From Screening to Treatment of Pancreatic Cancer: A Comprehensive

Muhammad Wasif Saif

Northwell Health Cancer Institute, Donald and Barbara Zucker School of Medicine, Feinstein Institute for Medical Research, Lake Success, NY, USA

ABSTRACT

Introduction Pancreatic adenocarcinoma is a devastating malignancy, associated with a grim prognosis, due to its silent presentation and lack of diagnostic tests. In addition, treatment options are limited to few agents, such as 5-FU, irinotecan, oxaliplatin, gemcitabine and nab-paclitaxel. Methods We performed a literature search for relevant published clinical trials, abstracts of trials in progress and ongoing or planned trials for the treatment of APC using Pubmed.com, ClinicalTrials.gov and American Society of Clinical Oncology (ASCO) abstract search as sources. We present an in-depth analysis of the phase I-III clinical trials determining the role and efficacy of different modalities. We also describe rationale for future investigation. Discussion Despite advances in first-line and second-line therapies for APC, median OS remains short of a year. We need collaborative efforts between the cooperative groups, institutions, community practices and industry to work together in enrolling these patients in clinical trials. In addition to use new technologies, such as organoids, we must pay attention to the palliative aspect of care for these patients from the beginning including nutritionist, social worker and supportive care health providers to assist with goals of care, symptom management and end of life discussions.

INTRODUCTION

Pancreatic cancer (PC) carries a poor prognosis and now ranks as the third leading cause of cancer-related deaths in the United States [1]. Unfortunately, due to lack of any diagnostic tools and non-specific symptomatology, majority of the patients are diagnosed with advanced disease with an abysmal 5-year-overall survival (OS) rate of only 7% [1]. Surgery is feasible in approximately 15–20% of the patients, and even if resected the 5-year survival remains only about 10% [2]. Therefore, it is considered the most fatal malignancy of all major cancers. The disease is rare before the age of 45, but the incidence increases intensely thereafter. Incidence and death rates vary by sex and race [3]. The incidence is greater in males than females (male-to-female ratio 1.3:1) and in blacks than in whites (14.8 per 100,000 in black males compared with 8.8 per 100,000 in the general population) [4].

To date, only two chemotherapy combination regimens, namely FOLFIRINOX (folinic acid, 5-fluorouracil, irinotecan, oxaliplatin) and gemcitabine plus nab-paclitaxel (nabPGem) have shown OS benefit in patients with metastatic disease but both regimens are associated with increased toxicity [5, 6]. Patients with APC refractory to first-line therapy have a dismal prognosis and limited therapeutic options, with only one option consisting of nanoliposomalirinotecan in combination with fluorouracil and folinic acid which was approved by FDA based upon results of the phase III NAPOLI-1 study [7]. Currently, FOLFIRINOX is probably the most widely used regimen in the first-line treatment of APC, hence, how this regimen fits in the algorithm of the treatment is not clear. At present time, screening for pancreatic cancer is not recommended by any society and national practice guidelines in the general population [8]. However, with better understanding of human genetics, recognition of risk factors, and development of diagnostic tools, it is generally recommended to perform endoscopic ultrasound (EUS), multi-detector computed tomography (MDCT), magnetic resonance cholangiopancreatography (MRCP), magnetic resonance imaging (MRI), and endoscopic retrograde cholangiopancreatography (ERCP) in high-risk individuals [9] as summarized in Figure 1. It is important to remind here that currently the application of these diagnostic tests is very limited for the general population.

We performed a literature search for relevant published clinical trials, abstracts of trials in progress and ongoing or planned trials for the treatment of APC using Pubmed.com, ClinicalTrials.gov and American Society of Clinical Oncology (ASCO) abstract search as sources. We present an in-depth analysis of the phase I-III clinical trials determining the role and efficacy of different modalities. We also describe rationale for future investigation.

• Sequential therapy
• apply metastatic regimens to earlier stages
• Precision Medicine
Pharmacogenetic and metabolic markers of Chemotherapeutic agents commonly used in PC

- Stromal Targeting agents
- Inflammatory Response
- Other agents
- Immunotherapy
- Surgical resection of hepatic metastases
- Radiation Therapy
- Liver-directed Therapy

**Sequential chemotherapy**

As mentioned earlier, the current guidelines recommend nabPGem or FOLFIRINOX as first-line treatment, followed by nal-IRI depending on the patient's PS. There is no randomized study III performed to date. Ramanathan et al performed a phase II study of induction therapy with gemcitabine and nab-paclitaxel followed by consolidation with modified FOLFIRINOX (mFOLFIRINOX with omission of bolus 5-FU and addition of growth factor every 2 weeks given for a maximum of 6 months) in patients with APC [10]. The study patients received induction therapy (gemcitabine and nab-paclitaxel weekly x 3 every 4 weeks for up to 6 cycles or earlier if progressive cancer followed by consolidation therapy (mFOLFIRINOX). The primary endpoint was to increase 1-year survival to more than 70%. The results were presented in an annual meeting in 2014 at which time the study had only accrued 26 patients. Among the 20 patients treated with the induction phase, 75% have had a significant decrease in CA 19-9 levels and achieved a 50% partial response (PR) but at the cost of grade ≥3 adverse events, including neutropenia, fatigue, thromboembolic events, and peripheral neuropathy. Other possible sequences of chemotherapy that were tested in small clinical trials or can be utilized in appropriate patients may include:

- Gemcitabine and nab-paclitaxel → nab-IRI with 5-FU and leucovorin versus mFOLFOX-6/5FU versus capcitabine
- mFOLFIRINOX → gemcitabine and nab-paclitaxel versus gemcitabine if patient has existing neuropathy

The absence of direct comparison of the two first-line regimens at present leaves the choice up to the treating physician and the patient depending on PS and toxicities associated with these regimens. In our experience, the sequence FOLFIRINOX followed by nab-Paclitaxel and Gemcitabine or vice versa lead to an equal OS outcome.

**Metastatic to Earlier Stage: Can we apply metastatic regimens to earlier stages (Locally advanced, adjuvant, and Neo-adjuvant therapy) to enhance the cure rate in pancreatic cancer?**

Until recently, the standard adjuvant therapy for PC following surgery was either 6 months of adjuvant gemcitabine alone or with capecitabine or 5-FU leucovorin or S-1 [11-14]. Role of radiation therapy in this setting remains to be confirmed based on the conflicts from many studies in the adjuvant setting [11, 15]. Moreover, the notion that pancreatic cancer is a systemic disease and R0 resection is not achieved in majority of the patients undergoing surgery, further underlines the importance of developing better therapies to improve the cure rate of those patients who are able to undergo surgery as well as selecting the right patient who should undergo surgery. These challenges and questions lead us to consider testing intensive regimens such as those proven to be beneficial in the metastatic setting: FOLFIRINOX or gemcitabine with nab-paclitaxel in earlier stages with a hope that the use of these regimens may enhance the cure rate if they are used in earlier stages of pancreatic cancer patients. PRODIGE/ACCORD study showed an impressive survival benefit with FOLFIRINOX over gemcitabine [15]. However, APACT study did not reach its end point to improve survival with addition of nab-paclitaxel to gemcitabine [16].

Similarly, nab-paclitaxel combination with gemcitabine was recently reported in LAPACT study for patients with locally advanced disease [17]. Median time to treatment...
failure (TTF) was 9.0 months (90% CI 7.3-10.1), median progression-free survival (PFS) was 10.9 months (90% CI 9.3-11.6), and median OS was 18.8 months (90% CI 15.0-24.0). Overall, the disease control rate was 77.6% (90% CI 70.3-83.5), including 33.6% PR. Toxicities were similar to previous studies and 15% were converted to resectable disease and underwent surgery. Though curative-intended surgical resection and adjuvant chemotherapy represents the current standard of care for pancreatic cancer, sadly these patients still have an unfavorable prognosis secondary to high risk of relapse. Borrowed from the data other resectable gastrointestinal cancers, especially esophagus and gastric cancer in which neoadjuvant or perioperative multimodal therapies have substantially improved the outcome, it seems very reasonable to postulate that use of the newer and intense chemotherapy regimens, such as FOLFIRINOX or nab-paclitaxel to gemcitabine may improve the outcome in resectable and borderline pancreatic cancer. Recent studies are aiming to investigate the benefit for obvious reasons enumerated below:

1. Potential downsizing of the tumor with subsequent higher proportion of R0 resections,
2. Neoadjuvant chemotherapy may be more effective than adjuvant treatment secondary to preserved anatomy and vasculature,
3. Pancreatic cancer is a systemic disease as these patients are likely to havemicrometastases even at the time of diagnosis of a small primary tumor, hence, there is benefit of the systemic effect of neoadjuvant chemotherapy,
4. Neoadjuvant chemotherapy also offers a “window of opportunity” to test the biology of the tumor, and
5. Finally, most patients can receive neoadjuvant chemotherapy compared to adjuvant therapy which can be achieved in approximately 60 – 70% due to perioperative morbidity.

**Precision Medicine**

**BRCA2 and Pancreatic Cancer** Patients with BRCA-1 and BRCA-2 germ line mutations are at an increased risk of developing pancreatic adenocarcinoma, especially BRCA-2 mutation [18]. A recent study of whole genome sequencing of 638 patients with familial pancreatic cancer showed mutations in the BRCA2 gene accounted for the largest fraction of known familial pancreatic cancer genes and was found in 5–10% of the families [19]. Among patients with no family history of PDAC, BRCA2mutation is found in 2% and BRCA1 mutation is found in 1% of the patients or less. In the Ashkenazi Jewish population with PDAC, a much higher incidence of BRCA mutations are found and seen in up to 13.7% of unselected cases.

Studies have revealed that the BRCA-2protein is involved in repair of double-stranded DNA breaks and such tumors deficient in deoxyribonucleic acid (DNA) repair mechanisms such as BRCA mutants show better responses to DNA alkylators such as irinotecan, cisplatin, oxaliplatin, mitomycin [20]. However, such tumors can utilize the poly(adenosine diphosphate [ADP]-ribose) polymerase (PARP) pathway as a salvage mechanism. Therefore, inhibition of PARP pathway could lead to tumor destruction and synthetic lethality in presence of BRCA mutation [21]. Various PARP inhibitors have been approved for treatment of patients with germline or somatic BRCA mutant breast and ovarian cancer. This provides basis of using PARP inhibitors in patients with pancreatic cancer that harbor BRCA mutation. A recent phase III Pancreas Cancer Olaparib Ongoing (POLO) study showed impressive results with near doubling of progression free survival compared to placebo (7.4 vs 3.8 months) [22]. These results highlight the importance of germline testing for all patients with pancreatic cancer and inclusion of additional deficiencies in homologous recombination repair (ATM and PALB2) including BRCA variants of uncertain significance should be further explored.

**HER2-amplified pancreatic cancers**

HER2 amplification occurs in 2% of pancreatic adenocarcinoma [23]. Studies have shown that HER2-amplified pancreatic cancers demonstrated a mRNA expression profile which clustered with the HER2-amplified intrinsic subtype of breast cancer using the PAM50 classifier a molecular level, and clinically, these tumors followed an atypical metastatic pattern characterized by sparing the liver and metastasizing to the lungs and brain – a finding similar one seen in HER2-amplified breast cancer [24]. Based on these data, the investigators explored the role of anti-HER2 therapy in HER2-amplified pancreatic cancers.

Three single arm phase II studies investigated anti-Her2 agents active in combination with cytotoxic agents in pancreatic cancer (Table 1). As evidenced from the table above, only 2 of the trials selected patients based on Her2 status, and utilized immunohistochemistry alone to detect HER2 overexpression.

**Pharmacogenetic and metabolic markers of Chemotherapeutic agents commonly used in PC**

Predicting response and limiting drug-induced toxicity for patients with any tumor type including pancreatic cancer are also critical. Inter-patient differences in tumor response and drug toxicity are common during chemotherapy. Genomic variability of key metabolic enzyme complexes, drug targets and drug transport molecules are important contributing factors, such as hent-1, DYPD, TYMS, TP, UGT1A1, CDA, DCK, MSI, etc. [28,29,30].

Currently, there is inconsistent use of these pharmacogenetic markers in the clinical setting secondary to both the lack of robust evidence as well as limit of financial resources. Patients’ selection and tailored treatments by the introduction of genetic testing in future studies is mandated. One such example is outline in Figure 2, with a proposed schema for such a study that will
hopefully allow better response prediction and limit drug-induced toxicity leading to improved patient outcomes in the most cost-effective way.

Stromal targeting agents

It has been suggested that the tumor microenvironment, such as desmoplastic reaction and stromal neighborhood in pancreatic cancer may act as a hindrance to chemotherapeutic agents, raising the possibility to develop agents that can target the environment and improve the delivery of chemotherapy [31]. Recently, multiple efforts have been made as well as undergoing on developing stroma-depleting agents into the treatment of pancreatic cancer, such as strategies targeting:

- Transforming growth factor (TGF-β),
- Hedgehog (Hh) pathway,
- Tumor necrosis factor (TNF) receptors,
- Degrading hyaluronic acid (HA) in the stroma, and
- Heparan sulfate proteoglycans (HSPGs).

Table 2 summarizes the stromal targeting agents either recently underwent evaluation or currently under evaluation to improve outcome of patients with PC:

<table>
<thead>
<tr>
<th>Anti-HER2 agent</th>
<th>Cytotoxic agent</th>
<th>HER2 status required</th>
<th>Method used to test HER2</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trastuzumab</td>
<td>Gemcitabine</td>
<td>Yes</td>
<td>IHC*</td>
<td>25</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>Capecitabine</td>
<td>Yes</td>
<td>IHC*</td>
<td>26</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>Gemcitabine</td>
<td>No</td>
<td>NA</td>
<td>27</td>
</tr>
</tbody>
</table>

*IHC: immunohistochemistry

Figure 2. Role of Pharmacogenetic Markers in development of Future clinical studies in pancreatic cancer.

Table 1: Studies that investigated anti-Her2 agents active in combination with cytotoxic agents in pancreatic cancer.

Transforming growth factor β (TGF-β) Kano et al. investigated the effect of inhibiting TGFβ signaling with a low-dose TGFβ type 1 receptor inhibitor in preclinical studies and observed reduction in the pericyte coverage of tumor vessels and enhancement of the accumulation of macromolecular nanomedicines in the area of the tumor [32]. However, this strategy did not reduce the abundant fibrous tissue in the tumor. Further studies are required to further investigate this pathway and develop more effective targets to demolish this pathway.

Hedgehog (Hh) pathway Hh signaling cascade regulates embryonic development and pathological activation of this pathway have shown to be oncogenic in many tumor types, including pancreatic cancer. Hh binds to the extracellular receptor, Patched, which releases Smoothened, which then acts to activate transcription factors which is considered as a possible mechanism involved in carcinogenesis [33]. Interestingly, Hh signaling in pancreatic cancer is limited to the stromal compartment and Sonic Hedgehog (Shh) and has been shown to produce a desmoplastic reaction in mice, which is not only a scintillating feature of pancreatic cancer but also associated with metastatic potential and pharmacologic barrier [34]. Olive et al. showed that inhibition of Shh resulted in improved gemcitabine delivery, depletion of the dense stroma, and increased vascularization of the tumors in preclinical studies [35]. This data led to a testing of Hh inhibitors in clinical setting. IPI-926, a small molecule SHh inhibitor was combined with gemcitabine 1000 mg/m2 IV in a phase I/II study (ClinicalTrials.gov Identifier: NCT01130142). Unfortunately, the trial was closed after preliminary interim analysis showed decreased survival in the IPI-926 plus gemcitabine arm, with median overall survival less than the historical median survival of gemcitabine alone of approximately 6 months [36]. Final results have not been published yet along with translational correlates.

Another agent, GDC-0449 (vismodegib) showed an acceptable toxicity profile and indicated some antitumor effects in a variety of solid tumors in a phase I study. Recently, the results of a study combining vismodegib with
nab-paclitaxel and gemcitabine showed a disease control rate in over 80% of the patients [37].

**Tumor necrosis factor (TNF) receptors** CD40 superfamily of tumor necrosis factor receptors have been found in pancreatic stroma and preclinical studies have indicated that CD40 agonists shrank stroma in pancreatic tumor models [38]. It is postulated that this effect is probably mediated by activation of the tumor-associated macrophages. A pilot study combined CD40 agonist (CP-870,893) with gemcitabine and showed PR of 19% among 21 evaluable patients. One dose-limiting toxicity was grade 4, cerebrovascular accident which occurred at the 0.2 mg/ kg dose level, and was estimated as the MTD [39]. The most common adverse event included cytokine release syndrome, usually grade 1 and 2. In addition, changes in FDG uptake detected on PET/CT imaging were intriguing. Phase II studies are warranted.

**Hyaluronic acid of the stroma** HA, a glycosaminoglycan is a major component of the stroma and frequently overproduced by various tumor types. In addition, presence of HA in tumors is associated with correlates with enhanced tumor growth, increased metastatic potential, rapid tumor progression, and elevation in tumor interstitial fluid pressure (IFP); hence acting as a barrier to chemotherapeutic agents [40]. PEGylated recombinant human hyaluronidase (PEGPH20) has shown to degrade HA in stroma and leading to better chemotherapy delivery to the tumor cells [41]. Based on the safety profile of the combination of PEGPH20 with gemcitabine, this agent underwent testing both with gemcitabine and nab-paclitaxel as well as FOLFIRINOX.

Encouraged by the preliminary data from phase I/II studies [42], the phase III HALO-109–301 compared PEGPH20 in combination with nab-paclitaxel/gemcitabine to nab-paclitaxel/gemcitabine alone in previously untreated patients with pancreatic tumors confirmed high expression of HA. Patients were randomized in 2:1 manner to receive the experimental arm [43]. The primary endpoint was overall survival. Five hundred patients were enrolled but sadly the study did not meet its primary endpoint of OS (11.2 months compared to 11.5 months (hazard ratio of 1.00 and \( p=0.096 \)). Since this announcement, all future development of PEGPH20 has been halted. Prior to the announcement of the results of HALO study, Ramanathan et al, presented similar negative data of Southwest Oncology Group (SWOG) 1313 that was conducted to determine the safety and efficacy of PEGPH20 in combination with modified version of FOLFIRINOX [44].

**Heparan sulfate proteoglycans** HSPGs are polysaccharide molecules bound to proteins associated with cell membrane of cells including tumor cells; contribute to tumor microenvironment by binding to factors that support tumor growth.

| Anti-diabetic | Insulin receptor-dependent mechanism | Metformin |

**Agents targeting the inflammatory response**

The rationale for this strategy arises from a few observations [47]:

- Inflammatory cytokine signaling does appear to be important both in disease initiation and progression in preclinical models of pancreas cancer,
- Majority of the patients with APC have both laboratory and clinical evidence of systemic inflammation, such as weight loss, decreased muscle mass, poor performance status (cachexia), and
- Patients who have an elevated C-reactive protein, a marker of systemic inflammation, have a worse prognosis.
- Given this rationale for disrupting systemic inflammation, many agents have undergone testing (Table 3).

<table>
<thead>
<tr>
<th>Stromal Targeting agents</th>
<th>Sonik Hedgehog has been shown to produce a desmoplastic reaction</th>
<th>TGF-β type 1 receptor inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transforming growth factor-β (TGF-β)</td>
<td>Reduction in pericyte coverage of tumor vessels and enhancing accumulation of macromolecular nanomedicines in the area of tumor</td>
<td>CP-870,893</td>
</tr>
<tr>
<td>Tumor necrosis factor receptors (TNF)</td>
<td>CD40 agonists shrank stroma in PC models; probably mediated by activation of the tumor-associated macrophages</td>
<td>PEGPH20</td>
</tr>
<tr>
<td>Hyaluronic acid (HA) of Stroma</td>
<td>HA is a major component of the stroma; presence of HA in tumors is associated with enhanced tumor growth, increased metastatic potential, rapid tumor progression, and elevation in tumor interstitial fluid pressure (IFP)</td>
<td>M402</td>
</tr>
<tr>
<td>Heparan sulfate proteoglycans (HSPGs)</td>
<td>HSPGs are polysaccharide molecules bound to proteins associated with cell membrane of cells including tumor cells; contribute to tumor microenvironment by binding to factors that support tumor growth</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2: Summary of Stromal Targeting agents undergoing evaluation in Pancreatic Cancer.**

**Table 3**
### Table 3: Agents targeting the Inflammatory Response.

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arachidonic acid Pathway</td>
<td>• LTB4 receptor antagonist</td>
</tr>
<tr>
<td>JAK/STAT Pathway</td>
<td>• JAK1 and JAK2 inhibitor</td>
</tr>
</tbody>
</table>

### Arachidonic acid Pathway (Lipoxygenase [LOX] Pathway)

Arachidonic acid is metabolized to leukotrienes and other inflammatory compounds via 5-lipoxygenase. Upregulation of 5-lipoxygenase has been reported in several cancer types, including pancreatic cancer [48]. Preclinical studies have revealed that lipoxygenase inhibitors inhibit cell proliferation and induce apoptosis [49]. Tong et al. 2012, suggesting that an inhibitor of 5-lipoxygenase may arrest the tumor growth. Unfortunately, a phase II randomized, double-blind study comparing LY293111, a LTB4 receptor antagonist, with gemcitabine to gemcitabine plus placebo, showed no difference in 6-month survival (p > 0.2) or PFS (p > 0.05) [50].

### JAK1 and JAK2

A randomized double-blind Phase II study the **RECAP study**, investigated Ruxolitinib, JAK1 and JAK2 inhibitor that blocks the stat transcription factor pathway and inflammatory cytokines versus placebo in combination with capcitabine in patients with metastatic pancreas cancer. Overall, the study did not meet the end point but when they looked at the patient population with elevated C-reactive protein levels, the investigators observed a strong efficacy signal [51]. The survival at 6 months was 42% with ruxolitinib versus 11% for placebo.

These results provide the proof of the principle with survival benefit in those patients with evidence of systemic inflammation. A randomized phase III study is underway to confirm these results.

### Immunotherapy and pancreatic cancer

Secondary to the relative lack of efficacy of traditional chemotherapy in patients with pancreatic cancer, investigators have also approached to other treatment modalities such as immunotherapy as it worked out in other chemo-refractory tumors such as melanoma. **Table 4** summarizes selected immunotherapy in PC.

### Immune checkpoint inhibitors

Approximately 1% of pancreatic cancers are associated with defective mismatch repair (dMMR/MSI-high) [52]. In the KEYNOTE-016 phase II trial of pembrolizumab for patients with advanced solid tumors with dMMR, 5 of 6 patients with pancreatic cancer responded to pembrolizumab [53]. Other agents in this class, such as ipilimumab are also undergoing investigation in pancreatic cancer [54]. A phase II study of FOLFRINOX followed by ipilimumab with an allogeneic tumor vaccine is underway in patients with APC [NCT01896869].

### Tumor vaccines

Whole tumor vaccines are promising cancer immunotherapies. Allogeneic pancreatic tumor vaccines are vaccines created from the tumor cells of one patient and given to another patient, with the hope that specific tumor antigens will be expressed and recognized by the new host’s immune system, creating an immune response directed toward the host’s own tumor cells [55]. **CRS-207** is a pancreatic cancer vaccine which uses a live-attenuated strain of *Listeria monocytogenes* that expresses mesothelin, a cell surface glycoprotein that is overexpressed in pancreatic tumors. The proposed mechanism of action is that the bacteria will invade phagocytes, produce mesothelin and, in turn, activate cytotoxic T cells against mesothelin, resulting in cell death of the mesothelin-expressing tumor cells. A recently completed phase II trial investigated the use of CRS-207 in conjunction with GVAX, a whole-cell vaccine expressing human granulocyte macrophage-colony stimulating factor. This study showed a statistically significant OS benefit in patients receiving the combination of GVAX and CRS-207 immunotherapies compared to patients receiving GVAX immunotherapy alone, with a mOS of 6.1 months compared with 3.9 months, respectively (p = 0.011) [56].

### Tumor-specific antibodies

Yttrium Y-90 clivatuzumabtetraxetan is a radio-immunoconjugate made of a monoclonal antibody directed against the pancreatic tumor antigen MUC 1 conjugated to the chelating agent tetra-azacyclodecanetetra-acetic acid and radiolabeled with the radioisotope yttrium Y90 [56]. A phase I trial showed promising activity with a good safety profile [57] and this agent is currently being investigated in a phase III trial.

### Modified lymphocytes

Another approach to immunotherapy is to use T cells that have been engineered to have a T-cell receptor (TCR) that recognizes a specific antigen by fusing the TCR to the antibody-binding domain of an immunoglobulin (Ig) [58]. IgCD28TCR is a T cell designed with an Ig portion that recognizes carcinoembryonic antigen (CEA), allowing T cells to recognize and destroy cells expressing CEA [59]. A phase II clinical trial is currently recruiting participants with any CEA expressing adenocarcinoma, including pancreatic adenocarcinoma.

### Other targets

Table 5 summarizes few other agents which have been tested or undergoing testing in pancreatic cancer.

### Surgical resection of hepatic metastases

Researchers have investigated to determine the benefit of metastatectomy such as simultaneous pancreatic and partial hepatic resection. An analysis of 109 patients with pancreatic adenocarcinoma was performed [64]. These patients were divided into two groups:

---

**Table 3**

**Arachidonic acid Pathway (Lipoxygenase [LOX] Pathway)**

Arachidonic acid is metabolized to leukotrienes and other inflammatory compounds via 5-lipoxygenase. Upregulation of 5-lipoxygenase has been reported in several cancer types, including pancreatic cancer [48]. Preclinical studies have revealed that lipoxygenase inhibitors inhibit cell proliferation and induce apoptosis [49]. Tong et al. 2012, suggesting that an inhibitor of 5-lipoxygenase may arrest the tumor growth. Unfortunately, a phase II randomized, double-blind study compared LY293111, a LTB4 receptor antagonist, with gemcitabine to gemcitabine plus placebo, showed no difference in 6-month survival (p > 0.2) or PFS (p > 0.05) [50].

**JAK1 and JAK2**

A randomized double-blind Phase II study the **RECAP study**, investigated Ruxolitinib, JAK1 and JAK2 inhibitor that blocks the stat transcription factor pathway and inflammatory cytokines versus placebo in combination with capcitabine in patients with metastatic pancreas cancer. Overall, the study did not meet the end point but when they looked at the patient population with elevated C-reactive protein levels, the investigators observed a strong efficacy signal [51]. The survival at 6 months was 42% with ruxolitinib versus 11% for placebo.

These results provide the proof of the principle with survival benefit in those patients with evidence of systemic inflammation. A randomized phase III study is underway to confirm these results.

**Immunotherapy and pancreatic cancer**

Secondary to the relative lack of efficacy of traditional chemotherapy in patients with pancreatic cancer, investigators have also approached to other treatment modalities such as immunotherapy as it worked out in other chemo-refractory tumors such as melanoma. **Table 4** summarizes selected immunotherapy in PC.

**Immune checkpoint inhibitors**

Approximately 1% of pancreatic cancers are associated with defective mismatch repair (dMMR/MSI-high) [52]. In the KEYNOTE-016 phase II trial of pembrolizumab for patients with advanced solid tumors with dMMR, 5 of 6 patients with pancreatic cancer responded to pembrolizumab [53]. Other agents in this class, such as ipilimumab are also undergoing investigation in pancreatic cancer [54]. A phase II study of FOLFRINOX followed by ipilimumab with an allogeneic tumor vaccine is underway in patients with APC [NCT01896869].

**Tumor vaccines**

Whole tumor vaccines are promising cancer immunotherapies. Allogeneic pancreatic tumor vaccines are vaccines created from the tumor cells of one patient and given to another patient, with the hope that specific tumor antigens will be expressed and recognized by the new host’s immune system, creating an immune response directed toward the host’s own tumor cells [55]. **CRS-207** is a pancreatic cancer vaccine which uses a live-attenuated strain of *Listeria monocytogenes* that expresses mesothelin, a cell surface glycoprotein that is overexpressed in pancreatic tumors. The proposed mechanism of action is that the bacteria will invade phagocytes, produce mesothelin and, in turn, activate cytotoxic T cells against mesothelin, resulting in cell death of the mesothelin-expressing tumor cells. A recently completed phase II trial investigated the use of CRS-207 in conjunction with GVAX, a whole-cell vaccine expressing human granulocyte macrophage-colony stimulating factor. This study showed a statistically significant OS benefit in patients receiving the combination of GVAX and CRS-207 immunotherapies compared to patients receiving GVAX immunotherapy alone, with a mOS of 6.1 months compared with 3.9 months, respectively (p = 0.011) [56].

**Tumor-specific antibodies**

Yttrium Y-90 clivatuzumabtetraxetan is a radio-immunoconjugate made of a monoclonal antibody directed against the pancreatic tumor antigen MUC 1 conjugated to the chelating agent tetra-azacyclodecanetetra-acetic acid and radiolabeled with the radioisotope yttrium Y90 [56]. A phase I trial showed promising activity with a good safety profile [57] and this agent is currently being investigated in a phase III trial.

**Modified lymphocytes**

Another approach to immunotherapy is to use T cells that have been engineered to have a T-cell receptor (TCR) that recognizes a specific antigen by fusing the TCR to the antibody-binding domain of an immunoglobulin (Ig) [58]. IgCD28TCR is a T cell designed with an Ig portion that recognizes carcinoembryonic antigen (CEA), allowing T cells to recognize and destroy cells expressing CEA [59]. A phase II clinical trial is currently recruiting participants with any CEA expressing adenocarcinoma, including pancreatic adenocarcinoma.

**Other targets**

Table 5 summarizes few other agents which have been tested or undergoing testing in pancreatic cancer.

**Surgical resection of hepatic metastases**

Researchers have investigated to determine the benefit of metastatectomy such as simultaneous pancreatic and partial hepatic resection. An analysis of 109 patients with pancreatic adenocarcinoma was performed [64]. These patients were divided into two groups:
Table 4: Immunootherapy in PC.

| Immune checkpoint inhibitors | Ipilimumab |
| Whole tumor vaccines | GVAX and CRS-207 |
| Tumor-specific antibodies | Yttrium Y-90 divatuzumabtetraxetan |
| Modified lymphocytes | IgCD28TCR |

Table 5: summarizes few other agents which have been tested or undergoing testing in pancreatic cancer.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Pathway</th>
<th>Study (I,II,III)</th>
<th>Outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evofosfamide</td>
<td>Hypoxia-activated prodrug of bromo-isophosphoramide mustard (Br-IPM) that is preferentially activated under hypoxic conditions</td>
<td>MAESTRO is an international, randomized, double-blind, placebo-controlled phase III trial of Evofosfamide/Gemcitabine vs Placebo/Gemcitabine (Clinical trial information: NCT01746979)</td>
<td>No survival benefit</td>
<td>60</td>
</tr>
<tr>
<td>PHY906/Yiv906</td>
<td>Chinese herbal drug that inhibits of NFK-b, VEGF and MMP.</td>
<td>II</td>
<td>Met the end point and improved 6-months survival</td>
<td>61</td>
</tr>
<tr>
<td>Metformin</td>
<td>AMPK-pathway and mTOR.</td>
<td>I</td>
<td>Proof of principle</td>
<td>62,63</td>
</tr>
</tbody>
</table>

Group 1 consisted of 33 patients with liver metastasis:
- Group 1-A: 11 patients to aggressive surgery, consisting of pancreatoduodenectomy and partial liver resection.
- Group 1-B: 22 patients to palliative bypass surgery.
- Group 2 consisted of 76 patients without liver metastasis:
  - Group 2-A: 37 patients to pancreatoduodenectomy.
  - Group 2-B: 39 patients to bypass surgery.

The researchers did not find any statistical differences in the median OS (6 months versus 4 months) between Group 1-A and Group 1-B. All the patients in Group 1-A patients succumbed to death within a year due to multiple recurrent liver metastases. Also, patients in the Group 1-A had significantly poorer survival compared to those in the Group 2-A.

However, as we evolved in the novel chemotherapeutic agents, newer data is showing a trend towards survival in selected patients with hepatectomy [65]. Cases of metachronous liver metastasis or synchronous liver oligometastases of pancreatic cancer after radical surgery, in which patients exhibit long-term survival without recurrence after hepatectomy, are reported from major cancer centers [66,67]. Hepatectomy may confer long-term survival, and the time to postoperative recurrence and the number of liver metastases may be useful criteria for deciding whether to perform hepatic resection. It mandates a careful selection of patients after primary chemotherapy in a multidisciplinary approach.

Radiation therapy

In comparison to conventional radiotherapy, stereotactic body radiation therapy (SBRT) may provide the opportunity to administer radiation in a shorter time frame with similar efficacy and reduced toxicity. In addition, SBRT involves more accurate patient immobilization and greater attention to accurate replication of the simulation position for treatment delivery, allowing for sub-centimeter precision [68]. The target tumor and the normal tissue avoidance structures are stereotactically registered to the treatment machine. Multiple non-coplanar fixed beams or arc fields are used in order to minimize normal tissue exposure and provide rapid fall-off of the radiation dose outside of the target area [69]. Finally, an ablative dose of ionizing radiation is delivered to the tumor, typically in one to five sessions. Many of the same principles are employed during stereotactic radiosurgery for brain lesions, but radiation oncologists are now adapting them to the treatment of extra-cranial tumors, such as pancreatic cancer. Multiple retrospective and prospective studies have explored the safety and efficacy of SBRT with and without chemotherapy in locally advanced pancreatic cancer and showed encouraging results with respect to local control of locally advanced pancreatic cancer [68,69,70]. Future studies are needed to address strategies for reducing long-term toxicities associated with SBRT, such as duodenal ulcer or perforation.

Liver-directed therapy

With the improvement in technology in other modalities, researchers have also investigated the role of chemo- or radio-embolization to the liver metastasis in patients with APC [71].

Trans-arterial chemoembolization

In one study, repetitive transarterial chemoembolization (TACE) in 34 patients of APC with liver metastases led to an overall disease control in 81% of the patients (9.37% partial response (PR) + 71.87% stable disease) with an overall median OS of 16 months [72].

Radio-embolization with Yttrium-90 microspheres (SIRT)

Others have looked in the role of radio-embolization with Yttrium-90 microspheres (SIRT) in APC patients with liver metastases and found an objective response up to 47% and a median OS of 9.0 months (range 0.9-53.0) [73]. Most acute toxicities such as nausea, vomiting, fatigue, fever and abdominal pain did not exceed grade 3. However, liver abscesses, gastroduodenal ulceration, cholestasis and cholangitis, ascites and spleen infarction were noticed as delayed complications secondary to Y-90
radio-embolization [74]. Our group also experienced benefit in selected cases [71]. It is mandatory that such an approach should be undertaken with the guidance of a multi-disciplinary team of experts.

**DISCUSSION**

It is evident that there are many challenges related to pancreatic adenocarcinoma ranging from its environment, relative chemo-resistance, to lack of screening tools, delayed diagnosis, diagnosis at an advanced stage, patient’s poor quality of life, lack of biomarkers (predictive or prognostic), variation in the management of patients across the globe, such as attitudes towards second-line therapy and use of radiotherapy especially for earlier stage patients. Access and funding for clinical trials remains limited and varied across the globe. So, to overcome these barriers and improve the outcome in patients with pancreatic cancer, we have made significant advances in our understanding of the biology of pancreatic cancer, and many novel drugs and biologics are now in the practice such as olaparib while others in pipeline as a result of those advances. I am hopeful that we will see a number of promising novel treatments for pancreatic cancer move into the clinic to benefit patients over the next few years. There is a long list of potential biomarkers, beyond pharmacogenetic markers that need to be validated not only to select the therapy but prognostic value too. Circulating tumor cells and circulating tumor DNAmay provide an early signal of treatment response or recurrence, and hence must be adapted immediately in the management of these patients. Future is also dependent on the organoids as well as tumor and patient profiling to evolve patient care in the era of precision medicine.

**Conflicts of Interest**

The authors report no conflict of interest.

**REFERENCES**

18. Lowery MA, Kelsen DP, Stadler ZK, Yu KH, JanJigian YY, Ludwig E, et al. An emerging entity: Pancreatic adenocarcinoma ranging from its environment, patient’s poor quality of life, lack of biomarkers (predictive or prognostic), variation in the management of patients across the globe, such as attitudes towards second-line therapy and use of radiotherapy especially for earlier stage patients. Access and funding for clinical trials remains limited and varied across the globe. So, to overcome these barriers and improve the outcome in patients with pancreatic cancer, we have made significant advances in our understanding of the biology of pancreatic cancer, and many novel drugs and biologics are now in the practice such as olaparib while others in pipeline as a result of those advances. I am hopeful that we will see a number of promising novel treatments for pancreatic cancer move into the clinic to benefit patients over the next few years. There is a long list of potential biomarkers, beyond pharmacogenetic markers that need to be validated not only to select the therapy but also prognostic value too. Circulating tumor cells and circulating tumor DNAmay provide an early signal of treatment response or recurrence, and hence must be adapted immediately in the management of these patients. Future is also dependent on the organoids as well as tumor and patient profiling to evolve patient care in the era of precision medicine.

The authors report no conflict of interest.


