HIGHLIGHT ARTICLE

Novel Agents for the Treatment of Pancreatic Cancer

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Summary

Metastatic pancreatic cancer continues to be a difficult disease to treat because of its aggressive nature, advanced stage at presentation and lack of treatment options. There is a need for the development of new agents directed against novel targets to improve outcomes for these patients. At the 2014 American Society of Clinical Oncology (ASCO) Gastrointestinal Cancers Symposium phase I/II trials provided information on three novel strategies for treating metastatic pancreatic cancer. Immunotherapy in the form of a vaccine (GVAX) followed with an immune stimulator (CRS-207) showed extended survival (Abstract #177). A monoclonal antibody (NEO-102) targeting MUC5AC also showed activity and was well tolerated (Abstract #243). A heat shock protein 90 (HSP90) inhibitor (ganetespib) showed modest effects but was well tolerated making it available for use with conventional chemotherapy (Abstract #297). The details of these presentations will be discussed.

Introduction

There are approximately 45,000 new cases of pancreatic adenocarcinoma diagnosed in the USA annually. Pancreatic cancer is considered incurable, with the expectation that all newly diagnosed cases will succumb to the disease [1]. Gemcitabine is still considered the backbone of treatment for patients with locally advanced or metastatic disease with no new chemotherapeutic agents having been approved for its treatment in recent years. The primary goals of treatment in these patients are improved survival and palliation. Novel agents targeting tumor specific pathways, using immunotherapy or biologic therapy are being developed and investigated as single agents or adjuncts to conventional chemotherapy.

Key words Antibodies, Monoclonal; Heat-Shock Proteins; HSP90 Heat-Shock Proteins; Listeria monocytogenes; mesothelin; Pancreatic Neoplasms; STA 9090; Vaccines

Abbreviations CRS-207: live attenuated double deleted *Listeria monoctogenes* strain; GVAX: granulocyte macrophage colony-stimulating factor gene-transduced tumor vaccine; HSP: heat shock protein; MUC5AC: mucin 5 subtype AC; RECIST: Response Evaluation Criteria in Solid Tumors

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This update will review data presented at the 2014 American Society of Clinical Oncology (ASCO) Gastrointestinal Cancers Symposium. Three abstracts will be reviewed: the first looks at a novel vaccine, granulocyte macrophage colony-stimulating factor gene-transduced tumor vaccine (GVAX) and live attenuated double deleted *Listeria monoctogenes* strain (CRS)-207, used to stimulate a broad antigenic response; the second looks at a monoclonal antibody (NEO-102) developed against mucin 5 subtype AC (MUC5AC) and the third explores the anti-heat shock protein (HSP) ganetespib.

Clinical Data

A Phase 2, Randomized Trial of GVAX Pancreas and CRS-207 Immunotherapy Versus GVAX Alone in Patients with Metastatic Pancreatic Adeno-carcinoma: Updated Results (Abstract #177 [2]).

Cellular mediated immunity relies on T lymphocytes to eradicate cells exhibiting aberrant differentiation, such as neoplastic cells or cells with foreign antigens such as bacteria or transplanted cells. Humoral immunity relies on both B and T lymphocytes, as well as dendritic cells and other antigen presenting cells, for the formation of antigen-specific antibodies. One approach to combat malignant cells is to stimulate the native immune system to a state of heightened activity. Immuno-

therapy is a promising adjunct to traditional chemotherapy.

Dung *et al*. introduced allogenic pancreatic cell lines (GVAX) and/or live-attenuated *Listeria monocytogenes* (CRS-207) in an effort to stimulate both the innate and adaptive immune responses [2]. Cyclophosphamide is given to inhibit T cell targeting of the allogenic pancreatic cells. This gives the humoral immune system access to pancreatic antigens which help generate a B cell mediated immune response. In this study, 90 patients with metastatic pancreatic cancer were randomized to two arms. In arm A patients received two doses of allogenic pancreatic cell lines with cyclophosphamide followed by four doses of live-attenuated *Listeria monocytogenes*. Arm B received six doses of allogenic pancreatic cell lines and cyclophosphamide only. The primary endpoint was overall survival between the arms with secondary endpoints of safety, clinical and immune responses.

Median overall survival was 6.1 months in the patients who received combined therapy (arm A; both GVAX and CRS-207). Patients who received monotherapy (arm B; GVAX) had a median survival of 3.9 months (P=0.01). There was also a dose dependent increase in survival in both arms by receiving 3 or more doses of therapy. Patients receiving 3 or more doses of combined therapy had a median survival of 9.7 months and patients receiving 3 or more doses of pancreatic cell lines alone had a survival of 4.6 months. CA 19-9 stabilization was not statistically significant between groups. Toxicities included local reactions after GVAX and transient fevers, rigors and lymphopenia after CRS-207.

In conclusion, patients with previously treated stage IV pancreatic cancer showed improved survival with combined therapy of allogeneic pancreatic cell lines and live-attenuated *Listeria monocytogenes*.

A Phase Ib/IIa Study of NEO-102: A Therapeutic Antibody to Treat Pancreatic and Colorectal Cancers (Abstract #243 [3])

Mucins are large extracellular proteins found on many cells. In normal tissues, they function to protect the epithelium by producing gels which hydrate, protect and lubricate the luminal surfaces [4]. The MUC family of mucins includes also transmembrane proteins that are overexpressed in malignancies and may confer a survival advantage to cancer cells. Recent studies have also shown that these proteins may play a crucial role in signal transduction by interacting with signaling pathways leading to alterations in cell growth, proliferation and cell survival. As such these proteins have also been found to be prognostic biomarkers in pancreatic cancer [5].

One such protein identified in pancreatic cancer is MUC5AC. Overexpression of this protein has been associated with shorter survival in patients with adenocarcinoma of the pancreas [5]. *In vitro* studies have shown that MUC5AC is upregulated by the GLI1, a downstream transcription factor in the Hedgehog signaling pathway. This upregulation leads to a disruption in the function of E-cadherin and beta-catenin and may be important in the pancreatic carcinogenesis [6]. Thus MUC5AC presents a therapeutic target for monoclonal antibody. NEO-101 (formerly named NPC-1C) was derived from tumor associated antigens from a colon cancer and has been found to react with MUC5AC related antigens in pancreatic cancer [7]. In a phase I study, NEO-101 was shown in to have activity in patients with refractory pancreatic cancer with 2 patients maintaining stable disease and obtaining an overall survival of greater than 12 months after having progressed on standard therapy. However, this formulation was not well tolerated and was associated with occasional red cell agglutination [8].

Patel *et al*. reported on their phase Ib/IIa, dose escalation study of NEO-102, a glycoengineered reformulation of NEO-101. This monoclonal antibody is directed against MUC5AC and was given to patients with advanced pancreatic or colorectal cancer refractory to standard therapy [3]. The primary objective of the study was to measure efficacy as assessed by pre- and post-CT scans using the Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Secondary objectives were to determine the safety and tolerability of escalating doses, assess pharmacokinetic parameters and assess immune responses to the antibody. Eleven patients have been enrolled in four different dose levels. Of the 11, two had pancreatic cancer. Both of these patients were enrolled on the second dose level (2 mg/kg) and were evaluable: one patient showed stable disease and the other had progressive disease. Grade 1/2 diarrhea, back pain and fatigue have been seen but no dose limiting toxicities have been seen. Median progression free survival in the intent to treat population with pancreatic cancer was 2.2 months. Based on these initial results, a phase II study of NEO-102 given in combination with gemcitabine is on-going in patients with refractory pancreatic cancer.

A Phase II Study of Ganetespib (G) as Second- or Third-Line Therapy for Metastatic Pancreatic Cancer (MPC) (Abstract #297 [9])

Heat shock protein 90 (HSP90) is a chaperone protein that regulates the folding and maturation of other client proteins. There are over 200 protein clients, such as ERBB4, c-MET, EGFR, IGF-1R, and PDGFR-alpha, that HSP90 may interact with making

it an attractive target in oncology. The client proteins that associate with HSP90, may be involved in multiple cancer processes such as apoptosis, growth signals, angiogenesis, metastasis and proliferation [10]. *In vitro* studies have shown that by blocking the action of HSP90, associated client proteins undergo aberrant conformations leading to ubiquitination and degradation of the proteins by proteosomes [11].

The first class of HSP90 inhibitors, including tanespimycin, showed some promise but the drugs were plagued by problems with formulations, drug resistance due to drug efflux and hepatotoxicity [10, 12]. Ganetespib (STA 9090) is a second generation HSP90 inhibitor structurally unrelated to tanespimycin that exhibits greater potency than the first generation agents and superior activity in preclinical studies. Kauh *et al*. reported on phase I data of ganetespib given in combination with docetaxel for patients with advanced solid tumors [13]. They showed that the combination was tolerated with side effects being neutropenia, diarrhea, nausea, fatigue and anemia. Some responses consisting of mainly stable disease were reported in this trial.

This year Thota *et al*. reported on their single arm, phase II trial of ganetespib in patients with refractory metastatic pancreatic cancer [9]. Patients receiving second- or third-line therapy were treated with ganetespib at 175 mg/m^2 i.v. on weekly 3 out of 4 weeks. The primary endpoint was disease control rate at 8 weeks. Secondary endpoints included overall survival, response rate by RECIST criteria, and safety. Seventeen patients were enrolled and 14 received ganetespib. Grade 3 toxicities seen were nausea and vomiting, abdominal pain, fatigue, diarrhea and hyponatremia. No grade 4 toxicities were noted. Disease control rate at 8 weeks was 21% and overall survival was 2.5 months. Early stopping rules for lack of efficacy resulted in the study being halted. Based on the modest effects on disease control and given data suggesting greater efficacy when used with conventional chemotherapy further trials are being considered.

Conclusion

Multiple new agents are being considered for use in the treatment of metastatic pancreatic cancer. Understanding the pathogenesis of pancreatic cancer will help in selecting novel targets for drug molecules. The use of immunotherapy continues to be an attractive strategy in these patients. The combination of a vaccine and immunostimulating agent, cyclophosphamide/GVAX and CRS-207, showed extended survival and minimal toxicities. The monoclonal antibody to MUC5AC, NEO-102, also showed activity as a single agent but may prove more efficacious in combination with gemcitabine. Future trials with this combination are on-going. Finally, the HSP90 inhibitor ganetespib showed modest response but may have greater activity when combined with conventional chemotherapy. Such combinations will be the focus of future trials.

Take Home Message

Novel strategies are being used to try and improve survival rates in patients with metastatic pancreatic cancer. The most promising of these strategies involves manipulation of the immune system through the use of a vaccine and immunostimulatory agents. Cyclophosphamide/GVAX followed by CRS-207 is currently enrolling patients on a phase IIb study. Also the monoclonal antibody against MUC5AC, NEO-102, is being further studied on two trials hoping to improve on its preliminary results (Table 1).

Conflict of interest The authors have no potential conflict of interest

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Table 1. Clinical trials [a].

Trial	Phase	Status
Efficacy of Combination *Listeria*/GVAX Immunotherapy in the Pancreatic Cancer Setting (ECLIPSE: NCT02004262)	Phase IIb	Active, enrolling
Vaccine Therapy with or without Cyclophosphamide in Treating Patients Undergoing Chemotherapy and Radiation Therapy for Stage I or Stage II Pancreatic Cancer That Can Be Removed by Surgery (NCT00727441)	N/A	Active, enrolling
Phase IIa Study of NPC-1C Chimeric Monoclonal Antibody to Treat Pancreatic and Colorectal Cancer (NCT01040000)	Phase IIa	Active, enrolling
NPC-1C with Gemcitabine for Advanced Pancreatic Cancer (NCT01714453)	Phase I/II	Active, not enrolling

[a] http://www.cancer.gov/cancertopics/pdq

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