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A RETROSPECTIVE COMPARATIVE STUDY OF TOXICITIES AND OUTCOMES BETWEEN GEMCITABINE + NAB PACLITAXEL AND FOLFIRINOX IN LOCALLY ADVANCED CA PANCREAS RECEIVING IN NEO-ADJUVANT CHEMOTHERAPY

Khawaja Amtul Raouf Qazi *, Mariam Abdul Samad, Nazneen Kouser, Maveya Afreen, Shaikmusaib Zubedi and Anupama Koneru

Department of Pharmacy Practice, Sultan-ul-uloom College of Pharmacy, Hyderabad - 500034, Telangana, India.

Keywords:

Locally advanced pancreatic cancer, Neo-adjuvant chemotherapy, Tumor response, Toxicities

Correspondence to Author:
Khawaja Amtul Raouf Qazi

Assistant Professor,
Department of Pharmacy Practice,
Sultan-ul-uloom College of Pharmacy,
Hyderabad - 500034, Telangana,
India.

E-mail: amtulraouf@sucp.ac.in

ABSTRACT: Neoadjuvant chemotherapy with Gemcitabine/nab-paclitaxel (Gemcitabine + Nab-Paclitaxel) And Folfirinox (Folfirinox) are two standard therapies for patients who has locally advanced pancreatic cancer (Lapc). We retrospectively compared the efficacy and safety of the two treatment regimens in patients with unresectable pancreatic cancer. The sample size consisted of 96 patients who has locally advanced pancreatic cancer. (Gnp) Gemcitabine and nab–paclitaxel is Group I (N=53), and Folfirinox consisting of leucovorin, fluorouracil, irinotecan and oxaliplatin is Group II (N=43). The Primary objectives of our study were to compare toxicities between gemcitabine + Nab-Paclitaxel And Folfirinox and to evaluate the safety of these regimens The secondary objective was % reduction of tumor, Surgery (% of patients who underwent surgery) and overall survival both estimated using the independent t- test and chi-square test. **Results:** The haematological toxicities rates were similar between the two groups (62% vs. 63%; $p > 0.05$), with similar anemia toxicities rates (62%). The neutropenia toxicity rates were similar (15% vs 16%; p>0.05) and febrile neutropenia, thrombocytopenia, and GI toxicities were higher in group II than group I. In analysis % reduction of tumor was similar between both groups with a P value of 0.3510, calculated by dependent t – test. Patients who underwent surgery were slightly more in Group I.

INTRODUCTION: Pancreatic cancer (PC) is one of the highest cancer mortality rates in the world [1]. There were an estimated 43,090 deaths from pancreatic cancer in the United States in 2017. In addition, the 5-year relative survival rate was only 8% and the long-term relative survival rate was only 3% [2]. Pancreatic cancer is now third leading cause of cancer-related deaths in the United States [3] and will become the second leading cause by 2030 [4].

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Since most end-stage cases are diagnosed as metastatic or locally advanced [5,6,7,8] radical surgical resection can only be performed in 15-20% of cases [9, 10] with the recent advent of more effective chemotherapy regimens, Neoadjuvant chemotherapy (NAC) has been used to increase R0 resection rates and convert inoperable, locally advanced tumors to potentially resectable tumors.

National Comprehensive Cancer Network also recommends NAC as the standard of care (NCCN) in BRP and LAPC [16]. Combination regimens such as Folfirinox [leucovorin, fluorouracil, irinotecan, and oxaliplatin] and GNP [gemcitabine and nab-paclitaxel] have shown significant improvement compared to single-agent gemcitabine. Both regimens have shown nearly 30% response rates and double survival compared to Gemcitabine

alone [17, 18]. Folfirinox and GNP have emerged as the two most popular approvals in the neoadjuvant setting for BRPC and LAPC, based on data from his PRODIGE4/ACCCORD11 and MPACT trials in the metastatic setting of. However, the efficacy and safety of Folfirinox and GNP as NACs for BRPC and LAPC are still controversial. Several studies have shown greater efficacy and longer survival with Folfirinox compared to GNP [19, 20]. However, in real-world settings outside of clinical trials, treatment with GNP was shown to be not inferior to Folfirinox in mitigation settings. GNP has been used in up to ECOG 2 patients with acceptable toxicity, whereas Folfirinox is only suitable for his patients with excellent performance status without associated comorbidities [21, 22].

Choosing an appropriate neoadjuvant strategy is critical for patients with BRPC and LAPC. This is the only chance to prolong survival due to pancreatic cancer's rapid progression and deadly nature [23].

This study is aimed to compare the toxicities and safety of neoadjuvant GNP and Folfirinox in patients with locally advanced pancreatic cancer.

METHODOLOGY:

Study Population: The patients who received consecutive treatment for LAPC using either FOLFIRINOX (FFX) OR gemcitabine + nab – Paclitaxel as the first line therapy were included in this study and the total patients were 96.

43 Patients treated with FFX out of the total 96 patients are labelled as Group I and the remaining 53 patients who were treated with GNP are labelled as Group II

Chemotherapy Regimen: Nab-paclitaxel (125-180 mg/m2) followed by gemcitabine (1000-1600 mg/m2) was administered intravenously on days 1, 8 and 15 every 4 weeks. Patients treated with FOLFIRINOX received oxaliplatin (85 mg/m2), irinotecan (150-180 mg/m2), leucovorin (400 mg/m2), and 5-fluorouracil (5-FU) (bolus (0-400 mg/m2)). mg/m2) + intravenous infusion (2400 mg/m2 for 46-48 hours) ON days 1, 15 every 4 weeks. Antiemetic prophylaxis with serotonin type 3 receptor antagonists and dexamethasone is commonly used. Recombinant human granulocyte colony-stimulating factor (G-CSF) and erythropoietin were administered as required by the physician.

Outcome Evaluation: Evaluation of toxicities and outcomes between Folfirinox and Gemcitabine + nab – Paclitaxel.

Statistical Analyses: All statistical analyses were performed using SPSS version 20 Confidence interval is 95%; hence P value <0.05 is considered significant. Test Performed: Independent t-test, Chi square test.

RESULTS:

Study Population:

Treatment Group: The number of patients who were receiving Gemcitabine+Nab-paclitaxel or FOLFIRINOX in neoadjuvant chemotherapy for locally advanced pancreatic adenocarcinoma were considered for the study.

TABLE 1: TREATMENT GROUP

Group	Treatment	N	%
I	Gemcitabine + Nab paclitaxel	53	55
II	FOLFIRINOX	43	45

The value in the above table was calculated to analyze the results for treatment group Patients, and it has been calculated that out of a total of 96 patients 55% were receiving gem+nabpaclitaxel (N=53) and 45% patients were receiving Folfirinox N=43).

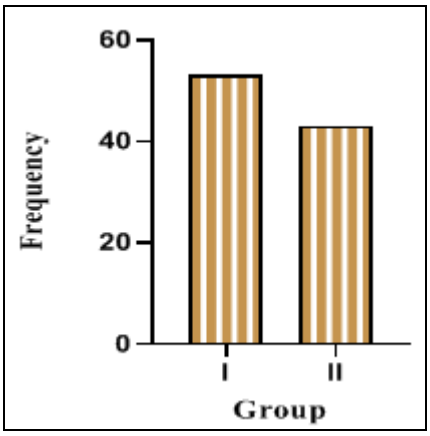

FIG. 1: TREATMENT GROUP

Age Distribution: The P-value below table were calculated by independent t-test to analyze the result for comparison of Age Distribution in both groups. Compared with the patients who received Gemcitabine +nab paclitaxel, those treated with Folfirinox were younger.

TABLE 2: AGE DISTRIBUTION

Group	Age (years)				P value
	Minimum	Maximum	Mean± SD	Median	
I	33	77	63.04±10.45	64	
II	33	63	51.70±7.99	54	<0.0001

Mean± SD of 63.04±10.45 with a minimum age of 33 and a maximum age of 77 years has been analyzed for the patients of Group I (N=53), Mean± SD of 51.70±7.99 with a minimum age of 33 and a maximum of 63 years has been analyzed for the patients of Group II (N=43).

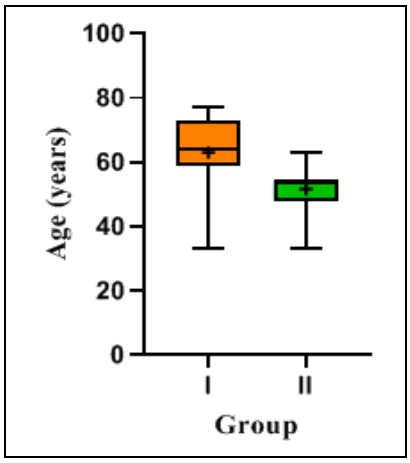

FIG. 2: AGE DISTRIBUTION

Gender Distribution: Male patients are significantly higher in Folfirinox regimen than in Gemcitabine+ Nab – paclitaxel group.

TABLE 3: DISTRIBUTION BASED ON GENDER

Gender	Group I (n=53)	Group II (n=43)	P value
Male	26(49)	40(93)	<0.0001
Female	27(51)	03(07)	

Male and Female patients were considered for the study, and it has been calculated out of 53 patients in group I 49% were male (N=26) and 51% were female (N=27) and in Group II out of 43 patients 93% were male (N=40) 75 were female (N=3).

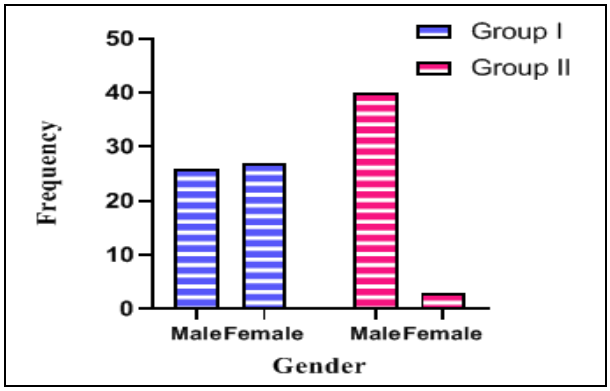

FIG. 3: DISTRIBUTION BASED ON GENDER

Number of Chemotherapy Cycles: The chemotherapy cycle of Nab-paclitaxel followed by gemcitabine was administered intravenously on days 1, 8 and 15 every 4 weeks. Patients treated with Folfirinox received chemotherapy on days 1 & 15 every 4 weeks. No. of cycles for each group varied according to clinicians.

TABLE 4: CYCLE

Cycle	Group I (n=53)	Group II (n=43)	P value
1	29(55)	10(23)	
2	9(17)	12(28)	0.0182
3	12(22)	12(28)	
4	2(04)	07(16)	
5	1(02)	02(05)	

For the patients in group I (receiving neoadjuvant gem+nabpaclitaxel therapy) out of 53 patients the results were 1% (N=1) patients received 5 cycles of chemotherapy, 4% (N=2) patients received 4 cycles, 22% (N=12) patients received 3 cycles of chemotherapy, 17% (N=9) patients received 2 cycles of chemotherapy, 55% (N=29) patients received 1 cycles of chemotherapy. For the patients in Group II (receiving neoadjuvant Folfirinox therapy) out of 43 patients the results were 5% (N=2) patients received 5 cycles of chemotherapy, 16% (N=7) patients received 4 cycles, 28% (N=12) patients received 3 cycles of chemotherapy, 28% (N=12) patients received 2 cycles of chemotherapy, 23% (N=10) patients received 1 cycles of chemotherapy.

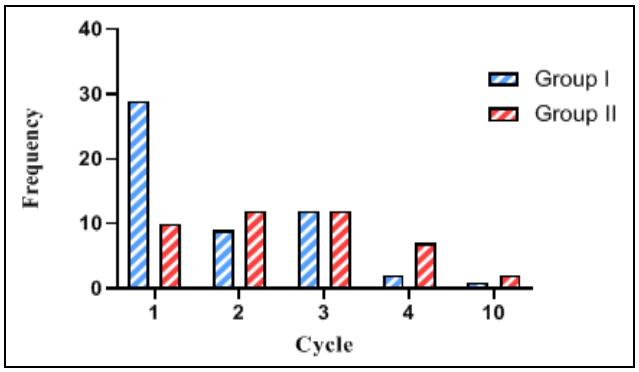

FIG. 4: CYCLE

Evaluation of Treatment:

Tumor Response: By calculating the percentage reduction of tumor, we can determine whether the

chemotherapy is effective and choose the best regimen. There is no significant difference, but the percentage of tumor reduction in group 2 is slightly higher than in group 1.

TABLE 5: % REDUCTION

Group	Reduction				P value
	Minimum	Maximum	Mean± SD	Median	
I	0	45	11.18±2.06	0	
II	0	54	8.37±2.13	0	0.3510

Mean± SD of 11.18±2.06 with a minimum of 0% and a maximum of 45% statistical reduction of tumor has been analysed for the patients of Group I (N=53). Mean± SD of 8.37±2.13 with a minimum of 0% and a maximum of 54% statistical reduction of tumour has been analysed for the patients of Group II (N=4).

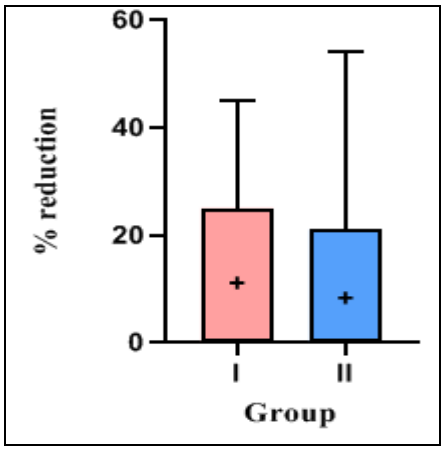

FIG. 5: % REDUCTION

Operability Rate: Cancer can only be cured through surgical resection. Locally advanced pancreatic cancer (LAPC), as we all know, is unresectable due to vascular involvement. The conversion of unresectable cancer to resectable cancer following neoadjuvant chemotherapy is an important parameter for assessing the regimen's efficacy.

Patients who underwent surgery following neoadjuvant chemotherapy were slightly more numerous in group II.

TABLE 6: SURGERY

Surgery	Group I		Group II	
	N	%	N	%
Yes	10	19	11	26
No	43	81	32	74

The above graph represents the percentage of patients in each respective group who underwent surgery after neo-adjuvant chemotherapy completion. Out of a total of 96 patients for the patients in Group I (N=53) the results were 19% (N=10) underwent surgery and 81% (N=43) did not underwent surgery, for the patients in Group II (N=43) the results were 26% (N=11) underwent surgery and 81% (N=32) did not underwent surgery.

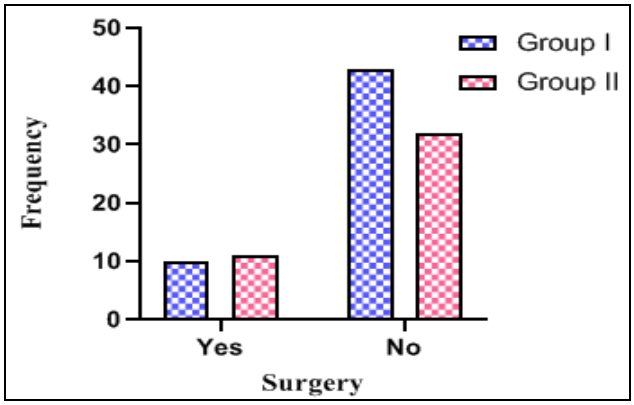

FIG. 6: SURGERY

Overall Survival: The p value in the table below was calculated by Chi-square and illustrates the comparison of Survival after treatment in both Groups.

TABLE 7: SURVIVAL

Survival	Group I (n=53)	Group II (n=43)	P value
Alive	36(68)	30(70)	0.8464
Dead	17(32)	13(30)	

FIG. 7: SURVIVAL

For the patients in Group I (N=53) 68 %(N=36) are Alive, 32 % (N=17) are Dead. For the patients

in Group II (N=43) 70 %(N=30) are Alive, 30 % (N=13) are Dead.

Toxicities:

Laboratory Parameters: To compare the toxicities between 2 group's lab parameters like Hb count, Neutrophils, Lymphocytes and Platelet count were considered. Chi-square and the above graph calculated the p value in the above table illustrates the comparison of laboratory parameters post initiation of neo- adjuvant chemotherapy.

TABLE 8: LABORATORY PARAMETERS

Parameter	Group I (n=53)	Group II (n=43)	P value
Hemoglobin			
Normal	17(32)	16(37)	0.5984
Abnormal	36(68)	27(63)	
WBC			
Normal	40(75)	35(81)	0.4851
Abnormal	13(25)	08(19)	
Neutrophil			
Normal	40(75)	35(81)	0.4851
Abnormal	13(25)	08(19)	
Lymphocytes			
Normal	41(77)	40(93)	0.0355*
Abnormal	12(23)	03(07)	
Platelet count			
Normal	42(79)	39(91)	0.1243
Abnormal	11(21)	04(09)	

Out of a total of 96 patients for patients in Group I out of 53 patients the results of hemoglobin post-chemotherapy were 32% (N=17) patients had normal values 68% (N=36) patients had abnormal values, patients in Group II out of 43 patients the results were 37%(N=16) patients had normal values 63% (N=27) patients had abnormal values with a P value of (0.5984). Statistically significant difference does exist as P<0.05. Out of a total of 96 patients for patients in Group I out of 53 patients, the results of WBC post-chemotherapy were 75% (N=40) patients had normal values 25% (N=13) patients had abnormal values, patients in Group II out of 43 patients the results were 81% (N=35) patients had normal values 19% (N=08) patients had abnormal values with a P value of (0.4851). A statistically significant difference does not exist as P>0.05. Out of a total of 96 patients for the patients in Group I out of 53 patients the results of Neutrophil post-chemotherapy were 75%(N=40) patients had normal values 25% (N=13) patients had abnormal values, patients in Group II out of 43 patients the results were 81% (N=35) patients had normal values 19% (N=08) patients had abnormal values with a P value of (0.4851). A statistically significant difference does not exist as P>0.05. Out of a total of 96 patients for the patients in Group I out of 53 patients the results of Lymphocytes post chemotherapy were 77% (N=41) patients had normal values 23% (N=12) patients had abnormal values, patients in Group II out of 43 patients the results were 93% (N=40) patients had normal values 07% (N=03) patients had abnormal values with a P value of (0.0355).Statistically significant difference does not exist as P>0.05. Out of a total of 96 patients for patients in Group I out of 53 patients the results of platelet count post-chemotherapy were 79% (N=42); patients had normal values 21% (N=11) patients had abnormal values, patients in Group II out of 43 patients the results were 91%(N=39) patients had normal values 09% (N=4) patients had abnormal values with a P value of (0.1243). A statistically significant difference does not exist as P>0.05.

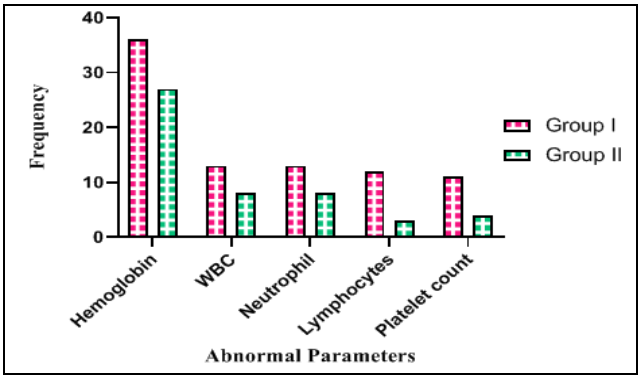

FIG. 8: ABNORMAL PARAMETERS

Comparison of Adverse Events: The p value in the below table was calculated by Chi-square and the above graph illustrates the comparison of Adverse events post initiation of neo-adjuvant chemotherapy.

TABLE 9:

Adverse Event	Group I (n=53)	Group II (n=43)	P value
Hematological toxicity	33(62)	27(63)	0.9577
Anemia	33(62)	27(63)	0.9577
Neutropenia	08(15)	07(16)	0.8737
Lymphopenia	06(11)	0	0.0227*
Febrile neutropenia	04(08)	05(12)	0.4952
Thrombocytopenia	03(06)	03(07)	0.7910
GI toxicity	01(02)	02(05)	0.4389
Diarrhea	01(02)	02(05)	0.4389

Out of a total of 96 patients for the patients in group I (N=53) patients the results of Hematological toxicity post-chemotherapy were 62 % (N=33), for patients in group II (N=43) patients, the results were 63 % (N=27) with a P value of (0.9577). A statistically significant difference does not exist as P>0.05. Out of a total of 96 patients for patients in Group I out of 53 patients the results of Anemia toxicity post-chemotherapy were 62% (N=33); patients in Group II out of 43 patients the results were 63% (N=27) with a P value of (0.9577). Statistically significant difference does not exist as P>0.05.

Out of a total of 96 patients in Group I out of 53 patients the results of Neutropenia toxicity post-chemotherapy were 15% (N=8); patients in Group II out of 43 patients the results were 16% (N=07) with a P value of (0.8737). A statistically significant difference does not exist as P>0.05. Out of a total of 96 patients for patients in Group I out of 53 patients, the results of lymphopenia toxicity post-chemotherapy were 11%(N=06); patients in Group II out of 43 patients the results were 0%(N=0) with a P value of (0.0227). The statistically significant difference does exist as P<0.05. Out of a total of 96 patients for patients in Group I out of 53 patients, the results of Febrile neutropenia toxicity post-chemotherapy were 08% (N=04); patients in Group II out of 43 patients, the results were 12% (N=05) with a P value of (0.4952). A statistically significant difference does not exist as P>0.05.

Out of a total of 96 patients for patients in Group I out of 53 patients, the results of Thrombocytopenia toxicity post-chemotherapy were 06% (N=03); patients in Group II out of 43 patients, the results were 07% (N=03) with a P value of (0.7910). A statistically significant difference does not exist as P>0.05.

Out of a total of 96 patients in Group I out of 53 patients, the results of GI toxicity and diarrhea post-chemotherapy were 02%(N=1), 02% (N=1) patients in Group II out of 43 patients, the results were 05% (N=02), 05%(N=02) with a P value of (0.4389) for GI toxicity, (0.4389) for diarrhea. A statistically significant difference does not exist as P>0.05.

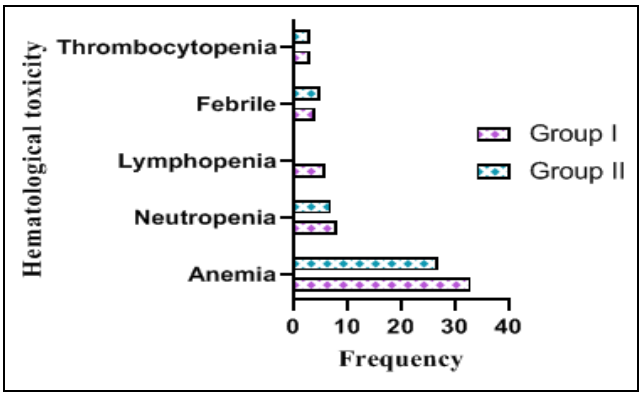

FIG. 9A: HEMATOLOGICAL TOXICITY

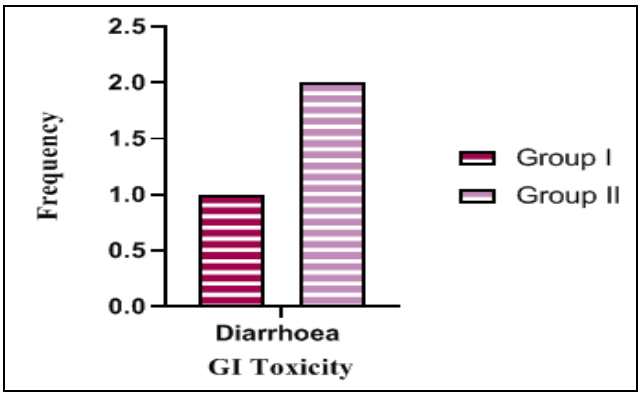

FIG. 9B: GI TOXICITY

Delay: The above graph compares the delay of chemotherapy after initiating neoadjuvant chemotherapy.

TABLE 10:

Delay	Group I (n=53)	%	Group II (n=43)	%
YES	03	06	07	16
NO	50	94	36	84

For the patients in Group I (N=53) 94% (N=50) did not have any delay in the chemotherapy cycle, 06% (N=03) had a delay in chemotherapy treatment.

For the patients in Group II (N=43) 16% (N=07) had any delay in the chemotherapy cycle, 84% (N=36) did not had delay in chemotherapy treatment.

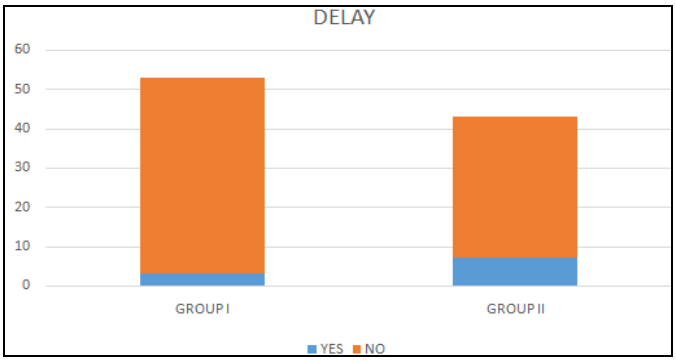

FIG. 10: DELAY

Cycle Completed: The p value in the above table were calculated by Chi-square and the above graph illustrates the comparison of completion of chemotherapy cycle.

TABLE 11:

Completed	Group I (n=53)	Group II (n=43)	P value
Yes	41(77)	34(79)	0.8402
No	12(23)	09(21)	

For the patients in Group I (N=53) 77% (N=41) completed their chemotherapy cycle, 23% (N=12) did not completed their chemotherapy cycle.

For the patients in Group II (N=43) 79% (N=34) completed their chemotherapy cycle, 21% (N=09) did not complete their chemotherapy cycle. With a P value of (0.8402), statistically significant difference does not exist as P>0.05.

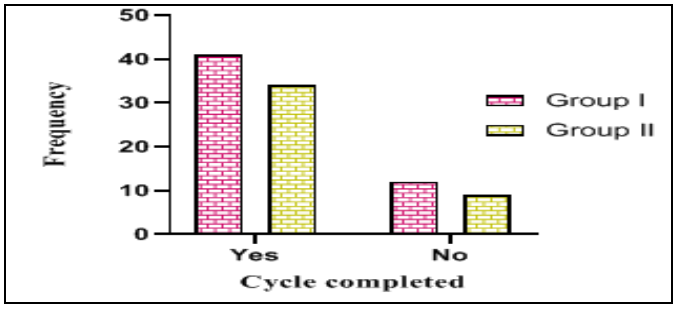

FIG. 11: CYCLE COMPLETED

Total Cycles: Evaluating the number of cycles completed by the patients of both groups will indirectly indicate the toxicity pattern of the regimen.

TABLE 12: TOTAL CYCLE

Total Cycle	Group I		Group II	
	N	%	N	%
2	10	19	05	12
3	12	23	06	14
4	14	26	16	37
5	04	8	05	12
6	13	24	11	25

For the patients in group I (receiving neoadjuvant gem+nabpaclitaxel therapy), out of 53 patients the results were 24% (N=13) patients received 6 cycles of chemotherapy, 8% (N=04) patients received 5 cycles, 26% (N=14) patients received 4 cycles of chemotherapy, 23% (N=12) patients received 3 cycles of chemotherapy, 19% (N=10) patients received 2 cycles of chemotherapy. For the patients in Group II (receiving neoadjuvant Folfirinox therapy) out of 43 patients the results were 25% (N=11) patients received 6 cycles of chemotherapy,

12% (N=05) patients received 5 cycles, 37% (N=16) patients received 4 cycles of chemotherapy, 14% (N=06) patients received 3 cycles of chemotherapy, 12% (N=10) patients received 1 cycles of chemotherapy

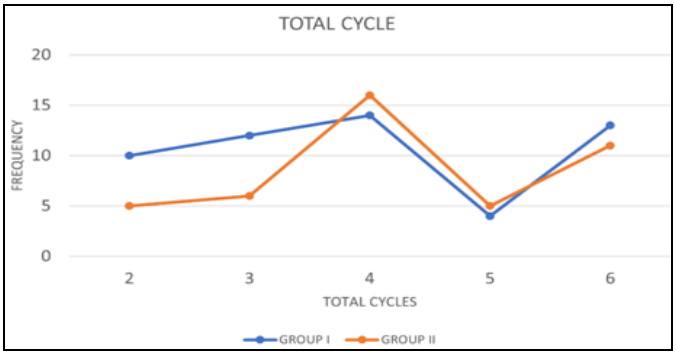

FIG. 12: TOTAL CYCLE

DISCUSSION: Considering the speedy development and lethal function of pancreatic cancer, it's far too essential for patients who must pick out their first neoadjuvant therapy strategy. Folfirinox and gemcitabine + nab - Paclitaxel were proven to be more effective chemotherapeutic alternatives as neoadjuvant chemotherapy in patients with locally advanced pancreatic cancer (LAPC) by analysing many studies [22, 23]. Although neoadjuvant remedy has been widely endorsed *via* many hints and NCCN recommendations for LAPC, the most reliable therapeutic routine remains controversial.

Folfirinox and GNP are the maximum frequently endorsed NAC strategies for LAPC. The standard in resectable disease is a surgical procedure with complete macroscopic resection accompanied by widespread adjuvant chemotherapy. For LAPC, R0 resection is the ultimate desire that majorly decides lengthy-time period survival. According to our retrospective study, neo-adjuvant chemotherapy with Folfirinox slightly improves surgical outcomes and results in a high % tumour reduction. In preceding research, Folfirinox is suitable for sufferers with first-rate performance without applicable comorbidities. Almost all the medical trials had a high chance of bias, for instance, patients of the Folfirinox group were with more youthful age and lower ECOG degrees in comparison with GnP group, which might impair the validity of the located results. As we mentioned before, Folfirinox had higher resection numbers and better % reduction of tumour compared with GnP, which isn't constant with consequences of chemotherapy response. This study also compared the toxicities of two common chemotherapy regimens. GnP was generally reserved for older and more vulnerable patients because patient groups were uneven in age. Also, in our study, we discovered that patients in the GnP group were older than those in the FFX group and that FFX treatment was most effective in male patients. The safety profile and quality of life should be considered when deciding between these two chemotherapy regimens. A drug regimen's safety may be determined by its toxicity or results. In our retrospective comparative analysis, we discovered that the two regimens had comparable rates of high-grade hematological damage.

Major Difference: FFX group had higher febrile neutropenia than GnP group.

CONCLUSION: In the first-line treatment of locally advanced pancreatic cancer, this retrospective comparative analysis shows that Folfirinox and Gemcitabine + nab - Paclitaxel had nearly equal effectiveness. The choice between Folfirinox and GEM-NAB as NAC in LAPC is based on many factors, including age, gender, and toxicities. Our retrospective comparative study concludes that both regimens have similar toxicity.

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CONFLICTS OF INTEREST: There author declares no conflict of interest.

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