How I treat pancreatic cancer

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ABSTRACT
Pancreatic adenocarcinoma (PA) represents 90% of solid pancreatic malignant tumours. With one of the worst prognoses in oncology (all stages 5-year overall survival (OS) of 9%), PA was the seventh-leading cause of cancer-related deaths worldwide in 2018, and during the last 20 years, there have been unexplained increases in its incidence and mortality. This article summarises how to manage, to our opinion, PA in everyday practice according to tumour staging into resectable, unresectable or metastatic disease. Surgery followed by consensus adjuvant chemotherapy is the first-intention treatment for resectable patients. Unresectable but non-metastatic PA should be treated with induction chemotherapy and optionally with chemoradiotherapy to enable when possible secondary surgical resection. First-line and second-line chemotherapy does improve quality of life and OS in the metastatic setting, FOLFIRINOX and gemcitabine + nab-paclitaxel being the two current standard first-line options. Molecular profiling of metastatic patients is emerging, as some personalised therapies are possible for rare subtypes such as MSI high, BRCA1-2 mutated and NRG1/NTRK fusion gene PA.

DIAGNOSIS, STAGING, AND FOLLOW-UP
The classical presentation of pancreatic adenocarcinoma (PA) includes epigastric pain with posterior irradiation (suggesting a non-resectable tumour because of coeliac plexus invasion), jaundice (if the tumour is located at the head of the pancreas) and impaired general condition. New-onset or decompensated diabetes, steatorrhoea, bowel obstruction, acute pancreatitis and thrombosis can also be related to PA.

PA appears as a hypoattenuating mass with indistinct margins on arterial phase CT scan. Recent (<4 weeks) thoracic-abdominal-pelvic CT scan with arterial and portal phases is mandatory for tumour staging to adequately guide therapeutic choices. Disease classification as resectable, locally advanced and metastatic PA seems more relevant than TNM staging. At diagnosis, 10%–20% of PAs are resectable, 30%–40% are locally advanced and 50%–60% are metastatic. Resectability is defined in non-metastatic PA according to vascular invasion in the absence of distant lymph node involvement. Echoendoscopy can be relevant for locally advanced tumours by providing pathological proof before the start of chemotherapy or if biliary stenting (with a metallic stent) is required. Liver MRI is needed for tumours considered resectable on CT, as diffusion sequences can reveal occult liver metastasis and avoid useless laparoscopy in 12% of PA cases.

Pretherapeutic blood tests should include blood cell count, creatinine, bilirubin, albumin, dipyrimidine dehydrogenase (DPD) deficiency screening (uracilaemia) if treatment with 5 fluoro-uracile (5FU) or capecitabine is planned and carbohydrate antigen 19–9 (CA 19–9), which provides prognostic information. 5FU-related cardiotoxicity (corony artery vasospasm and heart rhythm disorders), though rare, justifies a baseline ECG before the first administration.

Each patient case should be discussed by a multidisciplinary board, including: oncologists, radiologists, surgeons, endoscopists, radiotherapists and pathologists. Whenever possible, patients should be included in clinical trials. Due to the aggressiveness of the disease, CT-scan assessment every 2 (rather than 3) months is recommended in non-resected patients on treatment. Pancreatic cancer management is summarized in figure 1.

RESECTABLE PA
Surgery is the only curative treatment of PA. Resectability of non-metastatic PA relies on the absence of arterial (coeliac axis (CA), superior mesenteric (SMA), and common hepatic arteries) and venous (portal (PV) and superior mesenteric vein (SMV)) tumour contact, in order to provide an R0 resection (>1 mm between tumour cells and margins). Venous tumour contact <180° can also be considered as resectable if there is no vein contour irregularity. Peripancreatic lymph nodes are compatible with resectability, unlike distant lymph nodes. Typical clinical-radiological presentation does not require histological proof and should be resected in first intention. Optimal surgical preparation consists of preoperative alcohol and tobacco withdrawal, nutritional support and perioperative immunonutrition. CA 19–9 levels, tumour size and pain will be taken into account for surgical
decision. The type of resection depends on the location of the PA: pancreaticoduodenectomy for PA of the head of pancreas; distal pancreatectomy with splenectomy for PA of the body and tail of pancreas; and total pancreatectomy may be discussed in the rare cases of diffuse degenerated intraductal papillary mucinous neoplasm or postoperative resectable recurrence. Peritoneal carcinomatosis or tumour invasion on the interaortocava lymph node picking, on fresh-mount microscopic study, contraindicates any pancreatic resection. After pancreatic resection, at least 15 lymph nodes should be harvested during dissection. Surgeons should ink resection margins to improve resection status examination. Pancreatic enzymes should be prescribed, especially if steatorrhoea occurs, and glycaemia should be monitored. Infectious complications of splenectomy are prevented by antibiotic
prophylaxis and vaccinations (meningococcus and pneumococcus). As the pancreatic surgery mortality rate after pancreatic surgery is around 8% and is lower in high-volume centres (OR 1.8 in low-volume centres), patients should be referred to high-volume centres for surgery (>65 PA surgeries per year) when possible. Morbidity rates after pancreatic surgery of 20%–60% and the 7%–40% risk of fistula remain challenging. Patients eligible for a curative surgery with jaundice should not undergo biliary stenting (preferentially fully covered self-expanding metal stents) before surgery as it is associated with complications that may significantly delay an urgent surgery; except if cholangitis, bilirubin >250 µmol/L or renal failure is observed.

Adjuvant chemotherapy for 6 months with modified FOLFIRINOX (mFOLFIRINOX: oxaliplatin, 85mg per square metre of body-surface area; irinotecan, 150mg per square metre; leucovorin, 400mg per square metre; and fluorouracil 2400mg per square metre given as a 46 hours infusion, every 2 weeks) is currently the reference, since the publication of the projet de recherche en oncologie digestive (PRODIGE) 24 trial, even in patients with R1 resection.1 Compared with gemcitabine, median disease-free survival and overall survival (OS) were significantly increased and respectively 22 vs 13 months and 54 vs 35 months, at the price of more neurological and gastrointestinal grade 3/4 adverse events. Adjuvant mFOLFIRINOX should start up to 3 months after surgical resection. Gemcitabine+capecitabine is an alternative for patients over 75 years old, with limited performance status (PS) or postoperative morbidity. Gemcitabine alone can also been discussed in these patients as 5FU alone in those not tolerating gemcitabine-based regimens. Adjuvant gemcitabine + nab-paclitaxel was compared with gemcitabine in the APACT phase III study with negative results.2 Chemoradiotherapy is also currently not recommended in the (neo)adjuvant setting. Many ongoing phase II and III randomised trials are currently assessing the interest of neoadjuvant chemotherapy for resectable PA.

Borderline or locally advanced PA should be treated with induction treatment with the aim of downstaging the tumour to attempt secondary curative intent surgery. Standard induction treatment remains gemcitabine, pending the results of ongoing phase III studies testing the more aggressive mFOLFIRINOX regimen. However, a meta-analysis of non-randomised patient cohorts has suggested that mFOLFIRINOX is effective and it is already used in many centres.3 Without progression after induction therapy, preoperative chemoradiotherapy seems to improve pathological results (R0 resection, ypN0 and major response) or stereotactic body radiation therapy, though not standard induction treatment remains gemcitabine, pending the results of ongoing phase III studies testing the more aggressive mFOLFIRINOX regimen. However, a meta-analysis of non-randomised patient cohorts has suggested that mFOLFIRINOX is effective and it is already used in many centres.3 Without progression after induction therapy, preoperative chemoradiotherapy seems to improve pathological results (R0 resection, ypN0 and major response rates), locoregional relapse-free survival and OS though these results need to be confirmed.4 Adjuvant chemotherapy can be administered, but its modalities are not well defined and trials are ongoing, with generally continuing the preoperative regimen for a total of 6 months. When the tumour is not resectable after induction chemotherapy, chemoradiotherapy (intensity modulated radiation therapy or stereotactic body radiation therapy), though not standard, may allow tumour shrinkage and secondary resection in a small percentage of patients. Otherwise, continuing

| Molecular alteration | Localisation | Frequency, % | Targeted treatment | Indication in M+PA |
|---------------------|--------------|--------------|--------------------|--------------------|
| BRCA 1 or 2 mutation | Germine      | 4–7          | Olaparib PARP inhibitor | Maintenance after response to platinum-based chemotherapy |
| MMR deficiency      | Tumour       | 1–2          | Pembrolizumab Anti-PD1 immunotherapy | MSI in IHC or NGS |
| NTRK fusion         | Tumour       | <1           | Larotrectinib Tyrosine kinase inhibitor | FISH or RT-PCR |
| NRG fusion          | Tumour       | 6            | Afatinib Tyrosine kinase inhibitor | FISH or RT-PCR |

ChT, chemotherapy; FISH, fluorescence in situ hybridisation; IHC, immunohistochemistry; M+, metastatic; MMR, mismatch repair; MSI, microsatellite instability; NGS, next-generation sequencing; PA, pancreatic adenocarcinoma; PARP, poly ADP ribose polymerase; RT-PCR, reverse-transcriptase PCR.

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CHEMOTHERAPY OR SWITCHING TO CHEMOREADIOThERAPY GAVE SIMILAR RESULTS IN TERMS OF PROGRESSION FREE SURVIVAL (PFS) AND OS, BUT CHEMOREADIOThERAPY MAY ALLOW TREATMENT HOLLIDAYS AND SEEMED TO AFFECT BETTER PREVENTION OF LOCOREGIONAL PROGRESSION. CHEMOREADOThERAPY CAN ALSO BE USEFUL AS A SYMPTOMATIC TREATMENT OF PA-RELATED PAIN IN UNRESECTABLE TUMOURS. ERLOTINIB DID NOT PROVIDE ANY BENEFIT IN PATIENTS WITH LOCALLY ADVANCED PA.

METASTATIC PA

Metastatic PA management consists of palliative chemotherapy and best supportive care. With better oncological outcomes compared with gemcitabine with PFS of 6.4 vs 3.3 months p<0.001 and OS of 11.1 vs 6.8 months (p<0.001), the FOLFIRINOX regimen (oxaliplatin, 85 mg per square metre of body-surface area; irinotecan, 180 mg per square metre; leucovorin, 400 mg per square metre and fluorouracil, 400 mg per square metre given as a bolus followed by 2400 mg per square metre given as a 46-hour continuous infusion, every 2 weeks) became the reference first-line chemotherapy for PS 0–1 patients <75 years old with blood bilirubin ≤1.5 ULN. However, the mFOLFIRINOX described in the adjuvant setting is also commonly used in metastatic setting and a 5FU maintenance could be an option after 4 months of induction chemotherapy. Gemcitabine + nab-paclitaxel represents an alternative for patients who cannot undergo FOLFIRINOX, as OS significantly improved compared with gemcitabine (8.5 vs 6.7 months, p<0.001). In frail patients, gemcitabine alone is also possible. A PS of 3 or 4, however, contraindicates any palliative chemotherapy and only allows best supportive care.

Half of metastatic PA patients are eligible for second-line chemotherapy. Patients progressing under FOLFIRINOX can be switched to gemcitabine + nab-paclitaxel (non-randomised data) or gemcitabine alone. Patients treated with gemcitabine-based first-line regimens should be treated with 5FU-based second-line regimens. A positive randomised phase III trial showed the superiority of 5FU plus liposomal irinotecan versus 5FU (OS 6.1 vs 4.2 months, p=0.012), whereas FOLFOX superiority to 5FU remains controversial.

Germline testing and tumour gene profiling should be proposed whenever possible and discussed at a dedicated board meeting (Table 1). Patients with metastatic PA who harbour germline BRCA1/2 mutations (4%–7% of patients) are eligible for olaparib poly ADP-ribose polymerase (PARP) inhibitor as oral maintenance therapy in the case of tumour control by induction chemotherapy containing oxaliplatin, with improved median PFS (7.4 vs 3.8 months, p=0.004). New tyrosine kinase inhibitors such as larotrectinib and afatinib seem promising, respectively, in the cases of tumour NTRK and NRG1 (up to 6%) gene fusions. Finally, immunotherapy seems useful in 1% of PA cases with mismatch repair deficiency, though data remain scarce to date.

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