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Retrospective Study

Safety and Efficacy of Biweekly Gemcitabine in Combination with Capecitabine in Elderly and Frail Patients with Resected Pancreatic Cancer

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ABSTRACT

Background
The European Study Group for Pancreatic Cancer (ESPAC-4) study showed that gemcitabine and capecitabine (GemCap) conferred a survival benefit over gemcitabine monotherapy in resected pancreatic cancer (PC) patients. ESPAC-4 included patients with a median age of 65-years (37-81) and Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0,1 in 97%. We present our experience with an adopted biweekly regimen of GemCap in patients who were ≥75-years old and deemed not suitable for the ESPAC-4 regimen.

Methods
Patients received a biweekly regimen of GemCap (gemcitabine 1000 mg/m^2 every 2-weeks and capecitabine 1000 mg/m^2 twice a day orally on days 1-7 every 2-weeks). Patients were evaluated for progression-free survival (PFS), overall survival (OS), and sites of recurrence. Toxicities were graded according to National Cancer Institute (NCI) common terminology criteria for adverse events (CTCAE) v5.0.

Results
Thirty-five (35) patients with a median age of 79-years were treated with biweekly GemCap adjuvant treatment. Seventy-two percent (72%) of patients had ECOG PS of 2. The median PFS and OS were 8-months and 22-months. Twenty-five percent (25%) had local recurrence, 60% had metastatic disease and 8.6% had no evidence of disease (NED). The most frequent toxicities were grades 1-2 anemia (20%), thrombocytopenia (8%), and hand-foot syndrome (HFS) (10%). Grade ≥3 included diarrhea (4%) and HFS (1%).

Conclusion
Our study showed that biweekly gemcitabine in combination with capecitabine can be an acceptable regimen with efficacy comparable to historical control and a favorable toxicity profile in elderly and frail patients. Patients on this regimen also make fewer visits to the oncologist. A biweekly GemCap regimen warrants further exploration in patients not suitable for FOLFIRINOX (a combination of bolus and infusional fluorouracil, leucovorin, irinotecan and oxaliplatin), full-dose GemCap, or a clinical trial.

Keywords
Gemcitabine; Capecitabine; Pancreatic cancer.

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INTRODUCTION

Pancreatic cancer is one of the most lethal solid organ malignancies. Surgical resection remains the primary treatment modality for patients with pancreatic cancer when feasible and offers the only potential for cure but is only possible in a minority of patients.[1] Even in those patients who receive adjuvant treatment, the majority of them succumb to death due to metastatic disease.[2,3] Treatment is often guided by resectability, but this may vary depending on surgical judgment and experience. Referral to a high-volume center should be considered.[4] The addition of postoperative chemotherapy improves overall survival, but the role of chemoradiation remains controversial (Table 1).[5-13]

Table 1. *PFS and Median Survival*

Study	Treatment	Impact of Adjuvant Therapy
GITSG[5]	Observation *vs.* 5-FU plus radiation therapy	Median survival improvement from 11-months to 20-months
EORTC[6]	Observation *vs.* 5-FU plus radiation therapy	A trend toward median survival improvement from 19-months to 24.5-months; *p*=0.208
ESPAC-1[7]	5-FU/L *vs.* Chemoradiation *vs.* Chemoradiation+5-FU/L *vs.* Observation	Chemotherapy *vs.* observation (20.1-months *vs.* 15.5-months; *p*=0.009) Chemoradiation *vs.* observation showed worse median survival (15.9-months *vs.* 17.9-months; *p*=0.05)
RTOG 9704[8]	5-FU with radiation *vs.* Gemcitabine plus 5-FU with radiation	Median survival (16.7-months *vs.* 18.8-months; *p*=0.047) (pancreatic head tumors only)
CONKO-001[9]	Gemcitabine *vs.* Observation	Disease-free survival doubled (13.4-months *vs.* 6.9-months) Trend toward overall survival benefit (22.1-months *vs.* 20.2-months; *p*=0.06)
ESPAC-3[10]	Gemcitabine *vs.* 5-FU *vs.* Observation	No difference in survival advantage between Gemcitabine and 5-FU however, safety and dose intensity favored gemcitabine
ESPAC-4[11]	Gemcitabine/Capecitabine *vs.* Gecitabine	Median OS for patients in gemcitabine plus capecitabine group was 28-months (95% CI 23.5-31.5) *vs.* 25 ·5-months (22.7-27.9) in gemcitabine group (HR 0.82 [95% CI 0.68-0.98], *p*=0 ·032)
JASPAC-01[12]	Gemcitabine *vs.* S-1	The two-year survival rates were 70% and 53% for S-1 and gemcitabine, The two-year relapse free survival rates were 49% and 29% for S-1 and gemcitabine
PRODIGE-24[13]	Gemcitabine *vs.* FOLFIRINOX	Median disease-free survival (DFS) was 21.6-months with FOLFIRINOX and 12.8-months with gemcitabine (HR, 0.58; 95% CI, 0.46-0.73, *p*=0.001). Median OS was 54.4-months with FOLFIRINOX and 35-months with gemcitabine (HR, 0.64; 95% CI, 0.48-0.86, *p*=0.003).

Historically, multiple randomized clinical studies have shown the role of 5-FU monotherapy or gemcitabine monotherapy[5-7,9] to improve OS for 6-months after surgical resection compared with surgery alone. More recent studies have looked at newer combination regimens, such as gemcitabine plus capecitabine or FOLFIRINOX (a combination of bolus and infusional fluorouracil, leucovorin, irinotecan and oxaliplatin) that might further improve outcomes after surgical resection.[11,13] In Asia, S-1 (tegafur, gimeracil, and uracil potassium), an oral 5-fluorouracil (5-FU) prodrug, which is designed to improve the antitumor activity of 5-FU by inhibiting dihydropyrimidine dehydrogenase (DPD), the key enzyme of 5-FU catabolism has established superiority over gemcitabine, but this agent is not available in the USA.[12]

For patients with good performance status, adjuvant FOLFIRINOX chemotherapy or the combination of gemcitabine and capecitabine are usually considered. However, for older patients or patients with marginal performance status, adjuvant gemcitabine or 5-FU monotherapy are acceptable options. S-1 is not available in the USA.

European Study Group for Pancreatic Cancer (ESPAC-4) study evaluated the efficacy and safety of gemcitabine and capecitabine (GemCap) compared with gemcitabine monotherapy in 732 patients with resected pancreatic cancer.[11] ESPAC-4 included patients with a median age of 65-years (37-81) and Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 (43%), 1 (54%), and 2 (2%) who received a median cumulative dose of gemcitabine of 15,000 mg/m^2 with capecitabine and the median cumulative dose of capecitabine was 162,680 mg/m^2. Despite these results being effective, GemCap was associated with increased toxicity, inconvenience to patients, and enhanced cost.

Prior studies have suggested a modified regimen of biweekly GemCap and a 7/7 schedule of capecitabine could lessen the adverse effects of the regimen while maintaining or enhancing efficacy.[14-16] Although promising, this regimen has not been evaluated further, especially in a patient population who have relatively poor performance status either related to co-morbid conditions or age. Management of these patients is quite limited and further hindered by the underrepresentation of this population in clinical trials.

Therefore, we performed a retrospective analysis at our centers with an adopted biweekly regimen of GemCap in pancreatic cancer patients who were ≥75-years-old and those who were deemed not suitable for ESPAC-4 regimen and/or FOLFIRINOX after surgical resection.

METHODS

This study was approved with written consent by our institution's Institutional Review Board (IRB). Ethics approval was not sought as this was a retrospective review. We performed a retrospective analysis of patients ≥75-years with resected PC with no prior treatments. Patients were treated with a modified regimen (GemCap) consisting of intravenous gemcitabine every 2-weeks

and capecitabine twice daily by mouth on days 1-7 every 2-weeks. Patients were evaluated for disease-free survival (DFS), overall survival (OS), and sites of recurrence. Toxicities were graded according to NCI CTCAE v5.0.[17]

Patients older than 75-years of age with resected pancreatic adenocarcinoma were eligible. Confirmation of histological diagnosis of adenocarcinoma was required. All patients had to have an Eastern Cooperative Oncology Group performance status of 0, 1, or 2. Patients were treated with this regimen based on the discretion of the treating physician. Decisions were based upon open discussions with the patients based on performance status, co-morbid conditions, or the patient's preference for not wanting to come to the treatment room for weekly treatments. There were no limitations based on comorbidities if performance status was adequate. Patients were chemo naïve as no previous treatment for pancreatic cancer was allowed.

Chemotherapy was administered on days 1 and 15 of a 28-day cycle. Patients received gemcitabine (1000 mg/m^2) every 2-weeks and capecitabine (1000 mg/m^2) days 1-7 every 2 weeks. Pre-medications and anti-emetics were ordered according to American Society of Clinical Oncology (ASCO) guidelines. Granulocyte-colony stimulating factor was also administered according to ASCO guidelines.[18] Treatment was continued for 6-months or until evidence of recurrence of disease progression or unacceptable toxicity.

Comprehensive physician office visits were conducted every 2-weeks before initiation of treatment and between each cycle of treatment. Detailed history and physical examination were performed at each clinic visit. Baseline information to assess disease status, such as level of resection, and site of primary tumor was also collected. Baseline blood work was obtained before initiating treatment as well as before each subsequent treatment. Laboratory values included a complete blood count, comprehensive metabolic panel, and cancer antigen 19.9 levels. Toxicities were assessed using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. Computed tomography imaging of the chest, abdomen, and pelvis was used to assess disease status every three months or as clinically indicated. All information was recorded in each patient's secure online medical electronic record.

Study endpoints that were evaluated included disease-free survival (DFS), OS, and toxicity profile. Descriptive statistics were used to evaluate demographic information, subsequent lines of treatment, as well as toxicity profile. DFS was calculated from the start of chemotherapy until disease progression or death, whichever came first. OS was obtained from the initiation of chemotherapy until death from any cause.

RESULTS

A total of 35 (22 male, 13 female) patients who received biweekly GemCap adjuvant treatment were evaluated. Demographic data are presented in Table 2.

Table 2. *Demographics of Patients*

Characteristic	Adjuvant treatment (n=35)
Age (years)	
Median	79
Range	75-97
Sex	
Female	13
Male	22
Location of primary tumor	
Head	26
Tail	5
Others	4
Co-morbid conditions	
Diabetes mellitus	15
Peripheral neuropathy	4
Cardiovascular disease	6

All patients were equal or older than 75-years of age with a median of age 79-years. Seven (28%) patients had an ECOG PS of 1 and 28 (72%) had an ECOG PS of 2. There were 5, 7, and 16 patients with stage I, borderline, and II pancreatic cancer respectively. The most common site was head (76%), followed by tail (15%), and others. Nine patients (25%) had R1 and 26 (75%) had R0 resection.

Most toxicities were rated as grade 2 or less and related to anemia, thrombocytopenia, neutropenia, hand-foot syndrome, fatigue, nausea, and skin rash. Grade 3 or higher toxicities were rare in our cohort: grade ≥3 neutropenia (5%), diarrhea (3%), fatigue (1%), infection (1%), and HFS (1%) (Figure 1).

Treatment compliance was approximately 94%. Delays were necessary in 7% of cases and dose reduction was required in 4% of cases. There were no treatment-related discontinuations. There was no treatment-related death.

Around 34% of patients received growth-factor support based on the ASCO guidelines. Although the standard to receive primary prophylaxis includes regimens where the risk of neutropenia is >20%, many patients in our analysis received growth-factor support largely due to older age and comorbidities. It has been shown that older patients aged greater than 65-years may be more vulnerable to chemotherapy-related febrile neutropenia. Furthermore, having more advanced cancer and comorbidities carries a higher-risk of complications from chemotherapy. In our analysis, no patients developed neutropenic fever.

The median disease-free survival (DFS) and overall survival (OS) were 8-months (range: 5.5-14) and 22-months (range: 17-27) respectively. Nine (25%) had local recurrence, 21 (60%) had metastatic disease and 3 (8.6%) had no evidence of disease (NED). Two patients were lost to follow-up.

DISCUSSION

Our experience with an adopted biweekly regimen of GemCap in

patients who were ≥75 years old and those who were deemed not suitable for ESPAC-4 regimen or FOLFIRINOX showed similar results to historical precedents. Relatively reduced toxicities associated with this regimen, convenience to patients, and potentially reduced healthcare costs make this regimen an optimal option in selected patients who were deemed not suitable for the ESPAC-4 regimen and/or FOLFIRINOX after surgical resection. Additionally, better tolerability and biweekly schedule allow for combination with a third agent, such as a targeted treatment or immunotherapy, especially as we enter the era of precision medicine in oncology. Though retrospective, this study underlines the need for further investigation, particularly in elderly patients with antigen-presenting cell (APC) to optimize outcomes while minimizing toxicities and preserving quality of life.

Although the results of the ESPAC-4 trial were promising and effective, they came at a cost of increased toxicity as well as practical disadvantages for the patients. ESPAC-4 study enrolled 732 patients enrolled, 366 in the gemcitabine arm and 364 in the GemCap arm.[11] All six cycles of planned GemCap were administered to 65% of patients in the gemcitabine group and 54% in the GemCap group. In this study, the median cumulative dose of gemcitabine was 16,750 mg/m^2 in the gemcitabine group and 15,000 mg/m^2 (median cumulative dose of capecitabine was 162,680 mg/m^2) in the GemCap group. In our study, delays occurred in 7% of cases and dose reduction was required in only 4% of the patients. There were no treatment-related discontinuations. However, the total dose of gemcitabine was lower than the ESPAC-4 study: patients received 1000 mg/m^2 every 2-weeks in our cohort (planned cumulative dose of 12,000 mg/m^2) instead of 1000 mg/m^2 weekly x 3 out of 4-weeks (planned cumulative dose of 18,000 mg/m^2). Our cohort of patients on a modified biweekly schedule showed lower grade 3 and 4 toxicities (Figure 1). As described earlier, approximately 35% of patients in our analysis received growth-factor support due to older age and comorbidities. No patients developed neutropenic fever in our study.

This alternative biweekly GemCap appears to have acceptable efficacy for a frail population when compared with the historical control from the ESPAC-4 trial.[11] ESPAC-4 study showed a median overall survival time of 25·5-months (22.7-27.9) in the gemcitabine group and 28-months (23.5-31.5) in the GemCap (HR 0.82 (95% CI 0.68-0.98), p=0.032).[11] Our cohort of patients had a median survival of 22-months (range: 17-27). ESPAC-4 study population had a median relapse-free survival of 13.1-months (11.6-15.3) in the gemcitabine group and 13.9-months (12.1-16.6) in the GemCap group (HR 0.86, 95% CI 0.73-1.02, p=0.082).[11] On the other hand, our patients had a median DFS of 8-months (range: 5.5-14). We acknowledge here that cross-over comparison from different studies lends to bias as different populations were evaluated. There is no direct comparison of demographic data and the lack of a control arm could limit the generalizability of results. The older population remains a heterogeneous group and difficult to treat based on unclear tolerability of treatments as well as exclusion from some clinical trials.[19] Prior studies have suggested a modified regimen of biweekly gemcitabine/capecitabine could lessen the adverse effects of the regimen while maintaining or enhancing efficacy.[14-16] These modified regimens have not been further assessed in a patient population who have relatively poor performance status either related to co-morbid conditions or age-related complications. Management of these patients is quite limited and further hindered by the underrepresentation of this population in clinical trials. Pancreatic cancer is known to be a disease of older adults, with a median age of 71-years at diagnosis in the USA.[20] In the ESPAC-4 study, only 3% of patients had ECOG PS of 2 in the GemCap arm.[11]

The findings from our study suggested that the adopted biweekly GemCap regimen not only maintains relative efficacy with considerable improvement in side-effect profile but could have an impact on healthcare costs. By eliminating day 8 of treatment, financial toxicity can be greatly reduced factoring in costs of chemotherapeutic agents, infusion-related costs, and personnel need at the cancer center. Furthermore, there is increasing awareness of quality-of-life measures in patients with cancer.[21] By reducing treatment room visits, patients may have considerable improvement in these measures related to convenience factors as well as transportation needs. This may also encompass more quality time with loved ones at home, which is of paramount importance for most patients with pancreatic cancer.[20] We did not include a quality-of-life (QoL) assessment in our study, but this could present an interesting area of research in this population.

Lastly, improvement in these toxicities while producing somewhat optimal results may allow for additional treatments. By preserving toxic side effects from treatment, further investigation can be performed with the addition of a third agent to this combination, especially targeted treatments, vaccines, and immunotherapies.

We acknowledge the limitations that accompany our study. This was carried out in a retrospective nature which included inherent biases such as the possibility of selection bias. A relatively small sample size is also a limitation as this was conducted solely at our institution as a retrospective analysis. However, keeping these points in mind, we believe our patients represented a reasonably similar profile to the general population in this patient population with pancreatic cancer. All patients were treated at the discretion of the treating physician. Patients were monitored as they would be in any clinical setting.

CONCLUSION

Our study showed that this schedule of biweekly GemCap regimen is an acceptable option for elderly, frail patients with PC and warrants further exploration in patients not suitable for FOLFIRINOX, full dose GemCap, or a clinical trial. This regimen required fewer dose reductions, omissions, or delays and allowed to administer of pegylated-filgrastim. Moreover, fewer visits to oncology clinics and related expenses do favor the benefit. Additionally, this tolerable regimen is ideal to be combined with immunotherapy in clinical trials for this patient population.

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INSTITUTIONAL REVIEW BOARD PERMISSION

This study was approved with written consent by our institution's Institutional Review Board. Ethics approval was not sought as this was a retrospective review.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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