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TOPIC HIGHLIGHT

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Adjuvant and neoadjuvant treatment in pancreatic cancer

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Abstract

Pancreatic adenocarcinoma is one of the most aggressive human malignancies, ranking 4th among causes for cancer-related death in the Western world including the United States. Surgical resection offers the only chance of cure, but only 15 to 20 percent of cases are potentially resectable at presentation. Different studies demonstrate and confirm that advanced pancreatic cancer is among the most complex cancers to treat and that these tumors are relatively resistant to chemotherapy and radiotherapy. Currently there is no consensus around the world on what constitutes "standard" adjuvant therapy for pancreatic cancer. This controversy derives from several studies, each fraught with its own limitations. Standards of care also vary somewhat with regard to geography and economy, for instance chemo-radiotherapy followed by chemotherapy or *vice versa* is considered the optimal therapy in North America while chemotherapy alone is the current standard in Europe. Regardless of the efforts in adjuvant and neoadjuvant improved therapy, the major goal to combat pancreatic cancer is to find diagnostic markers, identifying the disease in a pre-metastatic stage and making a curative treatment accessible to more patients. In this review, authors examined the different therapy options for advanced pancreatic patients in recent years and the future directions in adjuvant and neoadjuvant treatments for these patients.

Key words: Pancreatic ductal adenocarcinoma; Adjuvant; Neoadjuvant; Fluorouracil; Gemcitabine

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INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is one of the most aggressive human malignancies, ranking 4th among causes of cancer-related death in the Western world[1].

Unlike most of the more frequent causes of cancer mortality (lung, colon, prostate and breast cancers) whose death rates are declining, the death rate for pancreatic cancer is relatively stable.

The poor prognosis is reflected by a median survival of 5-8 mo and a 5-year survival of less than 5% when all stages are combined[1-3].

PDAC is characterized by a rapid disease progression

and absence of specific symptoms, largely precluding an early diagnosis and curative treatment[3,4].

In most cases, PDAC is already locally advanced at time of diagnosis and only approximately 10%-20%[1,5] of patients are considered candidates for curative resection. The majority of patients (50%-60%) present with metastatic disease, and thus palliative chemotherapy remains the only option for almost all of these patients[6]. Owing to the high recurrence rate, surgical PDAC patients require adjuvant chemotherapy with or without radiotherapy providing a 5-year survival rate of 15%-25%[7] (Table 1).

Due to the described overall prognosis for all pancreatic cancer patients, systemic chemotherapy, radiation therapy or a combination of both is used following surgical resection (adjuvant therapy) and also prior to the tumor resection (neoadjuvant therapy) to improve cure rates.

Although the benefit of adjuvant and neoadjuvant therapy has been improved in recent years, the best choice of treatment modality still remains highly controversial.

The objective of this review is to examine therapies received by advanced pancreatic cancer patients in recent years and to examine the principal chemotherapeutic agents or molecular-targeted therapies useful for clinicians.

Table 1 Staging of pancreatic cancer

Stage	TNM classification	Clinical classification	5-year percent survival (mo)
Stage 0	TisN0M0	Resectable	
Stage Ⅰ A	T1N0M0	Initial	31.4
Stage Ⅰ B	T2N0M0		27.2
Stage Ⅱ A	T3N0M0		15.7
Stage Ⅱ B	TXN1M0	Locally advanced	7.7
Stage Ⅲ	T4NXM0		6.8
Stage Ⅳ	TXNXM1	Metastatic	2.8

Tis: Cancer *in situ*: T: Size and/or extent of invasion; N: Extent of lymph node involvement; M: Whether distant metastases are present.

ADJUVANT THERAPY

In an effort to improve the outcome in patients undergoing potentially curative resection, systemic chemotherapy (Table 2), radiotherapy or a combination of both have been applied following surgery.

SYSTEMIC THERAPY

Chemotherapy

The first randomized controlled trial of adjuvant therapy in pancreatic cancer was designed by the Gastrointestinal Tumor Study Group, which concluded that treatment with 5-fluorouracil (5-FU) plus radiation followed by two years of weekly 5-FU maintenance provided better outcomes than surgery alone[8]. Although this trial was criticized for many reasons, it served to establish 5-FU as the only standard adjuvant therapy for many years in pancreatic cancer. Different drugs and combinations have emerged and been incorporated for the best treatment of these patients (Table 2).

5-FU: 5-FU is a thymidylate synthase inhibitor that blocks the synthesis of pyrimidine thymidine, a nucleotide required for DNA replication.

5-FU had been considered the only chemotherapeutic option for about 20 years until the registration of gemcitabine. Several trials conducted in the late 1970s and early 1980s demonstrated that adjuvant chemotherapy using bolus 5-FU therapy conferred a survival benefit in patients with resected pancreatic cancer[8].

Different studies in the last years have demonstrated a survival benefit from six months of postoperative leucovorin-modulated 5-FU in patients with resected pancreatic cancer, compared to those receiving no adjuvant chemotherapy (median overall survival 19.7 mo *vs* 14 mo respectively, statistically significant)[9-11].

Although for locally advanced and metastatic patients this drug leads to an improved survival compared to the best supportive care[12,13], the combination of 5-FU with other drugs such as doxorubicin or mitomycin did not prove superior to the antimetabolite alone. Similar results were obtained comparing single agent 5-FU to 5-FU plus cyclophosphamide, methotrexate and vincristine[14] as the combination did not offer a survival advantage over 5-FU alone.

Only the combination of 5-FU/irinotecan/oxaliplatin (FOLFIRINOX) has been associated with a high objective response rate based on imaging study, and this finally is the preferred regimen for patients who have good performance status and a normal serum bilirubin level[15].

In the last years, new fluoropyrimidines that mimic the effect of a continuous infusion of 5-FU have been approved. One of the most common but not available in all countries is S-1, an orally active fluoropyrimidine, with favorable antitumor activity in gemcitabine-refractory disease[16,17].

Capecitabine: Capecitabine is an orally administered fluoropyrimidine that is absorbed intact through the intestinal wall and then converted to 5-FU in three sequential enzymatic reactions: carboxylesterases, cytidine deaminase and thymidine phosphorylase. The last enzyme is present at consistently higher levels in tumor rather than normal tissue, thereby providing the basis for enhanced selectivity and better tolerability[18]. The efficacy of capecitabine in monotherapy was shown with high clinical response rate (24%) but low objective response (7%)[19]; however, no advantage using capecitabine in monotherapy over gemcitabine alone has been demonstrated.

Gemcitabine: The development of gemcitabine may be considered a major advance in the treatment of pancreatic cancer. This drug is a difluorinated analog of deoxycytidine. As a prodrug, gemcitabine must be phosphorylated by cytoplasmic and mitochondrial enzymes to its active metabolites, gemcitabine diphosphate and gemcitabine triphosphate. The cytotoxic effect of this drug is attributed to a combination of two actions of the

Table 2 Mode of action of principal drugs used in pancreatic cancer

Agent	Mode of action
5-FU	5-FU is a folate antimetabolite that forms a ternary complex involving 5-fluoro-2-deoxyuridine-5-monophosphate, thymidylate synthase, and 5,10-methylene THF. The formation of this complex thereby inhibits thymidylate synthase activity, which subsequently depletes intracellular thymidylate levels and ultimately suppresses DNA synthesis Also, two metabolites of 5-FU, 5-fluoro-2-deoxyuridine-5-triphosphate and 5-fluorouridine-5-triphosphate, can be incorporated into DNA and RNA, respectively, resulting in DNA instability and interfering with RNA processing and function
Gemcitabine (Gemzar®)	Gemcitabine is an S-phase nucleoside analogue (diflourodeoxycytidine) that is phosphorylated to difluorodeoxycytidine triphosphate by deoxycytidine kinase. Gemcitabine also stimulates deoxycytidine kinase and inhibits both ribonucleotide reductase and deoxycytidine monophosphate deaminase. Gemcitabine triphosphate is incorporated into nascent DNA to inhibit DNA synthesis
Capecitabine (Xeloda®)	Capecitabine an oral, tumor-selective fluoropyrimidine carbamate that is sequentially converted to 5-FU by three enzymes located in the liver and in tumors. The final step is the conversion of 5'-deoxy-5-fluorouridine to 5-FU by thymidine phosphorylase in tumors
Platinum analogues	Platinum forms adducts with DNA inhibiting transcription and replication causing cell death. Oxaliplatin is a third-generation platinum analogue (a diaminocyclohexane platinum derivative) that may have activity in tumors resistant to cisplatin or carboplatin and may have an additive/synergistic activity in doublet or triplet therapy
Taxanes	The taxanes include paclitaxel and docetaxel (Taxotere®) and are semi-synthetic microtubule inhibitors with a different mechanism of action from the vinca alkaloids. Taxanes bind to β-tubulin, promoting microtubule assembly and preventing depolymerisation thus forming stable non-functional complexes and inhibiting the function of the mitotic spindle; This results in cell cycle arrest and increased sensitivity to radiation
Irinotecan (CPT11, Camptosar®)	Irinotecan is a topoisomerase I inhibitor that impedes the DNA helix tortional stress-relieving activity of DNA topoisomerases and also prevents their release from the DNA thus prompting apoptosis

5-FU: 5-fluorouracil.

diphosphate and triphosphate nucleosides, which leads to inhibition of DNA synthesis[20,21].

The first pivotal trial found that gemcitabine is more effective than 5-FU in alleviation of some disease-related symptoms in patients with advanced, symptomatic pancreatic cancer, conferring a modest survival advantage over treatment with 5-FU. As the treatment with gemcitabine was associated with significant clinical response and better survival, this drug was approved for first-line therapy of metastatic pancreatic cancer. This pivotal phase Ⅲ trial demonstrated improvement in median overall and 1-year survival compared to 5-FU (5.7 mo *vs* 4.4 mo and 18% *vs* 2%, respectively)[22].

Many phase Ⅱ studies have demonstrated the efficacy of gemcitabine combination treatments, but not all of the phase Ⅲ trials confirmed the improvement in overall survival (OS) of gemcitabine-based regimens compared to gemcitabine alone. However, an improvement in six-month survival was seen by combining gemcitabine-fluoropyrimidine analogues and gemcitabine-platinum analogues, as demonstrated in the meta-analysis of Heinemann and colleagues[2].

Due to the results obtained in monotherapy, gemcitabine has been combined with many other active cytotoxic agents including 5-FU, cisplatin, docetaxel, oxaliplatin and irinotecan, in an attempt to improve the response in pancreatic cancer patients and each will be discussed here separately.

Gemcitabine and 5-fluorouracil: Based on the complementary pharmacology of their mechanisms of action, the combination of 5-FU and gemcitabine has been evaluated in phase Ⅰ, Ⅱ and Ⅲ trials. Finally, phase Ⅲ trials showed that there is no significant improvement in median OS and median progression-free survival when evaluating the combined regimen compared to that of gemcitabine alone[23-26].

Gemcitabine and capecitabine: Different phase Ⅲ trials have shown that patients who received gemcitabine and capecitabine compared to gemcitabine alone have a significant improvement in survival[27,28].

These data and the meta-analysis performed by these authors suggest that the combination of gemcitabine plus capecitabine should be considered a standard first-line option for locally advanced and metastatic pancreatic cancer.

Gemcitabine and platinum combinations: Since gemcitabine enhances the formation of cisplatin-DNA adducts, an effect that may be due to suppression of nuclear excision repair by gemcitabine, and the platinum may augment the incorporation of gemcitabine triphosphate into DNA[29], the gemcitabine and platinum combination has been assessed in different trials.

Although in preclinical studies the combination of gemcitabine and cisplatin is synergistic, at least three phase Ⅲ trials comparing gemcitabine to the combination of gemcitabine plus cisplatin showed no significant survival advantage for this approach[30-32]. Furthermore, the combination of gemcitabine and platins has not shown improvement in terms of response and is not a considered option for pancreatic cancer patients.

Gemcitabine and irinotecan: As irinotecan (a topoisomerase inhibitor) had minimal clinical activity in patients with advanced pancreatic cancer, combined therapy with gemcitabine is not recommended[33,34] and in some

cases the combination could lead to major toxicity.

Gemcitabine and taxanes: Antitumoral action of taxanes is due to their mechanism of microtubule stabilization and consequently to cell cycle arrest. The association of gemcitabine with paclitaxel or docetaxel in advanced pancreatic patients was studied in different trials and has shown encouraging response rates[35,36]. A phase Ⅲ trial has not yet been completed. Thus, whether this regimen represents an improvement over gemcitabine alone is unclear.

The available data suggest that if there is a benefit to gemcitabine combination therapy compared to gemcitabine alone, it is modest and best documented for capecitabine plus gemcitabine. Today, only gemcitabine alone and the combination of gemcitabine plus capecitabine represent good options for initial therapy.

In summary, adjuvant fluorouracil has been shown to be of benefit for patients with resected pancreatic cancer but gemcitabine is the most effective agent in advanced disease. Compared with the use of fluorouracil, gemcitabine does not result in improved overall survival in patients with completely resected pancreatic cancer[37].

Combined therapies

As compared with gemcitabine, FOLFIRINOX was associated with a survival advantage and had increased toxicity. FOLFIRINOX is an option for the treatment of patients with metastatic pancreatic cancer and good performance status[38].

Targeted molecular therapy

Based on the biological properties of pancreatic cancer, new systemic therapies have been tried. The most common molecular targets have been epidermal growth factor receptor (EGFR)/KRAS, human epidermal growth factor receptor type 2 (HER2) and vascular endothelial growth factor (VEGF), as these genes are overexpressed or mutated in pancreatic tumors.

Targeting EGFR: Currently, there are two approaches targeting the EGFR system: monoclonal antibodies (i.e., cetuximab/Erbitux®) and small molecule tyrosine kinase inhibitors. In spite of promising preclinical trials, cetuximab as monotherapy, or in combination with other cytotoxic agents such as gemcitabine or with radiotherapy, has failed to improve the outcome of PDAC patients[39,40].

Up to now, the only EGFR targeting demonstrating a clinical benefit is erlotinib (Tarceva®, OSI 774), a tyrosine kinase inhibitor that inhibits ErbB-1 phosphorylation. One phase Ⅲ trial of erlotinib with gemcitabine was able to show at least a small gain in the survival of patients with advanced PDAC[41]. Although erlotinib obtained Food and Drug Administration approval and access in clinical application in 2005, the therapeutic benefit for patients with advanced PDAC remains poor.

Targeting HER2: In several studies, HER-2 overexpression in pancreatic cancer has been reported to vary widely (10%-82%)[42,43] and it does not correlate with poor prognosis[44]. Although studies in a mouse model have shown that combination of anti-HER2 antibodies (i.e., trastuzumab) and other chemotherapy may be effective for HER2-overexpressing pancreatic cancer patients[45], the clinical significance is uncertain. A phase Ⅱ clinical trial of trastuzumab for pancreatic cancer has been conducted and showed only 6% response to combined therapy with trastuzumab and gemcitabine in patients with metastatic pancreatic cancer, which is not superior to therapy with gemcitabine alone[46].

Currently, anti-Her2 therapy is experimental and still under investigation for the treatment of pancreatic cancer.

Targeting VEGF: A phase Ⅲ trial concluded that there is no benefit for the addition of bevacizumab to gemcitabine *vs* gemcitabine alone and *vs* gemcitabine and cetuximab[47].

Also some studies have failed to demonstrate a benefit for adding axitinib (an oral inhibitor of VEGF receptors 1, 2 and 3) to gemcitabine[48,49]. Currently, the anti-VEGF approach is not recommended in pancreatic cancer.

Hormonal therapy

Tamoxifen and octreotide are not indicated in metastatic pancreatic cancer because both of them have failed to demonstrate any survival advantage for treated patients[50,51].

RADIOTHERAPY

The use of adjuvant radiotherapy for pancreatic cancer is controversial and the role of radiation therapy continues to be investigated. Currently, the addition of radiotherapy depends on the country in which a patient is being treated[52].

Chemo-radiotherapy followed by chemotherapy is considered the optimal therapy in North America (Gastrointestinal Tumor Study Group; Radiation Therapy Oncology Group) while chemotherapy alone is the current standard in Europe (European Study Group for Pancreatic Cancer; Charité Onkologie)[10,53,54].

The rationale for adjuvant radiotherapy for pancreatic cancer is to improve loco-regional control. Modern radiation delivery techniques, such as intensity-modulated radiation therapy or image-guided and stereotactic body radiation therapy, permit dose escalation in order to reduce normal tissue toxic effects and simultaneously deliver increased doses of radiation to affected areas[55,56]. It is clear that breakthroughs in the treatment of this devastating disease will come mostly from advances in systemic therapy, so radiotherapy should not be abandoned, but rather, intensified.

Intraoperative radiotherapy has also been considered, since local recurrence rates are very high. In general, intraoperative radiotherapy can slightly increase survival rates among patients with pancreatic cancer in localized

stages. There is no clear evidence to indicate that intraoperative radiotherapy is more effective than other therapies in treating pancreatic cancer in locally advanced and metastatic stages[57].

CHEMORADIOTHERAPY

Some studies demonstrated improved survival when radiotherapy was combined with 5-FU chemotherapy compared with radiotherapy alone, in patients with locally advanced unresectable pancreatic cancer[58]. This combined therapy has been applied to patients undergoing RO resection to improve surgical cure rate.

In locally advanced pancreatic cancer, recent evidence using modern radiotherapy techniques and dosing suggests a continued role for radiotherapy. In both resected and unresected disease, further studies are needed to define optimal radiation dose, field size, and technique, and to assess the effect of radiotherapy not only on survival, but also on local disease control and quality of life[59].

NEOADJUVANT THERAPY

The low rate of resectability and the poor outcomes following pancreaticoduodenectomy have led to the investigation of preoperative and postoperative therapies to identify those patients who are not candidates for surgery and who could benefit from neoadjuvant chemotherapy and/or radiotherapy.

The initial reports using radiation therapy with or without 5-FU did not demonstrate an obvious improvement in either resectability or overall survival[60,61]. Subsequent studies improved the treatment by increasing radiotherapy dose, adding intraoperative radiotherapy and using combined chemotherapy. The drugs tested were mitomycin, 5-FU, 5-FU and cisplatin, and paclitaxel, but their efficacy remains uncertain[62-64].

Subsequent reports used gemcitabine-based chemotherapy which provided an enhanced local effect, although with potentially more toxicity than 5-FU-based regimens. Gemcitabine has also been combined with radiotherapy and cisplatin[65,66].

Currently, neoadjuvant radiation is associated with improved survival in patients with resectable pancreatic cancer[67] but chemotherapy alone without radiotherapy is beginning to be studied and the experience is limited[68,69].

ADJUVANT *VS* NEOADJUVANT THERAPY

Although the median survival times reported from some uncontrolled trials of neoadjuvant therapy compare favorably to those reported with adjuvant therapy approaches[65,70,71], the question as to whether preoperative therapy is better than postoperative therapy is uncertain as there are no randomized trials comparing the two approaches.

One advantage of neoadjuvant therapy is that it avoids the morbidity of pancreaticoduodenectomy in patients who have occult, micrometastatic disease that becomes evident during therapy. A second advantage is that in patients undergoing surgery, prolonged recovery prevents the delivery of postoperative adjuvant chemotherapy in about a quarter of them[72].

Recent studies have shown that neoadjuvant therapy is associated with a lower rate of lymph node positivity and improved overall survival and should be considered an acceptable alternative to the surgery-first paradigm in operable pancreatic cancer[73].

SECOND-LINE THERAPY

There are few trials of second-line therapy in patients who have failed chemotherapy, and there is no widely accepted standard of care.

For patients who retain a good performance status after failing initial gemcitabine therapy, benefit has been suggested from a second-line therapy based on oxaliplatin/fluoropyrimidine combination such as 5-FU and oxaliplatin[65,70,71]. Other oxaliplatin combinations are also acceptable with the agents gemcitabine, irinotecan or capecitabine[74-76].

There are no data for patients who fail initial 5-FU and oxaliplatin, but a reasonable option is gemcitabine as monotherapy.

CONCLUSION

All the treatment options examined in this review demonstrate and confirm that advanced pancreatic cancer is among the most complex cancers to treat.

Currently there is no consensus regarding the optimal management of patients after resection of an exocrine pancreatic cancer, and the approach is different in Europe and in the United States. Most European clinicians use chemotherapy alone after resection of a pancreatic neoplasm. The American approach more often includes chemoradiotherapy as well as adjuvant chemotherapy.

Although it is mainly accepted that a 6-mo course of systemic chemotherapy with gemcitabine or 5-FU should be part of any adjuvant treatment, there is no single adjuvant regimen of chemotherapy or chemoradiotherapy that can claim unequivocal superiority over others. Among these options there are no differences in outcome but fewer side effects occur with gemcitabine, and this is nowadays the preferred regimen.

Based on current data, it is clear that treatment with gemcitabine or 5-FU results in a median survival of just a few months[77,78]. The limitation of this treatment is mainly due to the profound resistance of PDAC cells towards anti-cancer drugs, emerging from the efficient protection against chemotherapeutic drugs by an altered balance of pro- and anti-apoptotic proteins which results in a markedly reduced apoptotic responsiveness[79,80].

Currently there are around 1070 clinical trials focusing on studying new biomarkers, different drug combinations and vaccines designed for pancreatic cancer (www.clinicaltrial.gov).

Regardless of these efforts in adjuvant and neoadjuvant therapy, the major goal to combat PDAC is to find diagnostic markers, identifying the disease in a pre-metastatic stage and making a curative treatment accessible to more patients. Given an earlier diagnosis, surgical interventions together with adjuvant radio/chemotherapy are the most promising options. Considering such evidence, the urgent need for an individualized and more effective adjuvant therapy is evident.

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