MINI REVIEW

New Developments in the Treatment of Pancreatic Cancer: Highlights from the 44th ASCO Annual Virtual Meeting, May 29-31, 2020

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ABSTRACT

Pancreatic cancer has the worst survival of any solid tumor. Overall, pancreatic cancer accounts for about 3% of all cancers in the US and about 7% of all cancer deaths. The American Cancer Society's estimates that 57,600 people (30,400 men and 27,200 women) will be diagnosed with pancreatic cancer in the United States for 2020 and approximately 47,050 people (24,640 men and 22,410 women) will die of this disease. FOLFIRINOX, or the combination of gemcitabine with nab-paclitaxel remain to be the major treatment options for these patients for both local and metastatic disease. This slow progress is a result of partly the complex pathogenesis of this disease, and partly the fact that window of opportunity to treat these patients is short as majority of them are diagnosed at an advanced stage. This is a real challenge but also provides an opportunity for new ideas and novel approaches. In this paper, we will present few interesting studies presented at the American Society of Clinical Oncology (ASCO) 2020 virtual Annual Meeting.

INTRODUCTION

Pancreatic cancer (PC) has the worst survival of any solid tumor. The American Cancer Society's estimates that 57,600 people (30,400 men and 27,200 women) will be diagnosed with PC in the United States for 2020 and approximately 47,050 people (24,640 men and 22,410 women) will die of PC [1]. Overall, PC accounts for about 3% of all cancers in the US and about 7% of all cancer deaths [1]. The incidence of PC is slightly more common in men than in women and more common in African-Americans than in Whites [2]. The average lifetime risk of developing PC is about 1 in 64, however, the individual's risks of developing PC can be impacted by certain risk factors, including both personal and genetic [3].

What We Knew Before the 2020 ASCO Annual Meeting?

Even though surgery is the only potentially curative treatment for patients with PC, but unfortunately less than 20% are resectable at the time of diagnosis [4, 5]. Chemotherapy for 6 months including FOLFIRINOX (5-fluorouracil, leucovorin, irinotecan, and oxaliplatin), gemcitabine plus capecitabine, gemcitabine alone, or S-1 alone (where it is available) is generally the accepted gold standard across the globe, except oncologists in USA still include radiation in selected cases [5, 6, 7, 8, 9]. Even in those patients who receive adjuvant chemotherapy, majority of them succumb to death due to metastases [4]. Neoadjuvant trials have been undergoing more aggressively to address this issue. On the other end, palliative chemotherapy remains the treatment of choice in the management of those with advanced pancreatic cancer (APC). Options in the first-line consist of single agent gemcitabine, the combination of gemcitabine with the epidermal growth factor (EGF) inhibitor erlotinib, FOLFIRINOX, or the combination of gemcitabine with nab-paclitaxel [10, 11, 12, 13]. Though few studies have tested few agents in the second-line, but liposome irinotecan with 5-FU and leucovorin is the only FDA-approved regimen in this setting [14]. It is evident that the currently available options are limited and the window of opportunity to offer treatment to these patients remain to be short, which further compounded by the deteriorated quality of life due to cancer-related symptoms. There it is imperative that we develop molecularly-targeted agents, biomarkers to select the available conventional chemotherapy to prevent toxicity, such as organoids and explore other pathways in the cascade of pancreatic carcinogenesis, including immunotherapy.

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Abbreviations PC Pancreatic Cancer; APC Advanced Pancreatic Cancer; EGF Epidermal Growth Factor; GEMCAP Gemcitabine Plus Capecitabine; CRT Chemoradiotherapy;
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What We Learnt at the 2020 ASCO Annual Meeting?

SWOG S1505 was presented at the meeting (NCT02562716) [15]. S1505 was a randomized phase II trial of peri-operative chemotherapy with mFOLFIRINOX versus gemcitabine/nab-paclitaxel (12 weeks pre-op,

12 weeks post-op) for resectable PC (PDA). A total of 147 patients were enrolled and out of them, 102 were found eligible. The outcomes of S1505 for each arm are summarized in **Table 1**. Overall, neither arm's 2-year OS estimate was statistically significantly higher than the a priori threshold of 40% (p=0.42 in Arm 1 and p=0.12 in Arm 2). Toxicities were consistent with previous studies. In summary, this study showed the feasibility of the use of both regimens but also failed to show any survival benefit compared to the historical standard.

Our European researchers presented the results of the ESPAC-5F (89500674), a 4-arm, prospective, multicenter, international randomized phase II trial to determine the feasibility and efficacy of a comparison of immediate surgery compared with neoadjuvant gemcitabine plus capecitabine (GEMCAP) or FOLFIRINOX or chemoradiotherapy (CRT) in patients with borderline resectable PC [16]. The primary objectives were recruitment rate and resection rate (R1/R0) and secondary objectives were to assess overall survival and toxicity. Patients were randomized to undergo immediate surgery, or receive neoadjuvant therapy of either 2 cycles of GEMCAP, or 4 cycles of FOLFIRINOX or 50.4Gy capecitabine-based CRT in 28 daily fractions over 5.5 weeks. Patients were restaged at an interval of 4-6 weeks and surgery was performed if stage remained to be borderline resectable. Following surgical resection, patients received adjuvant therapy.

18 of 20 patients received 2 cycles of GEMCAP while the rest 2 did not receive any chemotherapy. 25% patients were able to complete the planned GEMCAP. 15 of 20 patients received the 4 cycles of mFOLFIRINOX while the rest 5 did not receive any chemotherapy. Akin to GEMCAP, 25% patients were able to complete the planned FOLFIRINOX. 12 of 20 patients received 5.5 weeks of CRT while 2 patients in this arm did not receive any treatment. 38% patients in this arm finished the planned CRT.

Resection rates (including R0 and R1) was 62% for those who underwent immediate surgery versus 55% for those who received neoadjuvant therapy (GEMCAP, FOLFIRINOX or CRT) with a p value of 0.668) while R0 resection rate was 15% and 23% for the two arms respectively (p=0.721). One-year survival rate was 40% [95% CI, 26% – 62%] for immediate surgery and 77% [95%CI, 66% - 89%] for neoadjuvant therapy with an HR ratio of 0.27 [95% CI, 0.13 – 0.55 and P value of <0.001 **(Table 2)**. The investigators concluded that there was no statistical difference in resection rates for immediate surgery versus neoadjuvant therapy. However, there was a significant survival advantage at one year for neoadjuvant therapy versus immediate surgery. Among the three treatment options, FOFIRINOX was the superior as shown below:

In short, neoadjuvant should be considered for patients with borderline resectable PC.

It is a known fact that age is a risk factor for PC and majority of the patients are above the age of > 70 years. ESPAC-4 study included patients with median age of 65 years (37-81) and ECOG performance status (PS) of 0 (43%), 1 (54%) and 2 (2%). Our group presented our experience with an adopted biweekly regimen of s-GEMCAP in patients who were ≥ 75 years and those who were deemed not suitable for ESPAC-4 regimen [17]. Thirty-five (22M, 13F) patients, ≥ 75 (median age 79), ECOG PS 1 in 7 (28%) patients and 2 in 28 (72%) who received a modified regimen of gemcitabine (1000-2000 mg/m2) every 2 weeks and capecitabine (800-1000 mg/m2) day 1-7 every 2 weeks. Patients were evaluated for DFS, OS and sites of recurrence. Toxicities were graded according to NCI CTCAE v5.0. Updated data at the conclusion of 38 months showed median DFS of 11 months and OS of 24.0 months. Nine (25%) had local recurrence, 21 (60%) had metastatic disease and 3 (8.6%) had NED. The most frequent toxicities were grades 1-2 anemia (20%), thrombocytopenia (8%) and hand-foot syndrome (HFS) (10%). Grade ≥3 included diarrhea (4%) and HFS (1%) with no treatment-related discontinuations. Treatment compliance was 100%. Delays were necessary in 7% of cases and dose reduction was required in 4% of cases. There was no treatment related death. This schedule of biweekly s-GEMCAP regimen suggests an acceptable option in for elderly, frail patients with PC and warrants further exploration in patients not suitable for FOLFIRINOX, full dose GEMCAP or a clinical trial. In addition, this schedule is optimum for administration of pegylated-filgrastim. Moreover, fewer

Table 1. Results of S1505 Study in Resectable PC.

	mFOLFIRINOX (n=55)	Gemcitabine/Nab-paclitaxel (n=47)
Started pre-op Chemotherapy	53 (96%)	45 (96%)
Completed pre-op Chemotherapy	46 (84%)	40 (85%)
Surgical resection	40 (73%)	33 (70%)
Complete or major pathologic response	10 (25%)	14 (42%)
Started post-op Chemotherapy	33 (60%)	28 (60%)
Completed full course of treatment	27 (49%)	19 (40%)
Median DFS (months) post-op	10.9m	14.2m
Median OS (months)	22.4m	23.6m
Two-year OS (%)	41.60%	48.80%

Table 2. One-year survival for ESPAC-5F.

	mFOLFIRINOX	GEMCAP	CRT	Surgery
1-year survival	84%	79%	65%	40%

Table 3. Studies related to KRAS presented at ASCO 2020.

Study	Method	No. of Patients or Specimens	Findings	Implications
1 [21]	NextGen sequencing (NGS) and whole transcriptome sequencing (WTS)	1164	In KRAS WT tumors, TA were seen in 22% by WTS and 52% by NGS. Key TA include BRAF, ALK, ROS1, NRG1, MSI-H, FGRF, MET, ERBB, RET, NOTCH1, Wnt, PI3K, etc.	The use of WTS with NGS was able to identify TA in most of the KRAS WT tumors, underlying the need for performing a comprehensive DNA and RNA profiling of PC to guide treatment possibilities beyond standard agents.
2 [22]	Know Your Tumor program	1475	PFS and OS were greater with KRAS G12V and G12R variants on 5FU-Based Therapy (e.g. FOLFIRINOX). KRAS Q61 seem to be associated with better outcome on gemcitabine/nab-paclitaxel	KRAS mutation status and its specific variants seem to be of value both prognostically as well as predictively.
3 [19]	Single arm study of gemcitabine plus Cobimetinib in patients with KRAS G12D, G12V, and G12R mutations	7 patients with KRAS G12D/G12V mutated PC. 6 patients with KRAS G12R mutated PC	Patients with KRAS G12D/G12V mutated PC did not get any benefit and died within 2 months. Patients with KRAS G12R mutated PC achieved median PFS of 6.0 months (95% CI 3-9.3 months) and median OS has not been reached	Patients with PC KRAS G12R mutated PC seem to derive benefit with this novel combination chemotherapy.

visits to oncology and related expense do favor towards benefit. Additionally, this tolerable regimen is ideal to be combined with immunotherapy in clinical trials for this patient population.

Many new agents were also presented at the meeting, such as CPI-613 (Devimistat) and Cobimetinib, MEK inhibitor and hopefully will be tested in randomized phase III studies to confirm their benefit towards APC [18, 19].

It is well-known that about 90% of PC tumors carry KRAS mutations [20, 21, 22]. Recently investigators have looked back at this abnormality to investigate the clinical and biological impact of KRAS variants and

The biological and clinical impact of common KRAS variants, such as G12D, G12V, G12R as well as explore any potential targetable alterations related to this pathway. Of note, three studies related to this topic were presented as summarized in **Table 3**.

What we need to do next?

It is extremely important to bear in mind that patients with pancreatic cancer should be referred to centers of excellence. Importance of multidisciplinary teams in order to improve survival in these patients cannot be over emphasized [23]. We need to develop of PC networks to improve access to trials and to coordinate collaboration between healthcare professionals and industry to improve outcomes. Cooperation between industry and academia needs to be further improved to ensure that trials are relevant to clinical practice as well as Improve access to newly registered drugs. Early introduction of palliative care alongside chemotherapy to improve quality of life, mood and outcomes. It is important that we standardize the management of PC across the globe and base treatment selection on evidence-based national and international guidelines. Randomized controlled trials using a standardized protocol for pancreatic specimen examination for ease of comparison between studies should be applied. Tumor and patient profiling are critical in understanding disease, developing new treatments and better selecting patients for optimal therapy. Less invasive strategies, such as profiling of CTDNA may overcome need to procure tumor tissue [24]. NCCN also recommends germline mutational analysis in patients with PC [25]. Detection and treatment in high-risk patients should continue with multidisciplinary teams, with comprehensive genetic testing, counseling services and development of screening markers.

Conflicts of Interest

All named authors hereby declare that they have no conflicts of interest to disclose.

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