ORIGINAL ARTICLE

Does Erlotinib Restore Chemosensitivity to Chemotherapy in Pancreatic Cancer? A Retrospective Analysis

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ABSTRACT

Background Erlotinib, an Epidermal Growth Factor Receptor (EGFR) inhibitor, in combination with gemcitabine was approved in 2005 as 1st-line therapy for patients with Advanced Pancreatic Cancer (APC). In the second line setting, erlotinib as monotherapy and in combination regimens was evaluated in small studies with limited benefit. We previously published a case series documenting a potential benefit of adding erlotinib to chemotherapy at the time of Progression of Disease (PoD) in patients with APC. **Patients and Methods** Here, we update our cohort of patients to a total of 27 diagnosed with APC who received erlotinib upon PoD to prior chemotherapy regimens. Final analysis of this cohort showed a PFS of 4.0 months (range: 2 - 11) with median OS of 10.1 months (range: 7 - 16). CA19-9 levels declined by greater than 50% in 23% of the patients, by 25 - 49% in 19% of the patients, and stable in 26% of the patients. Radiological response included partial response in one patient, and stable disease in 17 patients. Toxicities were manageable, including grade 1-2 rash in 44.4% of patients. Other less common adverse effects were diarrhea (33.3%), anorexia (25.9%), hypomagnesemia (22.2%). **Conclusion** Our study showed that the addition of erlotinib to prior chemotherapy regimens at PoD provided meaningful disease control with improved PFS. The results confer with the preclinical and clinical findings that the addition of erlotinib may circumvent chemoresistance in chemotherapy-refractory tumors. These findings are like those seen in colorectal cancer following administration of cetuximab in irinotecan-failure patients and warrant prospective studies.

INTRODUCTION

Pancreatic cancer is an inherently chemoresistant tumor. Erlotinib, an epidermal growth factor receptor (EGFR) inhibitor, in combination with gemcitabine was approved in 2005 as 1st-line therapy for patients with advanced pancreatic cancer (APC). A phase III National Cancer Institute of Canada Clinical Trials Group study showed a statistically significant survival benefit of the combination of gemcitabine with the epidermal growth factor receptor (EGFR) inhibitor erlotinib compared with gemcitabine alone [1]. The combined treatment arm demonstrated an 18% reduction in the risk of death or an overall 22% improvement in survival than the gemcitabine alone arm and it was statistically superior in 1-year survival (23.8% *vs* 19.4%, respectively; p=0.028) and in median survival (6.4 *vs* 6.0 months, respectively) [1]. Based on these data, the Food and Drug Administration (F.D.A.) of the U.S.A. granted approval for erlotinib to be administered in combination with gemcitabine for the treatment of advanced pancreatic cancer. In the second line setting, erlotinib as monotherapy and in combination regimens was evaluated in small studies with limited benefit [2, 3, 4]. Encouraged by these studies, others have investigated potential role of erlotinib in earlier stages and different combinations as well [5, 6, 7].

The most common side-effect in patients receiving erlotinib is skin rash, as discussed below, and diarrhea [1, 2, 3, 4, 5, 6, 7, 8]. Other reported side effects include interstitial lung disease, especially following therapy with gemcitabine and erlotinib, possibly due to drug interaction. Skin rash is the most common side-effect of erlotinib administration in metastatic pancreatic cancer patients sometimes leading to the discontinuation of this potentially beneficial treatment. Furthermore, treatment of this group of patients is mainly palliative and preservation of the quality of life should be the main priority of the treating physician. Skin rash often significantly hampers the quality of life and, therefore, needs insistent management [8].

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Erlotinib is a highly specific HER1/EGFR Tyrosine Kinase Inhibitor (TKI) [9]. It inhibits ATP binding to HER1/EGFR tyrosine kinase in normal and tumor cells. Several human malignancies are associated with aberrant EGFR expression. The latter has been related to chemoresistance and poor prognosis [10]. Tyrosine kinase HER1/EGFR is a potential target for therapeutic intervention in ovarian, head, neck, lung, breast, bladder, and other squamous cell carcinomas. In preclinical models, the combination of an EGFR TKI and gemcitabine resulted in enhanced cytotoxicity of gemcitabine and induced apoptosis in tumor cells [11, 12, 13, 14, 15]. The mechanisms of the synergy between EGFR TKIs and gemcitabine are not fully elucidated. The cytotoxicity of gemcitabine may be enhanced by an EGFR TKI through the inhibition of the phosphorylation of EGFR.

Preclinical studies have shown synergism between erlotinib and antifolates as well as gemcitabine in solid tumors, even in presence of KRAS mutation [6, 12, 15]. The effectiveness of the combination of irinotecan and cetuximab in patients with irinotecan-refractory colon cancer tumors suggests that cetuximab may circumvent irinotecan resistance [16]. Three hundred and twenty-nine patients with colorectal cancer whose disease had progressed during or within three months after treatment with an irinotecan-based regimen were randomized to receive both cetuximab and irinotecan or cetuximab monotherapy. In cases of disease progression, the addition of irinotecan to cetuximab monotherapy was permitted. The rate of response in the combination-therapy group was significantly higher than that in the monotherapy group (22.9% *vs* 10.8%, respectively; p=0.007). The median time to progression was significantly greater in the combination-therapy group (4.1 *vs* 1.5 months, respectively; p<0.001).

Based on these data and the extensive experience of this research group in patients with APC this report describes cases showing that the is akin to cetuximab, another anti-EGFR inhibitor that showed synergy with chemotherapeutic agents in colorectal cancer patients who are no longer responsive to chemotherapy alone suggesting a mechanism of overcoming chemoresistance. We previously published a case series documenting a potential benefit of adding erlotinib to chemotherapy at the time of progression of disease (PoD) in patients with APC and in this retrospective study, we analyzed additional cases with refractory APC to analyze the efficacy of adding erlotinib to chemotherapy at the time of progression of disease (PoD) [16, 17].

PATIENTS AND METHODS

A retrospective chart review was conducted of 27 patients with APC who received erlotinib upon PoD to prior chemotherapy regimens which include combinations of gemcitabine, nab-paclitaxel, oxaliplatin, cisplatin, capecitabine, 5 fluorouracil (5-FU), and irinotecan. **Table 1** shows few examples. The side effects of the combination treatment were closely monitored and the dosage of erlotinib and additional agent were modified when the side effects reached severe as per general guidelines for both agents, including management of rash and HFS.

Imaging was performed every four cycles (8-9 weeks), and serum CA19-9 was measured every 3-4 weeks. Response to treatment was assessed using Response Evaluation Criteria in Solid Tumors (RECIST) parameters. The best response seen at either 8 weeks or 16 weeks was considered. CA19-9 response was defined as drop of at least 25% from baseline at the time of start of CAP-ERL. Toxicity was graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. Progression-free survival was defined as time from initiation of treatment until disease progression or death. OS was defined as time from initiation of treatment until death or last known follow up.

RESULTS

All the patients had advanced stage (median age: 64 years [range: 46 – 78]; male:female = 15:12; median ECOG PS of 1 [range: 0-2]. Majority had liver metastases (58%), lungs (34%), peritoneal (7%), distant lymph nodes (1%). Since the population studied in this study was treated before the general utilization of NGS, genetic data was available only on limited patients: 3 with KRAS wild and 5 with mutant KRAS mutant, BRCA1/2 negative in 3 patients, and 1 MSS.

Erlotinib at an initial dose of 100 mg/day was added to different agents, including gemcitabine (12), capecitabine (12), irinotecan (2) and docetaxel (1) at PoD in patients with APC (**Table 1**). Erlotinib was escalated to 150 mg in 7 patients due to a rise in CA19-9 or lack of rash after initiating 100mg dose.

Table 1. Chemotherapy regimens in few patients included in the study.

First-line	Second-line	Third-line	Fourth-line
GTX	Irinotecan	Irinotecan + Cetuximab	
Gemcitabine with S-1	Irinotecan	Irinotecan + Erlotinib	
Gemcitabine and Oxaliplatin	Gemcitabine-erlotinib		
Gem-capecitabine	Gem-erlotinib		
Gem-Ox	gemcitabine-capecitabine	Docetaxel	Erlotinib + Docetaxel
Gemcitabine	FOLFOX-6, Gem-Ox, Irinotecan and Capecitabine	Capecitabine + Erlotinib	

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PFS was 4.0 months (range: 2 - 11) with median OS of 10.1 months (range: 7 - 16). CA19-9 levels declined by greater than 50% in 23% of the patients, by 25 - 49% in 19% of the patients, and stable in 26% of the patients. Radiological response included partial response in one patient, and stable disease in 17 patients.

Toxicities were manageable. Grade 1-2 rash was the most common adverse effect seen in 44.4% of patients. Other less common adverse effects were diarrhea (33.3%), anorexia (25.9%), hypomagnesemia (22.2%). Majority of the adverse effects were grade 1-2. No grade 4 adverse events occurred.

DISCUSSION

Our study showed that the addition of erlotinib to prior chemotherapy regimens at PoD provided meaningful disease control with improved PFS. The results confer with the preclinical and clinical findings that the addition of erlotinib may circumvent chemoresistance in chemotherapy-refractory tumors. As a survival response to chemotherapy, pancreatic cancer cells have been shown to increase EGFR phosphorylation which leads to downstream effects of increase cell proliferation, invasion, angiogenesis and decrease apoptosis [18]. Erlotinib inhibits this process, thereby restoring the cytotoxic apoptosis of cancer cells by chemotherapy [12, 14, 15]. Erlotinib has also been shown to induce upregulation of thymidine phosphorylase, and reduce thymidylate synthase expression, which potentiate the therapeutic effect of capecitabine and 5-FU.

When drugs are used in this setting, their clinical benefit should be considered more important than their anti-tumor activity. The data of the present study incite new hypothesis to explore the role of erlotinib in the second-line therapy after failing gemcitabine. Now that gemcitabine is commonly used in the adjuvant setting also, this topic becomes more important. Increased understanding of the EGFR pathway may permit the use of other targeted agents to either augment therapeutic efficacy or circumvent resistance. It is warranted to develop strategies to truly target therapy with the EGFR agents by identifying those patients who are most likely to derive benefit and achieve meaningful responses.

CONCLUSION

Larger studies are required to study the role of erlotinib akin to cetuximab in colorectal cancer overcoming irinotecan resistance.

CONFLICT OF INTEREST

None

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