Recent Combined Modality in Treatment of Pancreatic Adenocarcinoma

An Essay

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By

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List of Abbreviations

APC : Advanced pancreatic cancer
CA : Celiac axis
CHA : Common hepatic artery
CRT : Chemoradiation
CTV : Clinical target volume
EBRT : External beam radiotherapy
EGFR : Epidermal growth factor receptor
EMT : Epithelial mesenchymal transition
ERCP : Endoscopic retrograde cholangiopancreatography
EUS : Endoscopic ultrasound
FDG : Fluorodeoxyglucose
FDR : Fixed Dose Rate
GTV : Gross target volume
Hh : Hedgehog
IORT : Intraoperative radiotherapy
IPMNs : Intraductal papillary mucinous neoplasms
JPS : Japan Pancreas Society
LANPC : Locally advanced non-resectable pancreatic cancer
LMWH : Low molecular weight heparin
MCNs : Mucinous cystic neoplasms
MDACC : MD Anderson Cancer Center
MRCP : Magnetic resonance cholangiopancreatography
NCPB : Neurolytic celiac plexus block
OAR : Organs at risk
OS : Overall survival
PAC : Pancreatic adenocarcinoma
PD : Pancreaticoduodenectomy
PFS : Progression free survival
PTV : Planning target volume
PV : Portal vein

RT : Radiotherapy
SMA : Superior mesenteric artery
SMV : Superior mesenteric vein
SUV : Standardized uptake value
SV : Splenic vein
UICC : International Union against Cancer
VEGF : Vascular endothelial growth factor
3D-CRT : 3D-conformal radiotherapy
IMRT : Intensity modulated radiotherapy
NCCN : National Comprehensive Cancer Network

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Introduction

Pancreatic cancer is one of the top ten incidence cancers in Europe and USA, with an overall 5-year survival rate of less than 5%. It is considered as well, to have one of the worst prognoses of all solid malignancies ***(Jemal et al., 2010).*** Pancreatic cancer, rank fourth among cancer-related deaths in the USA ***(Hidalgo, 2010).***

In Egypt, pancreatic cancer represented 2% of all cancer cases in Gharbia cancer registry 2000-2002 ***(Ibrahim et al., 2007).***

The main histological pattern of pancreatic cancer is infiltrating ductal adenocarcinoma, accounting for up to 90% of all pancreatic malignancies ***(Cascinu et al., 2010).***

Evaluation of a patient in whom pancreatic cancer is suspected should focus on diagnosis and staging of the disease, assessment of resectability, and palliation of symptoms ***(Hidalgo, 2010).***

Pancreatic cancer is staged according to the most recent edition of the American Joint Committee on Cancer TNM classification, which is based on assessment of resectability by means of helical CT. T1, T2, and T3 tumors are potentially resectable, whereas T4 tumors, which involve the superior mesenteric artery or celiac axis, are unresectable ***(Edge and Compton, 2010).***

Patients with pancreatic cancer are best cared for by multidisciplinary teams that include surgeons, medical and radiation oncologists, radiologists, gastroenterologists, nutritionists, and pain specialists ***(Katz et al., 2009).***

The aim of combined modality treatment schedules is to achieve increased killing in the tumor cell populations without an equivalent increase in normal tissue damage. There is, however, some increased risk of normal tissue toxicity that must be taken into account when assessing the therapeutic potential. Mechanisms involved in combined modality therapy include, increased radiosensitivity, inhibition of cellular proliferation, or independent additive toxicities, improvement the chances of achieving a therapeutic gain ***(Stewart, 1991).***

For patients with resectable disease, surgery remains the treatment of choice ***(Shaib et al., 2007).***

In patients with resectable disease, adjuvant chemotherapy allows to improve the 5 year survival rate, from about 10% with surgery alone, up to 20% with post-operative chemotherapy. Gemcitabine or 5FU are today the drugs of choice for adjuvant chemotherapy which is indicated in all patients with a resectable Pancreatic Adenocarcinoma (PAC). Whereas, adjuvant chemoradiotherapy (CRT) is still controversial, and its benefit may be restricted to patients with R1 resection ***(Ghaneh et al., 2010).***

An emerging strategy in patients with resectable pancreatic cancer is the use of preoperative (neoadjuvant) treatment. Nonrandomized, phase 2 studies suggest that this approach is at least as effective as postoperative treatment and may decrease the rate of local failures and positive margins after surgery ***(Evans et al., 2008).***

These findings are particularly relevant for patients who have so-called borderline-resectable tumors with limited vascular involvement; in these patients, preoperative treatment may result in tumor-free resection margins ***(Katz et al., 2008).***

The aim of treatment of patients with advanced locoregional disease is palliative. Management options range from systemic chemotherapy alone to combined forms of treatment with chemoradiation therapy and chemotherapy. A series of randomized trials conducted over the past two decades established that chemoradiation therapy was superior to radiation therapy alone in these patients. The results of more recent studies suggest that chemotherapy is indeed the critical component and that combined treatment with chemotherapy and chemoradiation therapy is an effective, though more toxic, approach ***(Huguet et al., 2007).***

The addition of erlotinib to gemcitabine demonstrated OS benefit, so that the Food and Drug Administration (FDA) and the European Medicines Evaluation Agency (EMA) have approved this combination for first-line treatment of advanced pancreatic cancer ***(Miksad et al., 2007).***

Recently, at the 2010 ASCO meeting, FOLFIRINOX regimen, which combines the three cytotoxics 5FU, irinotecan and oxaliplatin, has shown a significant benefit on progression free survival and overall survival in comparison with gemcitabine alone ***(Conroy et al., 2010).***

Intractable pain is a major problem and often necessitates the use of high-dose opiate analgesia. Complementary approaches include intraoperative, percutaneous CT-guided or EUS neurolytic coeliac plexus block ***(Suleyman et al., 2004).***

Finally, combination of locoregional approaches such as surgery and radiotherapy, along with systemic therapies, should be considered both for patients who are operative candidates and for those with locally advanced, unresectable disease. How best to combine these modalities in terms of schedule, timing, and choice of agents is a question that continues to be actively investigated. Some of these data are equivocal or conflicting; thus standards of care for combined-modality treatment have not been uniformly accepted to date ***(Ko et al., 2007).***

So, combination therapies, together with improved diagnostic tools are ultimately hoped to improve the whole outlook for patients diagnosed with pancreatic cancer ***(Wong and Lemoine, 2009).***

Aim of the Work

The aim of this study is to review the characteristic features of pancreatic adenocarcinoma and highlight the recent effective combined modalities in treatment of pancreatic adenocarcinoma.

Anatomy and Physiology of the Pancreas

▪ Anatomy:

A-Gross anatomy:

The pancreas, named for the Greek words *pan* (all) and *kreas* (flesh), is a 12-15 – cm long J-shaped (like a hockey stick), soft, lobulated, retroperitoneal organ. It lies transversely, although a bit obliquely, on the posterior abdominal wall behind the stomach, across the lumbar (L1-2) spine ***(Gray and Lewis, 2000).***

The pancreas is prismoid in shape and appears triangular in cut section with superior, inferior, and anterior borders as well as anterosuperior, anteroinferior, and posterior surfaces. The head of the pancreas lies in the duodenal C loop in front of the inferior vena cava (IVC) and the left renal vein. The uncinate process is an extension of the lower (inferior) half of the head toward the left. The body and tail of the pancreas run obliquely upward to the left in front of the aorta and left kidney. The pancreatic neck is the arbitrary junction between the head and body of the pancreas. The narrow tip of the tail of the pancreas reaches the splenic hilum in the splenorenal (lienorenal) ligament. The pancreatic head constitutes about 50% and the body and tail the remaining 50% of the pancreatic parenchymal mass ***(Kapoor, 2006).***

▪ Blood supply:

The celiac trunk comes from the anterior surface of the aorta at the level of T12–L1. It has a short length of about 1 cm

and trifurcates into the common hepatic artery (CHA), splenic artery, and left gastric artery (LGA). The CHA runs toward the right on the superior border of the proximal body of the pancreas, and the splenic artery runs toward the left on the superior border of the body and tail of the pancreas ***(Gray and Lewis, 2000).***

The superior mesenteric artery (SMA) comes off from the aorta just below the origin of the celiac trunk at the level of L1 behind the neck of the pancreas. The gastroduodenal artery (GDA), a branch of the CHA, runs down in front of the neck of the pancreas and divides into the right gastro-omental (gastroepiploic) artery (RGEA) and superior pancreaticoduodenal artery (SPDA). The inferior pancreaticoduodenal artery (IPDA) arises from the SMA. Veins accompany the SPDA and IPDA. Superior pancreaticoduodenal veins (SPDVs) drain into the portal vein and inferior pancreaticoduodenal veins (IPDVs) drain into the superior mesenteric vein (SMV) ***(Kapoor, 2006).***

▪ Nerve supply:

The pancreatic innervation comes from the parasympathetic and sympathetic branches of the autonomic nervous system. The parasympathetic fibers are responsible for the regulation of the pancreatic exocrine secretion, by means of the vagus nerve. The sympathetic fibers arrived from the celiac ganglion and are responsible of the pancreatic vascular innervation and the pain transmission ***(Eynard et al., 2008).***

▪ Lymphatic drainage:

The head of the pancreas drains into pancreaticoduodenal lymph nodes and lymph nodes in the hepatoduodenal ligament,