Advanced pancreatic cancer: The standard of care and new opportunities

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Abstract

Presentation of pancreatic cancer is localized, locally advanced or metastatic. With the later represented the main bulk (more than 80%). Despite the significant innovation in molecular analysis and therapeutic approach in many types of cancer in the last two decades, still the outcome of advanced pancreatic cancer is disappointing and the mortality rate approximately unchanged. In this mandated review we intended to highlight the standard of care and emerging agents for advanced pancreatic cancer treatment.

Introduction and scope of the problem

An estimated 53,670 new cases of pancreatic cancer (PC) in the US and approximately 43, 0690 will die in 201. Roughly, the incidence is equal in both sexes; however, it is higher in African American than white American.[1] It is the fourth most common cause of cancer death after lung, prostate and colorectal cancer, and expected by 2030 to be the second.[2] Due to nonspecific symptoms, it is usually presented at advanced stage with less than 10% of patients are potentially candidate to curative surgical resection. Although with this small percentage, there are many obstacles to surgical approach including; a significant morbidity and mortality up to 10% associated with prolonged recovery period and hospital stay. Moreover, approximately 30% of patients do not receive the proper post-operative therapy.[3]

Stage for stage, PC is often considered the poorest prognosis in comparison to any other cancer type. The 5-year survival for localized, locally advanced and metastatic cases is approximately 26%, 10% and 2%, respectively. Median survival is 10-12 months with treatment and 5-6 months without treatment.[1] We present in this review a brief of the standard of care in ductal advanced pancreatic cancer (dAPC) and new being under investigations aiming to improve the outcome of this devastating disease.

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The current management

PC staging is based on TNM staging along with the extent of resectability. The most appropriate imaging modality for diagnosis is Computed Tomography (CT), along with Magnetic resonance imaging (MRI) in addition to PET/CT in special consideration. Usually, the biopsy is a safe procedure either from primary/metastatic sites; with endoscopic ultrasound-directed is preferred over CT-guided approach. Before thinking about alternative diagnosis, at least two or three biopsies should be evaluated. Cancer Antigen 19.9 (CA19-9) may be helpful for diagnosis and evaluating treatment response.[4]

First-line systemic therapy

The goals of systemic therapy must be discussed with the patients, and enrollment in a clinical study is strongly recommended. Treatment selection is based mainly on performance status (PS).

Gemcitabine monotherapy

Gemcitabine, the anti-metabolite and deoxycytidine analogue works by inhibiting DNA repair and synthesis through DNA incorporation. It is established as standard treatment for APC more than 20 years ago. In 1997, Burris et al. demonstrated its benefit vs. bolus 5-fluorouracil (5-FU). The improvement in OS and quality of life was marginal, which necessitated the need for further combination regimens to get better outcome.[5]

Later, several clinical trials had evaluated gemcitabine in combination with potentially synergistic chemotherapeutic agents (*e.g.* irinotecan, oxaliplatin, cisplatin, 5FU). But most of them have failed to show statistically significant results. However, two randomized controlled trials (RCTs) showed border line significant with use of gemcitabine combination against gemcitabine monotherapy, but on the expense of increased toxicity.[6,7]

Gemcitabine plus Albumin-bound (nab) paclitaxel

Nab paclitaxel, a nanoparticle form of paclitaxel, is approved

for first line treatment of APC based on MPACT trial; phase III randomized, international, open-label evaluated gemcitabine ± nab-paclitaxel, in 861 patients with dAPC, treatment naive, bilirubin ≤ upper lower limit (ULN), PS ≥70. The trial met its primary end point; OS (8.5 months *vs* 6.7 months: 0.72 (0.62-0.83); P<0.001) and secondary end points; PFS (5.5 months *vs* 3.7 months: 0.69 (0.58-0.82); P<0.001) favoring the combined arm. Moreover, the addition of nab-paclitaxel improves 1-year survival by 35%. Although the hematological adverse effects (AEs) were common in combined arm, the AEs related death was equal. Updated results showed that 3% of patients in nab-paclitaxel were a live 42 months while all patients in gemcitabine montherapy arm were expired. The poor PS and presence of liver metastasis were associated with poor survival outcome.[8] Secreted protein acidic and cysteine rich (SPARC), the transporter of nab paclitaxel inside the cell, is generally over expressed on PC, due to this characteristic, Nab-paclitaxel could possibly deliver intracellular.

Owing to hydrophilic characters of gemcitabine, the passive diffusion is not enough and need transporter. Human equilibrative nucleoside transporter 1 (hENT1) is responsible for this process; moreover, the phosphorylation occurs intracellular. Actually there are controversies about the use of hENT1 as predictive biomarkers for benefit from gemcitabine in adjuvant sitting. Subanalysis to ESPAC-3 and ROTG 9704 trials revealed that high level hENT1 was associated with better response and survival outcome to gemcitabine. However, CONKO-001 trial and AIO-PK0104 trial were unable to confirm this positive results.[9,10] In the metastatic sitting, unfortunately hENT1 could not be validated in the LEAP trial.[11] There is no clear explanation for this difference, the unavailability of approved test or standard antibody may be accused.

FOLFIRINOX therapy

FOLFIRINOX regimen is a combination of chemotherapeutic agents; 5FU, leucovorin, irinotecan and oxaliplatin validated as first line therapy in dAPC in young/fit patients based on phase III randomized trial (PRODIGE trial) comparing it *vs* gemcitabine monotherapy; included 340 patients. Eligibility criteria was; dAPC without prior chemotherapy, PS 0/1, adequate organ function and bone marrow reservoir. The results showed improvement in both median OS: 11.1 months *vs* 6.8 months HR: 0.57 (95% CI: 0.45-0.73; P<0.001) and median PFS: 6.4 months *vs* 3.3 months HR: 0.47 (95% CI: 0.37-0.59; P<0.001), in favor FOLFIRINOX arm.[12] Although, the results of PRODIGE trial were strong, some concern about the toxicity profiles. The grade ¾ toxicity rate including hematological; neutropnia, febrile neutropnia, and thrombocytopenia; diarrhea, and sensory neuropathy were statistically significant more in FOLFIRINOX arm. Nevertheless, the toxicity rate was not associated with toxic related death and less degradation in QoL. The NCCN panel appreciates that toxicity can be managed by different ways.

Gemcitabine plus erlotinib

Although, the preliminary results of phase II trials using gemcitabine in combination with target therapy as cetuximab and bevacisumab were encouraging, phase III studies revealed negative results except the combined gemcitabine plus erlotinib. NCIC CTG PA.3 is an international, double-blind, placebo-controlled, randomized phase III trial of 569 patients with dAPC assigned to receive gemcitabine ± erlotinib. The results showed median OS was 6.2 months *vs* 5.9 months and 1-year OS was 23% *vs* 17%, in favoring the erlotinib arm. Surprisingly, the improvement in OS and response to erlotinib were associated with the occurrence of grade two or more skin rash. Consequently, the investigators advised stopping erlotinib if no skin rash appeared within two months from treatment.[13] We conclude from this, only small set of patients get small benefit, it is often used to highlight the divergence between statistically significant and clinically meaningful results.

Other agents

Gemcitabine plus cisplatin

Data regarding the value of this combination is debating. Most trials had failed to proof significant survival benefit over gemcitabine monotherapy. However, selected patients may get benefit from it based on the expected role in tumors with BRCA mutations as extrapolation from ovarian or breast cancer management. Accordingly, gemcitabine plus cisplatin may be considered as an alternative to FOLFIRINOX in patients with dAPC carrying the features of hereditary cancer syndrome affecting DNA repair mutation (such as BRCA mutations).[14]

Gemcitabine plus fluoropyrimidine

A number of trials had evaluated the value of gemcitabine plus capecitabine, *vs* gemcitabine single agent. The results were conflicting, Cunningham D et al. demonstrated better response rate, PFS and a trend to improve OS.[15] However, results obtained from analysis of 8 RCTs did not demonstrate OS benefit in gemcitabine plus capecitabine arm.[16]

The addition of docetaxel (GTX) or oxaliplatin (GEMOXEL) to gemcitabine plus capecitabine improve the response and disease control compared to gemcitabine monotherapy but with more toxicity.[17,18] The gemcitabine plus capecitabine based combinations may be considered an option in dAPC, a signed as category 2A by NCCN panel.ECOG E2297 is a phase III trial failed to demonstrate a statistically significant survival benefit of combined gemcitbine plus 5-FU over single agent gemcitabine.[19] Nevertheless, recent trial evaluating the addition of S1, oral fluoropyrimidine to gemcitabine may improve the response and survival in patients with dAPC.[20]

Second-line systemic therapy

As validated in many trials, chemotherapy is better than the best supportive care as regard survival outcome, in candidate patients.[21]

FOLFOX

Until recently, FOLFOX regimen was the de facto choice post gemcitabine, but with mixed results.

CONKO-003 is a phase III trial revealed a statistically significant improvement in both PFS and OS with the use of FOLFOX regimen.[22]

However, the results from trial PANCREOX, open labeled phase III trial showed detrimental effect with the use of FOLFOX regimen as second line in dAPC post gemcitabine based protocol.[23]

Nanoliposomal irinotecan plus 5-FU/LV

In Oct 22, 2015, FDA approved liposomal irinotecan, previously called MM-398 in combination with 5-FU/LV as a treatment for post gemcitabine based regimen in dAPC. Liposomal formulation is characterized by longer half-life, slower clearance and increased AUC, with subsequently increased tumor exposure and conversion to its active form, SN38. The approval was based on the results of NAPOLI-1 trial. It is international controlled phase III included 417 patients with APC post gemcitabine-based therapy with PS≥70. Randomization was nanoliposomal irinotecan monotherapy, 5-FU/LV or nanoliposomal irinotecan plus 5-FU/LV. The results revealed 1.9 month improvement in OS in combination arm with the median OS was 6.1 months compared with 4.2 months with 5-FU /LV arm (HR, 0.57; 95% CI, 0.41-0.80; P=0.0009). In addition, the PFS was 3.1 months *vs* 1.5 months, favoring the nanoliposomal irinotecan plus 5-FU/LV. Because the considerable hematological and non-hematological toxicity of nanoliposomal irinotecan (≥3 adverse effect) it was approved along with a boxed warning concerning severe diarrhea and neutropenia.

The update of NAPOLI-1 trial published in April 2017 recommended using growth factors or dose reduction to limit the considerable toxicity and advice to check *UGT1A1* gene status in all patients being candidate for nanoliposomal irinotecan treatment.[24] Figure 1 illustrates provisional treatment cascade for APC based on previous lines of treatment, for first line (Figure 1A) and after progression (Figure 1B).

Emerging agents

Despite the introduction of new and to some extent effective treatment options, we did not change the course or biology of the disease sufficiently. We have 4 classes of novel therapeutics under investigation; novel cytotoxics, stromal-depleting agents, molecularly targeted agents, and immunotherapies. Table 1 summarized some of these agents.

Novel cytotoxics

TH-302 (evofosfamide), hypoxia-activated pro drug evaluated in combination with gemcitabine and nab-paclitaxel in PC. The trial has been terminated earlier following the company decision (ClinicalTrials.gov Identifier: NCT02047500).[25]

Radiotherapy

Regarding the movement of abdominal organs during the respiration cycle, SBRT (Stereotactic body radiotherapy) had a limited clinical value in PC. CyberKnife® is a device that can follow the tumors' motion and carry out real-time scene modulations. Recent data from a study done by Song *et al*., on 59 locally APC evaluating the use of CyberKnife® reported good clinical efficacy with minimal toxicity.[26]

Chemoembolization

Liver metastasis is not uncommon cause of treatment failure in dAPC. There is emerging data about the benefit of drug eluting beads (DEB) in treating liver metastasis from PC, either in R0 or R1. As we are considering PC is systemic disease, so this approach should be combined with systemic chemotherapy. However, this strategy had some limitation on the form of highly selected patients with different bead sizes and doses depending on physician's decisions. Meanwhile, most of the trials had small sampled sized.[27]

Table 1. Selected investigational agents for advanced pancreatic cancer.

Category	Examples
Novel cytotoxics	1-MM-398 (nanoliposomal irinotecan) 2-evofosfamide), hypoxia-activated pro drug
Stromal-depleting agents	PEGPH20 (recombinant hyaluronidase) Vitamin D analogues Necuparanib
Signal transduction inhibitors	BTK inhibitors (*e.g.*, ibrutinib) Bispecific anti-IGFR/HER3 mAbs (*e.g.*, istiratumab) PARP inhibitors (*e.g.*, olaparib) STAT3 inhibitors (*e.g.*, napabucasin [BBI608]) Notch inhibitors (*e.g.*, demcizumab, tarextumab) JAK inhibitors (*e.g.*, ruxolitinib)
Immunotherapies	Vaccines Algenpantucel-L-Negative CRS-207 (mesothelin-expressing Listeria) + GVAX-Negative Reolysin-Negative Immune checkpoint inhibitors Anti–CTLA-4 antibodies (*e.g.*, tremelimumab, ipilimumab) Anti–PD-1/PD-L1 mAbs (*e.g.*, nivolumab, pembrolizumab,) IDO inhibitors Anti-CD40 mAbs Multiple agents CAR T-cells Ongoing studies targeting EpCAM, HER2, mesothelin, and MUC1

Electroporation

It is a new local ablation treatment technique. The name electroporation came from creating nanopores in the cell membrane leading to increase the cell membrane permeability and later cell death through direct current pulses sent through the tumor. Depending on the number and duration of pulses, the permeability changes became reversible (allow non-permeable chemical agents, such as proteins or drugs, to pass through cell membrane) or irreversible leading to tumor necrosis.[28] The safety of ultrasound guided percutaneous irreversible electroporation (IRE) in patients with APC was evaluated in phase I study. The results were promising as regarding efficacy with acceptable safety profile.[29] Moreover, the preliminary results from combined IRE with chemotherapy or radiation therapy revealed improvement in survival in comparison to historical controls. These results expect that local control of primary tumor may have positive impact on survival.[30]

Stromal-depleting agents

Hyaluronan, also called hyaluronic acid, represented the main components of the extracellular matrix, involved in cell proliferation, migration, and may be in tumor progression. Theoretically, its degradation may normalize tumor interstitial pressure and subsequently improving drug delivery.[31]

PEGPH20, a recombinant human hyaluronidase, investigated in combination with gemcitabine/nab-paclitaxel in APC in HALO-109-202 trial. It is multicenter, randomized, phase II open-label study with two cohorts. First one is to compare the treatment effect of nab-paclitaxel and gemcitabine ±. PEGPH20.Second cohort is to study the safety and tolerability. The treatment continues until progression, intolerable toxicity, death, or choice to discontinue. The preliminary results showed the benefit of PEGPH20 is limited to patients with high hyaluronic acid. In addition, the higher rate of thromboembolic events on PEGPH20-containing arm (42% *vs* 25%); mandated the addition of prophylactic low molecular heparin.[32]

SWOG S1313 is another phase Ib/II trial investigated the addition of PEGPH20 to mFOLFIRINOX in APC. Notably, this trial is temporarily closed enrollment due to the initial results suggested PEGPH20 treatment unlikely to improve OS. Further analysis of the data set based on hyaluronic acid level is to follow (ClinicalTrials.gov.NCT01959139).

Immunotherapies

Immune checkpoint inhibitors, Despite the success in programmed death-1 (PD-1) and programmed death-1 ligand-1 (PD-L1) blocking in many types of cancers, its use in PC is not effective.[33] PC is considered a nonimmunogenic tumor. Early response to immunotherapy dominated by immune-suppressive cells, in part due to tumor-associated macrophages, myeloid-derived suppressor cells, and regulatory T-cells which is called a complex tumor microenvironment (TME).[34] Notably, about 1% of PC associated with defective mismatch repair (dMMR/MSI-high), and based on accelerated FDA approval on May 23, 2017, pembrolizumab (Anti-PD-1) can be used for all metastatic or unresectable MSI-H or MMR-deficient solid tumors after failure of standard treatment.[35] In a phase II trial, pembrolizumab evaluated in 21 patients with dMMR advanced previously-treated cancers. The results

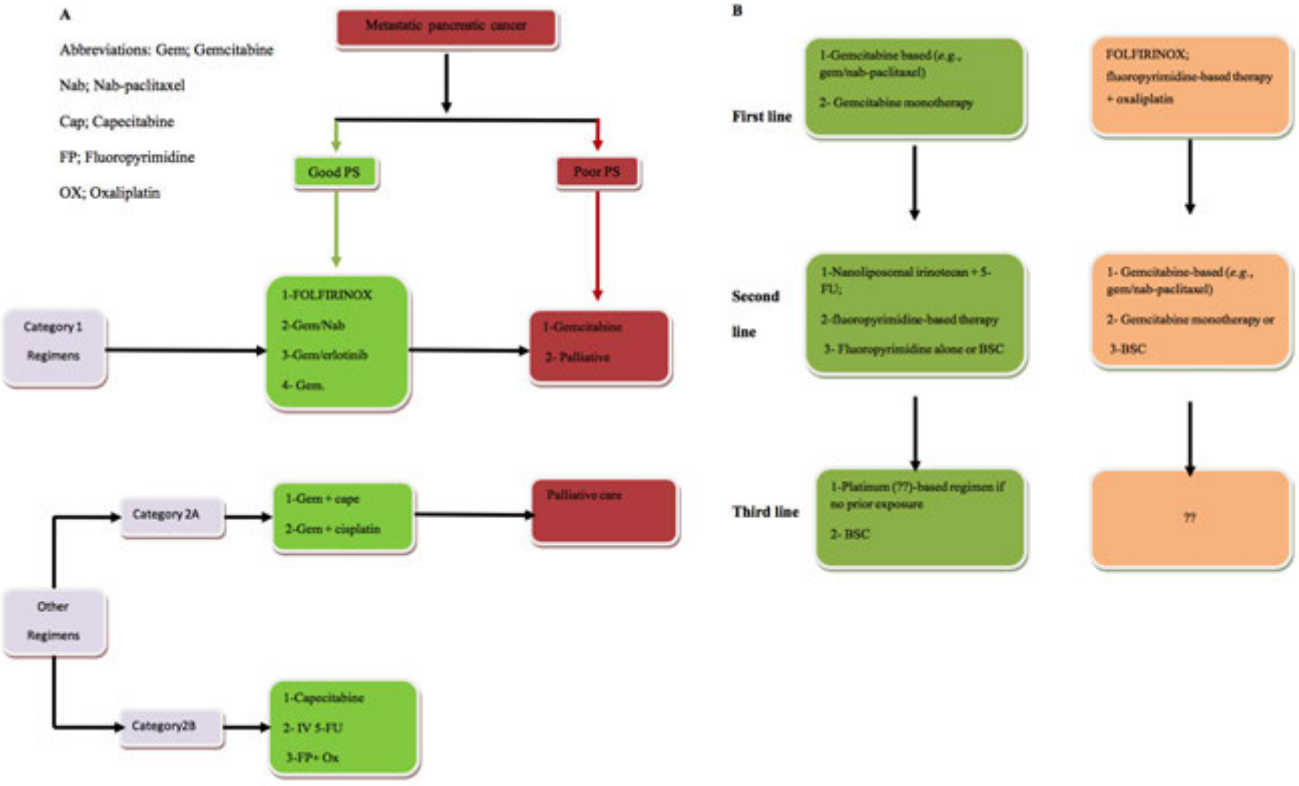

Figure 1. A) Proposed algorithm for chemotherapy in dAPC, for first line; B) chemotherapy after progression on first-line treatment.

revealed two of four patients with APC on pembrolizumab had objective response.[36]

Cancer vaccine

Preparing the immune cells to recognize and kill tumor cells in vivo is the rationale to use cancer vaccine. Whole cell, antigen pulsed-DC vaccines, peptide/DNA, and mAb treatments represent the main types of immunotherapy that are currently being evaluated in clinical trials for dAPC.[37] Although the clinical efficacy of cancer vaccines remains unsatisfying, some recent data showed the possibility of personalized vaccination. Clinical application of dendritic cells-Cytokine-induced killer (DC-CIK) immunotherapy has been reported in clinical trials for dAPC.[38-41] However, the best results showed in the combination of DC-CIK immunotherapy and chemotherapy indicated by improvement in survival.[42]

Signal transduction inhibitors

Epidermal growth factor receptor (EGFR) is expressed in up to 50% of PC and is required for carcinogenesis even with K-ras mutation. The erlotinib, is small TKI inhibitor, the only approved target therapy combined with gemcitabine in APC based on NCIC CTG PA.3 (explained in previous part).[43] Nimotuzumab, matuzumab, and panitumumab are anti-EGFR monoclonal antibodies proved prolonged 1-year OS in combination with gemcitabine vs. single agent gemcitabine in primary results from phase I and II trials.[44-46] However, cetuximab failed to improve the outcome.[47]

Janus kinase inhibitors

Also called JAK inhibitors, act through interfering with the JAK-STAT signaling pathway. Ruxolitinib, is JAK inhibitor evaluated in combination with capecitabine *vs* monotherapy capecitabine in dAPC after gemcitabine, failed to significantly improve the survival outcome.[48]

Discussion

PC is a devastating disease; scarcely respond to conventional therapies, and a leading cause of cancer related mortality. Still, treatment of dAPC is a challenging, possibly because of the lacking adequate screening tools, nonspecific presentations make most of the cases diagnosed in advanced stages, and distinguish biology resulting in rapid development of therapy resistance.

Typically, cancer management is multidisciplinary team and according to World Health Organization (WHO), palliative care is appropriate for involving early in the disease course. Temel and colleagues evaluated the impact of early incorporation of palliative care in metastatic non-small-cell lung cancer, and reported that the early referral to palliative care was associated with improvement in quality of life and survival.[49] Moreover, in a large based study involved 416 patients with multiple cancer sites revealed the same findings.[50]

Many factors must be in mind before choosing the therapy. PS is a critical factor of selecting treatment for patients with dAPC to determine who is more likely to benefit from chemotherapy. Good PS (90%-100%) is usually associated with chemotherapy benefit, in contrary, patients with poor PS (60-80%) only gains toxicity without survival outcome. Other factors included co morbidity conditions (*e.g.*, preexisting sensory neuropathy), patient's preference, appropriateness, cost of treatment course, and lacking of predictive biomarkers.[51] Involvement in patients in treatment decision and discussing the aims of therapy is an essential part of treatment plan, and participation in clinical studies is recommended.

Two front line regimens, gemcitabine plus Albumin-bound and FOLFIRINOX, have demonstrated survival benefit of patients with APC in phase III trials (MPACT and PRODIGE, respectively). Due to imminent side effects, the investigators advised to use modified FOLFIRINOX in the form of doses attenuation or omitting bolus 5-FU and used growth factor support with encouraging results in form of improved safety profile with maintained efficacy.[52]

However, to maximize the response, we need optimal treatment based on predictive markers which are deficient, in dAPC management. The value of measuring the hENT1 and SPARC in selecting gemcitabine and nap-paclitaxel containing regimens are conflicting and need more active research. A question appeared on the scene in the last period about the role of maintenance therapy in dAPC. Management of treatment free periods is a matter of debate after first line systemic therapy and before disease progression. Generally, the options include stopping the toxic drugs, stopping the treatment or use different agents for maintenance. PACT-12 is a randomized phase II trial evaluating the sunitinib after first line chemotherapy *vs* observation. The results failed to validate the role of maintenance treatment of PC. Despite the improvement in 1- and 2-year survival rate in sunitinib arm suggesting its possible value in subset of patients, which may need additional trials to be validated.[53]

Historically, about 50% of patients were suitable candidates for second line treatment and until recently, we did not have a clear guideline after first line failure. Second-line/salvage treatment of nanoliposomal irinotecan plus 5-FU/LV following gemcitabine-based therapy is evidenced based. Because the lack of competence of nanoliposomal irinotecan monotherapy and significant toxicity. The FDA emphasized in that the approval for combined manner and not approved for use as single agent.

A lot of known genetic syndromes as Lynch syndrome (HNPCC) and familial breast cancer (BRCA2) may increase an individual risk of evolving PC. The genetic events are either inherited or acquired leading to PC development over years passing by three steps known as pancreatic intraepithelial neoplasia (PanIN). The early stage ((PanIN-1) is characterized by small number of gene changes with little changes in pancreatic cells, in contrast, the PanIN-3 changes occurred in several genes with marked anaplasia in cells. *KRAS* oncogene, which controls on cell cycle growth, is the most common, affected one. Efforts are needed to diagnose it in the pre-cancerous stage even in pancreatic juice collected during an endoscopic retrograde cholangiopancreatography (ERCP). Right now; genetic tests are optional for patients with strong family history and are not recommended for general use.

Novel therapeutics under investigation may one day complement, but is unlikely to replace standard cytotoxic agents include immunotherapies, stromal-depleting agents, and signal transduction inhibitors. The molecular sub classification of PC is a new avenue may help in personalized therapies.

Conclusions

Causes, diagnosis, and treatment of PC is an active area of

research, need more efforts. There is more pressing need to think about second-line therapies and beyond. Novel chemotherapeutic agents (*e.g.*, nab-paclitaxel and nanoliposomal irinotecan) may gain more value when combined with target agents. Also, we are in urgent need for biomarkers that allow molecular monitoring during the disease course.

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