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Multi-Disciplinary Management of Metastatic Pancreatic Cancer

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1. Introduction

Pancreatic cancer (PC) is a devastating disease with the worst mortality rate and an overall 5-year survival rate lower than 5% (2% in distant cases; 9% in regional cases and 22% in localized cases). Although accounting for only 3% of all cancers, this disease is the fourth leading cause of death and represents 6 – 7 % of all cancer related deaths. In males, the incidence ASR is 8.2 and 2.7 and the mortality ASR is 7.9 and 2.5 in more developed areas and less developed areas, respectively.

In females, the incidence ASR is 5.4 and 2.1 and the mortality ASR is 5.1 and 2.0 in more developed areas and less developed areas, respectively.

We noticed that the incidence and the mortality rates are very close (*Jemal et al. 2011*). Also, the death rate is increasing from 9.28 per 100,000 in 1991 to 9.48 in 2006 with an absolute change of 0.2 (2.1%). (*Jemal et al. 2010*).

In the United States, the overall incidence is about 8–10 cases per 100,000 persons/year and rises slowly over the years with 43 140 new cases in 2010.

Pancreatic cancer remains one of the most difficult to treat due to late initial diagnosis and to intrinsic resistance to conventional treatments. About 50% of patients have distant disease at the time of diagnosis (locally advanced stage) and in 40% the tumor has spread (metastatic stage).

2. Risk factors

Risk factors have been identified, molecular pathogenesis has been elucidated, but advances in early detection and efficient treatments remain rather disappointing despite tremendous efforts.

Studies results show that long-term diabetes, even though risk diminishes over time, remains a risk factor for PC independent of obesity and smoking with a latency period of more than 5 years. Type 3 diabetes mellitus is an effect, and therefore a harbinger, of pancreatic cancer in at least 30% of patients (*Magruder JT et al, 2011; Li D et al. 2011*).

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After a pooled analysis of 14 cohort studies, a review study noted that, coffee consumption was inversely associated with pancreatic cancer (RR, 0.82; 95% CI, 0.69-0.95) (Yu X *et al*, 2011).

Although there have not been a sufficient number of clinical trials, promising dietary factors to prevent pancreatic cancer include citrus fruits, flavonoids, curcumin, folate, and vitamin D. Phase II clinical trials of curcumin have shown encouraging chemoprotective effects in patients with pancreatic cancer and have determined that curcumin can be safely administered to patients at oral doses up to 8 g/d.

Several flavonoids found in a variety of fruits and vegetables have also been shown to inhibit pancreatic cancer at various molecular targets including cell-cycle, Akt, NFkB, ERK, and many others. Currently, there is one on-going phase II clinical trial on the use of genistein in treating resectable pancreatic cancer patients. However, more clinical trials are needed to explore the efficacy and application of these factors in treating pancreatic cancer.

The use of citrus fruit extracts to treat pancreatic cancer has become of interest only in the past few years. Using citrus fruit extracts instead of individual compounds to treat pancreatic cancer is of great interest because it allows the use of low doses of multiple bioactive compounds and nutrients instead of large doses of single compounds, and therefore reducing the possibility of reaching toxic effects.

When comparing the inhibitory effects of different extraction methods of lime juice on pancreatic cancer, it was found that the methanol extract exhibited the highest inhibitory effect. Although the results from this study provide insight into the best options for extracting citrus fruits, more research needs to be conducted on various types of citrus fruits extracts and their mechanisms of action by which they affect pancreatic cancer.

Folate and vitamin D have good epidemiological evidence that shows that consumption of either of these nutrients leads to a reduced risk of pancreatic cancer. However, both of the nutrients have few experimental studies needed to help draw conclusions about either of their impacts on pancreatic cancer. (Jodee Johnson *et al*. 2011).

The pooled data of 6 studies involving a total of 2335 patients suggests an association between infection with *H. pylori* and the development of pancreatic cancer ((AOR 1.38, 95% CI: 1.08-1.75; P=0.009). (Trikudanathan G *et al*, 2011)

As is the case in other complex diseases, common, low-risk variants in different genes may act collectively to confer susceptibility to pancreatic cancer in individuals with repeated environmental exposures, such as smoking and red meat intake. Clarification of gene-gene and gene-environmental interaction is therefore indispensable for future studies. To address these issues, a rigorously designed molecular epidemiologic study with a large sample is desirable. (Yingsong Lin *et al*, 2011.)

3. Diagnosis

Pancreatic cancer is usually detected at an advanced stage and responds poorly to treatment.

Ductal adenocarcinoma and its variants account for over 90% of pancreatic malignancies. The presenting symptoms of the disease can include weight loss, jaundice, floating stools,

pain, dyspepsia, nausea and depression. However, no early warning signs of pancreatic cancer have been established. As previously noted, long term diabetes is a risk factor thus diagnosis of pancreatic cancer should be considered in diabetic patients with continuous weight loss and abdominal symptoms. All patients for whom there is clinical suspicion of pancreatic cancer or evidence of dilated duct should undergo initial evaluation by dynamic-phase CT scan. Subsequent decisions regarding diagnostic management and resectability should involve multidisciplinary consultation with reference to appropriate radiographic studies to evaluate the extent of the disease (*Agarwal B et al, 2001. Johnson CD. 2010*)

The principles of diagnosis and staging are:

1. Decisions about diagnostic management and resectability should involve multidisciplinary consultation with reference to appropriate radiographic studies to evaluate the extent of disease. Resections should be done at institutions that perform a large number (15-20) of pancreatic resections annually.
2. Imaging should include specialized pancreatic CT scan. CT should be performed according to a defined protocol such as triphasic cross-sectional imaging and thin slices.
3. The role of PET/CT scan remains unclear. PET/CT may be considered after formal pancreatic CT protocol in high risk patients to detect extra-pancreatic metastases. It is not a substitute for high quality contrast enhanced CT scan.
4. Endoscopic Ultrasound (EUS) may be complementary to CT for staging.
5. EUS directed fine needle biopsy is preferable to a CT-guided FNA in patients with resectable disease because of lower risk of peritoneal seeding with EUS FNA when compared with the percutaneous approach. Biopsy proof of malignancy is not required before surgical resection and a non diagnostic biopsy should not delay surgical resection when the clinical suspicion for pancreatic cancer is high.
6. Diagnostic staging with laparoscopy to rule out subradiologic metastases (especially for body and tail lesions) is used routinely in some institutions prior to surgery or chemoradiation or selectively in patients who are at higher risk for disseminated disease (borderline resectable disease, markedly elevated CA 19-9, large primary tumors or large regional lymph nodes).
7. Positive cytology from washings obtained at laparoscopy or laparotomy is equivalent to M1 disease. If resection has been done for such a patient, they should be treated as for M1 disease.

The key advances are:

In 2010 new insights were added to the complex biology of pancreatic cancer offering new opportunities for early diagnosis and treatment.

The first comprehensive analysis of pancreatic tumors and their metastases describes the patterns of genomic instability and estimates the time from tumor initiation to metastatic spread to be at least 10 years (*Yachida, S. et al, 2010*).

Genome-wide association studies point towards multiple common disease alleles with small effects influencing pancreatic cancer risk (*Petersen, G. M. et al. 2010; Low, S. K. et al. 2010*).

The ESPAC-3 trial reported that gemcitabine did not result in improved overall survival compared with fluorouracil plus folinic acid in patients with resected pancreatic cancer (*Neoptolemos, J. P. et al. 2010*).

Superior values for diagnostic performance were shown for MIC-1, PAM4, OPN, HSP27, TPS, TSGF, and CAM17.1 as individual markers. Panels of biomarkers comprised CA 19-9, MCSF, CEA, SAA, Haptoglobin, TSGF, CA 242, and HSP27. Individually or in concerted form, sensitivity and specificity ranged from 77 to 100% and 84-100%, respectively. While these markers show high screening potential for pancreatic cancer, standardized validation studies using multiplex assays are required to pave the way for clinical routine application (Bünger *S et al*, 2011).

4. Treatment

There is consensus on the fact that surgical removal of the tumor represents the best option for pancreatic cancer treatment; to be resectable, tumors need to be small and strictly localized to pancreas without invasion into surrounding organs and evidence of metastasis. However, only 15–20% of all patients are candidates for potentially curative surgery. Depending on the tumor localization, pancreaticoduodenectomy, distal or total pancreatectomy can be performed. However, even with an optimal curative surgery, metastases often occur. Median survival time without evidence of recurrent disease is 21.2 months after resection.

Systemic therapy is used in the adjuvant setting and in the management of locally advanced unresectable and metastatic disease.

4.1 Neoadjuvant resectable / borderline resectable

No standard treatment regimen currently exists for neoadjuvant resectable or borderline resectable pancreatic cancer. Neoadjuvant therapy for patients with resectable tumors should ideally be conducted on a clinical trial. Generally, use similar paradigms as for locally advanced unresectable disease:

- Upfront 5-FU or Capecitabine based chemoradiation
- Upfront gemcitabine-based chemoradiation therapy
- Induction chemotherapy (2 to 4 cycles) followed by 5-FU or Gemcitabine based chemoradiation therapy.

Ideally, surgical resection should be attempted 6 to 8 weeks following chemoradiation. Surgery can be performed after 8 weeks following chemoradiation however radiation induced fibrosis may potentially make surgery more difficult.

4.2 Chemoradiation therapy for locally advanced disease

Chemoradiation is a conventional option for the management of unresectable locoregional pancreatic cancer, although the utility of chemoradiation in this population of patients is controversial.

4.3 Post-operative adjuvant treatment

Clinical trial preferred or Systemic Gemcitabine or 5-FU/Leucovorin before or after chemoradiation (fluoropyrimidine or gemcitabine based) or chemotherapy alone Gemcitabine (category 1) or 5-FU/Leucovorin (category 1) or Capecitabine (Category 2B).

4.4 Chemotherapy for locally advanced and metastatic disease

The primary goals of treatment for advanced pancreatic cancer are palliation and improved survival. Although some effect on survival may be achieved, these benefits are usually limited to patients with adequate performance status (ECOG 0-2). Patients who present with very poor performance status may benefit from the administration of Gemcitabine, but comfort-directed measures are always paramount. Before initiating cytotoxic therapy, an open dialogue regarding the goals of treatment should take place, and adjunctive strategies should be discussed (including nonsurgical bypass, celiac block for pain; of note debilitated patients with advanced disease may have abrupt changes in clinical status. Therefore, if treatment is begun, it should proceed with close follow-up. Patients may experience sudden onset of bleeding or thromboembolism, rapidly escalating pain, biliary stent occlusion, cholangitis, or other infections. Moreover, clinically meaningful tumor progression may develop quickly, and tumor-related symptoms may be inappropriately attributed to chemotherapy or other causes. For instance, patients who complain of intractable nausea and vomiting may have gastric outlet obstruction rather than chemotherapy-induced emesis. Peritoneal carcinomatosis may manifest as ascites or in its more subtle form, as abdominal bloating, decreased oral intake and constipation.

Prior to approval of Gemcitabine, 5-FU was the most extensively evaluated agent for PC, either alone or in combination without survival advantage. Gemcitabine, with or without Erlotinib, has been the standard chemotherapy in APC. The FDA approval in 1997 was based on the results of the randomized trial where Gemcitabine was compared to 5-FU in previously untreated patients. Patients treated with Gemcitabine had a median survival of 5.65 months, compared to 4.41 months ($p < 0.05$) in those treated with 5-FU. Twenty-four percent of patients treated with gemcitabine were alive at 9 months, compared to 6% of patients treated with 5-FU. In addition, more clinically meaningful effects on disease-related symptoms were seen with gemcitabine (23.8%) than with 5-FU (4.8%). (Burris HA 3rd, Moore MJ, Andersen J et al. 1997).

Platinum compounds have been widely evaluated. A pooled analysis of two randomized trials indicates that the combination of gemcitabine with a platinum analog such as oxaliplatin or cisplatin significantly improves progression-free (PFS) and overall survival (OS) when compared to gemcitabine alone (HR for PFS: 0.75 with $p=0.0030$; HR for OS: 0.64 with $p=0.063$ in favour of the GP combination). The benefit from combination therapy is predominantly detected in patients with a good performance status. (V. Heinemann, Labianca R, Hinke A, Louvet C. et al. 2007).

Among the numerous randomized phase III studies comparing gemcitabine as single agent to gemcitabine combined to a new agent, only the gemcitabine-erlotinib combination has shown a small, but statistical improvement in survival. A trend to better survival was also observed with a gemcitabine-capecitabine regimen. The use of low-weight heparin may be of value to reduce venous thromboembolic events

The various combinations of new generation drugs showed 13% - 28.7 % RR with the Gemcitabine/Oxaliplatin, 8.2% - 17.3% with Gemcitabine alone, 12.8 % with Gemcitabine/CPT-11, 16% - 23% with Gemcitabine/Capecitabine, 22% with Oxaliplatin/Capecitabine and 10% with Oxaliplatin and 5-FU, 12.9% with Cisplatin / Gemcitabine, 13 % with Bevacizumab/Gemcitabine, 8.6 % with Erlotinib/Gemcitabine and 12.5 % with Cetuximab/Gemcitabine and 31% with the Folfirinox regimen.

The addition of Cisplatin, Bevacizumab, Cetuximab to Gemcitabine did not improve survival compared with patients treated with Gemcitabine alone in APC patients. The OS ranged between 5.8 and 9 months (table 1).

(G. Stathopoulos, K. Syrigos, G. Aravantinos, et al. 2006; V. Heinemann, T. Hoehler, G. Seipelt et al. 2008; K. Song, Y. Do, H. Chang et al. 2008; M. Moore, D. Goldstein, J. Hamm et al. 2007; Hedy Lee Kindler et al. 2010; Philip A. Philip. 2010; Giuseppe Colucci et al. 2010; E. Popli, Y. Feng, J. Berlin et al. Phase III, 2009; Jürg Bernhard et al. 2008; J. C. Bendell, S. Britton, M. R. Green et al. 2011; P. E. Oberstein, M. Saif. First 2011).

Reference	Regimen	Clinical benefit	ORR	median PFS	median survival
Berlin et al. JCO 2002	5FU + Gem	23.8%	6.9%	3.4 mo	6.7 mo
	Gem	4.8%	5.6%	2.2 mo	5.4 mo
Colucci et al. JCO 2010	Gem + Cisplatin	15.1%	12.9%	3.8 mo	7.2 mo
	Gem	23.0%	10.1%	3.9 mo	8.3 mo
Louvet et al. JCO 2005	Gem + Oxaliplatin	38.2%	26.8%	5.8 mo	9 mo
	Gem	26.9%	17.3%	3.7 mo	7.1 mo
Poplin et al. JCO 2009	Gemox	ND	9.0%	2.7 mo	5.7 mo
	Gem fixed dose rate	ND	10.0%	3.5 mo	6.2 mo
	Gem	ND	6.0%	2.6 mo	4.9 mo
Heinemann et al Ann Oncol 2007	Gem + Platinum	ND	22.0%	24 weeks	36 weeks
	Gem	ND	14.0%	15 weeks	29 weeks
Ghosn et al. Am J Clin Oncol 2007	Gem + Oxaliplatin + 5FU/LV	62.0%	27.5%	4 mo	7.5 mo
Bernhard et al. JCO 2008	Gem + Capecitabine	26.0%	ND	ND	ND
	Gem	25.0%	ND	ND	ND
Philip et al. JCO 2010	Gem + Cetuximab	49.5%	12.5%	3.4 mo	6.3 mo
	Gem	44.1%	14.0%	3 mo	5.9 mo
Kindler et al JCO 2010	Gem + Bevacizumab	13.0%	13.0%	3.8 mo	5.8 mo
	Gem	10.0%	10.0%	2.9 mo	5.9 mo
Moore et al. JCO 2007	Gem + Erlotinib	57.5%	8.6%	3.75 mo	6.24 mo
	Gem	49.2%	8.0%	3.55 mo	5.91 mo

Table 1. Summary of Results of some important Gemcitabine-based regimen

Oxaliplatin is one of the investigational active agents used in APC. With its synergistic effect, Oxaliplatin shows a higher RR when combined with other drugs. With 5-FU, preclinical data suggested synergistic efficacy which led to investigate the combination in many clinical trials. In a phase II trial in pancreatic cancer patients, this combination was explored and showed encouraging RR which deserve more evaluation (M. Ducreux, 2004; C. Louvet, R. Labianca, P. Hammel et al. 2005; C. Louvet, T. Andre, G. Liedo et al. 2002).

Recent publication of the results of a phase II trial performed by our group and assessing the combination of the FOLFOX 6 regimen showed promising results (27.5% partial response and 34.5% stable disease resulting in tumor growth control in 62% of the patients). Grade III

or IV toxicities were mild. The median time to progression and the median survival time were 4 and 7.5 months respectively (*M. Ghosn et al, 2007*).

Results from the randomized phase III study PRODIGE 4/ACCORD 11 trial evaluating the regimen of FOLFIRINOX vs. Gemcitabine alone in patients with APC and good performance status showed dramatic improvements in both progression-free survival (6.4 months vs. 3.3 months, $p < 0.001$) and median overall survival (11.1 months vs. 6.8 months, $p < 0.001$) in favor of the group receiving FOLFIRINOX. Because of these strong results, NCCN classified FOLFIRINOX as a category 1 recommendation for first-line treatment of good performance status patients with either metastatic or locally advanced disease.

There are however some concerns about the toxicity of the FOLFIRINOX regimen. The grade ≥ 4 toxicities rates were 12.3% for diarrhea, 15.6% for nausea, 17.2% for vomiting, 24% for fatigue, 47.9% for neutropenia and 5.7% for febrile neutropenia. Despite the high level of toxicity, no toxic deaths have been reported.

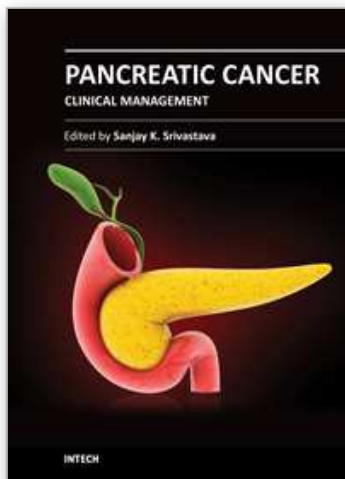
The high level of toxicity highlight the need to identify which patients will ultimately benefit from this more aggressive approach.

Summary: Gemcitabine (with or without erlotinib or capecitabine) is still the reference treatment in patients with ECOG performance status 2. **Folfirinox** is a new more toxic and more efficient regimen that may be considered in patients with good performance status. There is a difficulty in improving outcomes in metastatic PC. This continues to be a field of intense interest and regimens that conclusively show benefit in this disease are likely to generate enthusiasm and rapid adoption into clinical practice.

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This book covers pancreatic cancer risk factors, treatment and clinical procedures. It provides an outline of pancreatic cancer genetic risk factors, biomarkers and systems biology for the better understanding of disease. As pancreatic cancer suffers from lack of early diagnosis or prognosis markers, this book encompasses stem cell and genetic makers to identify the disease in early stages. The book uncovers the rationale and effectiveness of monotherapy and combination therapy in combating the devastating disease. As immunotherapy is emerging as an attractive approach to cease pancreatic cancer progression, the present book covers various aspects of immunotherapy including innate, adaptive, active, passive and bacterial approaches. Management of anesthesia during surgery and pain after surgery has been discussed. Book also takes the reader through the role of endoscopy and fine needle guided biopsies in diagnosing and observing the disease progression.

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