

Post-chemotherapy incidence of haematological adverse events have been explored in several studies and the speculated risk factors for such effects have been documented. A multivariant analysis has revealed that patients aged <20 years, poor ECOG performance status and malnutrition were statistically significant factors for the severe suppression of the bone marrow.[36] The number of chemotherapeutic agents in a specific treatment protocol and the intensity of the regimens are also speculated as the risk factors for severe myelosuppression.[36,37] However, the present study found almost identical adverse haematological effects for the two agents (Group II) and three agents (Group I) NACT regimens (Figure 4), where the mild adverse effects (Grade I plus II) were observed in 63.3% (Group I) and 64.8% (Group II) while the severe adverse effects (Grade III plus IV) were observed in 36.7% (Group I) and 35.2% (Group II) (Figure 4). Other studies have reported older age, low baseline blood cell counts, advanced disease and specific genetic polymorphisms as the risk factors for the incidence of adverse haematological effects.[38]

The adverse haematological effects found in the present study are consistent with the previous reports. For example, Grade III or IV neutropenia and neutropenia of CCRT with cisplatin and docetaxel has been documented in 32 % and 36% of patients with LANPC, respectively.[11] Another study demonstrated the development of Grade II neutropenia in 50%, while Grade III or IV neutropenia in 13.5% of patient.[39] A recent phase III trial reported that neoadjuvant gemcitabine plus cisplatin chemotherapy led to the incidence of Grade III or IV neutropenia in 28.0%, thrombocytopenia in 11.3%, anaemia in 9.6% patients with LANPC.[40] Li *et al*. reported Grade III or IV toxicities in 72.8% (174/239) LANPC patients when treated with the TCF-based NACT[41]; this study reported one TPF-related death after one cycle of NACT, because of neutropenia. Overall, these studies indicate that NACT with either TPF or GC regimen integrated with CCRT offer significant survival benefits in LANPC patients with adverse haematological toxicities of varying severities.

Multiple factors contribute to the toxicity associated with the chemotherapy agents employed in this study (i.e., cisplatin, docetaxel, gemcitabine, and fluorouracil). The reduction of glutathione is proposed as a potential contributor to haematological toxicity. Additionally, the generation of reactive oxygen species is suggested to trigger oxidative stress, consequently diminishing the antioxidant capacity and defence mechanisms in the body. Other factors, including the creation of non-enzymatic molecules and alterations in antioxidant enzymes, are implicated in the substantial chemotherapy-related toxicity.[42] Given the use of identical chemotherapy agents under various protocols, the reported toxicities in the abovementioned studies remain consistent.

CONCLUSION

Haematological toxicity profiles for LANPC patients treated with TFC (Group I) or GC (Group II) and CCRT revealed that the majority of patients experienced low-grade anaemia and lymphopenia, high-grade l neutropenia and mixed pattern of thrombocytopenia. The toxicity profiles in Group I and II were consistent.

AUTHORS' CONTRIBUTION

Conceptualization: ABR, GH, AaR, SNK, SS, RM, YRK, A, AS, MAA. Data curation: ABR, YRK, A, AS, MAAFormal analysis: AbR, AAR, SNK, SS, RMInvestigation: AbR, AaR, SNK, SS. Methodology: AAR, SNK, SS, RM, YRK. A Project administration: ABR, GH. Resources: ABR, GH. Supervision: GHValidation: SNK, SS, RM, YRK, A, AS, MAA. Visualization: SNK, SS, RM, YRK, A, AS, MAA. Writing – original draft: AbR, GH, AAR, SNK, SS, RM, YRK, A, AS, MAA. Writing – review & editing: AbR, GH, AAR, SNK, SS, RM, YRK, A, AS, MAA

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Address for Correspondence:

Abdul Rehman, Jinnah Postgraduate Medical Centre (JPMC) Karachi-Pakistan
Cell: +92 333 254 3060
Email: soomrorehman@gmail.com