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Highlight Report

Pancreatic Cancer Workshop: Treatment approaches in metastatic pancreatic cancer

Friday 29 April

The recent Asia Pacific Gastroenterology Cancer Summit (APGCS) held in Bangkok, Thailand, provided a forum for physicians to gain an up-to-date understanding on:

- how gastrointestinal (GI) malignancies develop
- advances in the treatment of these malignancies
- practical recommendations for how community oncologists can apply the findings from these data.

During this congress, a workshop was held to specifically discuss the management of metastatic pancreatic cancer. Despite having the highest mortality rate of all major cancers, there are only a few approved treatments for this type of metastatic cancer (Table 1).[1] This workshop sought to share country-specific treatment patterns, exchange best practices and experiences, and approach a general consensus on treatment strategies specific to patients suffering from this disease in the Asia-Pacific (APAC) region. The workshop was moderated by Professor Thomas Seufferlein, GI Oncologist, Ulm University, Germany, and Dr Shaheenah Dawood, Consultant Medical Oncologist, Dubai Hospital, United Arab Emirates (UAE), and attended by medical oncologists, clinical oncologists, and GI oncologists, as well as physicians from Hong Kong, India, Malaysia, Singapore, and Thailand. The format of the workshop included presentations from experts, discussion of case studies of Asian patients, and polling of attendees for their opinions.

Table 1. Available treatments for metastatic pancreatic ductal adenocarcinoma[1]

Treatment for mPDAC	Year of FDA approval
Gem	1996
Gem + Erlotinib	2005
FOLFIRINOX*	Has not been approved by FDA
Gem + nab-paclitaxel	2013
Nal-IRI	2015

FDA, US Food and Drug Administration; Gem, Gemcitabine; mPDAC, metastatic pancreatic ductal adenocarcinoma; nab-paclitaxel, Paclitaxel albumin-stabilized nanoparticle formulation; Nal-IRI, Nanoliposomal irinotecan.
*Combination of 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin.

Welcome address & workshop objectives

Dr Shaheenah Dawood, UAE

The objectives of the workshop were to:

- review the current state of affairs in the treatment of pancreatic cancer, specifically metastatic disease
- discuss country-specific treatment patterns and cases
- approach a general consensus on treatment strategies in APAC.

Overview of the current treatment landscape and unmet needs

Prof Thomas Seufferlein, Germany

Pancreatic ductal adenocarcinoma (PDAC) mortality rates are set to rise as populations continue to age. There are currently up to four approved regimens available for first-line treatment of metastatic PDAC (mPDAC):

- gemcitabine (Gem)
- Gem + Erlotinib (Erl)
- FOLFIRINOX

[1] Data from http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. Accessed July 2016.

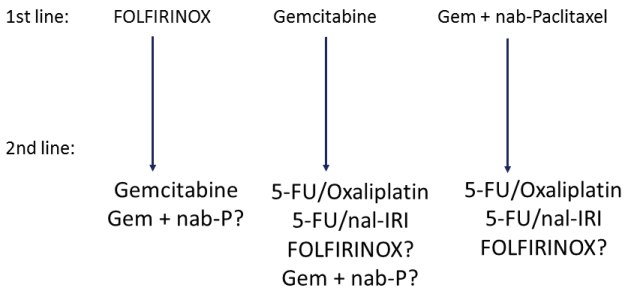
- Gem + paclitaxel albumin-stabilized nanoparticle formulation (nab-P)*

**At the time of the workshop, nab-P was not approved in Malaysia and Thailand for the treatment of mPDAC.*

The current treatment algorithm for determining individualized treatment of patients with mPDAC was presented (Figure 1), as were the options available for second-line treatment (Figure 2). The current data gaps in mPDAC treatment were considered to be the following:

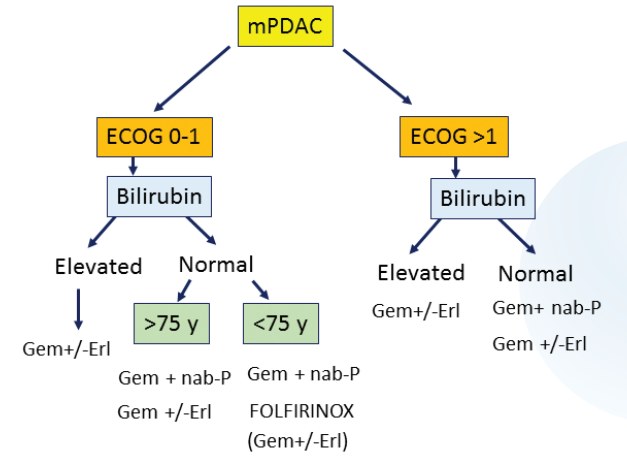
- What should be the duration of treatment in first-line therapy?
- Is there an optimal therapeutic sequence?
- How can novel strategies be implemented into the therapeutic setting?
- How can tumor evolution be monitored, and how should subsequent treatments be chosen?

Figure 1. Treatment algorithm for mPDAC



5-FU, fluorouracil; Gem, Gemcitabine; nab-P, paclitaxel albumin-stabilized nanoparticle formulation; nal-IRI, nanoliposomal irinotecan

Figure 2. Treatment algorithm for mPDAC



ECOG, Eastern Cooperative Oncology Group score; Erl, Erlotinib; Gem, Gemcitabine; mPDAC, metastatic pancreatic ductal adenocarcinoma; nab-P, paclitaxel albumin-stabilized nanoparticle formulation

Of the nine respondents, for most (89%, n = 8), 40–70% of their patients present with Stage 4 *de novo* disease every year. Seventy per cent (7 out of 10 attendees) indicated that some combination of tumor burden, performance status, age, and any prior therapy received impacted their choice of first-line therapy in mPDAC.

Treatment strategies in metastatic pancreatic cancer: Do we have a consensus?

The focus of the workshop was to present cases that highlighted different strategies and challenges faced by oncologists in the management of metastatic pancreatic cancer, with a view towards determining a consensus approach to treatment.

Patient Case: First-line Gem-based doublet therapy

Dr PK Das, India

A 45-year-old male with a history of chronic pancreatitis presented with ascites, a 26 mm lesion in the head of the pancreas, enlarged duodenal lymph nodes (< 12 mm), and splenic and superior mesenteric vein thrombosis. In this case a Gem-based (Gem + Erl) doublet therapy was used as first-line treatment. In the registrational Phase III study,[2] the Gem + Erl treatment combination demonstrated a median 0.3-month survival improvement over Gem alone. Although many attendees agreed that this was not a striking difference, the combination of Gem + Erl could still be considered as an option in selected cases because of its better toxicity profile. FOLFIRINOX and Gem + nab-P are more active players in the treatment landscape along with certain other Gem doublet therapies. However, the lack of a head-to-head trial of FOLFIRINOX and Gem + nab-P was identified as a clinical data gap.

Patient cases: Choice of first-line treatment for metastatic pancreatic cancer patients

Dr Stephen Chan, Hong Kong

Two cases where Gem + nab-P was used as first-line therapy at the Prince of Wales Hospital in Hong Kong were discussed. The first was a 62-year-old female who presented

[2] Moore MJ, *et al. J Clin Oncol* 2007;25:1960–6.

with obstructive jaundice, a pancreatic body mass, and multiple liver metastases. The second patient was a 70-year-old male with previous good health, who presented with multiple bi-lobed liver metastases (seven lesions in total). Patient age and bone marrow reserve were indicated as major decision factors when choosing FOLFIRINOX versus Gem + nab-P for first-line therapy. The lower toxicity and flexibility in dose adjustment of Gem + nab-P were the main reasons cited for being favored over FOLFIRINOX. In Hong Kong, prophylactic granulocyte-colony stimulating factor (G-CSF) is used during Gem + nab-P therapy in elderly patients to bolster lower bone marrow reserve and treat neutropenia. Several attendees from other countries explained that they often opt to administer reduced doses of Gem (600–800 mg/m^2) + nab-P (75–100 mg/m^2) in their older/lower performance status patients to manage toxicity issues. It was discussed that while ethnicity is not a major determinant in treatment selection in mPDAC, there are certain exceptions. For example, patients of Indian origin have less tolerance to capecitabine due to greater incidence of certain adverse events.

Patient case: Using a modified FOLFIRINOX regimen

Dr Choo Su Pin, Singapore

A case of a 66-year-old female patient who presented with abdominal pain, no weight loss, a pancreatic mass encasing the celiac axis and superior mesenteric artery, and multiple small lung metastases, who was given a modified FOLFIRINOX (mFOLFIRINOX) treatment regime was discussed. The FOLFIRINOX regimen was modified by omitting the 5-fluorouracil (5-FU) bolus, with subcutaneous G-CSF being administered 24 hours after completion of chemotherapy, and subsequent dose reductions of 20% for all FOLFIRINOX components as necessary. The interval between treatment cycles was also increased from 2-weekly to 3-weekly, and then 4-weekly to manage toxicity in the patient. An approach for modifying the FOLFIRNOX regimen was presented.

Table 2. Choice of first-line treatments for Asian mPDAC patients

	Choice of first-line therapy for Asian mPDAC patients*						
Patient status	**FOLF-IRINOX/ mFOLFIRI-NOX**	**Gem alone**	**Gem + nab-P**	**Gem doublet (non-nab-P)**	**Capecit-abine -based regimen**	**S-1**	**Others**
ECOG 0 (n = 9)	78%	-	22%	-	-	-	-
ECOG 0-1 (n = 11)	55%	-	45%	-	-	-	-
ECOG 2 (n = 12)	-	25%	58%	17%	-	-	-
Heavy tumor burden† (n = 12)	83%	-	8%	8%	-	-	-
Elderly (age ≥75 yrs), ECOG 0-1 (n = 11)	-	45%	55%	-	-	-	-
Elderly (age ≥75 yrs), ECOG 2 (n = 12)	-	67%	-	-	-	-	33%‡
Elevated bilirubin level (n = 10)	-	60%§	10%	-	-	10%	20%

ECOG, Eastern Cooperative Oncology Group; Gem, Gemcitabine; mPDAC, Metastatic pancreatic ductal adenocarcinoma; nab-P, Paclitaxel albumin-stabilized nanoparticle formulation; S-1, 5-FU prodrug.
*Values represent percentage of respondents; †assuming good performance status and normal bilirubin levels; ‡best supportive care; §dependent on bilirubin level

- Select only fit and motivated patients.
- Omit initial bolus of 5-FU.
- Dose reduction (by ≥ 20%) as necessary to manage toxicity.
- Support with prophylactic G-CSF.*
- Extension of chemotherapy intervals to manage side effects.

**The majority of the attendees agreed that G-CSF should be used for all patients, but it would have a significant impact on treatment costs, depending on the region.*

From discussions, it was found that **all attendees (100%) prefer to use mFOLFIRINOX regimens over the full-dose regimen in their practice due to toxicity concerns.** Discussions further revealed some trends in the choice of first-line treatments for mPDAC patients (Table 2). The attendees acknowledged that although there was no strong evidence to support the policy of maintenance therapy, 70% (7 out of 10 respondents) would give it. Five of eight attendees (63%) cited Gem alone as the maintenance therapy of choice when treating mPDAC patients.

Patient case: Choice of second-line treatment after progression on first-line therapy

Dr Virote Sriuranpong, Thailand

A case of an 88-year-old patient who had progressed after first-line treatment with Gem alone was presented. The patient was diagnosed with a liver abscess 7 months prior to presentation, and had developed a 1.4 x 1.2 cm enhancing lesion at the pancreatic neck. Capecitabine and oxaliplatin were given as second-line therapy, and at the last follow up in early April 2016, the patient (now 93 years old) had an Eastern Cooperative Oncology Group (ECOG) score of 0. This case highlights that there are several other treatment options for metastatic pancreatic cancer that are still under consideration. Performance status (i.e. ECOG score) was the key factor impacting the choice of second-line treatment for 85% (11 of 13) of the attendees. The preferred second-line therapy choices for Asian mPDAC patients with a good performance status were either FOLFIRINOX/mFOLFIRINOX, or Gem + nab-P, depending on the first-line treatment they had previously received (Figure 3). **Ninety per cent (nine of 10 attendees) reported that more than 50% of their patients progressed to second-line therapies.**

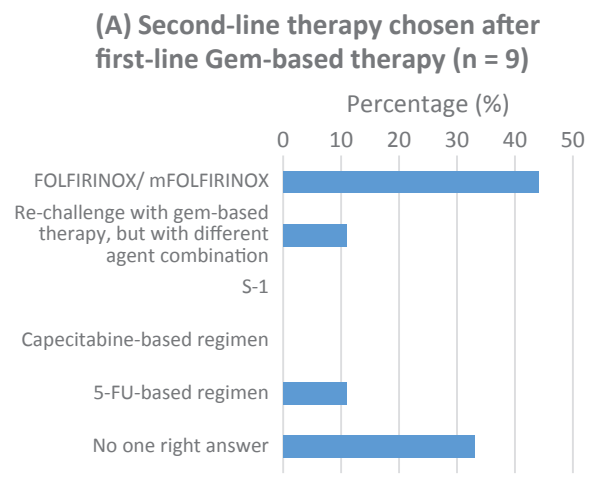
Future outlook and emerging therapies in metastatic disease

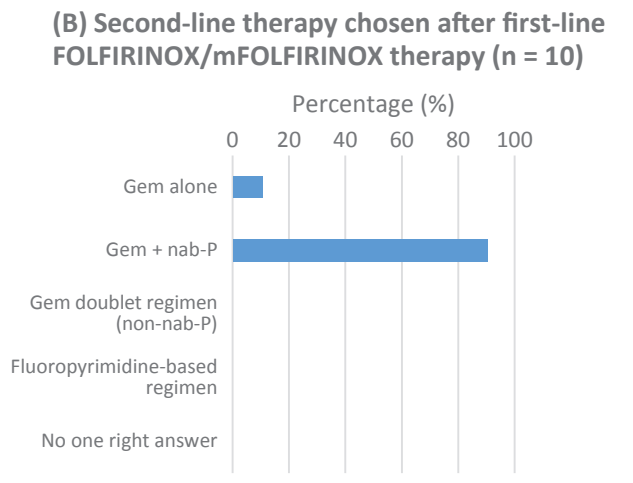
Prof Thomas Seufferlein, Germany

Looking ahead, some of the key issues in the development of emerging therapies for mPDAC were outlined.

- Gradual molecular stratification of PDACs.
- Stromal reprograming.
- Caution in extrapolations of subgroups from small Phase II trials.
- Monitoring of the disease and tumor evolution as a novel option.

Figure 3. Choices for second-line therapy if patient previously received (A) Gem-based therapy or (B) FOLFIRINOX/mFOLFIRINOX





Therapy with Gem + nab-P represents an ideal option as a 'backbone' for future therapies because of its efficacy, low toxicity (relative to FOLFIRINOX), and compatibility with other drugs. Some interesting therapeutic targets for mPDAC were also discussed amongst the attendees, such as poly ADP ribose polymerase (PARP), the tumor stroma, immune checkpoint inhibitors such as programmed death-ligand 1 (PD-L1), and tumor stem cells.

Summary of treatment consensus and closing remarks

Dr Shaheenah Dawood, UAE

The following key points emerged after intense discussions.

- The inherent heterogeneity in Asian populations significantly affects the generalizability of data from Western clinical studies and the choice of treatments in mPDAC patients.
- Dose reductions in first-line therapy are commonly adopted by the workshop attendees in their practices.
- Age (and, therefore, bone marrow status) is a more important factor than performance status when selecting a first-line therapy.
- FOLFIRINOX is almost always given in a modified form (i.e. 5-FU bolus omitted, ± dose reduction) to patients by the workshop attendees, often with prophylactic G-CSF support.
- A significant proportion of patients in Asia (> 50%, based on survey responses) progress to second-line therapy.

In closing, the idea of establishing a web-based prospective APAC registry to collect data on the treatment approaches adopted by physicians in the region was proposed. Data compiled in the registry could potentially form the basis of future discussions at APGCS 2017, and eventual development of consensus statements on the optimal treatment of mPDAC in APAC.