DOI: https://doi.org/10.54393/pjhs.v5i12.1989

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 5, Issue 12 (Deccember 2024)

Original Article

OPEN ACCESS

Effectiveness of Gemcitabine with or without Radiotherapy in Gallbladder Carcinoma

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ARTICLE INFO

Keywords:
Carcinoma, Chemotherapy, Gallbladder, Gemcitabine, Radiotherapy, Karnofsky performance score

How to Cite:
Luqman, A. (2024). Effectiveness of Gemcitabine with or without Radiotherapy in Gallbladder Carcinoma: Gemcitabine in Gallbladder Carcinoma. Pakistan Journal of Health Sciences,5(12), 62-67. https://doi.org/10.54393/pjhs.v5i12.1989

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Received Date: 20th August, 2024
Accepted date: 24th December, 2024
Published date: 31st December, 2024

ABSTRACT

Gallbladder carcinoma is the most common malignancy of the hepatobiliary tract and the 5th most common cancer of the gastrointestinal tract. **Objective:** To compare the efficacy of gemcitabine as a single agent or in combination with radiation in terms of response rate and relief of symptoms in gallbladder carcinoma. **Methods:** This retrospective study was accomplished at the department of oncology, Nishter Hospital Multan, Pakistan, from January 2021 to December 2022. Inclusion criteria were patients with a histopathologically proven diagnosis of gallbladder carcinoma, and they were advised gemcitabine with or without radiation therapy as per the treating physician's discretion. The treatment response rate and alleviation of symptoms were noted. **Results:** Among a total of 50 patients, 40 (80.0%) were female. The mean age was 56.58 ± 6.14 years. At baseline, 33 (66.0%) patients had stable disease, while the remaining 17 (34.0%) had progressive disease. Gemcitabine alone revealed stable disease, and progressive disease in 14 (56.0%), and 11 (44.0%) patients, respectively, whereas among patients receiving gemcitabine plus radiotherapy, partial response, stable disease, and progressive disease were observed in 7 (28.0%), 14 (50.0%), and 4 (16.0%) patients, respectively (p=0.006). Regarding symptom relief, 8 (32.0%) patients in the gemcitabine alone group had pain relief versus 20 (80.0%) in the gemcitabine plus radiotherapy group (p=0.001). **Conclusion:** Gemcitabine plus concomitant radiotherapy was more effective in achieving higher response rates and alleviation of symptoms when compared to gemcitabine alone in gallbladder carcinoma patients.

INTRODUCTION

Gallbladder carcinoma is known to be the commonest hepatobiliary tract malignancy, and the 5th most frequent gastrointestinal tract related carcinoma [1]. The incidence of gall bladder cancer shows regional variation; it is more common in whites than in black women and more common in Native Americans and Mexican Americans. In Asian countries, there is a much higher incidence in Japan, Thailand, Korea, and the subcontinent [2]. Gallbladder carcinoma usually has a silent course and a dismal prognosis [3]. Initial symptoms of gall bladder carcinoma include pain in the abdomen, more often confined to the right hypochondrium, vomiting, loss of appetite, early satiety, and jaundice [4]. Initially, the disease does not create an alarming state, and thus, patients usually present late when the disease is advanced or often unresectable [5]. Various risk factors associated with this gall bladder disease include obesity, the presence of gall stones, choledochal cysts, estrogen excess, typhoid carriers, porcelain gallbladder, and multiparity [6, 7]. As gallbladder carcinoma is not very common, not much is stated about the standard regimen for managing these cases, but surgery, radiation therapy, and chemotherapy have their roles in the palliation and control of disease [8]. Surgical resection is the only curative option in gallbladder carcinoma. With localized disease, surgery, either simple cholecystectomy or extended radical cholecystectomy, plays an important role and offers better disease control for gallbladder carcinoma [9]. As gallbladder carcinoma usually presents in advanced stages, adjuvant therapy is usually required in most of the patients [10]. Depending on the stage of the disease, chemotherapy and radiotherapy are used in addition to surgery. Various chemotherapeutic

DOI: https://doi.org/10.54393/pjhs.v5i12.1989

agents have been used in different settings. Various trials have shown that gemcitabine is effective in gallbladder cancer, especially when used in combination with cisplatin [11, 12]. Initial phase 1 and 2 trials have produced encouraging results, but it is still not considered a standard drug as the available data are of short duration and the number of patients accrued in these trials is small [13, 14]. Radiation therapy has a palliative role, and it has been used in advanced stages for relief of pain and pressure effects. Radiation therapy has also been used in addition to surgery, and it has proved to be beneficial for longer disease control [15]. To improve the response rate in gallbladder cases with radiation alone, the dose of radiation has to be increased, which can lead to high hepatic toxicity [16]. A better reaction and a lower radiation dosage are obtained by using a radiosensitizer. Although gemcitabine has been characterized as a strong radiosensitizer, the ideal dose for radiosensitization is still up for debate. Doses ranging from 200 mg to 600 mg have been used concurrently with radiation [13, 14]. It was hypothesized that gemcitabine combined with radiation may be better in terms of relief of symptoms when compared to gemcitabien alone.

The aim of this study was to compare the efficacy of gemcitabine as a single agent or in combination with radiation in terms of response rate and relief of symptoms in gallbladder carcinoma.

METHODS

This retrospective study was carried out at the department of oncology, Nishter Hospital Multan, Pakistan, from January 2021 to December 2022. Ethical approval was obtained from the Institutional Ethical Review Board of Nishtar Medical University, Multan, under Reference Number 428.The inclusion criteria were record of patients of either gender, irrespective of age, with a histopathologically proven diagnosis of gallbladder carcinoma, adequate marrow reserve (Hb ≥ 9 g/dl, WBC ≥ 4000/mm3, ANC > 2000/mm3, platelet count > 100,000/mm3), renal parameters within the normal range, liver function tests not deranged, Karnofsky performance score of 60 or above, life expectancy of 3 months or greater, a normal x-ray chest, and were admitted to the oncology department during the study period. A record of patients was included if they were advised to take gemcitabine with or without radiation therapy as per the treating physician's discretion. The exclusion criteria were patients who had prior chemotherapy or radiotherapy. The sample selection was done using a non-probability convenience sampling technique. During the study period from January 2021 to December 2022, data of total 75 patients with gallbladder carcinoma were reviewed. Out of these, 50 patients met the inclusion acriteria and were reviewed in the study. The remaining 25 patients were excluded due to factors such as prior chemotherapy or radiotherapy, inadequate marrow reserve, deranged liver function tests, or a Karnofsky performance score below 60. Demographic data like gender, age, residential status, presenting symptoms, and their duration were noted. WHO performance status was graded as 0 (fully active, able to carry on all pre-disease activities without restriction), 1 (restricted in physically strenuous activity but ambulatory and able to carry out light work), 2 (ambulatory and capable of all self-care but unable to work; up and about more than 50% of waking hours), 3 (capable of only limited self-care; confined to bed or chair for more than 50% of waking hours), or 4 (completely disabled; cannot carry out any self-care; totally confined to bed or chair). Patients who received chemotherapy were given gemcitabine 1000 mg/m2 (on days 1, 8, and 22 for a total of three cycles), while gemcitabine 200 mg was given in addition to radiation therapy (commencing with the first scheduled radiation treatment day and continuing every week until the radiation is accomplished) to the remaining patients. The intended radiation dosage involved employing the shrinking field approach to administer a 4500 cGy midway tumor dose to the right hypochondrium. Radiation therapy was administered for five weeks at a dose of 180 cGy each day, five days a week. The first port, which included the gallbladder bed and local lymph nodes, was marked. For the first 14 days, a radiation dose of 180 cGy was administered. After 14 days, by ultrasound evaluation, the portal was reduced to the tumor site. The liver's tolerance limit was taken into consideration when choosing this approach. The tumor area was radiated for the remainder of the treatment once a smaller portal was created. At follow-ups, patients underwent a thorough physical examination and a history taking. The primary endpoint was the determination of the response rate (effectiveness). The effectiveness was assessed based on how the tumor responded to the treatment. The categories for response included Complete Response (CR) as complete disappearance of all clinically detectable disease, Partial Response (PR) as at least a 50% reduction in measurable disease, Stable Disease (SD) as Neither sufficient shrinkage to qualify as PR nor sufficient increase to qualify as PD, or Progressive Disease (PD) as growth in measurable disease or the appearance of new lesions. The secondary endpoint was the alleviation of symptoms and it was labeled as reduction in reported and relevant complaint when compared to the baseline severity. All the concerned statistics were gathered using a specifically predesigned proforma. The analysis of the data was conducted through "IBM-SPSS statistics" version 26.0. The quantitative variables like age, height, and weight were shown in the form of a mean and a Standard Deviation (SD). For the qualitative variables like gender, the level of response, and elevated symptoms, frequencies and

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percentages were calculated. Applying the chi-square test, different variables were assessed for any relationship between them. A p-value ≤ 0.05 was taken as standard to mark significance.

RESULTS

The records of 50 patients, matched as per inclusion and exclusion criteria, were analyzed for this study. Among a total of 50 patients, 40 (80.0%) were female, representing a female-to-male ratio of 4:1. The mean age was 56.58 ± 6.14 years, ranging between 42 and 75 years. The residential status of 34 (68.0%) patients was rural. The socio-economic status of 28 (56.0%) patients was low. The presence of gallstones, and jaundice were noted in 41 (82.0%) and 23 (46.0%) patients, respectively. At baseline, 33 (66.0%) patients had stable disease, while the remaining 17 (34.0%) had progressive disease. Table 1 showed characteristics of patients (Table 1).

Table 1: Baseline Characteristics of Patients (N=50)

Variables	Categories	Gemcitabine Alone N (%)	Gemcitabine and Radiotherapy N (%)	p-value
Socioeconomic Status	Male	4 (16.0%)	6 (24.0%)	0.480
	Female	21 (84.0%)	19 (76.0%)	
Age Groups (Years)	40-50	4 (16.0%)	2 (8.0%)	0.596
	51-60	10 (40.0%)	9 (36.0%)	
	61-70	11 (44.0%)	13 (52.0%0	
	71-80	-	1 (4.0%)	
Residence	Urban	6 (24.0%)	10 (40.0%)	0.225
	Rural	19 (76.0%)	15 (60.0%)	
Socioeconomic Status	Low	13 (52.0%)	15 (60.0%)	0.838
	Middle	8 (32.0%)	7 (28.0%)	
	High	4 (16.0%)	3 (12.0%)	
WHO Performance Status	1	1 (4.0%)	3 (12.0%)	0.181
	2	11 (44.0%)	15 (60.0%)	
	3	13 (52.0%)	7 (28.0%)	
TNM Stage	$T_3 N_{0/1} M_0$	6 (24.0%)	9 (36.0%)	0.507
	$T_{3/4} N_{1/2} M_0$	14 (56.0%)	10 (40.0%)	
	$T_{3/4} N_{1/2} M_1$	5 (20.0%)	6 (24.0%)	
Presence of Gallstones		18 (72.0%)	23 (92.0%)	0.066
Presence of Jaundice		11 (44.0%)	12 (48.0%)	0.777
Loss of Appetite		21 (94.0%)	23 (92.0%)	0.384
Abdominal Pain		24 (96.0%)	24 (96.0%)	1
State of Disease	Stable Disease	18 (72.0%)	15 (60.0%)	0.370
	Progressive Disease	7 (28.0%)	10 (40.0%)	

Overall, a partial response rate was seen in 7 (14.0%) patients, stable disease was seen in 28 (56.0%), and the remaining 15 (30.0%) had a progressive disease. None of the patients reported a complete response. When both groups were compared, Gemcitabine alone revealed a stable disease, and progressive disease in 14 (56.0%) and 11 (44.0%) patients, respectively, whereas among patients receiving gemcitabine plus radiotherapy, partial response, stable disease, and progressive disease were observed in 7 (28.0%), 14 (50.0%), and 4 (16.0%) patients, respectively. The overall comparison of response rates among patents of both study groups revealed statistically significant differences favoring gemcitabine plus radiotherapy (p=0.006), and the details are shown in Figure 1.

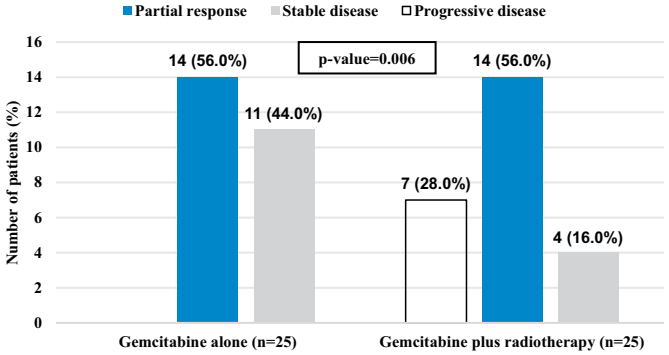

Figure 1: Comparison of Response Rate between Study Groups (N=50)

Regarding symptom relief, 8 (32.0%) patients in gemcitabine alone group had pain relief versus 20 (80%) in gemcitabine plus radiotherapy group (p=0.001), as shown in Table 2.

Table 2: Treatment Outcomes in Patients Receiving Chemo Alone and Chemo Plus RT (N=50)

Symptoms Relief	Chemo Alone N (%)	Chemo Plus RT N (%)	p-Value
Yes	8 (32.0%)	20 (80.0%)	0.007
No	17 (68.0%)	5 (20.0%)	

Nausea/vomiting, anorexia, and abdominal pain were the most frequent treatment related side-effects, noted in 25 (50.0%), 15 (30.0%), and 7 (14.0%) patients, respectively. None of the side effects were serious and no treatment breaks required in both groups. Symptomatic medication relieved the side effects. Mucositis was significantly associated with chemo alone group (p=0.018). Abdominal pain was significantly more prevalent in chemo plus RT group (24.0% versus 4.0%, p=0.042). Anorexia was significantly associated with chemo plus RT group (44.0% versus 16.0%, p=0.031). Table 3 is showing comparison of treatment related side-effects in both treatment groups (Table 3).

Table 3: Comparison of Treatment Related Side-Effects in both Study Groups (N=50)

Side-Effects	Category	Chemo Alone N (%)	Chemo Plus RT N (%)	p-Value
Neutropenia	Yes	3 (12.0%)	0	0.074
	No	22 (88.0%)	25 (100%)	
Nausea/ Vomiting	Yes	11 (44.0%)	14 (56.0%)	0.396
	No	14 (56.0%)	11 (44.0%)	
Diarrhea	Yes	3 (12.0%)	0	0.074
	No	22 (88.0%)	25 (100%)	

DOI: https://doi.org/10.54393/pjhs.v5i12.1989

Mucositis	Yes	5 (20.0%)	0	0.018
	No	20 (80.0%)	25 (100%)	
Abdominal Pain	Yes	1 (4.0%)	6 (24.0%)	0.042
	No	24 (96.0%)	19 (76.0%)	
Anorexia	Yes	4 (16.0%)	11 (44.0%)	0.031
	No	21 (84.0%)	14 (56.0%)	

DISCUSSION

In this study, 80.0% of patients with gallbladder carcinoma were female. The literature describes a high predominance of female gender among patients with gallbladder carcinoma, so these findings are pretty consistent with what has already been described earlier [17]. It was noted that the mean age mean of patients with gallbladder carcinoma was 56.58 ± 6.14 years. A local study from Karachi showed the mean age of patients with gallbladder carcinoma to be 52.8 ± 8.4 years [18, 19]. The age group involved, the 5th and 6th decade of life, seems to be the most probable age groups for gallbladder carcinoma. For advanced gallbladder carcinoma disease, adjuvant therapy is commonly utilized all over the globe, including radiation therapy and chemotherapy [15]. While 5FU has long been the standard chemotherapy medicine, more recent studies have looked into different medications. Of all the novel drugs, gemcitabine, a purine analogue, has shown promising results [10]. The study's findings showed that chemo-radiation or combination treatment offered improved palliation, disease management, and symptom relief for issues like pain and anorexia. One study conducted at the University of Chile Clinical Hospital showed gemcitabine as an effective drug with a 37% response rate. Treatment related to toxicity was mild. Researchers have shown that response rates with gemcitabine range between 8 and 30%, while it seems to be a well-tolerated and clinically active drug in unresectable gallbladder carcinoma [17-21]. It has been discovered that using radiation treatment in combination to chemotherapy or the medication used as a radiosensitizer, such as gemcitabine, cisplatin, and 5FU, is beneficial in managing pain and lessening the effects of pressure [22]. According to published data, radiation therapy has been used in a variety of settings, including intra-operative and conformal radiotherapy. The results have demonstrated that adding radiation therapy to chemotherapy or surgery has significantly improved disease control without having a noticeable negative impact on side effects [23, 24]. Some others have also revealed that postoperative gemcitabine significantly delays the recurrence of disease following a complete resection of pancreatic cancer compared to observation alone. These findings endorse the use of gemcitabine as an adjuvant chemotherapy [24]. A systematic review conducted by Dingle and colleagues exhibited that surgery offered the best chance of survival for people with gallbladder cancer or cholangiocarcinoma and should continue to be the main course of treatment. However, gemcitabine, either by itself or in conjunction with a fluoropyrimidine (such as 5-fluorouracil or capecitabine), proved to be a reasonable substitute for the finest supportive treatment for patients who were not candidates for surgery but were able and willing to take chemotherapy [24]. Possible limitations of this study could include a retrospective design, a small sample size, which may limit the generalizability of the results, potential variability in patient response due to individual differences in tumor biology, and the challenge of accurately measuring symptom relief. The study might face difficulties isolating the effects of gemcitabine from those of radiation when used in combination. Future studies should include prospective data collection to ensure comprehensive reporting of adverse events, which is crucial for evaluating the overall safety and tolerability of these treatment modalities.

CONCLUSIONS

Gemcitabine plus concomitant radiotherapy was revealed to be more effective in achieving higher response rates and alleviation of symptoms when compared to gemcitabine alone in gallbladder carcinoma patients. Further randomized controlled trials evaluating the longer duration of follow-ups are required to ascertain the impact of various management approaches among patients with gallbladder carcinoma.

Authors Contribution

Conceptualization: AL
Methodology: AL
Formal analysis: AL
Writing, review and editing: AL

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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