

New Frontiers in the Neoadjuvant Therapy of Pancreatic Adenocarcinoma: Apart from Therapeutical Protocols

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Pancreatic adenocarcinoma is the fifth leading cause of cancer death, with over 40,000 death/year in Europe and nearly 30,000 death/year in the USA [1, 2, 3, 4, 5]. In recent years, the incidence of exocrine pancreatic carcinoma has demonstrated a slow but constant increase. This disease quickly results in death because, at the time of diagnosis, it is locally advanced or with distant metastasis; more than 90% of patients cannot undergo surgery and other efficacious therapies are not available. Surgery remains the only curative treatment, but no more than 5-10% of patients can undergo surgery. The median survival rate is about 13-18 months [6, 7]. Disease recurrence following a potentially curative pancreaticoduodenectomy remains common, and long-term survival is seen in only 10-20% of patients who undergo potentially curative surgery. Among patients treated with surgery alone, local recurrence occurs in up to 50-80% of cases, peritoneal recurrence in 25% and liver metastases in 50% [8].

Over the last few years, efforts have been directed towards the development of adjuvant and neoadjuvant therapies in an attempt to improve survival outcome.

Only a few studies have focused on the role of preoperative therapy in pancreatic adenocarcinoma. Phase II trials suggest a role for preoperative radiotherapy and

chemoradiation in the control of locoregional disease, but without benefiting survival.

Chemoradiation has been administered to patients with locally advanced, unresectable pancreatic cancer in an effort to improve survival duration and, more recently, to downstage advanced local-regional disease to allow surgical resection.

Because surgical resection of the primary tumor remains the only potentially curative treatment for pancreatic cancer, preoperative chemoradiation has been studied for its ability to convert locally unresectable pancreatic cancer to resectable disease.

In 1969, Moertel *et al.* published the first study which used 5-fluorouracil (5-FU) in combination with radiotherapy for the treatment of locally advanced pancreatic cancer [9].

The GITSG (Gastrointestinal Tumor Study Group) confirmed the findings of Moertel *et al.* that median survival was improved from 6 to 10 months with the use of chemoradiation rather than radiation alone.

The GITSG demonstrated that a split-course of radiotherapy associated with 5-FU was superior to radiotherapy alone [10]. Subsequently, the GITSG suggested that chemotherapy in combination with SMF (streptozotocin, mitomycin C, 5-FU) produces a significantly inferior survival result for the

patient with locally regionally unresectable disease than does 5-FU plus radiotherapy followed by SFM [11].

The Eastern Cooperative Oncology Group (ECOG) study failed to demonstrate this advantage and found that the toxicity of treatment was substantial [12].

Two British randomized studies of chemotherapy versus best supportive care have shown a survival advantage for chemotherapy with no deterioration in quality of life for patients with inoperable pancreatic cancer [13, 14].

5-Fluorouracil-based chemotherapy has been the mainstay of treatment for 30 years with response rates varying from 15 to 28%.

It was used in combination with cisplatin (100 mg/m²) with initial effectiveness [15] but, in a more recent randomized trial, although there was a trend to improvement in overall survival, the same authors documented a significant toxicity in the combination therapy (48% as compared to 20% for 5-FU alone) [16].

Another antineoplastic agent employed in the neoadjuvant treatment of locally advanced pancreatic cancer has been the thymidylate synthase inhibitor, raltitrexed. In 42 patients with advanced pancreatic cancer, disappointingly only two partial responses were seen [17].

Initial work with the taxane, docetaxel, was encouraging with a response rate of 29%. Unfortunately, a confirmatory phase II study at the Memorial Sloan Kettering Cancer Centre demonstrated only a 17% response rate [18].

One of the drugs which has recently generated the greatest interest in the treatment of pancreatic cancer is gemcitabine. An initial phase II study showed a low response rate (11%), but a substantial number of patients had stable disease and/or improvement in quality of life [19].

In another trial, chemo-naïve patients were randomized to either gemcitabine or 5-FU obtaining a statistically significant advantage of gemcitabine over 5-FU in terms of survival and "clinical benefit response" [20]. Clinical

benefit response was a new endpoint which took into account reduction in pain intensity, reduction in daily analgesic requirement, and improvement in Karnofsky performance status.

In an additional study, patients in whom 5-FU chemotherapy was not effective were treated with gemcitabine as a second line of therapy with an advantage in terms of clinical benefit response [21]. Radiotherapy combined with continuous infusion 5-FU and gemcitabine with additional systemic therapy consisting of gemcitabine and cisplatin pre- and post-chemoradiation, has also been investigated showing a significant local tumor response in a small group of patients [22].

Recently, other trials of preoperative chemoradiation have been conducted, employing different regimens of chemotherapy and radiotherapy. These trials have each reported surgical complications and mortality rates similar to those of patients without preoperative treatment and lower rates of local recurrence [23, 24, 25, 26].

Conversion to resectability was noted to occur rarely (0-5%), with pain relief occurring in the majority of patients. Several factors support the preoperative use of chemoradiation; positive gross or microscopic margins of resection along the right lateral border of the superior mesenteric artery are common following a pancreaticoduodenectomy, suggesting that surgery alone may be an inadequate strategy for local tumor control. Moreover, postoperative recovery does not affect the delivery of multimodality therapy since chemoradiation is given before surgery; in fact, complications and prolonged recovery time after a pancreaticoduodenectomy can interfere with postoperative chemoradiation in at least 25-30% of eligible patients.

Utilizing a preoperative approach, overall treatment time is reduced because patients with disseminated disease evident on restaging studies after chemoradiation are spared a non-therapeutic laparotomy. Since the prognosis is generally poor, the identification of early responders to chemotherapy is important in order to avoid

unnecessary toxicity in patients who are not responding. The real problem is that response assessment by conventional radiographic methods is problematic because the treatment induces fibrosis and makes tumor measurements difficult. It has been difficult to compare many of the treatments for locally advanced pancreatic tumors as response rates have been very variable, mainly due to difficulty in imaging the pancreas and providing bidimensional measurements.

With preoperative therapy, a greater proportion of patients receive all the components of the treatment while, more than one-fourth of patients do not complete planned adjuvant therapy due to surgical complications or a delay in postoperative recovery of performance status. It has been suggested that preoperative chemoradiation, by providing better tumor cell oxygenation, might have the advantage over post-operative chemoradiation when we know that pancreatic tumors show hypoxia.

Additional large multicentric studies are required to evaluate the efficacy of this form of treatment.

Keywords Combined Modality Therapy; Neoadjuvant Therapy; Pancreatic Neoplasms

Abbreviations 5-FU: 5-fluorouracil; ECOG: Eastern Cooperative Oncology Group; GITSG: Gastrointestinal Tumor Study Group; SMF: streptozotocin, mitomycin C, 5-FU

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