Clinical Roundtable Monograph

Clinical Advances in Hematology & Oncology November 2017

Recent Advances in the Treatment of Pancreatic Adenocarcinoma

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Abstract: Although pancreatic cancer is rare, it is the fourth-leading cause of cancer-related mortality. Pancreatic adenocarcinoma is the most common type of pancreatic cancer, accounting for approximately 95% of cases. At diagnosis, it is estimated that less than 10% of patients have localized disease, 29% have regional disease, and 52% have distant metastases and might be eligible for palliative treatment only. Optimal management of pancreatic cancer requires early referral to a medical oncologist. Therapeutic goals should address both symptom improvement and survival. In the metastatic setting, advances in systemic therapy are improving outcome. For years, the standard therapy was single-agent gemcitabine, and this approach is still used for patients who have a poor performance status, who are elderly, or who have comorbidities. More recent strategies include oxaliplatin, irinotecan, fluorouracil, and leucovorin (FOLFIRINOX) and gemcitabine plus albumin-bound (nab)-paclitaxel. In 2015, the US Food and Drug Administration approved the use of nanoliposomal irinotecan in combination with fluorouracil and leucovorin for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy. Multiple novel strategies are being evaluated for patients with pancreatic cancer. A multidisciplinary team that includes an interventional gastroenterologist is appropriate for all patients with pancreatic cancer, regardless of disease stage. Proactive management of potential complications is essential for maintaining adherence to treatment and maximizing clinical outcomes.

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Target Audience

This activity has been designed to meet the educational needs of oncologists and nurses involved in the management of patients with pancreatic cancer.

Statement of Need/Program Overview

Pancreatic adenocarcinoma is the most common type of pancreatic cancer, accounting for approximately 95% of cases. For years, the standard therapy was single-agent gemcitabine, and this approach is still used for patients who have a poor performance status, who are elderly, or who have comorbidities. For patients eligible for more aggressive therapy, options include oxaliplatin, irinotecan, fluorouracil, and leucovorin (FOLFIRINOX) and gemcitabine plus albumin-bound (nab)-paclitaxel. A newer therapy that has shown a significant benefit in overall survival is nanoliposomal irinotecan, which is approved by the US Food and Drug Administration (FDA) for use in combination with fluorouracil and leucovorin for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy. With these newer treatment regimens, a small percentage of patients are surviving for multiple years after a diagnosis of metastatic pancreatic cancer. This monograph describes the latest clinical data and provides insight into the best use of available therapies, including sequencing and management of adverse events.

Educational Objectives

After completing this activity, the participant should be better able to:

- Explain how a patient's disease stage, age, and comorbidities influence selection of treatment for pancreatic adenocarcinoma
- Discuss when to initiate palliative care
- Describe data from the latest clinical trials of therapies in pancreatic adenocarcinomas
- Devise management strategies based on guidelines from the National Comprehensive Cancer Network and the European Society for Medical Oncology

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Unmet Needs in the Management of Pancreatic Adenocarcinoma

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Although pancreatic cancer accounts for only 3% of new cancer diagnoses in the United States, it is the fourth-leading cause of cancer-related death.[1] The incidence of pancreatic cancer is increasing, and outcomes remain poor. By 2030, pancreatic cancer is expected to become the second-leading cause of cancer-related mortality.[2] The incidence is highest among individuals ages 65 to 74 years.[3]

Pancreatic adenocarcinoma is the most common type of pancreatic cancer, accounting for approximately 95% of cases. Another 4% are pancreatic neuroendocrine tumors, which include functional tumors that secrete neuroendocrine substances and nonsecreting or nonfunctional tumors. The remaining pancreatic tumor types are uncommon histologies, such as acinar cell carcinoma, as well as metastases to the pancreas arising from the kidney and other organs.

Detection of pancreatic cancer is hampered by a lack of available screening modalities and the absence of hereditary factors in most patients.[4] A small fraction of pancreatic cancers can be attributed to inherited genetic causes, such as the very rare hereditary pancreatitis syndrome. However, other prevalent conditions include Lynch syndrome (germline mutations of *MLH1*, *MSH2, MSH3*, *EPCAM*, *PMS2*, or *MSH6* genes), hereditary breast and ovarian cancer syndrome (germline *BRCA1*, *BRCA2*, or *PALB2* mutations), Li–Fraumeni syndrome (germline *TP53* mutation), ataxia-telangiectasia syndrome (*ATM* mutation), familial melanoma (*CDKN2A* germline mutation), familial adenomatous polyposis (germline *APC* mutation), and Peutz–Jeghers syndrome (germline *STK11* mutation), among others.[4]

Most patients with pancreatic cancer are diagnosed with locally advanced unresectable disease or metastatic disease. At diagnosis, it is estimated that only less than 10% of patients have resectable disease, while 29% have regional/borderline resectable disease. Approximately 52% present with distant metastases and might be eligible for palliative treatment only.[3] In the past 10 years, a new category known as borderline resectable has been delineated. Borderline resectable refers to patients in whom neoadjuvant chemotherapy, with or without radiation therapy, has the potential to allow conversion to surgical resectability.[5]

Outcome for patients with pancreatic cancer remains dismal. The median overall survival for patients with locally advanced disease is approximately 20 months, even with adjuvant therapy.[6] Adjuvant chemotherapy has shown clinical benefit in patients with resectable pancreatic adenocarcinoma, with gemcitabine demonstrating a significant survival advantage compared with observation.[7] For many years, single-agent gemcitabine had been the only standard-of-care systemic adjuvant therapy, and it was added to radiation therapy when indicated (based on the status of lymph nodes and resection margins). Data from the ESPAC-4 trial (European Study Group for Pancreatic Cancer trial 4) recently showed that the combination of gemcitabine plus capecitabine improved overall survival vs gemcitabine alone (median overall survival, 28.0 vs 25.5 months; hazard ratio, 0.82; P=.032).[8]

In the metastatic setting, a variety of systemic therapies are used. For years, the standard therapy was single-agent gemcitabine, and this approach is still used for patients who have a poor performance status, who are elderly, or who have comorbidities.[9] For patients eligible for more aggressive therapy, the National Comprehensive Cancer Network (NCCN) guidelines[9] recommend oxaliplatin, irinotecan, fluorouracil, and leucovorin (FOLFIRINOX), based on results from the ACCORD trial (Actions Concertées dans les Cancers Colorectaux et Digestifs),[10] or gemcitabine plus albumin-bound (nab)-paclitaxel, based on results of the MPACT trial (A Randomized Phase III Study of Weekly ABI-007 Plus Gemcitabine Versus Gemcitabine Alone in Patients With Metastatic Adenocarcinoma of the Pancreas).[11,12]

In a real-world analysis of patients receiving selected therapies for metastatic pancreatic cancer, 49% received nab-paclitaxel, 32% received FOLFIRINOX, and 19%

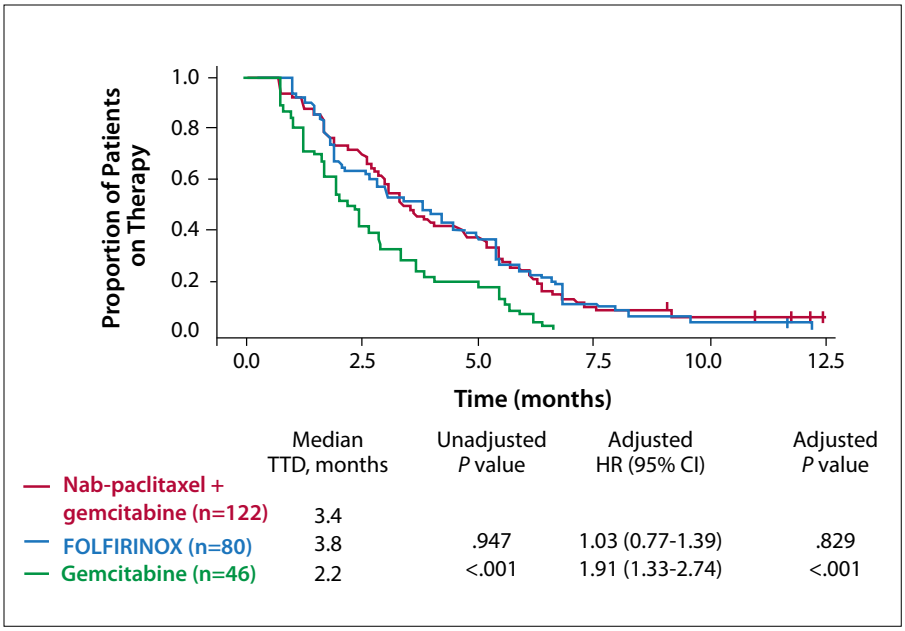

Figure 1. The proportions of patients with metastatic pancreatic cancer who remained on treatment in a real-world analysis. HR, hazard ratio; TTD, time to treatment discontinuation. Adapted from Braiteh F et al. *Cancer Manag Res*. 2017;9:141-148.[13]

Table 1. Use of Supportive Care: Doses per 100 Days

	Nab-Paclitaxel Plus Gemcitabine (n=122)	FOLFIRINOX (n=80)	Gemcitabine (n=46)	*P* Value[a]	*P* Value[b]
Antianxiety/antiemetic agents	6.94	6.30	5.22	.057	<.001
Erythropoiesis-stimulating agent	0.90	0.13	0.54	<.001	.033
Granulocyte colony-stimulating factor	2.02	4.41	0.73	<.001	<.001
Corticosteroids	7.89	5.79	5.38	<.001	<.001

[a]*P* value for nab-paclitaxel plus gemcitabine vs FOLFIRINOX.

[b]*P* value for nab-paclitaxel plus gemcitabine vs gemcitabine.

FOLFIRINOX, folinic acid, 5-fluorouracil, irinotecan, and oxaliplatin.

Adapted from Braiteh F et al. *Cancer Manag Res*. 2017;9:141-148.[13]

received single-agent gemcitabine.[13] In this analysis, nab-paclitaxel plus gemcitabine and FOLFIRINOX appeared to have comparable effectiveness. Patients treated with nab-paclitaxel plus gemcitabine remained on therapy longer than patients who were treated with gemcitabine alone (Figure 1). Nab-paclitaxel plus gemcitabine was associated with a lower incidence of adverse events and fewer requirements for granulocyte-colony stimulating factor support. However, this regimen required more frequent use of erythropoiesis-stimulating agents, antiemetic agents, and corticosteroids (Table 1).

The combination of gemcitabine and erlotinib, which targets the human epidermal receptor growth factor receptor 1/epidermal growth factor receptor, is also included in the NCCN guidelines.[9] However, the combination provides only a 2-week improvement in survival over gemcitabine alone.[14]

Clearly, there is an unmet clinical need for additional options for the treatment of pancreatic cancer. In the second-line setting, clinical trials had been limited primarily to small institutional and single-arm studies. Regimens under evaluation in clinical trials have included FOLFIRINOX[10]; oxaliplatin, folinic acid, and fluorouracil (5-FU)[15]; oxaliplatin plus 5-FU and leucovorin (LV; FOLFOX)[16]; and capecitabine plus oxaliplatin.[17] None of these trials led to significant changes in the treatment landscape. One regimen that has demonstrated a significant survival benefit is the combination of nanoliposomal irinotecan plus 5-FU/LV, which showed a significant survival improvement over 5-FU/LV alone in the

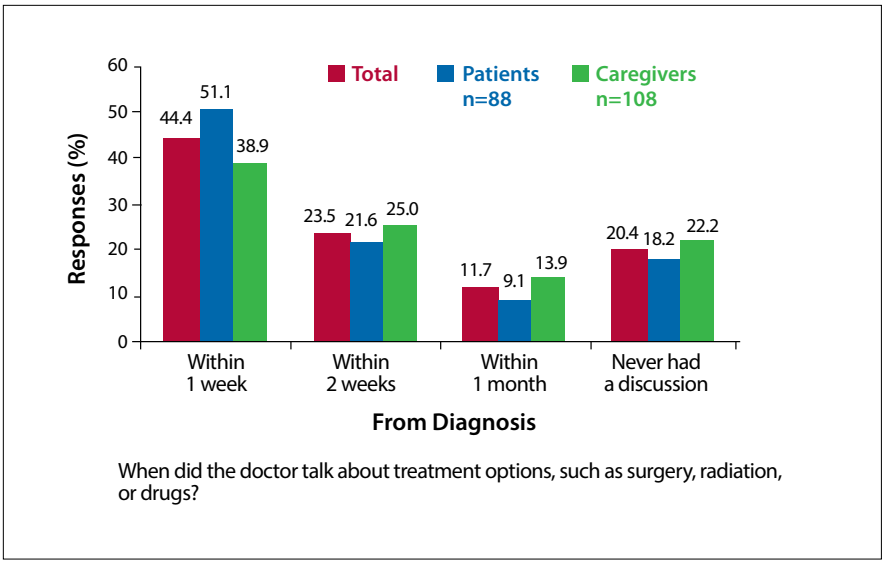

Figure 2. In a survey of patients with pancreatic cancer and their caregivers, 20.4% of respondents reported that the diagnosing physician did not discuss treatment options. Adapted from Engebretson A et al. *J Gastrointest Oncol.* 2016;7(2):228-233.[20]

randomized, phase 3 NAPOLI-1 trial (Nanoliposomal Irinotecan).[18]

Challenges in Pancreatic Cancer Treatment

Several other factors negatively impact outcomes for patients with pancreatic cancer. Studies have shown undertreatment of patients with both localized and advanced disease.[19] In a 2013 survey of patients with pancreatic cancer and their caregivers, 20.4% of respondents reported that the diagnosing physician did not discuss treatment options (Figure 2).[20] The most common reasons for not receiving treatment were that the doctor said nothing could be done (42.1%) and the patient did not think therapy would help (36.8%).[20] Undertreatment is particularly relevant to older patients, in whom comorbidities and polypharmacy are more common than younger patients.[21] Older patients are also less likely to enroll in clinical trials.[21]

The state of patients' general health can present challenges for the treatment of pancreatic cancer. There is often a high burden of symptoms at diagnosis, including cachexia, weight loss, anorexia, immune system dysfunction, and thromboembolic disease. These conditions can interfere with treatment and quality of life, particularly in older patients with comorbidities.

Pancreatic cancer is associated with a high incidence of depression. Although this association may not be surprising given the prognosis, approximately half of patients have signs of depression in the year prior to diagnosis, suggesting that there is a physiologic component.[22] Pancreatic cancer is also associated with a high incidence of pancreatic exocrine insufficiency, a condition in which pancreatic enzymes important for digestion are not properly secreted by the pancreas, resulting in malnutrition caused by a lack of vitamins and other nutrients.[23] In some cases, the onset of pancreatic exocrine insufficiency precedes the diagnosis of pancreatic cancer. Pancreatic exocrine insufficiency is often overlooked by physicians, who may not address the condition until it progresses to steatorrhea, the presence of high fat content in the stool that is associated with abdominal pain, flatulence, and weight loss.[23] However, once steatorrhea is identified, the patient's vitamin and nutrient absorption has already been compromised.

Another challenge for patients with pancreatic cancer is pain. Even patients with locally advanced disease can develop complex pain that includes visceral, somatic, and neuropathic components.[24] Pain associated with pancreatic cancer requires early introduction of opioids, with dose adjustments as appropriate and measures to prevent opioid-induced constipation, which can exacerbate symptoms. Interventional pain services may be considered to assist in pain control.

These symptoms and others not only cause problems for patients, but they also can interfere with the delivery of appropriate treatment.[25] It is essential that patients receive appropriate care to maximize outcomes. Early palliative care consultations have been shown to improve pain management and reduce visits to emergency departments related to pain.[25] A multidisciplinary care team that includes an interventional gastroenterologist is appropriate for all patients with pancreatic cancer, regardless of disease stage. Proactive management of potential complications (eg, opioid-induced constipation, cholestasis, stent infection, and pancreatic exocrine steatorrhea) is essential for maintaining adherence to treatment and maximizing clinical outcomes. Thus, therapeutic goals

should address both symptom improvement and survival. Enrollment in clinical trials should always be considered when formulating the treatment plan.

Disclosure

Dr Braiteh has received honoraria from Amgen, BMS, Genentech, AstraZeneca, Insys, Incyte, Ipsen, and Tesaro. He is a consultant or advisor for Amgen, Genentech, AstraZeneca, Insys, Incyte, Ipsen, and Lexicon. He is a member of the speakers bureaus of Amgen, BMS, Genentech, Boehringer Ingelheim, AbbVie, AstraZeneca, Celgene, Pfizer, Clovis, Lexicon, and Taiho.

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Development of New Pharmaceutical Therapies for Pancreatic Adenocarcinoma

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Despite substantial research efforts undertaken to identify new effective therapies for the treatment of pancreatic adenocarcinoma, progress has been slow. Among the novel approaches that have shown initial activity but yielded negative results in randomized trials are the hypoxia-activated prodrug evofosfamide,[1] the Janus kinase 1/2 inhibitor ruxolitinib,[2] the oral tyrosine kinase inhibitor masitinib,[3] the vaccine product algenpantucel-L,[4] the radiolabeled ^{90}Y-clivatuzumab tetraxetan,[5] and PEGPH20 administered in combination with FOLFIRINOX.[6]

One approach that has shown a significant benefit in overall survival in patients with pancreatic cancer is nanoliposomal irinotecan, which is approved by the US Food and Drug Administration (FDA) for use in combination with 5-FU/LV for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy.[7] This indication encompasses not only the second-line setting, but also patients who have received prior gemcitabine as an adjuvant treatment. For these patients, nanoliposomal irinotecan can be used in the first-line metastatic setting. The irinotecan preparation uses a novel nanoliposomal product that has been designed to enhance drug delivery to tumors.[8]

Preclinical Rationale for Nanoliposomal Drug Delivery

The development of nanoliposomal drug delivery systems was based on the observation that liposomes deposited into tumors are scavenged by tumor-resident macrophages that take in the encapsulated product. Nanoliposomal irinotecan is converted by macrophages to its more active metabolite, SN-38. The nanoliposomal drug is also passively targeted to tumor sites owing to the hypervascular nature of tumors and their enhanced permeability to macromolecules, a property known as the enhanced permeability and retention effect.[8,9] In animal studies, nanoliposomal irinotecan demonstrated a 70-fold increase in the area under the curve compared with conventional irinotecan; increased drug concentrations were detectable in the plasma, blood, and tumor.[10] Together, these data provided a strong rationale for the investigation of a nanoliposomal drug delivery system in pancreatic cancer.

Clinical Trials of Nanoliposomal Irinotecan in Pancreatic Cancer

Nanoliposomal irinotecan was initially evaluated in a phase 1 dose-escalation study, which showed favorable pharmacokinetics and suggested potential antitumor activity in patients with solid tumors.[11] Subsequently, a phase 2 trial evaluated the activity and safety of nanoliposomal irinotecan as monotherapy in 40 patients with gemcitabine-refractory pancreatic cancer.[12] The agent was associated with a 3-month overall survival rate of 75%. Median progression-free survival was 2.4 months, and median overall survival was 5.2 months. The safety profile was acceptable.

Outcomes in the phase 2 trial led to the initiation of the global, randomized, open-label, phase 3 NAPOLI-1 trial, in which 417 patients with metastatic pancreatic ductal adenocarcinoma previously treated with gemcitabine-based therapy were randomly assigned to nanoliposomal irinotecan plus 5-FU/LV (n=117), nanoliposomal irinotecan monotherapy (n=151), or 5-FU/LV (n=149).[13] The combination of nanoliposomal irinotecan plus 5-FU/LV was significantly more effective than 5-FU/LV. Median overall survival was 6.1 months with nanoliposomal irinotecan plus 5-FU/LV vs 4.2 months for 5-FU/LV alone (hazard ratio, 0.67; 95% CI, 0.49-0.92; *P*=.012; Figure 3).[13] Nanoliposomal irinotecan plus 5-FU/LV also improved median progression-free survival compared with 5-FU/LV alone (3.1 months vs 1.5 months; unstratified hazard ratio, 0.56; 95% CI, 0.41-0.75; *P*=.0001; Figure 4). The median overall survival with single-agent nanoliposomal irinotecan was 4.2 months. A per-protocol analysis of the NAPOLI trial included patients who had received at least 80% of the scheduled doses during the first 6 weeks of treatment (n=66 in the nanoliposomal irinotecan plus 5-FU/LV arm vs n=71 in

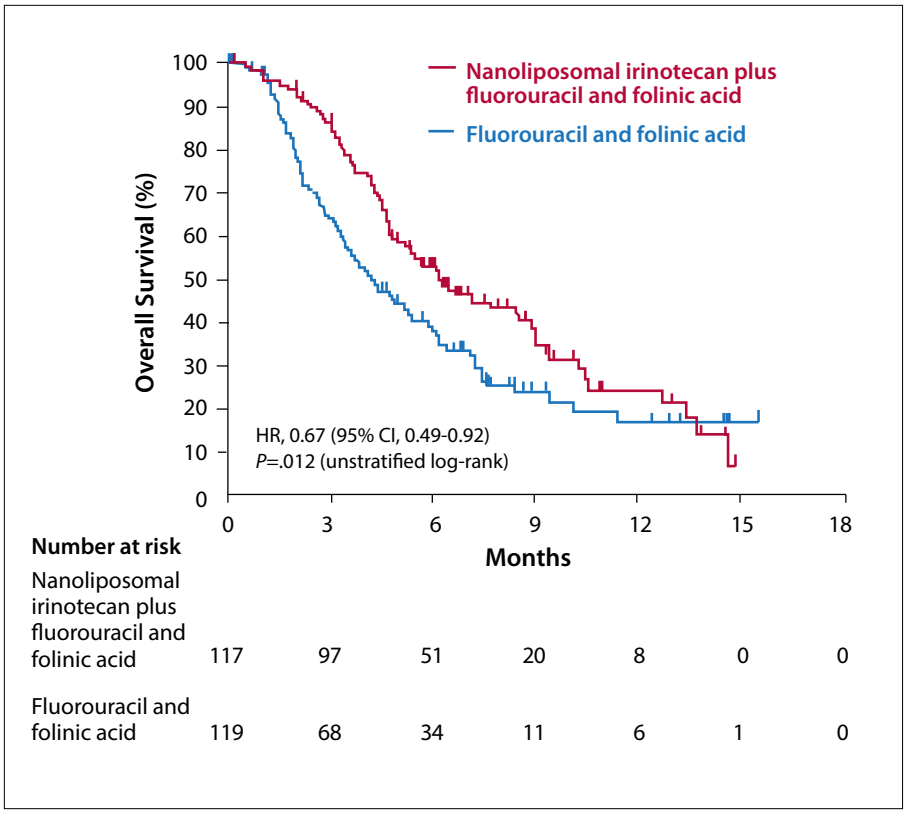

Figure 3. Median overall survival in the phase 3 NAPOLI-1 trial. HR, hazard ratio; NAPOLI-1, Nanoliposomal Irinotecan. Adapted from Wang-Gillam A et al. *Lancet.* 2016;387(10018):545-557.[13]

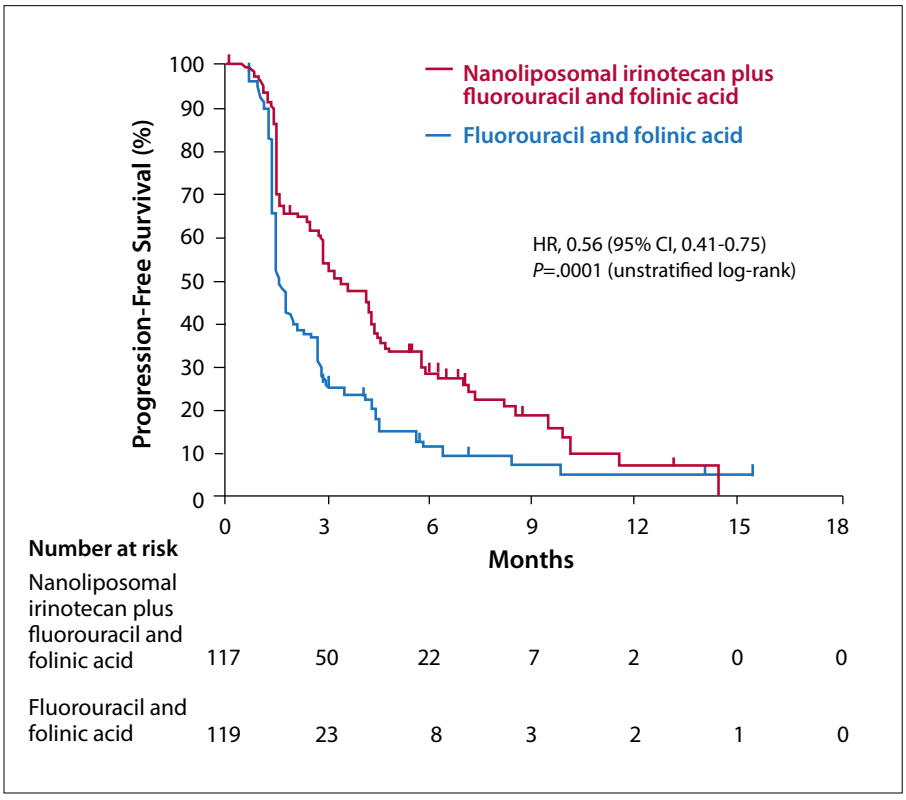

Figure 4. Progression-free survival in the phase 3 NAPOLI-1 trial. HR, hazard ratio; NAPOLI-1, Nanoliposomal Irinotecan. Adapted from Wang-Gillam A et al. *Lancet.* 2016;387(10018):545-557.[13]

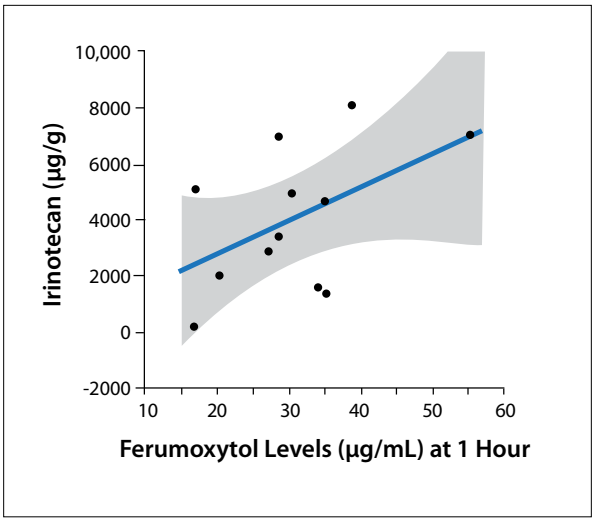

Figure 5. Relationship between lesion ferumoxytol concentrations measured at 1 hour and the average irinotecan concentrations measured in biopsies. Adapted from Ramanathan RK et al. *Clin Cancer Res*. 2017;23(14):3638-3648.[22]

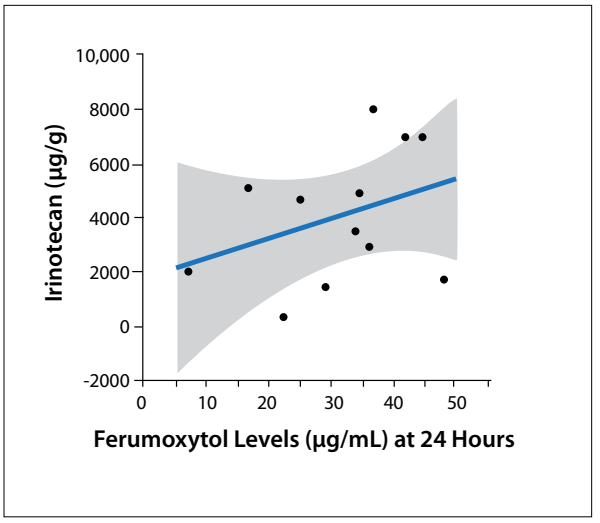

Figure 6. Relationship between lesion ferumoxytol concentrations measured at 24 hours and the average irinotecan concentrations measured in biopsies. Adapted from Ramanathan RK et al. *Clin Cancer Res*. 2017;23(14):3638-3648.[22]

the 5-FU/LV arm).[14] The median overall survival was 8.9 months in patients treated with nanoliposomal irinotecan plus 5-FU/LV vs 5.1 months for those treated with 5-FU/LV alone (stratified hazard ratio, 0.47; *P*=.0018).

The grade 3/4 toxicities that were more common with nanoliposomal irinotecan plus 5-FU/LV compared with the control arm of 5-FU were neutropenia (27% vs 1%), diarrhea (13% vs 4%), vomiting (11% vs 3%), and fatigue (14% vs 4%).

Based on the trial results and subsequent FDA approval of nanoliposomal irinotecan, this regimen should be considered a standard second-line regimen for patients who develop progressive disease after gemcitabine. One notable point about the NAPOLI-1 trial is the treatment history of enrolled participants. Because the trial was initiated before the common use of gemcitabine and nab-paclitaxel, only 13% of patients had received this combination as first-line therapy. However, 55% had received combination therapy with gemcitabine, and based on the nonoverlapping mechanisms of action with gemcitabine and nab-paclitaxel, the combination of nanoliposomal irinotecan plus 5-FU/LV as second-line therapy is reasonable and supported by the NCCN guidelines.[15]

Other Novel Strategies

Multiple other novel strategies are being evaluated for patients with pancreatic cancer. PEGPH20 combined with FOLFIRINOX showed no benefit at the interim futility analysis of a phase 2 trial,[6] but it continues to be evaluated in combination with other active agents based on promising activity in preclinical studies. One trial is evaluating PEGPH20 in combination with gemcitabine and nab-paclitaxel.[16] A recent abstract presentation of the HALO-109-201 study suggested that high levels of tumor hyaluronan may predict benefit from PEGPH20 used in combination with gemcitabine/nab-paclitaxel, indicating a potential biomarker for PEGPH20 responses.[17] Based on the encouraging results of the HALO-109-201 study, a randomized, placebo-controlled phase 3 study known as HALO-109-301 has been initiated in patients with tumors showing high expression of hyaluronan.[18]

Ibrutinib, a Bruton tyrosine kinase inhibitor, is also being evaluated in combination with gemcitabine/nab-paclitaxel in late-stage clinical trials.[19] Ibrutinib inhibits mast cell degranulation, causing stromal weakening, and it may also have immunostimulatory properties.

Another promising agent being evaluated in phase 3 trials is the signal transducer and activator of transcription 3 (STAT 3)-targeting drug napabucasin, which aims to inhibit cancer stem cell signaling pathways. In a phase 1/2 study in 66 patients with metastatic pancreatic cancer, the combination of napabucasin, nab-paclitaxel, and gemcitabine appeared to have antitumor activity, with an overall response rate of 55%.[20] The randomized, open-label, multinational CanStem111P trial is evaluating the addition of napabucasin to gemcitabine and nab-paclitaxel in approximately 1132 patients with metastatic pancreatic cancer.[21]

Work is also ongoing to develop biomarkers to assess

the activity of nanoliposomal irinotecan. Tumors with high concentrations of macrophages in the stroma may be more susceptible to nanoliposomal irinotecan based on higher concentrations of SN-38. One potential tool for measuring local macrophage concentrations is uptake of the iron-replacement agent ferumoxytol. The level of ferumoxytol in the tumor, as assessed by quantitative magnetic resonance imaging, appeared to correlate with responses to nanoliposomal irinotecan in preliminary studies (Figures 5 and 6).[22] Work is ongoing to further evaluate ferumoxytol as a biomarker for response to nanoliposomal irinotecan.

Disclosure

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Advances in the Management of Pancreatic Adenocarcinoma: Guidelines and Clinical Practice

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Optimal management of pancreatic cancer hinges upon early referral to a medical oncologist for a proper assessment. Performance status is a key consideration in treatment planning. Patients with a poor performance status (>2) are not likely to benefit from anticancer therapy and should instead receive best supportive care. It should be noted, however, that patients with a new diagnosis of pancreatic cancer could have functional limitations related to symptoms caused by the cancer itself. In such patients, it may be possible to improve performance status so that active treatment may become an option.

It is also important that, whenever possible, patients with pancreatic cancer receive care in a specialized center that is familiar with current practices. This approach may reduce the likelihood of less-optimal treatment.[1] Although treatment in specialized cancer centers was thought to benefit primarily those with early-stage cancers, recent data suggest that patients with complex conditions, such as pancreatic cancer, benefit from referral to specialized care centers regardless of stage.[2]

Clinical trial participation is a key aspect of pancreatic cancer treatment, as addressed in multiple treatment guidelines. Clinical guidelines from the NCCN[3] clearly state that a clinical trial is the best management option for patients with a diagnosis of cancer, and those from the National Cancer Institute[4] recommend that patients always be considered for clinical trials prior to initiating palliative therapy. Participation in clinical trials remains a challenge, as they are often available only in larger academic centers, and many eligible patients may not have access for various reasons. Unfortunately, only approximately 12% of US patients with pancreatic cancer enroll in clinical trials.[5] Efforts to educate physicians as well as patients regarding the importance of referral to a clinical trial, whenever possible, may improve access and overall outcomes.

Although survival rates for patients with pancreatic cancer remain bleak, outcomes have improved, albeit modestly, in recent years, with 5-year overall survival rates improving from approximately 4% in the early 2000s to 8% following the year 2010.[6] These trends highlight that, in small steps, strides are being made in the treatment of pancreatic cancer, primarily owing to improvements in systemic therapy. Newer treatment regimens, including gemcitabine and nab-paclitaxel, FOLFIRINOX, and nanoliposomal irinotecan plus 5-FU/LV, have changed the landscape in such a way that a small percentage of patients are surviving for multiple years after a diagnosis of metastatic pancreatic cancer. For example, in the phase 3 MPACT trial, 3% to 4% of patients receiving gemcitabine and nab-paclitaxel were still alive after 3 years, compared with no patients receiving gemcitabine alone.[7] These outcomes reflect a slow movement toward survival targets that were thought to be impossible in this disease.

Clinical Guidelines for Pancreatic Cancer

The guidelines primarily utilized in the community are those from the NCCN, which are updated frequently (most recently in September 2017), and those from the European Society for Medical Oncology (ESMO), which are published approximately every 3 years.[3,8,9] The ESMO guidelines are occasionally updated electronically to reflect treatment advances; they were most recently updated in June 2017 to add nanoliposomal irinotecan and 5-FU/LV for pancreatic cancer.[8,9]

The NCCN guidelines tend to be more extensive than the ESMO guidelines. They categorize treatments based on levels of evidence. Current NCCN guidelines recommend nanoliposomal irinotecan and 5-FU/LV as a category 1 option for the second-line treatment of patients with metastatic pancreatic cancer who have good performance status and disease progression.[3]

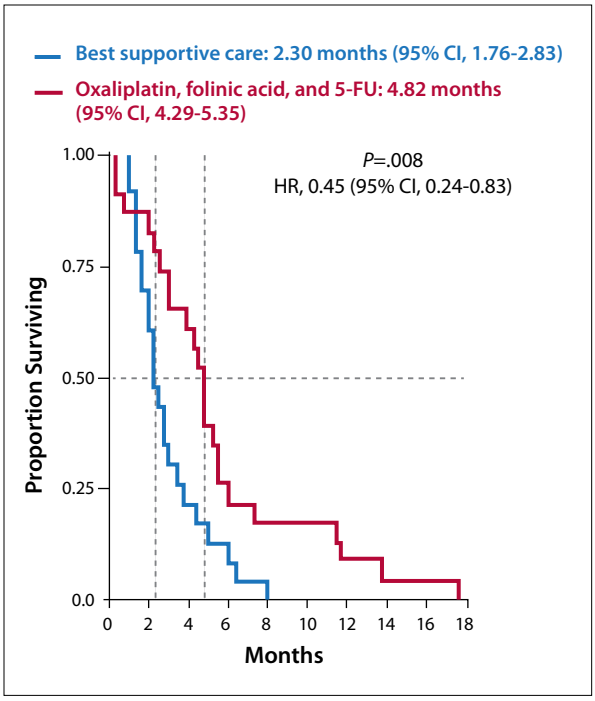

Figure 7. A trial from the CONKO study group showed a significant benefit with oxaliplatin, folinic acid, and 5-FU vs supportive care in the second-line setting. CONKO, German Charité Onkologie; 5-FU, fluorouracil; HR, hazard ratio. Adapted from Pelzer U et al. *Eur J Cancer*. 2011;47(11):1676-1681.[14]

Selecting Systemic Therapy in Pancreatic Cancer

Although there are some differences between the guidelines from the NCCN and ESMO, both promote the general aim of treating the right patient with the right regimen, with the goal of providing adequate palliation and extending survival. As newer regimens are introduced, treatment decisions become more complicated. The optimal sequencing of therapies has recently been brought into question. Clinicians often use FOLFIRINOX as initial therapy for patients who are relatively younger (typically <70 years old) and/or those with a great performance status. Another approach would be to start with gemcitabine plus nab-paclitaxel, regardless of the patient's age and performance status, leaving more therapy options for the second-line or even third-line settings. The choice between FOLFIRINOX and gemcitabine plus nab-paclitaxel in the first-line setting is largely driven by relative physician bias, given that the 2 regimens have not been compared in randomized studies. Historically and in separate studies, the median overall survival was 11.1 months with FOLFIRINOX vs 6.8 months with gemcitabine (P<.001),[10] and 8.7 months with gemcitabine plus nab-paclitaxel vs 6.6 months with gemcitabine (P<.0001).[7] However, a number of notable differences make the interpretation of the historical results very difficult, including the fact that the FOLFIRINOX trial enrolled a more highly selected patient population and included only subjects treated in French Centers of Excellence.[10]

In a real-world analysis of outcomes in patients with metastatic pancreatic cancer, Braiteh and colleagues found similar outcomes whether patients started with FOLFIRINOX or gemcitabine plus nab-paclitaxel.[11] The widespread use of FOLFIRINOX in the first-line setting is limited by the greater level of toxicity, and decreases salvage options beyond the first-line setting. In my practice, I tend to generally use a less-intensive biweekly regimen of gemcitabine plus nab-paclitaxel in the first-line setting,[12] reserving other therapies for later lines. This approach allows the use of nanoliposomal irinotecan plus 5-FU/LV as a second-line option. It is then possible to utilize a platinum-based therapy in the third-line setting, allowing a potential path for 3 lines of therapy while using a "gentler" treatment approach that maintains clinical benefit. Sequencing strategies, rather than a "kitchen-sink approach," are already widely adopted in the palliative setting of most other malignancies. Real-world data suggest that this approach does not compromise survival compared with the use of more aggressive initial therapy.[11]

Treatment Considerations for Patients With BRCA *Mutations*

A group of patients who require consideration of a different course of initial treatment are those with *BRCA1/2* mutations. These patients have an enhanced sensitivity to platinum agents and/or topoisomerase inhibitors, and therefore a regimen such as FOLFIRINOX or gemcitabine/cisplatin may be more beneficial earlier in the disease course.[13]

Choice of Second-Line Therapy

The selection of a second-line regimen depends on the type of exposure in the first-line setting. Historically, selection had been an ongoing challenge for oncologists. Traditionally, after gemcitabine/nab-paclitaxel, most clinicians in the United States have tended to use FOLFOX, based on the German Charité Onkologie (CONKO) study group trial showing a significant benefit with oxaliplatin, folinic acid, and 5-FU (OFF) vs supportive care in the second-line setting (Figure 7).[14] In contrast, the PANCREOX study (A Randomized Phase III Study of Fluorouracil/Leucovorin With or Without Oxaliplatin for Second-Line Advanced Pancreatic Cancer in Patients Who Have Received Gemcitabine-Based Chemotherapy)

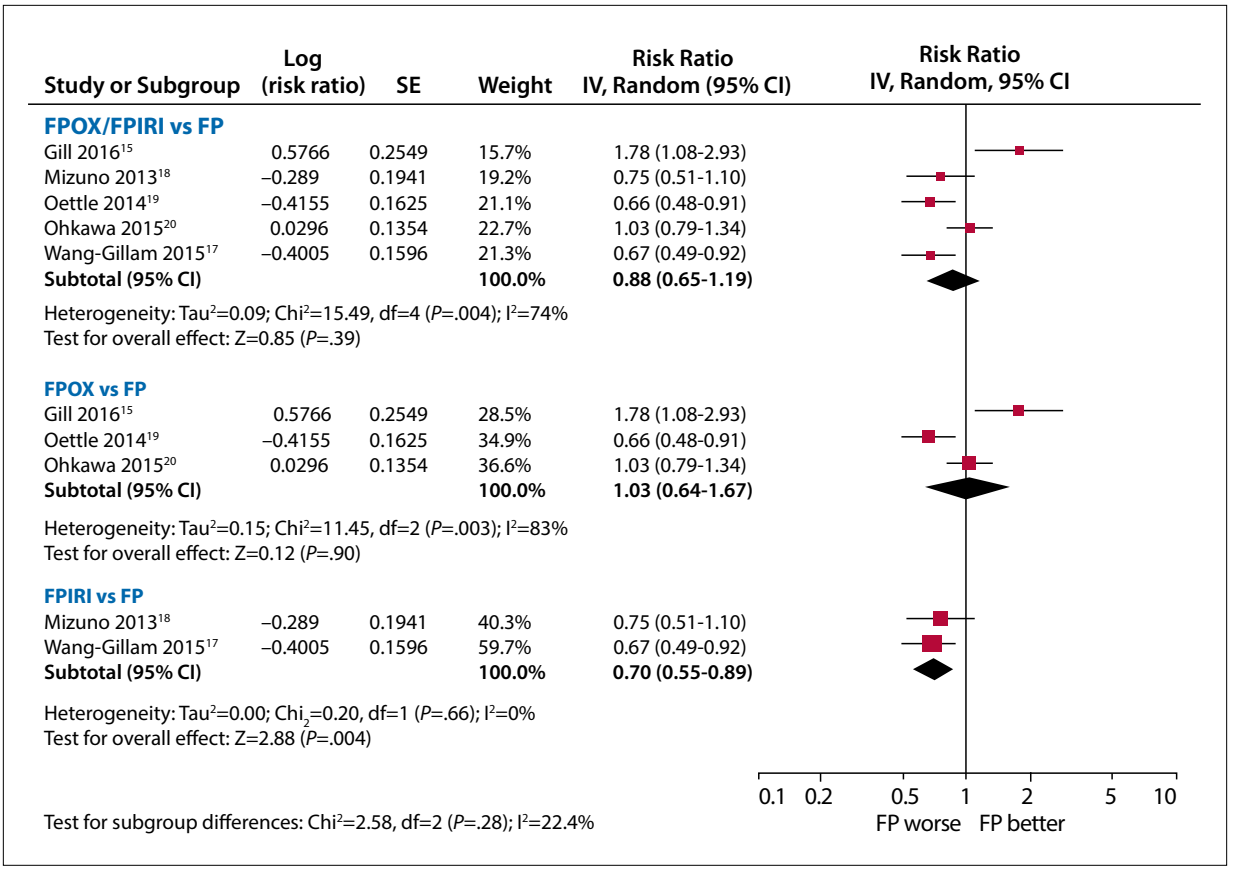

Figure 8. Comparison of overall survival in a meta-analysis evaluating second-line treatment in patients with pancreatic ductal adenocarcinoma. df, degrees of freedom; FP, fluoropyrimidine; FPIRI, fluoropyrimidine with irinotecan; FPOX, fluoropyrimidine with oxaliplatin; IV, inverse variance; SE, standard error. Adapted from Sonbol MB et al. Second-line treatment in patients with pancreatic ductal adenocarcinoma: a meta-analysis [published online August 17, 2017]. *Cancer*. doi:10.1002/cncr.30927.[16]

showed no benefit and added toxicities with the addition of oxaliplatin to 5-FU/LV vs 5-FU/LV alone.[15]

We recently published a meta-analysis evaluating all randomized, controlled trials of oxaliplatin-based and irinotecan-based regimens for the treatment of patients with progressive disease after first-line treatment of metastatic pancreatic cancer.[16] Only irinotecan-containing combinations appear to improve overall survival compared with fluoropyrimidine monotherapy (Figure 8), suggesting that nanoliposomal irinotecan plus 5-FU/LV should be the preferred option over FOLFOX for second-line treatment following disease progression on a gemcitabine-based regimen.

Managing Adverse Events

Combination regimens for the treatment of pancreatic cancer can have substantial toxicities. Patients who develop toxicities during treatment with FOLFIRINOX often require multiple dose reductions and growth-factor support.[10] Additionally, the regimen of gemcitabine and nab-paclitaxel has its own limiting toxicities. In particular, adequate delivery of weekly gemcitabine singly or in combination is notoriously difficult to maintain. Dose interruptions may be needed to manage cytopenias or other toxicities, as observed in clinical trials.[7] Neuropathy is of particular concern with nab-paclitaxel. Grade 3/4 peripheral neuropathy occurs in approximately 17% of patients receiving weekly gemcitabine and nab-paclitaxel.[7] Among patients treated with nab-paclitaxel, peripheral neuropathy leads to dose reductions in 10% and discontinuations in another 8%.[7] A modified biweekly regimen can be considered as a possible alternative. In a retrospective analysis, biweekly administration of gemcitabine and nab-paclitaxel was better tolerated while maintaining efficacy when compared with the historical weekly regimen (Figure 9).[12] Efforts are underway to have a direct comparison between biweekly and weekly dosing regimens. The toxicities associated with the nanoliposomal irinotecan and 5-FU/LV regimen are similar to what would be expected from an

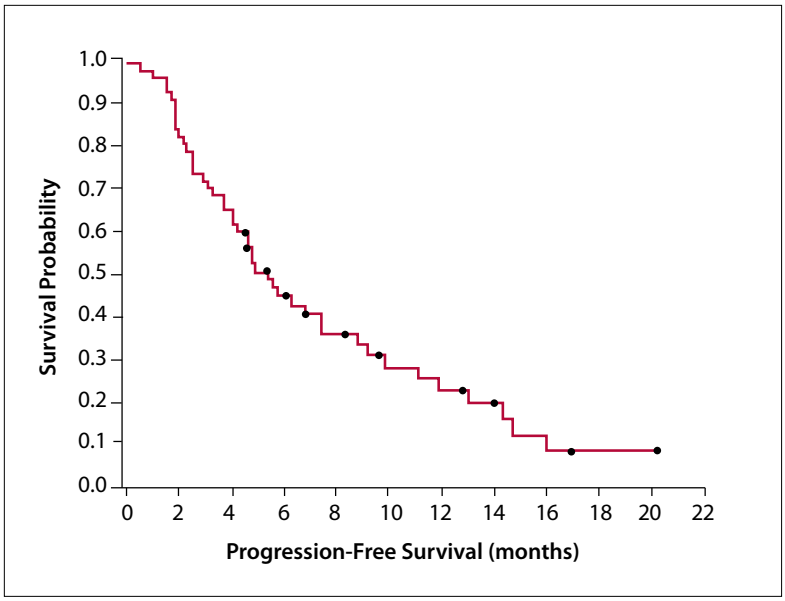

Figure 9. Progression-free survival among patients with metastatic pancreatic cancer who received first-line treatment with a modified regimen of gemcitabine (1000 mg/m^2) and nab-paclitaxel (125 mg/m^2) on days 1 and 15 of 28-day cycles. Adapted from Ahn DH et al. *Ther Adv Med Oncol*. 2017;9(2):75-82.[12]

irinotecan-based regimen, aside from a much lower rate of alopecia with the formulation.[17] Overall, it is essential to follow patients very closely, intervene with supportive measures, and use dose modifications as indicated to ensure exposure to optimal dose intensity while maximizing a balance between treatment efficacy and tolerability. With this comprehensive approach, one would maximize a balanced outcome of palliation and prolongation of survival.

Disclosure

Dr Bekaii-Saab has no real or apparent conflicts of interest to report.

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Recent Advances in the Treatment of Pancreatic Adenocarcinoma: Further Observations

Ramesh K. Ramanathan, MD, and Tanios Bekaii-Saab, MD

H&O How might drug development in pancreatic cancer evolve?

Ramesh K. Ramanathan, MD The development of new drugs for pancreatic cancer has been difficult—more so than for other cancers. Researchers have struggled to develop targeted agents and immunotherapeutic approaches that are effective in pancreatic cancer. Multiple targeted and immunotherapeutic approaches have shown a lack of efficacy in clinical trials; this does include some agents that showed only minimal activity in early studies. Perhaps there was too much of a rush on some of these agents. In order to effectively employ immunotherapy against pancreatic cancer, researchers will need to devise rational combinations of costimulatory molecules and understand the mechanisms behind the poor immune responses observed in pancreatic cancer.[1]

Tanios Bekaii-Saab, MD I agree; pancreatic cancer has the unfortunate reputation of being the "graveyard" of drug development. However, in the past few years, several studies have shown that we have the ability to move the needle and improve outcomes with a lot of work and more investment in this space.

Today, we know of 2 subsets of pancreatic cancer patients who will respond to specific therapies. Less than 1% of patients with pancreatic cancers have high expression of microsatellite instability (MSI-H), either in the setting of Lynch syndrome or through somatic acquisition. In this setting, the checkpoint inhibitor pembrolizumab, which binds to the programmed cell death protein 1 (PD-1) receptor, has shown significant activity[2] and is now approved by the FDA. I have firsthand experience treating a patient with a history of Lynch syndrome, who eventually developed MSI-H pancreatic cancer. She was initially treated with chemotherapy. She rapidly progressed and then was referred to my clinic for further management. She received single-agent pembrolizumab, and attained a complete response lasting more than 2 years now.

The other subset of patients includes those with tumors harboring *BRCA/PALB* mutations. Patients with germline *BRCA* mutations represent only approximately 3% to 4% of all cases, and another 5% to 6% have somatic mutations. There is another subset of patients who will have other homologous repair deficiencies (HRDs), accounting for close to 10% of pancreatic cancers. Patients with *BRCA/PALB* mutations exhibit significant responses to platinum-based and/or irinotecan-based therapies. Additionally, ongoing efforts to evaluate poly (ADP-ribose) polymerase (PARP) inhibitors in this subset of patients (with *BRCA/PALB* mutations and other HRDs) are underway. Olaparib[3] and rucaparib,[4] but not veliparib, have demonstrated preliminary single-agent activity in patients with pancreatic cancer with *BRCA* mutations.

We have a great need to continue expanding our understanding of the molecular biology and genetics of pancreatic cancer. Recent research suggests that as we further refine different subgroups, we may be able to target these cancers more precisely.

Disclosures

Dr Ramanathan is a consultant for Pharmacyclics. He has received research support from AbbVie, Merck, Celgene, Berg, Boston Biomedical, and Ipsen. Dr Bekaii-Saab has no real or apparent conflicts of interest to report.

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2. Diaz LA, Marabelle A, Delord JP, et al. Pembrolizumab therapy for microsatellite instability high (MSI-H) colorectal cancer (CRC) and non-CRC [ASCO abstract 3017]. *J Clin Oncol.* 2016;34(15 suppl).
3. Kaufman B, Shapira-Frommer R, Schmutzler RK, et al. Olaparib monotherapy in patients with advanced cancer and a germline *BRCA1/2* mutation. *J Clin Oncol.* 2015;33(3):244-250.
4. Domchek SM, Hendifar AE, McWilliams RR, et al. RUCAPANC: an open-label, phase 2 trial of the PARP inhibitor rucaparib in patients (pts) with pancreatic cancer (PC) and a known deleterious germline or somatic *BRCA* mutation [ASCO abstract 4100]. *J Clin Oncol.* 2016;34(15 suppl).

Slide Library

Pancreatic Cancer

- The fourth-leading cause of cancer-related death in the United States[1]
- Most patients are diagnosed with locally advanced unresectable disease or metastatic disease
- The most common type is pancreatic adenocarcinoma, which accounts for approximately 95% of cases

1. Siegel RL et al. CA Cancer J Clin. 2017;67(1):7-30.

Pancreatic Exocrine Insufficiency

- Pancreatic cancer is associated with a high incidence of pancreatic exocrine insufficiency, a condition in which pancreatic enzymes important for digestion are not properly secreted by the pancreas, resulting in malnutrition caused by a lack of vitamins and other nutrients[1]
- If overlooked, pancreatic exocrine insufficiency can progress to steatorrhea, which further compromises the patient's absorption of vitamins and nutrients[1]

1. Vujasinovic M et al. Nutrients. 2017;9(3).

Optimal Management of Pancreatic Cancer

- Optimal management of pancreatic cancer hinges upon early referral to a medical oncologist for a proper assessment
- Performance status is a key consideration in treatment planning. Patients with a poor performance status (>2) are not likely to benefit from anticancer therapy and should instead receive best supportive care
- Whenever possible, patients with pancreatic cancer should receive care in a specialized center that is familiar with current practices
- Clinical trial participation is a key aspect of pancreatic cancer treatment, as addressed in multiple treatment guidelines

Challenges in the Treatment of Pancreatic Cancer

- Studies have shown undertreatment of patients with both localized and advanced disease[1]
- There is often a high burden of symptoms at diagnosis, including cachexia, weight loss, anorexia, immune system dysfunction, and thromboembolic disease
- Pancreatic cancer is associated with a high incidence of depression[2]
- Even patients with locally advanced disease can develop complex pain that includes visceral, somatic, and neuropathic components[3]

1. Erewood L et al. J Gastrointest Cancer. 2015;46(1):9-20. 2. Mayr M, Schmid RM. BMC Cancer. 2010;10:569. 3. Lahoud MJ et al. World J Gastrointest Oncol. 2016;8(6):599-606.

Systemic Treatment of Pancreatic Adenocarcinoma

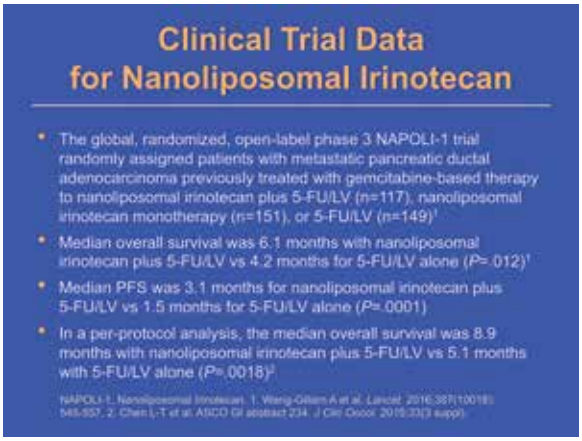
- In the metastatic setting, a variety of systemic therapies are used
- For years, the standard therapy was single-agent gemcitabine, and this approach is still used for patients who have a poor performance status, who are elderly, or who have comorbidities[1]
- For patients eligible for more aggressive therapy, options include[1,2]:
  - Oxaliplatin, irinotecan, fluorouracil, and leucovorin
  - Gemcitabine plus albumin-bound (nab)-paclitaxel

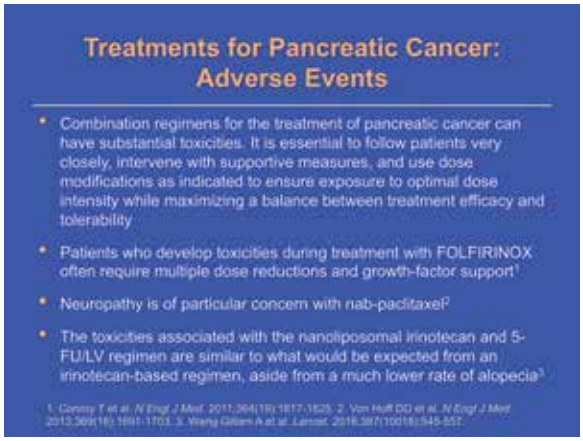
1. NCCN Clinical Practice Guidelines in Oncology. Pancreatic adenocarcinoma. Version 3.2017. https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf. Updated September 11, 2017. Accessed September 20, 2017. 2. Conroy T et al. N Engl J Med. 2011;364(19):1817-1825.

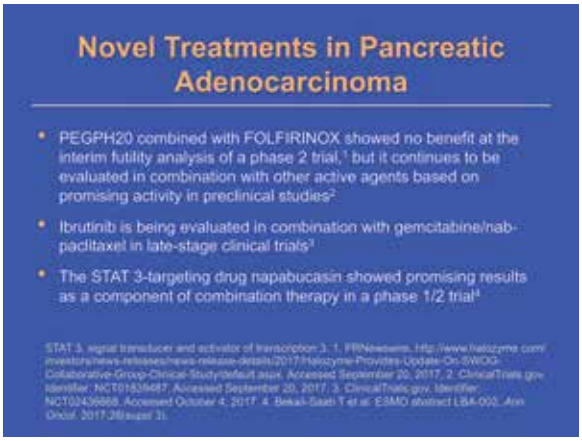
Newer Treatment Approaches for Pancreatic Adenocarcinoma

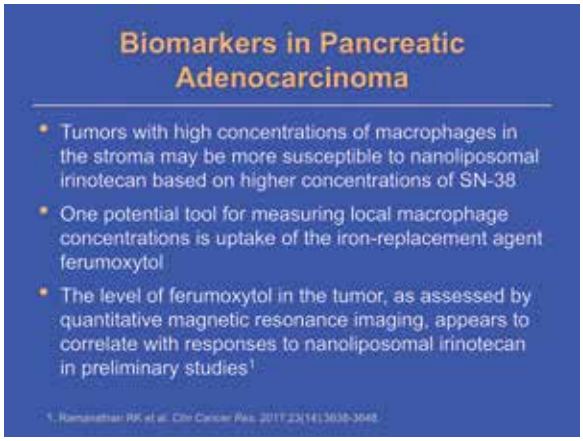
- Despite substantial research efforts undertaken to identify new effective therapies for the treatment of pancreatic adenocarcinoma, progress has been slow
- Nanoliposomal irinotecan is approved by the FDA for use in combination with fluorouracil and leucovorin for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy
- This indication encompasses not only the second-line setting, but also patients who have received prior gemcitabine as an adjuvant treatment. For these patients, nanoliposomal irinotecan can be used in the first-line metastatic setting

FDA, US Food and Drug Administration









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http://www.hematologyandoncology.net

NOTES

Recent Advances in the Treatment of Pancreatic Adenocarcinoma

CME Post-Test: *Circle the correct answer for each question below.*

1. Which type of pancreatic cancer is the most common?

   a. Acinar cell carcinoma
   b. Pancreatic adenocarcinoma
   c. Pancreatic neuroendocrine tumors
   d. Signet ring cell carcinomas

2. Most diagnoses of pancreatic cancer are made when the patient has:

   a. In situ disease
   b. Localized disease
   c. Regional disease
   d. Distant metastases

3. The most relevant consideration when planning treatment is:

   a. Age
   b. Ethnicity
   c. Performance status
   d. Sex

4. The symptom burden of pancreatic cancer is not likely to include:

   a. Depression
   b. Fever
   c. Malnutrition
   d. Thromboembolic disease

5. Which treatment approach was the previous standard and still used for patients who have a poor performance status, who are elderly, or who have comorbidities?

   a. FOLFIRINOX
   b. FOLFOX
   c. Gemcitabine
   d. Nab-paclitaxel

6. In a real-world analysis of patients receiving treatment for metastatic pancreatic cancer, which therapy was the most common?

   a. Nab-paclitaxel
   b. FOLFIRINOX
   c. Single-agent gemcitabine
   d. Gemcitabine plus capecitabine

7. In a real-world analysis of outcomes in patients with metastatic pancreatic cancer, which treatment was associated with a better outcome?

   a. FOLFIRINOX
   b. Gemcitabine plus nab-paclitaxel
   c. Outcomes were similar with FOLFIRINOX and gemcitabine plus nab-paclitaxel

8. In the phase 3 NAPOLI-1 trial, the combination of nanoliposomal irinotecan plus 5-FU was associated with a median overall survival of:

   a. 3.3 months
   b. 4.7 months
   c. 5.8 months
   d. 6.1 months

9. Which novel agent targets the signal transducer and activator of transcription 3 (STAT 3)?

   a. Evofosfamide
   b. Masitinib
   c. Napabucasin
   d. Tetraxetan

10. Which therapy was added as second-line treatment in 2017 versions of guidelines from the NCCN and ESMO?

    a. Evofosfamide
    b. Masitinib
    c. Nanoliposomal irinotecan
    d. PEGPH20

Evaluation Form: Recent Advances in the Treatment of Pancreatic Adenocarcinoma

If you wish to receive acknowledgment for completing this activity, please complete the post-test by selecting the best answer to each question, complete this evaluation verification of participation, and fax to: (303) 790-4876. You may also complete the post-test online at www.cmeuniversity.com. On the navigation menu, click on "Find Post-tests by Course" and search by **project ID 12748**. Upon successfully registering/logging in, completing the post-test and evaluation, your certificate will be made available immediately.

1. What degree best describes you?

❒ MD/DO ❒ PA/PA-C ❒ NP ❒ RN ❒ PharmD/RPh ❒ PhD
❒ Other, please specify:

2. What is your area of specialization?

❒ Oncology, Medical ❒ Oncology, Hematology/Oncology ❒ Oncology, Other

3. Which of the following best describes your *primary* practice setting?

❒ Solo Practice ❒ Group Practice ❒ Government
❒ University/teaching system ❒ Community Hospital
❒ HMO/managed care ❒ Non-profit/community ❒ I do not actively practice
❒ Other, please specify:

4. How long have you been practicing medicine?

❒ More than 20 years ❒ 11-20 years ❒ 5-10 years ❒ 1-5 years
❒ Less than 1 year ❒ I do not directly provide care

5. Approximately how many patients do you see each week?

❒ Less than 50 ❒ 50-99 ❒ 100-149 ❒ 150-199 ❒ 200+
❒ I do not directly provide care

6. How many patients do you currently see each week who have pancreatic cancer?

❒ Fewer than 5 ❒ 6-15 ❒ 16-25 ❒ 26-35 ❒ 36-45 ❒ 46-55
❒ 56 or more ❒ I do not directly provide care

7. Rate how well the activity supported your achievement of these learning objectives:

Explain how a patient's disease stage, age, and comorbidities influence selection of treatment for pancreatic adenocarcinoma

❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

Discuss when to initiate palliative care

❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

Describe data from the latest clinical trials of therapies in pancreatic adenocarcinoma

❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

Devise management strategies based on guidelines from the National Comprehensive Cancer Network and the European Society for Medical Oncology

❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

8. Rate how well the activity achieved the following:

The faculty were effective in presenting the material

❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

The content was evidence based

❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

The educational material provided useful information for my practice

❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

The activity enhanced my current knowledge base

❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

The activity provided appropriate and effective opportunities for active learning (e.g., case studies, discussion, Q&A, etc.)

❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

The opportunities provided to assess my own learning were appropriate (e.g., questions before, during or after the activity)

❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

9. Based upon your participation in this activity, do you intend to change your practice behavior? *(choose only one of the following options)*

❒ I do plan to implement changes in my practice based on the information presented

❒ My current practice has been reinforced by the information presented

❒ I need more information before I will change my practice

10. Thinking about how your participation in this activity will influence your patient care, how many of your patients are likely to benefit?

Please use a number (for example, 250):

11. If you plan to change your practice behavior, what type of changes do you plan to implement? *(check all that apply)*

❒ Apply latest guidelines ❒ Choice of treatment/management approach
❒ Change in pharmaceutical therapy ❒ Change in current practice for referral
❒ Change in nonpharmaceutical therapy ❒ Change in differential diagnosis
❒ Change in diagnostic testing ❒ Other, please specify:

12. How confident are you that you will be able to make your intended changes?

❒ Very confident ❒ Somewhat confident ❒ Unsure ❒ Not very confident

13. Which of the following do you anticipate will be the primary barrier to implementing these changes?

❒ Formulary restrictions ❒ Insurance/financial issues ❒ Time constraints
❒ Lack of multidisciplinary support ❒ System constraints
❒ Treatment-related adverse events ❒ Patient adherence/compliance
❒ Other, please specify:

14. Was the content of this activity fair, balanced, objective and free of bias?

❒ Yes ❒ No, please explain:

15. Please list any clinical issues/problems within your scope of practice you would like to see addressed in future educational activities:

Request for Credit (*required fields)

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Degree*_____

Organization_____

Specialty*_____

City, State, ZIP*_____

Telephone_____ Fax_____

E-mail*_____

Signature*_____ Date*_____

For Physicians Only:

I certify my actual time spent to complete this educational activity to be:

❒ I participated in the entire activity and claim 1.00 credits.
❒ I participated in only part of the activity and claim _____ credits.

Post-test Answer Key

1	2	3	4	5	6	7	8	9	10

Project ID: **12748**