REVIEW PAPER

From Screening to Treatment of Pancreatic Cancer: A Comprehensive Review

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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].

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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.

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 $\geq$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 →nal-IRI with 5-FU and leucovorin versus mFOLFOX-6/OFF versus capecitabine
- 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.

Until recently, the standard adjuvant therapy for PC following surgery was either 6 months of adjuvant gemcitabine alone or withcapecitabineor 5-FU leucovorin or S-1 [11,12,13,14]. 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 inresectableand 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 mall primary tumor, hence, there is benefit of the systemic effect of neoadjuvant chemotherapy,
4. Neoadjuvantchemotherapy 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.

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, *BRCA2*mutation 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-2 protein is involved in repair of double-stranded DNA breaks and such tumors deficient in deoxyribonucleic acid (DNA) damage 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.

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