Original Article

# A phase II trial of gemcitabine and erlotinib followed by ChemoProton therapy plus capecitabine and oxaliplatin for locally advanced pancreatic cancer

**Samrat M. Sanghvi[1], Alex R. Coffman[2], Chung-Tsen Hsueh[3], Joseph Kang[1], Annie Park[3], Naveenraj L. Solomon[4], Carlos A. Garberoglio[4], Mark E. Reeves[4], Jerry D. Slater[1], Gary Y. Yang[1]**

[1]Department of Radiation Medicine, Loma Linda University, Loma Linda, CA, USA; [2]Green Bay Oncology, Green Bay, WI, USA; [3]Department of Medical Oncology, Loma Linda University, Loma Linda, CA, USA; [4]Department of Surgical Oncology, Loma Linda University, Loma Linda, CA, USA

*Contributions:* (I) Conception and design: All authors; (II) Administrative support: All authors; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

*Correspondence to:* Gary Y. Yang. 11234 Anderson Street, Suite A-875, Loma Linda, CA 92354, USA. Email: GYang@llu.edu.

**Background:** Epidermal growth factor receptor (EGFR) is overexpressed in pancreatic cancer. EGFR expression plays a potentially important role in modulation of tumor sensitivity to either chemotherapy or radiotherapy. Erlotinib is a receptor tyrosine kinase inhibitor with specificity for EGFR/HER1. A phase II trial was conducted to explore the efficacy of a regimen utilizing erlotinib and proton therapy.

**Methods:** Patients with unresectable or borderline resectable non-metastatic adenocarcinoma of the pancreas were included. Patients received 8-week systemic treatment with gemcitabine 1,000 mg/m$^2$ and erlotinib 100 mg (GE). If there was no evidence of metastatic disease after GE, then patients preceded with proton therapy to 50.4 Gy in 28 fractions with concurrent capecitabine 825 mg/m$^2$ (CPT). This was followed with oxaliplatin 130 mg/m$^2$ and capecitabine 1,000 mg/m$^2$ (CapOx) for 4 cycles. The primary study objective was 1-year overall survival (OS). The benchmark was 43% 1-year survival as demonstrated in RTOG/NRG 98-12. The Kaplan-Meier method was used to estimate the one-year OS and the median OS and progression-free survival (PFS).

**Results:** The study enrolled 9 patients ages 47–81 years old (median 62) between January 2013 and March 2016, when the trial was closed due to low patient accrual. The 1-year OS rate was 55.6% (95% CI: 31% to 99%). The median OS was 14.1 months (95% CI: 11.4–NE) and the median PFS was 10.8 months (95% CI: 7.44–NE). A majority of patients completed CPT and GE, but only 33.3% completed the four cycles of CapOx. A third of patients experienced grade 3 toxicities, which were all hepatic along with one patient who also had grade 3 diarrhea. There were no grade 4 or 5 toxicities. Four patients were enrolled with borderline resectable disease, three of which were eligible for pancreaticoduodenectomy after GE and CPT treatment. One of two patients who underwent resection had a negative margin.

**Conclusions:** This regimen for locally advanced pancreatic cancer (LAPC) exceeded the pre-specified benchmark and was safe and well tolerated. Additional investigations utilizing more current systemic treatment regimens with proton therapy are warranted.

**Trial Registration:** ClinicalTrials.gov identifier (NCTNCT01683422).

**Keywords:** Locally advanced pancreatic cancer (LAPC); proton radiation therapy; chemotherapy; targeted therapy; erlotinib

Submitted Apr 08, 2022. Accepted for publication Jul 04, 2022.
doi: 10.21037/jgo-22-327
**View this article at:** https://dx.doi.org/10.21037/jgo-22-327

 

## Introduction

Pancreatic cancer remains a highly lethal malignancy despite advances in treatment. The estimated incidence of pancreatic cancer in the United States in 2020 is 57,600 cases with an estimated 47,050 deaths (1). At present, complete surgical resection offers the best chance of cure. However, because of the invasion of major vessels, at initial diagnosis, 50% of patients present with metastatic disease, 30% present with a locally advanced tumor, and only 20% are potentially resectable. The prognosis for locally advanced pancreatic cancer (LAPC) lies between those for metastatic and resected disease, which is approximately 9 to 13 months in modern trials (2-5).

Combined therapy for LAPC continues to evolve with goals of radiotherapy in LAPC including improvement in local control and palliation of pain and/or obstructive symptoms. Survival in trials of chemoradiotherapy (CRT) versus chemotherapy alone in LAPC have reported mixed findings (2,3,5-7). This points to the idea that the benefit of CRT for LAPC is likely confined to a carefully selected group of patients. The dose distribution patterns achievable with proton therapy could potentially offer important clinical advantages relative to those achievable with photons in this population of patients. This is due to the Bragg peak of proton beam therapy which could allow reduced dose to nearby normal tissues. Several dosimetric and phase I studies have shown that it is effective and feasible in treating pancreatic cancer regardless of the degree of tumor size, and presence or absence of combined therapies (8-11).

The epidermal growth factor receptor (EGFR) is a cell surface receptor for epidermal growth factor and transforming growth factor-alpha, which is overexpressed by a number of human tumors. In particular, EGFR is overexpressed in pancreatic cancer and plays a potentially important role in modulation of tumor sensitivity to chemotherapy or radiotherapy (12). Erlotinib is a receptor tyrosine kinase inhibitor with specificity for EGFR. The FDA approved Erlotinib in combination with gemcitabine for the treatment of patients with locally advanced, unresectable, or metastatic pancreatic carcinoma in 2005. This approval was based on the study by Moore *et al.* illustrating a 1-year survival and median survival benefit of gemcitabine and erlotinib versus gemcitabine and placebo for patients with locally advanced or metastatic pancreatic cancer (13). The CAPOX regimen utilized in this trial has been proven to be active in gemcitabine-pretreated patients with advanced pancreatic cancer (14).

The primary objective of this study was to determine the 1-year overall survival (OS) of a regimen utilizing erlotinib and proton therapy for patients with LAPC. The secondary objectives included: evaluate the local control (LC) and progression-free survival (PFS) rates, evaluate the frequency of serious adverse events, determine the predictive value of CA 19-9 for prognosis, and to evaluate quality of life and clinical benefit response. We present the following article in accordance with the TREND reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-327/rc).

## Methods

### *Patient selection*

Patients were enrolled with pathologically confirmed unresectable or borderline resectable non-metastatic adenocarcinoma of the pancreas as defined by the 2012 NCCN guidelines. Radiological resectability was defined by the following criteria on abdominal imaging: no evidence of tumor extension to the celiac axis, hepatic artery or superior mesenteric artery; no evidence of tumor encasement or occlusion of the superior mesenteric vein (SMV) or the SMV/portal vein confluence; and no evidence of visceral or peritoneal metastases. Unresectable or borderline resectable cases were defined as those that do not meet the above criteria.

Other eligibility criteria for inclusion included Eastern Cooperative Oncology Group (ECOG) performance status of less than or equal to 2 and age greater than or equal to 18. Patients also needed to have adequate hematologic reserve, hepatic reserve, and renal function including: white blood cell (WBC) >2,000 cells/mm$^3$, absolute neutrophil count (ANC) >1,500 cells/mm$^3$, platelets >100,000 cells/mm$^3$, serum bilirubin ≤2.5 mg/dL, serum creatinine ≤2 times the upper limit of normal or creatinine clearance ≥30 mL/min, alanine aminotransferase (ALT) <3 times the upper limit of normal, aspartate aminotransferase (AST) <3 times the upper limit of normal, and albumin >3.2 g/dL. Patients were not eligible if there was evidence of metastatic disease in the major viscera or peritoneal seeding, there was biliary or gastroduodenal obstruction, the patient had prior radiation to the planned field, or the patient had prior chemotherapy. Female participates of child-bearing age were required to have a negative urine or serum pregnancy test prior to registration. Perimenopausal participants had to be amenorrheic for greater than 12 months to be considered not of child-bearing potential. The study was conducted in accordance with the Declaration of Helsinki (as revised

 

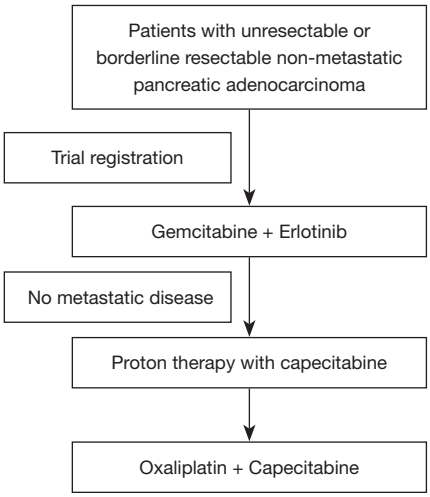


**Figure 1** Trial schema.

in 2013). The study was approved by the institutional ethics board of Loma Linda University (No. 5110324) and all patients signed a study-specific consent form prior to treatment.

### *Study design*

The schema for the study is shown in *Figure 1*. First, patients received gemcitabine plus erlotinib (GE) for 8 weeks prior to ChemoProton therapy (CPT). Gemcitabine was given weekly 1,000 mg/m$^2$ as an intravenous infusion on days 1, 8, 15, 29, 36, and 43. Erlotinib was taken 100 mg by mouth daily on days 1 through 43. Patients that did not develop metastatic disease by computed tomography (CT) continued to CPT, which started 4 to 8 weeks after completion of GE.

CPT consisted of 50.4 Gy in 28 fractions with concurrent capecitabine taken 825 mg/m$^2$ by mouth twice daily on Monday through Friday. The Post-CPT systemic treatment began 4 to 6 weeks after the completion of CPT and consisted of oxaliplatin 130 mg/m$^2$ intravenously on day 1 and capecitabine 1,000 mg/m$^2$ by mouth twice daily on days 2 to 15. The capecitabine and oxaliplatin (CapOx) regimen was repeated every 3 weeks for a total of 4 cycles.

### *Radiotherapy*

All patients were immobilized in a supine position using a cylindrical whole body immobilizer or pod, as previously described (15). A CT scan from T5 to L5/S1 with intravenous and oral contrast was performed. The gross tumor volume (GTV) was defined as the primary tumor and any involved regional lymph nodes. There was no elective nodal irradiation. The clinical target volume (CTV) was defined as the GTV plus a 1 cm margin. The spirometry based motion management system SDX was used for voluntary breath hold to account for motion management in patients that could tolerate it. Each of the two to four passively scattered proton fields was optimized to account for range uncertainty, depth dose, beam modulation, Bragg peak, and energy optimization. Beams were chosen to avoid nearby critical structures. Standard fractionation of 1.8 Gy per day was used to a total dose of 50.4 Gy. Each plan was evaluated to ensure the 90% isodose line was covering the CTV. The critical normal structures that were outlined included: small bowel with duodenum as a distinct volume, spinal cord, liver, and bilateral kidneys.

### *Patient evaluation*

The pretreatment evaluation of all patients included a history and physical examination; CT scan of the chest, abdomen, and pelvis; complete blood count, serum chemistries, liver function tests, amylase and lipase, and CA 19-9; and histologic confirmation of malignancy. Patients were seen on a weekly basis for history, physical examination, vitals, performance status, laboratory values, and adverse events assessment.

### *Toxicity related therapy adjustment*

Acute toxicities were defined according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Late toxicity was scored per RTOG guidelines as was defined as those toxicities occurring 3 months or greater after the completion of treatment. Standard medical supportive care for nausea and vomiting was provided prior to considering dose modification.

### *Statistical analysis and end points*

The median and 1-year PFS and OS rates were measured from the date of study enrollment to the date of death or last follow-up estimated using the Kaplan-Meier method. The NRG/RTOG 98-12 phase II study for LAPC demonstrated a 43% 1-year survival, which was the benchmark for this study (16). This comparison was chosen as NRG/RTOG 98-12 showed promising survival

 

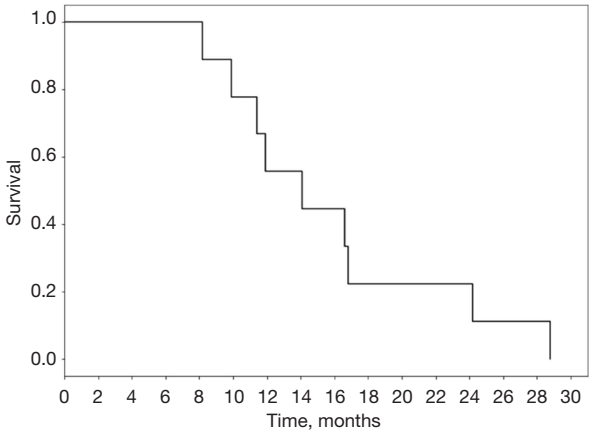


**Figure 2** Survival curve for all 9 patients.

in unresectable pancreatic patients as compared to previous historical studies (17-19). Using the method of Dixon and Simon (20), a goal sample size of 39 analyzable patients followed over 12 months ensured at least 90% probability of detecting a minimum of 17% improvement in the 1-year survival rate compared to NRG/RTOG 98-12 at the 0.10 significance level with a one-sided test. We adjusted this figure by 10% to allow for patient ineligibility or loss with a final sample size goal of 43 patients. The tumor response was determined by comparison of the pre-treatment and post-treatment CT scans and assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines, version 1.1 (21).

## Results

### *Patient characteristics*

A total of 9 patients were enrolled between January 2013 and March 2016 when the trial was closed early due to poor accrual. All patients were evaluable for survival and toxicity. The median age was 62 years (range, 47 to 81 years). All patients had an ECOG of 0-1 and 5 of 9 (55.6%) were female. The median follow-up was 14.1 months.

### *Outcomes*

The median OS was 14.1 months [95% CI, 11.4 months to not reached (NR)] (*Figure 2*) and the median PFS was 10.8 months (95% CI, 7.44 months to NR). The 1-year OS rate was 55.6% (95% CI, 31% to 99%). Four patients were enrolled with borderline resectable disease per 2012 NCCN guidelines, three of which were eligible for pancreaticoduodenectomy. One patient declined surgery, one of two patients who elected to proceed with surgery had a negative margin.

### *Treatment compliance*

The compliance was high in terms of neoadjuvant gemcitabine and erlotinib. All patients received six infusions of gemcitabine and eight of nine patients (88.9%) completed at least five of the six weeks of erlotinib. Two patients had dose reduction in both gemcitabine and erlotinib due to transaminitis. Two patients required filgrastim myeloid growth factor support due delayed neutropenia recovery. In terms of the CPT, all patients received at least 48 Gy dose of radiotherapy. During CPT, seven of nine patients (77.8%) completed the entire course of concurrent capecitabine with one patient stopping after two weeks because of side effects and one patient discontinuing due to noncompliance. Post-CPT CapOx was poorly tolerated as only three of nine patients (33.3%) completed all four cycles with three patients receiving no cycles of CapOx and three of nine (33.3%) receiving two or less cycles of CapOx.

### *Toxicity*

During pre-CPT chemotherapy with gemcitabine and erlotinib all patients had at least grade 1 toxicity. Two patients experienced grade 3 hepatic toxicity. Grade 2 toxicities include two patients with rash, one patient with diarrhea, and one patient with hepatic toxicity. During CPT one patient had a grade 3 hepatic toxicity, one patient had a grade 3 vomiting toxicity requiring hospitalization and discontinuation of capecitabine but there was no other grade 2 or higher toxicities.

For the post-CPT CapOx, three patients declined treatment and three patients requested to stop treatment early due to toxicities. One patient had grade 3 emesis and grade 3 diarrhea but completed all four cycles of CapOx. One patient experienced grade 2 diarrhea. One patient suffered from grade 3 encephalopathy and grade 3 abdominal infection during cycle 1 treatment requiring discontinuation of CapOx and hospitalization twice. There was no grade 4 or grade 5 toxicities.

## Discussion

The role of combined therapy for LAPC continues to

 

evolve. The biology of the disease can become evident over a period of chemotherapy, and this can be used to better select patients who will benefit from CRT. This seems like the most pragmatic way to proceed with LAPC patients until we have a better means of predicting tumor behavior and more active systemic agents. This has led to increased interest in treatment regimens incorporating induction chemotherapy with target agent followed by CRT and additional chemotherapy for diseases that carry a high risk for systemic relapse.

The PA.3 trial was the first phase III trial in advanced pancreatic cancer to show a survival advantage with the addition of a second drug, in this case the oral EGFR inhibitor Erlotinib to gemcitabine. The approval provides an important proof of concept regarding the use of newer targeted therapies in pancreatic cancer. Additionally with personalized genomic testing becoming more widely available, future studies will hopefully be able to determine the best patient groups who may benefit from the addition of targeted therapies (13).

The goals of radiotherapy in LAPC include improvement in local control and palliation of pain. Trials of CRT versus chemotherapy alone in LAPC have reported mixed findings regarding survival (3,5-7,22). In a trial conducted by the Gastrointestinal Tumor Study Group the effect of concurrent CRT versus chemotherapy alone in LAPC was evaluated and a benefit in survival from combined modality therapy was noted. The CRT arm consisted of radiation combined with 5-fluorouracil (5-FU) to a total dose of 54 Gy in 1.8 Gy fractions followed by maintenance streptozotocin, mitomycin and 5-FU (SMF). The chemotherapy-only arm was SMF combination chemotherapy for two years or until progression. In this trial, the one-year OS was 41% in the CRT arm compared to 19% in the chemotherapy alone arm (P<0.02) (7).

Modern chemotherapy and radiation techniques have been tested in multiple phase III trials evaluating the efficacy of CRT. In the trial by the Eastern Cooperative Oncology Group (E4201), patients with LAPC were randomly assigned to CRT (50.4 Gy in 28 fractions) with concurrent gemcitabine followed by 5 cycles of gemcitabine alone versus gemcitabine alone for 7 cycles. This trial showed that CRT was associated with a slightly improved survival (11.1 *vs.* 9.2 months, P=0.017) (3).

In a study by Chauffert *et al.* reported in 2008, CRT was delivered to a total dose of 60 Gy concurrently with cisplatin and 5-fluorouracil *vs.* gemcitabine alone followed by maintenance gemcitabine in both arms. OS in this trial was shorter in the CRT arm (13.0 *vs.* 8.6 months, P=0.044) and these patients experienced a higher rate of grade 3–4 toxicity compared with the chemotherapy arm (66% *vs.* 40% respectively; P=0.0008). A potential explanation for increased toxicity is the combination of aggressive chemotherapy delivered with concurrent radiation (60 Gy followed by high-dose weekly maintenance Gemcitabine). Due to inferior survival in the CRT arm, this study was stopped prior to the planned enrollment (5).

In a study by Hammel *et al.* reported in 2016, LAPC patients were randomized to gemcitabine alone *vs.* gemcitabine plus erlotinib and if tumor was controlled were randomized to chemotherapy *vs.* CRT. CRT was 54 Gy concurrently with capecitabine twice daily on days of radiation therapy. This trial did not show a significant difference in OS with CRT compared with chemotherapy alone, but it did show decreased local progression (32% *vs.* 46% respectively, P=0.03) with CRT. It also failed to show a benefit with the addition of erlotinib in the maintenance setting. This contrasts with the PA.3 trial and this study which used it in the upfront setting, however this still calls into question the ideal patient population and timing for the addition of erlotinib (2).

Alliance A021501 phase II trial enrolled 126 patients with borderline resectable pancreatic adenocarcinoma and randomized them to 8 cycles of 5-FU, leucovorin, irinotecan, and oxaliplatin (modified FOLFIRINOX; mFOLFIRINOX) or 7 cycles of mFOLFIRINOX followed by 5 days of hypofractionated radiation. The primary endpoint was the 18-month OS rate. Patients without disease progression following preoperative treatment received pancreatectomy and 4 cycles of adjuvant chemotherapy with oxaliplatin and 5-FU (FOLFOX). The R0 resection and pathologic complete response rate in patients receiving pancreatectomy was 74% and 11% in the neoadjuvant treatment with mFOLFIRINOX plus hypofractionated radiation therapy arm compared to 88% and 0% in the chemotherapy arm. Patients in chemotherapy arm had an 18-month OS rate of 66.4% *vs.* 47.3% for the group receiving chemotherapy plus hypofractionated radiation therapy. However, the radiation arm had to be closed early due to the lower rate of patients who proceeded to pancreatectomy than seen in other high-volume pancreatic cancer centers (23). In an update of the Dutch randomized PREOPANC phase III trial with longer term follow-up, OS was superior in the neoadjuvant gemcitabine-based CRT arm compared to upfront surgery followed adjuvant gemcitabine arm for both the resectable and the

 

borderline resectable subgroups (24). These studies add to the growing body of opinion that the benefit of neoadjuvant CRT for LAPC is likely confined to a carefully selected group of patients who did not develop early metastatic disease; this proportion of patients will continue to increase as systemic therapies improve.

With combined modality therapy in LAPC, toxicity does limit the ability of most patients tolerating the full treatment paradigm. Proton beam therapy may result in lower toxicity, enhanced efficacy and could contribute to improved local control of patients with LAPC.

The current study demonstrated the safety and tolerability of concurrent chemoradiation therapy with proton beam radiation therapy. During CPT one patient had a grade 3 hepatic toxicity, but there was no other grade 2 or higher toxicities. In the SCALOP trial which examined gemcitabine *vs.* capecitabine chemoradiotherapy (CRT) for LAPC patients, grade 3 or 4 toxicity was 12% which is similar to the 11% in this study. At least 27 of the planned 28 fractions of radiation was given to all the patients which is improved as compared to SCALOP although with low patient numbers it is difficult to compare. Adjuvant CapOx was not as well tolerated in this study with only one third of patients tolerating the regimen which is why there is also a rationale to moving more of the systemic therapy into the neoadjuvant setting (25).

The limitations of this study include the small patient numbers as the trial was closed early due to slow patient accrual. Even with this limitation, it does show that this regimen was well tolerated with an encouraging one-year survival in appropriately selected patients. This trial also combined both unresectable and borderline resectable patients which could potentially complicate the interpretation of the results. Future studies should aim to divide this heterogeneous group to help determine which patient group would be best fit for a particular treatment paradigm.

In conclusion, this regimen for LAPC was safe and well tolerated. Additional investigations utilizing more current systemic treatment regimens with proton therapy are warranted.

## Acknowledgments

Abstract was presented as a poster during ASTRO 2020 and at ISGIO in 2019.

*Funding:* This research was sponsored by the Del E Webb Endowed Chair.

## Footnote

*Reporting Checklist:* The authors have completed the TREND reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-327/rc

*Data Sharing Statement:* Available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-327/dss

*Peer Review File:* Available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-327/prf

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-327/coif). GY serves as the Editor-in-Chief of *Journal of Gastrointestinal Oncology*. CG, CTH and JS serve as unpaid editorial board members of *Journal of Gastrointestinal Oncology* from January 2021 to December 2022. The other authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics board of Loma Linda University (No. 5110324) and informed consent was taken from all individual participants.



## References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020;70:7-30.
2. Hammel P, Huguet F, van Laethem JL, et al. Effect of Chemoradiotherapy vs Chemotherapy on Survival in Patients With Locally Advanced Pancreatic Cancer

Controlled After 4 Months of Gemcitabine With or Without Erlotinib: The LAP07 Randomized Clinical Trial. JAMA 2016;315:1844-53.
3. Loehrer PJ Sr, Feng Y, Cardenes H, et al. Gemcitabine alone versus gemcitabine plus radiotherapy in patients with locally advanced pancreatic cancer: an Eastern Cooperative Oncology Group trial. J Clin Oncol 2011;29:4105-12.
4. Crane CH, Winter K, Regine WF, et al. Phase II study of bevacizumab with concurrent capecitabine and radiation followed by maintenance gemcitabine and bevacizumab for locally advanced pancreatic cancer: Radiation Therapy Oncology Group RTOG 0411. J Clin Oncol 2009;27:4096-102.
5. Chauffert B, Mornex F, Bonnetain F, et al. Phase III trial comparing intensive induction chemoradiotherapy (60 Gy, infusional 5-FU and intermittent cisplatin) followed by maintenance gemcitabine with gemcitabine alone for locally advanced unresectable pancreatic cancer. Definitive results of the 2000-01 FFCD/SFRO study. Ann Oncol 2008;19:1592-9.
6. Klaassen DJ, MacIntyre JM, Catton GE, et al. Treatment of locally unresectable cancer of the stomach and pancreas: a randomized comparison of 5-fluorouracil alone with radiation plus concurrent and maintenance 5-fluorouracil--an Eastern Cooperative Oncology Group study. J Clin Oncol 1985;3:373-8.
7. Treatment of locally unresectable carcinoma of the pancreas: comparison of combined-modality therapy (chemotherapy plus radiotherapy) to chemotherapy alone. Gastrointestinal Tumor Study Group. J Natl Cancer Inst 1988;80:751-5.
8. Zurlo A, Lomax A, Hoess A, et al. The role of proton therapy in the treatment of large irradiation volumes: a comparative planning study of pancreatic and biliary tumors. Int J Radiat Oncol Biol Phys 2000;48:277-88.
9. Kozak KR, Kachnic LA, Adams J, et al. Dosimetric feasibility of hypofractionated proton radiotherapy for neoadjuvant pancreatic cancer treatment. Int J Radiat Oncol Biol Phys 2007;68:1557-66.
10. Bouchard M, Amos RA, Briere TM, et al. Dose escalation with proton or photon radiation treatment for pancreatic cancer. Radiother Oncol 2009;92:238-43.
11. Hong TS, Ryan DP, Blaszkowsky LS, et al. Phase I study of preoperative short-course chemoradiation with proton beam therapy and capecitabine for resectable pancreatic ductal adenocarcinoma of the head. Int J Radiat Oncol Biol Phys 2011;79:151-7.
12. Ng SS, Tsao MS, Nicklee T, et al. Effects of the epidermal growth factor receptor inhibitor OSI-774, Tarceva, on downstream signaling pathways and apoptosis in human pancreatic adenocarcinoma. Mol Cancer Ther 2002;1:777-83.
13. Moore MJ, Goldstein D, Hamm J, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 2007;25:1960-6.
14. Xiong HQ, Varadhachary GR, Blais JC, et al. Phase 2 trial of oxaliplatin plus capecitabine (XELOX) as second-line therapy for patients with advanced pancreatic cancer. Cancer 2008;113:2046-52.
15. Wroe AJ, Bush DA, Schulte RW, et al. Clinical immobilization techniques for proton therapy. Technol Cancer Res Treat 2015;14:71-9.
16. Rich T, Harris J, Abrams R, et al. Phase II study of external irradiation and weekly paclitaxel for nonmetastatic, unresectable pancreatic cancer: RTOG-98-12. Am J Clin Oncol 2004;27:51-6.
17. Moertel CG, Childs DS Jr, Reitemeier RJ, et al. Combined 5-fluorouracil and supervoltage radiation therapy of locally unresectable gastrointestinal cancer. Lancet 1969;2:865-7.
18. Moertel CG, Frytak S, Hahn RG, et al. Therapy of locally unresectable pancreatic carcinoma: a randomized comparison of high dose (6000 rads) radiation alone, moderate dose radiation (4000 rads + 5-fluorouracil), and high dose radiation + 5-fluorouracil: The Gastrointestinal Tumor Study Group. Cancer 1981;48:1705-10.
19. Radiation therapy combined with Adriamycin or 5-fluorouracil for the treatment of locally unresectable pancreatic carcinoma. Gastrointestinal Tumor Study Group. Cancer 1985;56:2563-8.
20. Dixon DO, Simon R. Sample size considerations for studies comparing survival curves using historical controls. J Clin Epidemiol 1988;41:1209-13.
21. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-47.
22. Hazel JJ, Thirlwell MP, Huggins M, et al. Multi-drug chemotherapy with and without radiation for carcinoma of the stomach and pancreas: a prospective randomized trial. J Can Assoc Radiol 1981;32:164-5.
23. Katz MHG, Shi Q, Meyers JP, et al. Alliance A021501: Preoperative mFOLFIRINOX or mFOLFIRINOX plus hypofractionated radiation therapy (RT) for borderline resectable (BR) adenocarcinoma of the pancreas. J Clin Oncol 2021;39:377.

 

24. Chen Y, Sun XJ, Jiang TH, et al. Combined radiochemotherapy in patients with locally advanced pancreatic cancer: a meta-analysis. World J Gastroenterol 2013;19:7461-71.

25. Mukherjee S, Hurt CN, Bridgewater J, et al. Gemcitabine-based or capecitabine-based chemoradiotherapy for locally advanced pancreatic cancer (SCALOP): a multicentre, randomised, phase 2 trial. Lancet Oncol 2013;14:317-26.

**Cite this article as:** Sanghvi SM, Coffman AR, Hsueh CT, Kang J, Park A, Solomon NL, Garberoglio CA, Reeves ME, Slater JD, Yang GY. A phase II trial of gemcitabine and erlotinib followed by ChemoProton therapy plus capecitabine and oxaliplatin for locally advanced pancreatic cancer. J Gastrointest Oncol 2022;13(4):1989-1996. doi: 10.21037/jgo-22-327

 