Pancreatic Cancer

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1 Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the fourth most frequent cause of tumor-related death in the Western world [24, 25]. Few data are published concerning PDAC frequency in tropical countries, but it may be less frequent than in more developed countries [1, 10, 15]. However, its incidence is increasing worldwide, and PDAC will become by 2020 the second leading cause of cancer-related mortality [16]. Median survival is 5–8 months and median 5-year survival is less than 5 % [23]. Majority of the patients are diagnosed with metastases and are candidates for palliative treatment.

2 Risk Factors

PDAC is usually sporadic but may be familial, needing attentive care to familial history.

Sporadic PDAC development is the result of a combination of different causes including somatic genomic, genetic, and epigenetic alterations and environmental factors, especially cigarette smoking and alcohol. Long-standing type 2 diabetes mellitus is also associated with an increased risk of pancreatic cancer [13]. Tropical calcific pancreatitis (TCP) has been described as a form of chronic nonalcoholic pancreatitis and is associated with a 4 % lifetime risk of developing cancer [19]. The

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typical clinical phenotype of TCP includes an onset at less than 30 years of age, a body mass index (BMI) less than 18 kg/m^2, absence of any other cause of pancreatitis, and presence of diabetes [5].

Hereditary basis of PDAC is traditionally found in 5–10 % of patients [20]. Subsets of familial pancreatic cancer involve germ line cationic trypsinogen or PRSS1 mutations (hereditary pancreatitis), BRCA mutations (usually in association with hereditary breast–ovarian cancer syndrome), CDKN2 mutations (familial atypical mole and multiple melanoma), or DNA repair gene mutations (e.g., ATM and PALB2, apart from those in BRCA) [29].

3 Diagnosis

Histological diagnosis should be obtained when nonsurgical treatment is considered, because 10 % of malignant tumors of the pancreas aren't exocrine and all pancreatic tumors are not malignant. If the tumor is resectable, a biopsy is not recommended/mandatory in order to avoid gesture's morbidity and theoretical risk of tumor seeding along the needle tract [6]. In case of diagnostic doubt (nodule of pancreatitis or a pseudotumor pancreatitis) and unresectable or metastatic tumor, a fine-needle cytology or tumor biopsy needs to be achieved. When endoscopic ultrasonography (EUS) is available, fine-needle aspiration may be EUS-guided (EUS-FNA). EUS may be also useful to detect vascular invasion and to treat pain through celiac plexus block and obstructive jaundice through biliary drainage [11]. If EUS is not available, ascites or hepatic metastases may be sampled under radiological guidance (ultrasound or CT scan).

A contrast-enhanced computed tomography of the chest, abdomen, and pelvis is the primary and easily available modality for both diagnosing and staging [2]. It is typically a multiphase thin-section imaging technique showing the primary tumor at the earlier phase, while the latter phase best demonstrates tumor involvement of venous structures and liver metastases [4]. Pancreatic magnetic resonance (MR) imaging may be useful but is not mandatory [21]. Likewise, 18FDG PET/CT also offers no benefit over CT scan in diagnosing pancreatic cancer [22].

The staging system for pancreatic exocrine cancer is defined by the 7th edition of the American Joint Committee on Cancer (AJCC)/TNM classification [9].

4 Treatment of Resectable Tumors

Resectable tumors include AJCC stages I and II. It concerns only 10–20 % of the patients. The surgical procedure for the pancreatic head's tumors is a pancreaticoduodenectomy or Whipple procedure involving the removal of the distal half of the stomach, gallbladder, distal portion of the common bile duct, as well as the head of the pancreas, duodenum, proximal jejunum, and lymph nodes. Three anastomoses are

required for reconstruction, namely, pancreaticojejunostomy, choledochojejunostomy, and gastrojejunostomy. As morbidity and mortality can be high following surgery, patients need to be addressed in high-volume centers [30]. Recurrences after initial surgery are frequent, and 5-year survival after surgical resection of PDAC is as poor as 18–27 % and correlates with resection margin status (R0 vs. R1) and lymph node metastases [14]. A 6-month adjuvant therapy with 5-FU or gemcitabine-based chemotherapy is recommended for all patients after pancreatic surgery, independently of the T and N stages [17, 18]. The median overall survival for patients with resected pancreatic cancer treated with adjuvant chemotherapy is approximately 2 years.

5 Treatment of Locally Advanced Unresectable Tumors

Locally advanced pancreatic cancers (stage III) are divided into borderline resectable or locally advanced unresectable tumors. They are separated according to the relationship of the tumor to the adjacent major vascular structures (superior mesenteric artery (SMA), celiac axis, and superior mesenteric and portal veins (SMV–PV)). Tumors without vessel involvement or with only focal involvement of the SMV–PV confluence are considered to be resectable, while patients whose cancers involve arteries or have more extensive involvement of the SMV–PV confluence are classified as having clinical stage III tumors. Their median survival in most historical studies ranges from 8 to 12 months. In this setting, treatment options include mostly chemotherapy (CT), chemoradiation (CRT), and surgery but strong evidences for therapeutic sequences are lacking. Controversies mainly exist about the place of radiation therapy, because the definition of locally advanced pancreatic cancers varies in published series, borderline resectable and unresectable tumors are both included in the same studies, and metastatic progression during or immediately after radiation is usual. Recently, the LAP 07 trial showed no benefit in survival for CRT after 4 months of gemcitabine-based induction CT over CT alone in locally advanced unresectable tumors. Despite these results, chemoradiation is not abandoned and remains investigated after more aggressive neoadjuvant CT (like FOLFIRINOX or nab-paclitaxel–gemcitabine). At least, due to the high rates of metastatic progression, it is recommended to use first induction CT which may subselect the proportion of patients who may benefit from subsequent CRT. In borderline resectable pancreatic cancer, the role of CRT remains less controversial and will be answered in future prospective phase III trials.

6 Metastatic Disease

Cytotoxic chemotherapy is the standard treatment option for stage IV pancreatic cancer patients. Between 1997 and 2011, gemcitabine monotherapy remained the standard treatment for metastatic patients with a median survival of 5–6 months in

the study by Burris et al. [8]. Since gemcitabine, two CT combinations demonstrated their superiority to gemcitabine alone. First, in 2011, Conroy et al. published the efficacy and safety results of the FOLFIRINOX combination CT regimen in the ACCORD 11 randomized phase III trial (Conroy et al.). FOLFIRINOX (leucovorin at 400 mg/m^2, fluorouracil at 400 mg/m^2, irinotecan at 180 mg/m^2, and oxaliplatin at 85 mg/m^2 given as a bolus, followed by 2,400 mg/m^2 given as a 46-h continuous infusion, every 2 weeks) demonstrated its superiority in comparison to gemcitabine alone in 342 chemotherapy-naive patients with metastatic pancreatic cancer with an ECOG PS of 0 or 1 and a serum bilirubin level < 1.5 times the upper limit of normal. The median overall survival, progression-free survival (PFS), and objective response rate were significantly higher with FOLFIRINOX (median overall survival, 11.1 vs. 6.8 months; PFS, 6.4 vs. 3.3 months; objective response rate, 32 % vs. 9 %). However, treatment-related toxicity was also significantly higher with FOLFIRINOX, including grade 3/4 neutropenia (46 % vs. 21 %), febrile neutropenia (5.4 % vs. 1.2 %), thrombocytopenia (9.1 % vs. 3.6 %), sensory neuropathy (9 % vs. 0 %), vomiting (15 % vs. 8 %), fatigue (23 % vs. 18 %), and diarrhea (13 % vs. 2 %). The same efficacy and safety results were obtained later in an Indian phase III trial, confirming the substantial activity of FOLFIRINOX in non-European populations [26].

Much recent progress in metastatic PDAC was obtained with the association of nab-paclitaxel and gemcitabine, whose superiority over gemcitabine monotherapy was shown in the multinational phase III Metastatic Pancreatic Adenocarcinoma Clinical Trial (MPACT). This study included 861 patients with previously untreated metastatic pancreatic adenocarcinoma [28]. Combination therapy was associated with a significantly higher objective response rate (23 % vs. 7 %) and significantly longer median overall survival (8.5 vs. 6.7 months) and PFS (5.5 vs. 3.7 months) compared with gemcitabine alone. Grade 3/4 adverse events occurred more often with combination therapy. They included neutropenia (38 % vs. 27 %), febrile neutropenia (3 % vs. 1 %), fatigue (17 % vs. 7 %), diarrhea (6 % vs. 1 %), and neuropathy (17 % vs. 1 %). In September 2013, nab-paclitaxel in combination with gemcitabine was approved by the FDA for the first-line treatment of patients with metastatic adenocarcinoma of the pancreas.

As no phase III study has compared the efficacy of FOLFIRINOX and gemcitabine plus nab-paclitaxel in first-line metastatic setting, they both are reasonable choices for first-line therapy in patients with good performance status (ECOG PS 0 or 1). However, recent Canadian cost and quality-of-life data suggest that FOLFIRINOX may be more cost-effective than gemcitabine or gemcitabine plus nab-paclitaxel in patients with metastatic pancreatic cancer [3, 12].

7 Palliative Care

Palliative care is very important in PDAC because 80–90 % of newly diagnosed tumors are not resectable or with distant metastases. The most common symptoms of PDAC are obstructive jaundice, gastric outlet obstruction, pain, weight loss, and

anorexia. About 90 % of the patients are diagnosed with obstructive jaundice. Biliary drainage can be achieved surgically (biliary bypass) or by endoscopic/percutaneous placement of stents with equivalent results [27]. Malignant gastric outlet obstruction can also be treated surgically with gastrojejunostomy or endoscopically with a self-expandable metallic stent. As pain incidence and severity tend to increase with disease progression, a good palliation is necessary. Opioid analgesics, radiation therapy, and celiac plexus neurolysis could be used, besides chemotherapy that has also a role in pain control. Even if weight loss has been found to have a prognostic effect on survival, few attentions are given to medical interventions that can prevent or reduce the progressive weight loss of the patients. Weight gain and higher daily total energy intake can be obtained with enteric-coated pancreatic enzyme supplements [7].

8 Conclusion

The treatment of PDAC combines, according to the disease stage, surgery and chemotherapy. The role of radiotherapy is not clearly established and should be reserved to clinical trials.

Palliative care should be introduced as early as possible because of the poor survival of the patients.

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