Does Erlotinib Restore Chemosensitivity to Chemotherapy in Pancreatic Cancer? A Case Series

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Abstract. *Erlotinib (Tarceva) in combination with gemcitabine is indicated for first-line treatment of patients with locally advanced, unresectable or metastatic pancreatic cancer. In preclinical models, exposure of pancreatic cancer cell lines to an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor plus gemcitabine suggested enhanced cytotoxicity of gemcitabine and induced apoptosis in tumor cells. Erlotinib inhibited gemcitabine-induced phosphorylation of EGFR, which may promote cytotoxicity from gemcitabine. The effectiveness of the combination of irinotecan and cetuximab in patients with irinotecan-refractory colon cancer tumors suggests that cetuximab may circumvent irinotecan resistance. This report describes the author's experience with the use of erlotinib in patients with pancreatic cancer and discusses the possible role of erlotinib in restoring chemosensitivity in pancreatic cancer.*

With approximately 37,680 new cases and 34,290 deaths, pancreatic adenocarcinoma represents the fourth leading cause of cancer-related deaths in the U.S.A. (1). At the time of diagnosis 80% of patients present with locally advanced, unresectable or metastatic disease, representing a significant therapeutic dilemma (2). Surgery is the only curative treatment for pancreatic cancer, but even then, long-term survival is less than 20%, suggesting the need of adjuvant treatment (chemotherapy or/and radiotherapy). Gemcitabine, a nucleoside analogue, has demonstrated modest benefit in overall survival and symptom control (3), while the addition of a second cytotoxic agent (namely 5-FU, cisplatin or oxaliplatin) has demonstrated a significant advantage in terms of response rates and progression-free survival, but does not yield a significant overall survival advantage (2). 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 (4). 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) (4). 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.

Erlotinib is a highly specific HER1/EGFR tyrosine kinase inhibitor (TKI) (5). 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 (5). Tyrosine kinase HER1/EGFR is a potential target for therapeutic intervention in ovarian, head, neck, lung, breast, bladder and other squamous cell carcinomas (5-7).

In preclinical models, the combination of an EGFR TKI and gemcitabine resulted in: enhanced cytotoxicity of gemcitabine and induced apoptosis in tumor cells (8, 9). 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 (10).

The most common side-effect in patients receiving erlotinib is skin rash, as discussed below, and diarrhea. Other reported side effects include interstitial lung disease (11, 12), especially following therapy with gemcitabine and erlotinib, possibly due to drug interaction (13). 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 particular group of patients is

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mainly palliative and preservation of the quality of life should be the main priority of the treating physician. Skin rash often hampers significantly the quality of life and, therefore, needs insistent management.

Case Series

The effectiveness of the combination of irinotecan and cetuximab in patients with irinotecan-refractory colon cancer tumors suggests that cetuximab may circumvent irinotecan resistance (14). 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 colorectal cancer, this report describes cases showing that the use of erlotinib may have a potential role in restoring chemosensitivity in pancreatic cancer.

Case 1: irinotecan → cetuximab + irinotecan.
The male patient presented at the age of 71 years with a dual diagnosis of prostate carcinoma and pancreatic carcinoma on the background of a significant family history of cancer. Initially, he received 22 cycles of GTX (docetaxel, capecitabine and gemcitabine) followed by single-agent irinotecan every three weeks for 27 cycles and then, weekly cetuximab was added to the regimen at cycle 28. His disease remained stable for an additional 13 months on the combination of cetuximab and irinotecan. He did not have mutated KRAS (15).

Case 2: irinotecan → erlotinib + irinotecan.
A 56-year-old Caucasian male patient with stage IV pancreatic cancer with liver metastasis initially received gemcitabine with S-1 on a clinical study. Upon progression he was switched to irinotecan 180 mg/m^2 q 14 days. His computed tomography (CT) scan showed progression with new liver lesions after four months of therapy with irinotecan. At that time, erlotinib was added. The patient enjoyed stable disease on the combination of irinotecan with erlotinib for an additional four months. The patient had wild-type KRAS.

Case 3: Gem-Ox → Gem-erlotinib.
A 63-year-old Caucasian male with locally advanced pancreatic cancer received Gem-Ox (gemcitabine and oxaliplatin) and remained stable on CT scan for four months. Unfortunately, he later developed ascites and the cytology was positive for malignancy. He was switched to gemcitabine-erlotinib at that time, as the patient refused infusional 5-FU and capecitabine was denied by his health insurance. Interestingly, he achieved stable disease on the combination Gem-erlotinib for nearly five months. The patient developed grade-2 rash. The KRAS status was not known due to lack of tissue.

Case 4: Gem-capecitabine → Gem-erlotinib.
A 69-year-old male with pancreatic tail adenocarcinoma and involving the splenic hilum and peritoneal implants involving the greater omentum received gemcitabine/cisplatin for two cycles. He developed progressive disease and therapy was switched to gemcitabine-erlotinib. A CT scan after two months showed stable disease. He remained on this combination for a total of six months. He developed grade-2 rash. The KRAS status was not known.

Case 5: taxotere → erlotinib + taxotere.
A 55-year-old Caucasian female with pancreatic head mass underwent Whipple surgery and was staged as T1N1 with 3/13 lymph nodes positive. Both perineural and lymphovascular invasion were identified and the lesion was felt to be infiltrative and in close proximity to the retroperitoneal margin. As an adjuvant therapy, the patient received Gem-Ox but developed sensory neuropathy. Therefore, the regimen was switched over to gemcitabine-capecitabine. The patient finished a total of 12 cycles with no further severe side effects to the chemotherapy. One year after diagnosis, her CA 19-9 was increasing, and a magnetic resonance imaging scan confirmed several enhancing lesions along the surface of the liver, as well as in the peritoneum, with the largest in Morrison's pouch, measuring 2 cm. Initially, the patient declined chemotherapy but later agreed to a minimal chemotherapy as per her concerns for quality of life and the palliative nature of the treatment. She was restarted on chemotherapy with single-agent docetaxel at 25 mg/m^2. Two months later, the patient had a CT scan which showed disease progression. She was started on erlotinib in addition to docetaxel. She achieved stable disease for four months along with stable CA 19-9. The KRAS status was not known.

Case 6: capecitabine → capecitabine + erlotinib.
A 62-year-old female with pancreatic cancer s/p resection and adjuvant gemcitabine developed recurrence in the pancreatic bed and peritoneal disease. She then was administered FOLFOX-6, Gem-Ox, irinotecan and capecitabine. The recent CT scan showed progressive disease and her treatment was switched to xeloda-erlotinib. She remains on the therapy beyond two months with stable disease and is tolerating the treatment well. The KRAS is wild-type.

Discussion

This report described the cases of six patients of pancreatic cancer who were able to achieve stable disease after the addition of EGFR inhibitors, erlotinib in five patients and cetuximab in one patient, after failing chemotherapy. This data is akin to the prior data in colorectal cancer which showed that the combination of irinotecan and cetuximab in patients with irinotecan-refractory tumors may circumvent irinotecan resistance (14).

Burris *et al*. performed a multi-centered randomized, phase III clinical trial that compared 5-FU to gemcitabine (3). Treatment with gemcitabine resulted in a relative improvement of 36% in median overall survival compared to 5-FU (5.7 *vs*. 4.2 months, respectively) and 1-year survival rates (18% *vs*. 2%, respectively). In addition to the survival benefit, gemcitabine was also superior to 5-FU in producing clinical benefit response (24% *vs*. 5%, respectively). This study led to the approval of gemcitabine as a first-line chemotherapy agent. Unfortunately, almost all patients fail gemcitabine treatment. Moreover, no second-line therapy exists for gemcitabine-refractory pancreatic cancer patients. Therefore, the present case series may incite new interest in exploring the role of EGFR inhibitors, especially erlotinib, in this setting. This issue is also important as the benefit of erlotinib in the study by Moore *et al*. was marginal (4).

Preclinical data suggest a similar role of EGFR inhibitors. Naruse *et al*. (16) evaluated the cellular mechanisms of ZD1839 action against human malignant cells and drug-resistant cells *in vitro*. Among the cell lines tested, ZD1839 showed a strong growth-inhibitory effect *in vitro* on human leukemic cells resistant to phorbol ester (K562/TPA). These results suggest that ZD1839 is highly active against tumor cells with non-P-glycoprotein-mediated multidrug resistance that express EGFR. Sclabas *et al*. (17) investigated the effects of inhibition of the EGFR signaling pathway with the anti-EGFR monoclonal antibody IMC-C225 (cetuximab) on constitutive NF-kappaB activation and regulation of apoptosis-related genes in human pancreatic cancer cells. They found that activation of EGFR can be blocked with the anti-EGFR antibody IMC-C225 in the human pancreatic cancer cell line MDA Panc-28, leading to a marked decrease in constitutive NF-kappaB DNA binding activity. Their data also suggested that down-regulation of NF-kappaB DNA binding activity by IMC-C225 leads to a decrease in bcl-xl and bfl-1 expression. Therefore, targeting the NF-kappaB signaling pathway with an anti-EGFR antibody may be one strategy to restore apoptosis in human pancreatic cancer cells, thereby enhancing the effect of chemotherapy and radiation therapy. Another study by Bandyopadhyay *et al*. (18) reported that anti-EGFR monoclonal antibodies (mAbs), and not EGFR ligands, trigger a specific early physical interaction between EGFR and a 350-kDa catalytic subunit of DNA or its regulatory heterodimeric complex Ku70/80 in a variety of cell types, both *in vivo* and *in vitro*. Inhibition of EGFR signaling by anti-EGFR mAb was accompanied by a reduction in the levels of the DNA-PK and its activity in the nuclear fraction. These findings demonstrate the existence of a cellular pathway in mammalian cells that involves physical interactions between EGFR and DNA-PK or Ku70/80 in response to inhibition of EGFR signaling.

Although, the limitations of any conclusions to be drawn from a case series are fully acknowledged, this report may generate new interest and hypothesis-driven studies to further explore the role of erlotinib in pancreatic cancers.

Treatment options for pancreatic cancer in advanced or metastatic settings remain limited. Gemcitabine and erlotinib are the only F.D.A.-approved drugs for use in these patients as first-line therapy. Unlike the first-line setting, there is no standard of care after gemcitabine failure. The use of second-line chemotherapy *vs*. best supportive care was established with the CONKO-003 trial, where patients were assigned to best supportive care with or without OFF chemotherapy (oxaliplatin, 5-FU, leucovorin) (19). Patients on chemotherapy had a longer median overall survival than those with the best supportive care. The addition of oxaliplatin to infusional 5-FU and leucovorin has also been shown to result in an improved overall survival of 26 weeks *vs*. 13 weeks when compared with 5-FU and leucovorin alone (20). The combination of gemcitabine and oxaliplatin has demonstrated efficacy as a second-line therapy in gemcitabine-refractory patients (21, 22). A clinical benefit has also been seen with the use of irinotecan and oxaliplatin in patients previously treated with gemcitabine (23, 24). XELOX, the combination of capecitabine and oxaliplatin, has also been used as second-line therapy after gemcitabine failure (25). Single-agent paclitaxel has also shown to be an effective second-line chemotherapy agent with a low toxicity profile (26).

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.

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