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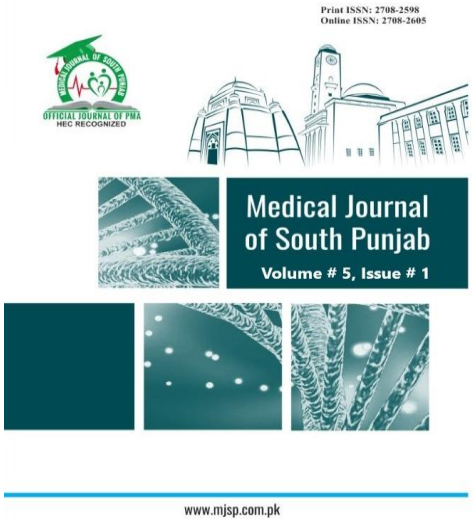


# Effects of two weekly gemcitabine in advanced stage head and neck cancers

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**Original Article**

# Effects of two weekly gemcitabine in advanced stage head and neck cancers

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## ABSTRACT

***Objective:*** *to assess the efficacy and toxicity of Gemcitabine in patients of Nasopharyngeal Carcinoma.*

***Methods:*** *A total of 29 patients of nasopharyngeal carcinoma stage three and four were studied in the study. Three cycles of Injection gemcitabine were given at a dose of 1000 mg/m2 on Day 1 and Day 8 of chemotherapy along with injection cisplatin 60 mg/m2 on Day 1 in 3 weekly cycles. After three cycles all the patients were planned for Concurrent chemoradiotherapy to the local tumor sites and regional lymph nodes. All demographic, laboratory and clinical parameters were noted. Primary end point was overall survival and progression. Secondary end points were adverse effects experienced due to treatment.*

***Results:*** *Mean age of patients was 53.14 ± 10.98 years. Survival was better in stage 3 patients as compared to stage 4 patients. Most common side effect was anemia at 62.1% of the patients experiencing it. Oral ulcers were only seen on 9 (31%) of patients.*

**Conclusion:** *This study illustrates that combination chemotherapy with cisplatin and Gemcitabine was beneficial in terms of disease progression and recurrence.*

***Keywords:*** *gemcitabine, nasopharyngeal carcinoma, chemoradiotherapy, adverse effects, efficacy*

## 1. INTRODUCTION

Cancer is fast emerging as one of the leading causes of death worldwide. WHO reported more than 19 million new cases and almost 10 million deaths related to cancer in just 2020[1]. Though it is amongst the leading causes of death in western countries, almost half of all new cancer case diagnosis are from Asia. Similarly, 58.3% of deaths related to cancer were reported from Asia.[1]

In Pakistan one of the leading cancer hospitals, Shaukat Khanum Memorial Hospital and research center published new neoplasms were diagnosed in the calendar year of 2021. Out of these 6894 were malignant.[2]

Head and Neck cancers rank sixth amongst all cancer by body regions. It is reported that almost 630,000 new cases and 350000 deaths are attributed to head and Neck cancers every year[3]. Common head and neck cancers include, but are not limited to, that of lip and oral cavity, pharynx, nasopharynx and larynx.[4] In Pakistan in 2020 larynx was the most common organ from head and neck region involved amongst males, followed by nasopharynx. While for females, tongue was the most common organ involved[2].

As per histology, an overwhelming majority of head and neck cancers are of the squamous cell variety. It may be further classified as keratinizing, non-keratinizing or large-cell. Head and neck cancers specially those of oral cavity and nasopharynx are more common in Asia. Almost, 70% of these cases are concentrated in south east Asia.[5]

Common etiological factors include consumption of tobacco, betel nut and EBV infections.[6] EBV DNA viral load has prognostic and therapeutic value as the treatment regimen employed may vary with viral load. However, our patients were not tested for EBV DNA viral load as only stage 3 and stage 4 patients were included in the study amongst whom the test loses significance[7].

Though radiotherapy remains the corner stone of treatment of carcinomas of head and neck, there are considerable treatment related adverse effects associated with it specially at higher doses.[8] Gemcitabine is a nucleoside analogue which not only increases cisplatin activity but is also postulated to increase the efficacy and penetration of radiotherapy. It is often included in Induction Therapy regimens before or simultaneously with radiotherapy.[9]

Though international studies are available on the subject, the only one published from Pakistan is more than a decade old. Hence a need for fresh data in population was felt. The aim of our study is to assess the frequency of treatment related adverse effects in patients of head and neck with gemcitabine injections and to determine its effect on survival and progression with various clinical characteristics and treatment modalities.

## 2. METHODOLOGY

A single centre prospective study was conducted at CMH Rwp from ---February 2020-- to February 2022. An Ethical review board approval was obtained vide letter number 529 dated 1.2.2024. Non-probability consecutive sampling was employed. All patients that reported to the department during the recruitment phase and met the criteria were included in the study. Pts were recruited in the first 3 months of the study. Written informed consent was taken from all patients.

Inclusion criteria included all patients with Nasopharyngeal carcinoma under the age of 75 years. Exclusion criteria included any pregnant or lactating females, any other comorbid illnesses, presence of metastatic lesion distant from the primary site detected on radiological studies. Patients with stage 1 or stage 2 Nasopharyngeal carcinoma were also excluded. Anyone with abnormal liver or renal functions or blood counts at baseline or those unwilling to participate in the

study were excluded from the study. Those lost to follow up at the end of the study period were excluded from the final statistical analysis.

Injection gemcitabine was given at a dose of 1gm/m2 on Day 1 and Day 8 of chemotherapy in 3 weekly cycles along with injection cisplatin 60 mg/m2 on Day 1. Three cycles of chemotherapy were given to each patient. All demographic data, disease staging, the administration of any prior or concurrent therapy, laboratory parameters and symptoms were noted at baseline. Patients were followed up for a period of six months after the end of the third gemcitabine cycle.

The primary end point was overall survival, tumor response to chemotherapy and progression. The secondary end points were adverse effects experienced due to treatment. Tumor response to chemotherapy was documented one month after the chemotherapy and survival was documented at the end of follow up period that is 6 months after the end of last chemotherapy cycle. While progression was defined as upstaging of tumor at any stage, expansion in the size of tumor or presence of metastatic lesions detected radiologically at any time during the study and follow up period.

The adverse effects that were observed were neutropenia, anemia, thrombocytopenia, and asthenia. Experiencing gastrointestinal symptoms by patients like nausea or vomiting and oral ulcers were also documented. Asthenia was defined as lack of energy to such an extent that the patient would require assistance to leave the room. Neutropenia was pre-decided as an absolute neutrophil count of less than 1500 cells per microliter of blood. Anemia and thrombocytopenia were set as a hemoglobin level of less than 10 microgram per deciliter and platelets below 100000 per microliter of blood.

Statistical analysis was carried out using SPSS version 23.0. Adverse effects experienced by patients were expressed as frequency and percentages while mean and standard deviation was calculated for the age of patients participating in the study. Pearson chi square test was employed to assess the relationship between survival and progression with stage of Nasopharyngeal carcinoma, any prior therapy received or concurrent therapy with cisplatin.

## 3. RESULTS

A total of 31 patients were enrolled during the study period. However, 2 were lost to follow up. Hence, statistical analysis was carried out on the remaining 29 participants. Mean age of patients was 53.14 ± 10.98 years as shown in table I. 18 (62.1%) patients were male while 11 (37.9%) were female. 65.5% of all patients were receiving concurrent therapy with Cisplatin. 17 (58.6%) patients were from stage 3 nasopharyngeal carcinoma while 12 (48.4%) were from stage 4. 9 (31%) had previously received some therapy prior to the initiation of chemotherapy.

Table 2 shows the frequency of adverse effects experienced by the patients enrolled in the study. Most common side effect was anemia. 18 out of 29 patients that is 62.1% experienced it. It was followed by nausea or vomiting at 55.2% and asthenia at 51.7%. Neutropenia and thrombocytopenia were seen in 13 (44.8%) and 8 (27.6%) patients respectively. Oral ulcers were only seen on 9 (31%) of patients.

Survival was compared between different stages of nasopharyngeal carcinoma and whether any prior therapy was being administered to patients. It was found that 12 (65.4%) patients of stage 3 and 9 (34.6%) patients of stage 4 survived at the end of study period. The p-value was 0.06 and hence the difference was non-significant. Concurrent therapy with cisplatin was followed by a survival of 61.5% while those who did not receive any cisplatin had a survival of 38.5%. The difference was not significant with a p-

value of 0.532. Similarly, 65.4% of patients without any form of prior therapy survived while 34.6% of those had received any prior therapy survived. The difference was nonsignificant with a p-value of 0.05.

Similar analysis compared progression with these clinical features. No significant difference was found with a p-value of 0.126, 1.000 and 0.205 for stage of nasopharyngeal carcinoma, concurrent cisplatin therapy and prior therapy received respectively.

**Table 1: Characteristics of patients involved in the Study**

| | |
|---|---|
| Age (mean ± SD) | 53.14 ± 10.98 years |
| Gender (%) | |
| Male | 18 (62.1%) |
| Female | 11 (37.9%) |
| Concurrent therapy with Cisplatin | 19 (65.5%) |
| Yes | 10 (34.5%) |
| No | |
| Stage of NPC | |
| Stage 3 | 17 (58.6%) |
| Stage4 | 12 (48.4%) |
| Prior therapy received | 9 (31%) |
| Yes | 20 (69%) |
| No | |

**Table 2: the frequency of Adverse effects experienced by the study population.**

| | |
|---|---|
| Neutropenia | 13 (44.8%) |
| Thrombocytopenia | 8 (27.6%) |
| Anemia | 18 (62.1%) |
| Oral ulcers | 9 (31%) |
| Nausea or vomiting | 16 (55.2%) |
| Asthenia | 15 (51.7%) |

**Table3: comparison of Survival amongst various patient groups**

| Factor Assessed | Did not Survive | Survived | P-value |
|---|---|---|---|
| Stage of NPC | | | |
| Stage 3 | 0 (0%) | 17 (65.4%) | 0.060 |
| Stage 4 | 17 (100%) | 9 (34.6%) | |
| Concurrent therapy with Cisplatin | | | |
| No | 0 (0%) | 10 (38.5%) | 0.532 |
| Yes | 3 (100%) | 16 (61.5%) | |
| Prior Therapy received | | | |
| No | 3 (100%) | 17 (65.4%) | 0.532 |
| Yes | 0 (0%) | 9 (34.6%) | |

**Table 4: comparison of progression amongst various patient groups**

| Factor Assessed | Did not Progress | Progressed | P-value |
|---|---|---|---|
| Stage of NPC | | | |
| Stage 3 | 8 (80%) | 9 (47.4%) | 0.126 |
| Stage 4 | 2 (20%) | 10 (52.6%) | |
| Concurrent therapy with Cisplatin | | | |
| No | 3 (30%) | 7 (36.8%) | 1.000 |
| Yes | 7 (70%) | 12 (63.2%) | |
| Prior Therapy received. | | | |
| No | 5 (50%) | 15 (78.9%) | 0.205 |
| Yes | 5 (50%) | 4 (21.1%) | |

## 4. DISCUSSION

Gemcitabine is a pyrimidine anti metabolite with activity against tumor cells in various carcinomas such as those of pancreas, cervix, urinary bladder, and most importantly squamous cell carcinoma of head and Neck[10]. The potentiating effect between Cisplatin and gemcitabine has been reported as far back as in 1995 by Peters et al[11]. Hitt et al were amongst the pioneers to suggest the schedule of cisplatin and gemcitabine dosing that has been employed in our study and has since become the standard of care [12].

In recent times, newer drugs in addition to the above combination have been explored. Huang et al experimented with toripalimab combined with gemcitabine and cisplatin. Treatment related adverse effects such as hematological abnormalities, asthenia, gastrointestinal symptoms, and hyperglycemia were documented. They ranged from 43.1% patients experiencing grade 1 intensity adverse effects to 8.7% patients experiencing grade 4. The treatment related adverse effects in our study were similar except for hyperglycemia. The most frequent adverse effects documented in our study were anemia by 62.1 % and thrombocytopenia by 27.6% of patients13.

A multi centre randomized controlled trial was conducted to assess the difference in outcomes when patients were given gemcitabine and cisplatin as induction therapy with chemoradiotherapy compared to just chemoradiotherapy. The three-year recurrence free survival was documented to be 85.3% in the experiment group. This is much higher than the survival reported in our study of 65.4% in stage three 34.6% in stage four nasopharyngeal carcinoma. This is despite their longer follow up time but perhaps attributable to their larger sample size of 480 patients[14].

A meta-analysis of existing literature on gemcitabine and cisplatin usage in combination with radio therapy revealed a dose dependant incidence of adverse effects. Those studies with a dose intensity of greater than 50mg/m2 per week were shown to have 74% incidence of grade 3 or 4 mucositis while it was significantly lower in those given low dose regimens. Only 31% of the patients recruited in our study experienced oral ulcers. This meta-analysis documented a 3-year survival of 50% with a non-significant difference between the two groups. This is like our study where no significant difference was found between those receiving cisplatin or not and those receiving any prior therapy or not[9].

Another study by Yang et al in 2019 studied a comparison of gemcitabine and cisplatin (experimental group) as compared to cisplatin and fluorouracil (control group). While the observed group not only had a statistically significant 1-year survival rate, but the adverse effects were also noted to be significantly less in the experimental group. The overall incidence of adverse effects was 10.91% in the group receiving gemcitabine and 33.33% in the group receiving fluorouracil with a p-value of 0.006. Leucopenia was noted in 2 out of 55 participants and thrombocytopenia in 1 out of 55 participants. Though the values seen in our study of neutropenia in 44.8% and thrombocytopenia in 27.6% are higher compared to this study the difference might be attributable to different cut-offs set for both studies[15].

Another recent study has focused on a rather rare adverse effect of taste alteration in pts of Nasopharyngeal Carcinoma receiving gemcitabine for chemotherapy. It was noticed that the incidence increased with every passing week of chemotherapy with a p-value of 0.001[16].Local studies are few and rare and most have focused on presentation of

nasopharyngeal carcinomas. One study from Lahore had a mean age of 48.8 years in males and 46.7 years in females which are both lower than the age of patients in our patients. This could be explained by our study being focused on mainly stage three and four nasopharyngeal carcinoma[17].

The only local study of the effect of gemcitabine in head and neck carcinomas was done more than a decade back in 2006. Grade 3 mucositis was seen in 71.8% of patients while grade 4 was seen in 5.1%. This study had a sample size of 39 patients which is not very different from our sample size of 29 patients. Though both studies recruited patients from stage 3 and stage 4 nasopharyngeal carcinomas, this study administered gemcitabine on D1, 8, 15, 22, 29 and 36 which was 4 additional doses as compared to our study. Hence, it could be postulated that frequency was adverse effects increased with more frequent dosing[18].

No study is without its limitations and ours being the short follow up time. In future local researchers could plan studies with larger sample size and longer follow-up time that would give a more realistic picture of survival and progression of disease.

## 5. CONCLUSION

In conclusion, it is emphasized that given the incidence of head and neck squamous carcinomas in our country, there is a need for more research and more data from our local population.

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