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Systemic treatments in pancreatic cancer: Taiwan pancreas society recommendation

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ABSTRACT

Pancreatic cancer is a highly aggressive malignancy with a poor prognosis. Over the past decade, significant therapeutic advancements have improved the survival rates of patients with pancreatic cancer. One of the primary factors contributing to these positive outcomes is the evolution of chemotherapy, from monotherapy to doublet or triplet regimens, and the integration of multimodal approaches. Additionally, targeted agents tailored to patients with specific genetic alterations and the development of cell therapies show promise in benefiting certain subpopulations. This article focuses on examining pivotal studies that explore the role of chemotherapy in neoadjuvant, adjuvant, maintenance, and salvage settings; highlights interesting findings related to cell therapy; and provides an overview of ongoing trials concerning metastatic settings. This review primarily aimed to offer recommendations based on therapeutic evidence, recent advancements in new treatment combinations, and the most innovative approaches. A unique aspect of this review is the inclusion of published papers on clinical trials and real-world data in Taiwan, thus adding a valuable perspective to the overall analysis.

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1. Introduction

Pancreatic cancer is a malignant tumor, with the worst prognosis among cancers. Taiwan Cancer Registry Annual Report 2020 found that the number of new cases of pancreatic cancer was approximately 3012, accounting for 4.88 % of all new cancer cases (13th). The incidence ranks 12th among males and 13th among females; however, the mortality ranks 8th among males and 5th among females [1]. The poor prognosis of pancreatic cancer is attributed to late diagnosis and low sensitivity to systemic chemotherapy.

Gemcitabine alone has become a standard treatment since 1997, which has better clinical benefits but with a low objective response rate (ORR) and a median overall survival (OS) of 6 months only [2]. Currently, irinotecan, oxaliplatin, fluorouracil, and leucovorin (LV) (FOLFIRINOX) or gemcitabine plus nab-paclitaxel (gem/nab-P) is the first-line therapy for metastatic pancreatic cancer worldwide [3,4]. Oral S-1 is an alternative treatment regimen for late-stage pancreatic cancer in East Asia and Taiwan [5]. In recent years, second-line treatment with liposomal irinotecan (nal-IRI) plus fluorouracil and LV (5-FU/LV) has been recommended by the National Comprehensive Cancer Network (NCCN) guidelines and approved by the Taiwan National Health Insurance [6].

Postoperative adjuvant chemotherapy demonstrates better survival benefits compared with placebo in resectable cases [7]. Induction chemotherapy for local/resectable pancreatic cancer followed by chemoradiation or conversion surgery has also been investigated [8]. Chemotherapy has become an important modality in multidisciplinary approaches for each stage of pancreatic cancer.

In recent years, advancements in next-generation sequencing (NGS) have significantly improved tumor genomic profiling, enabling the exploration of therapeutic targets in a tumor-agnostic manner [9]. Basket trials targeting driver mutations across organs, including those in *HER2*, *BRAF*, *BRCA1/2*, and mismatch repair genes, are currently ongoing. Additionally, rapid advancements in cancer studies have yielded novel agents for the treatment of various cancer types worldwide, offering hope to patients with advanced pancreatic cancer. Owing to the numerous treatment options available, clinical oncologists must choose wisely to treat this fatal cancer. The Taiwan Pancreas Society aims to unite experts to create a consensus to guide clinical oncologists in Taiwan regarding the treatment of patients with pancreatic cancer.

2. Patient selection and initial assessment

Evaluation of the baseline performance status (PS) and comorbidity profiles of patients is crucial. Although old age is generally associated with a poorer prognosis in pancreatic cancer, elderly patients with adequate PS can still benefit from therapy [10].

Evolution of multidisciplinary approaches has improved the survival of patients with pancreatic cancer. Furthermore, chemotherapy enhances quality of life, despite its associated toxicities [3,6,11]. Considering the specific adverse effects associated with each chemotherapy regimen is essential as they can significantly affect patients' quality of life [12]. Thus, informing patients about the potential benefits and limitations of treatment choices is imperative for effectively managing their expectations.

Germline and somatic genetic mutations may affect treatment choices. Despite the relatively high cost of genetic testing, it is necessary for physicians to engage in discussions with patients regarding this aspect. Selecting an appropriate tissue sampling method to obtain an adequate amount of tissue is necessary to identify somatic mutations. However, patient safety and facility experience should be considered before proceeding with tissue sampling.

Overall, considering these factors and engaging in comprehensive evaluations, discussions, and informed decision-making processes are vital for providing optimal care and treatment outcomes for patients with pancreatic cancer.

3. Neoadjuvant therapy for resectable pancreatic cancer

3.1. Rationale of neoadjuvant therapy

According to the NCCN guidelines for resectable pancreatic cancer, treatment choices include upfront surgery or neoadjuvant therapy. The rationale for neoadjuvant therapy is the high R1 resection rate and lymph node positivity in adjuvant therapy clinical trials [13,14], and up to 60 % of patients omit adjuvant therapy owing to postoperative complications [15]. Neoadjuvant therapy may eradicate micrometastases, increase R0 resection rate, select unfavorable biology, and demonstrate in vivo chemosensitivity. However, physicians face risks of tumor progression and chemotherapy toxicity and the requirement for tissue confirmation before treatment. Therefore, the NCCN guidelines suggest considering neoadjuvant therapy only for patients with high-risk features, including markedly elevated cancer antigen 19-9 level, large primary tumors, large regional lymph nodes, excessive weight loss, and extreme pain; however, there is no clear definition regarding the above factors.

3.2. The regimen of neoadjuvant therapy

A large meta-analysis compared neoadjuvant therapy with upfront surgery in resectable or borderline resectable cases [16], including 38 studies involving 3484 patients from 2000 to 2016. This study showed increased OS and higher R0 resection rates in patients who received neoadjuvant therapy. The phase III PREOPANC-1 study [17] was the first randomized controlled trial to demonstrate that neoadjuvant gemcitabine-based chemoradiotherapy had better OS, compared with upfront surgery, in resectable and borderline resectable pancreatic cancer. However, in the resectable subgroup, which represented 53 % of the cases, there was no significant difference in median OS (14.6 vs. 15.6 months) or R0 resection rate (66 % vs. 59 %). Other phase II trials using mFOLFIRINOX [18], gem/nab-P [19], gemcitabine plus S-1 [20], or a real-world study [21] showed different benefits in terms of OS or R0 resection rate. However, the sample size was small, and the results were inconclusive.

Therefore, neoadjuvant therapy for resectable pancreatic cancer may increase the R0 resection rate and prolong OS; however, it is still not a standard of care in clinical practice owing to the lack of large, randomized studies. The optimal regimen and duration of neoadjuvant therapy also remain unknown. Multidisciplinary discussions are necessary before initiating neoadjuvant therapy for resectable pancreatic cancer.

3.3. Recommendations

- Neoadjuvant therapy for resectable pancreatic cancer can be considered in patients with high-risk features.
- Multidisciplinary discussions and a definitive diagnosis before initiating neoadjuvant therapy for resectable pancreatic cancer are mandatory.
- There is no standard neoadjuvant regimen for resectable pancreatic cancer, and the choices include chemoradiation with gemcitabine or combination chemotherapy. Therefore, the participation of well-designed clinical trials is recommended.

4. Adjuvant treatment after surgical resection

Considering the poor results of surgery alone in pancreatic cancer, several efforts involving chemotherapy, radiotherapy, or both have been made to improve the 5-year survival of these patients.

4.1. Adjuvant chemotherapy

Postoperative adjuvant chemotherapy has been evaluated in several

randomized trials. The reference trials are as follows.

4.1.1. 5-FU/LV

The role of adjuvant chemotherapy was established in a multicenter 2 × 2 factorial randomized trial, in which 289 patients were treated with one of four therapeutic modalities: adjuvant chemotherapy (5-FU/LV), chemoradiation only (split course 40 Gy plus 5-FU), or chemoradiation followed by chemotherapy or surveillance alone [22]. Patients who received chemotherapy had a longer median survival (20.1 vs. 15.5 months; hazard ratio [HR], 0.71; 95 % confidence interval [95 % CI], 0.55–0.92; P = 0.009), compared with patients who did not.

4.1.2. Gemcitabine

The CONKO-001 trial, comparing gemcitabine to observations, confirmed the benefits of adjuvant chemotherapy [23]. Gemcitabine administered for 24 weeks improved recurrence-free survival (RFS) (13.4 vs. 6.7 months; HR, 0.55; 95 % CI, 0.44–0.69; P < 0.001) and median OS (22.8 vs. 20.2 months; HR, 0.76; 95 % CI, 0.61–0.95; P = 0.005).

4.1.3. Gemcitabine or 5-FU/LV

The ESPAC-3 trial compared the administration of adjuvant chemotherapy with six cycles of 5-FU/LV or gemcitabine [24]. No significant differences were observed in terms of OS, RFS, or quality of life. Recently, 5-FU/LV and gemcitabine are considered the standard of care for fragile patients.

4.1.4. Gemcitabine plus capecitabine

In the ESPAC-4 study, gemcitabine plus capecitabine demonstrated superior survival over gemcitabine monotherapy in resected pancreatic cancer with a median OS periods of 28.0 months and 25.5 months, respectively (HR, 0.82; 95 % CI, 0.68–0.98; P = 0.032) [13].

4.1.5. FOLFIRINOX

The PRODIGE 24-ACCORD trial demonstrated that adjuvant modified-FOLFIRINOX was superior to gemcitabine, with median RFS periods of 21.6 and 12.8 months (HR, 0.58; 95 % CI, 0.46–0.73; P < 0.001) and median OS periods of 54.4 months and 35.0 months (HR, 0.64; 95 % CI, 0.48–0.86; P = 0.003), respectively [14]. Adjuvant modified FOLFIRINOX regimen led to significantly longer survival but was associated with a higher incidence of grade 3–4 toxicities (76.9 % vs. 52.9 %).

4.1.6. S-1

In the JSPAC-01 study, S-1 was superior to gemcitabine (HR, 0.57; 95 % CI, 0.44–0.72; P < 0.0001 for noninferiority, P < 0.0001 for superiority) with 5-year OS rates of 24.4 % (95 % CI, 18.6–30.8) and 44.1 % (95 % CI, 36.9–51.1) in the gemcitabine and S-1 groups, respectively [25]. Grade 3–4 stomatitis and diarrhea were more frequently experienced in the S-1 group than in the gemcitabine group.

4.2. Adjuvant chemoradiation

Three randomized trials compared the benefits of adjuvant chemoradiation with surveillance alone, and two studies (EORTC [26] and ESPAC-1 trial [22] trials) failed to demonstrate survival benefits. Only one study showed a favorable outcome in chemoradiation, but this study was prematurely stopped owing to low patient accrual after enrolling 43 patients [27].

4.3. Timing of postoperative chemotherapy

A meta-analysis showed no conclusive evidence suggesting improved survival in patients starting treatment at various time cut-offs [28]. Based on our understanding of the natural history and biology of pancreatic cancer, time-to-treatment should be optimized to deliver treatment as soon as the patient has recovered from surgery and is able to tolerate chemotherapy. The initiation of adjuvant therapy within 12 weeks postoperatively is recommended.

4.4. Recommendations

- A multidisciplinary team is necessary.
- Adjuvant treatment with modified FOLFIRINOX, S-1, and gemcitabine plus capecitabine is recommended for fit patients, and gemcitabine monotherapy or 5-FU/LV is reserved for less fit patients.
- Routine chemoradiation is not recommended to patients after surgery, except in clinical trials.

5. Treatment of borderline resectable and locally advanced unresectable diseases

Only approximately 20–25 % of tumors are radiologically resectable upon diagnosis. Approximately 30–40 % of patients whose tumors are localized in the pancreatic region remain unsuitable for curative resection and are divided into borderline resectable and locally advanced diseases based on the severity of vessel invasion [29].

5.1. Borderline resectable disease

Previous studies showed that a short course of neoadjuvant therapy (usually for 2 months) before curative surgery resulted in higher R0/R1 resection rate at 64–85 %, and 12-month OS rate at 77 %, compared with only 40 % in the upfront surgery group. A longer course of neoadjuvant chemotherapy (usually up to 4 months) had an 18-month survival rate of 67 % [30]. In the PREOPANC-1 clinical trial, the subgroup analysis revealed improved OS in patients with borderline resectable disease who received neoadjuvant chemoradiotherapy compared with upfront surgery (17.6 vs. 13.2 months; HR, 0.62; 95 % CI, 0.40–0.95; P = 0.029) [31]. The R0 resection rate was also higher in the chemoradiotherapy group than in the upfront surgery group (71 % vs. 40 %, P < 0.01). The 5-year OS rate was 20.5 % in the neoadjuvant chemoradiotherapy group compared with 6.5 % in the upfront surgery group, with a longer median OS (15.7 vs. 14.3 months; HR, 0.73; 95 % CI, 0.56–0.96; P = 0.025) [17]. In another ESPAC-5 study, either short-course (2 months) neoadjuvant chemotherapy with gemcitabine plus capecitabine, FOLFIRINOX, or gemcitabine-based chemoradiotherapy resulted in better 1-year OS, compared with immediate surgery, in patients with borderline resectable disease (78 %, 84 %, 60 %, and 39 % respectively; P = 0.0028) [32]. It also improved the 1-year RFS in the short-course neoadjuvant treatment group, regardless of the treatment type, compared with immediate surgery. Yamaguchi et al. found that neoadjuvant chemotherapy with FOLFIRINOX or gem/nab-P followed by curative surgery was feasible and well-tolerated, with an R0 resection rate improving to 67.4 %, and the 3-year survival rate was 54.7 % [33]. However, the role of chemoradiation remains undetermined as the add-on of stereotactic body radiation therapy (SBRT) seemed to have a deleterious effect, compared with mFOLFIRINOX alone, in the A021501 trial (18-month OS rate 47.3 % vs. 66.7 %; median OS, 17.1 vs. 29.8 months) [34].

5.2. Recommendations

- Short courses of neoadjuvant therapy, including chemotherapy alone or gemcitabine-based chemoradiotherapy, are recommended for borderline resectable disease.
- Neoadjuvant chemotherapy may be more preferred than neoadjuvant chemoradiotherapy based on current evidence.
- No definite preference for chemotherapy regimens has been suggested. FOLFIRINOX and gem/nab-P are reasonable choices to get borderline tumor downsizing of the tumor is therapeutic goal, but this is not achieved by gemcitabine alone with a RR of 9 %.

Therefore, we may consider combination chemotherapy in this situation. FOLFIRINOX or gemcitabine/nab-P are reasonable choices.

5.3. Locally advanced disease

Resection of apparently unresectable pancreatic cancer following induction therapy, although relatively controversial, is an important development for selected patients based on remarkable advancements in surgical techniques and the more confident use of combination chemotherapy regimens and chemoradiotherapy. The NCCN guidelines recommend 4–6 months of induction combination chemotherapy followed by conventional chemoradiotherapy or SBRT for selected patients without systemic metastases, followed by surgical resection [35]. Gem/nab-P is similarly active and safe as sequential gem/nab-P, followed by FOLFIRINOX as multidrug induction chemotherapy regimen, with a relatively similar surgical conversion rate (35.9 % and 43.9 % respectively; P = 0.38) [36]. In the CONKO-007 trial, additional radiotherapy after induction chemotherapy with gemcitabine or FOLFIRINOX did not affect progression-free survival (PFS) or OS [37]. Su et al. found that induction chemotherapy with GOFL and mFOLFIRINOX followed by chemoradiotherapy provided similar clinical outcomes in patients with locally advanced pancreatic cancer [38,39].

5.4. Recommendations

- Up to 4–6 months of induction chemotherapy combined with chemoradiotherapy is recommended for locally advanced disease.
- Surgical exploration should be considered if the disease is under control after induction therapy.
- Both FOLFIRINOX and gem/nab-P, or sequential therapy, are safe and tolerable for locally advanced disease. No preference suggestions can be made based on the current evidence.
- Some new radiotherapy treatment choices, including proton and carbon, may be considered.

6. First-line chemotherapy for patients with metastatic pancreatic cancer

Combination chemotherapy demonstrates significantly better survival, compared with monotherapy. Therefore, gemcitabine- or fluorouracil-based combination chemotherapy is recommended as the first-line regimen, whereas monotherapy is recommended for fragile patients.

6.1. Monotherapy

6.1.1. Gemcitabine monotherapy

Gemcitabine monotherapy became the standard of care in advanced pancreatic cancer in 1997 based on the randomized phase III trial with median OS periods of 5.65 and 4.41 months for the gemcitabine and 5-FU arms, respectively (P = 0.0025) [2]. Combination chemotherapy is recommended for fit patients, whereas gemcitabine monotherapy remains an option for fragile patients.

6.1.2. S-1 monotherapy

In the large randomized phase III GEST study that recruited 834 patients with advanced pancreatic cancer, S-1 was comparable to gemcitabine in terms of ORR (21.0 % vs. 13.3 %) and OS (9.7 vs. 8.8 months; HR, 0.96; 97.5 % CI, 0.78–1.18; P < 0.001 for noninferiority) [5].

6.2. Combination chemotherapy

6.2.1. Gemcitabine plus erlotinib

The add-on of erlotinib to gemcitabine achieved a modest improvement of OS, compared with gemcitabine monotherapy (HR, 0.82; 95 % CI, 0.69–0.99; P = 0.038), in nonselective patients [40].

6.2.2. FOLFIRINOX

FOLFIRINOX is recommended as a first-line regimen only for fit patients (Eastern Cooperative Oncology Group [ECOG] PS 0–1). The PRODIGE 4/ACCORD 11 study demonstrated that FOLFIRINOX was superior to gemcitabine monotherapy as a first-line therapy for advanced pancreatic cancer, with median OS periods of 11.1 and 6.8 months, respectively (HR, 0.57; 95 % CI, 0.45–0.73; P < 0.001) [3]. However, FOLFIRINOX was highly toxic and intolerable in Asian patients [41], and modified FOLFIRINOX (omit bolus 5-FU and dose reduction of irinotecan to 150 mg/m^2) should be considered in Asian patients [42].

6.2.3. Nab-paclitaxel plus gemcitabine

The MPACT study demonstrated that gem/nab-P resulted in a better ORR and survival than gemcitabine alone; however, significant toxicities remained a concern. The median OS period was 8.5 months in the gem/nab-P group compared with 6.7 months in the gemcitabine group (HR, 0.72; 95 % CI, 0.62–0.83; P < 0.001) [4].

6.2.4. NALIRIFOX

NALIRIFOX (5-FU/LV, nal-IRI, and oxaliplatin) demonstrated superior survival benefit over gem/nab-P, with median OS periods of 11.1 and 9.2 months, respectively (HR, 0.83; 95 % CI, 0.70–0.99; P = 0.0355) in the randomized phase III NAPOLI-3 trial [43].

6.3. Recommendations

- Chemotherapy remains the standard of care in metastatic pancreatic cancer.
- Gemcitabine- or fluorouracil-based combination chemotherapy is recommended for fit patients, whereas monotherapy is recommended for fragile patients.

7. Taiwan experience of first-line treatment

Owing to the delayed reimbursement of the approved FOLFIRINOX and gem/nab-P in advanced pancreatic cancer, some phase I/II clinical trials and real-world data were developed in Taiwan.

7.1. GOFL

Biweekly GOFL is a triplet regimen consisting of gemcitabine, oxaliplatin, fluorouracil, and LV. In the phase II trial, the ORR was 33.3 %, with significant grade 3–4 toxicities of neutropenia (28.9 %) and diarrhea (6.7 %) [44].

7.2. SLOG

Biweekly SLOG was derived from the GOFL regimen using oral S-1/LV instead of infusion of 5-FU/LV. A phase I/II trial in patients with metastatic pancreatic cancer showed an ORR of 40.7 %, median PFS period of 7.6 months, and median OS period of 11.4 months. The common grade 3–4 toxicities included neutropenia (40.7 %), diarrhea (7.4 %), and oral mucositis (5.6 %) [12].

7.3. Modified GSL

In a phase II trial in elderly patients aged ≥70 years and ECOG PS ≤2, the results showed an ORR of 26.5 %, median PFS period of 6.6 months, and median OS period of 12.5 months. The common grade 3–4 toxicities were neutropenia (18.4 %) and mucositis (12.2 %), with improved quality of life, indicating that a modified GSL regimen is valuable for Asian elderly patients with advanced pancreatic cancer [10].

7.4. S-1 based regimens

The reimbursement of S-1 since June 2014 has changed treatment patterns and improved survival in a multi-institute cohort study [45]. Real-world data showed that gemcitabine plus S-1 as a first-line treatment was acceptable for patients with advanced pancreatic cancer [46].

7.5. Gemcitabine plus erlotinib

A randomized phase II trial was conducted to compare gemcitabine plus erlotinib with gemcitabine alone in patients with metastatic pancreatic cancer. The treatment efficacy was significantly better in the combination group than in the monotherapy group. Epidermal growth factor receptor mutations in exons 18–21, but not Kirsten rat sarcoma viral oncogene homologue (*KRAS*) mutations, were independent predictors of erlotinib benefit [47].

7.6. Recommendations

- The above regimens can serve as alternative first-line treatments for Taiwanese patients with pancreatic cancer, depending on physicians' choices, patient requests, reimbursement policies, and the balance between efficacy and toxicities.

8. Second-line treatment for advanced and metastatic pancreatic cancer

As patients progress from the first-line chemotherapy, they usually receive different second-line treatment regimens. However, the options for second-line treatments are limited because only a few successful trials significantly improve survival [48]. A systematic review of clinical trials that evaluated the effectiveness of subsequent chemotherapy after gemcitabine failure in pancreatic cancer showed survival benefits, compared with the best supportive care [49]. The choice of second-line chemotherapy depends on the chemotherapy used in the first-line regimen, adverse effects, PS, age, and comorbidities.

Currently, there are two main combination chemotherapy regimens in the first-line setting. After first-line treatment with gemcitabine-based chemotherapy, the advice is to select 5-FU-based chemotherapy; in the case of front-line therapy with 5-FU-based treatment, the indication is gemcitabine-based chemotherapy.

8.1. Second-line chemotherapy after treatment with gemcitabine-based combination therapy

Currently, international cancer treatment guidelines recommend 5-FU-based therapies, including FOLFIRI, nal-IRI + 5-FU, oxaliplatin plus 5-FU/LV (OFF), FOLFOX or capecitabine plus oxaliplatin, and monotherapy with 5-FU, capecitabine, or S-1 for patients previously treated with gemcitabine-based chemotherapy.

8.1.1. Nal-IRI + 5-FU/LV

In the NAPOLI-1 phase III randomized trial, patients with metastatic pancreatic cancer who previously received gemcitabine-based therapy were randomized to receive nal-IRI monotherapy, 5-FU/LV, or both [6]. Median PFS (3.1 vs. 1.5 months; HR, 0.56; 95 % CI, 0.41–0.75; $P < 0.001$) and median OS (6.1 vs. 4.2 months; HR, 0.67; $P = 0.012$) were significantly greater in patients who received nal-IRI with 5-FU/LV compared with those who received 5-FU/LV alone. The most frequent grade 3–4 side effects of combination therapy were neutropenia, diarrhea, emesis, and fatigue [50]. Nal-IRI combined with 5-FU/LV was later approved by the FDA as a treatment option after gemcitabine-based therapy in patients with metastatic disease.

Some retrospective studies in Korea and Taiwan have confirmed these data [51–54]. In Taiwan, real-world data support the use of the NAPOLI-1 nomogram for risk stratification to predict the OS with metastatic pancreatic cancer [55]. Moreover, the starting dose [56], pre-emptive dose [52], dose pattern, early cumulative dose [57], preoperative albumin combined with neutrophil-to-lymphocyte ratio [58], spleen volume [59], and previous conventional irinotecan treatment [60] also affect the treatment results of nal-IRI in real-world practice.

8.1.2. Fluoropyrimidine and oxaliplatin-based regimens

Another option in the second-line setting is an OFF regimen consisting of 5-FU/LV and oxaliplatin. In the CONKO-003 trial, compared with 5-FU/LV, oxaliplatin/5-FU/LV had significantly higher median OS (5.9 vs. 3.3 months) and median PFS (2.9 vs. 2 months) [61]. The PANCREOX trial compared the modified FOLFOX6 (mFOLFOX6) protocol with 5-FU/LV. The combination did not improve PFS, and the median OS was shorter in the mFOLFOX6 arm than in the 5-FU/LV arm [62].

8.1.3. Irinotecan- and 5-FU-based regimens

A prospective multicenter study evaluated the use of second-line 5-FU + LV + irinotecan (FOLFIRI) in patients who progressed to first-line therapy with gemcitabine and platinum (cisplatin or oxaliplatin) [63]. Among the 50 enrolled patients, four partial responses (8 %) were observed, with disease stability in 28 %, whereas PFS and OS were 3.2 and 5.0 months, respectively.

In the single-arm, multicenter phase II study conducted by Chung et al., in 48 patients receiving modified FOLFIRINOX, the ORR, disease control rate, median PFS period, and OS period were 18.8 %, 62.5 %, 5.8 months, and 9.0 months, respectively, with significant toxicity (neutropenia grade 3–4 rate, 64.6 %; febrile neutropenia, 16.7 %) [64]. Highly toxic triplet therapy is unsuitable as second-line palliative treatment in patients with a nonoptimal PS and is reserved for only a few patients.

8.2. Second-line chemotherapy after FOLFIRINOX treatment

There is no consensus on the second-line treatment after progression to FOLFIRINOX because no prospective randomized trials have been conducted in this setting. The choice is generally a gemcitabine-based treatment, which can include gemcitabine monotherapy or gemcitabine-based combination therapy.

8.2.1. Gemcitabine monotherapy

Only a series of retrospective studies have evaluated the efficacy of gemcitabine as second-line monotherapy after FOLFIRINOX failure [65,66]. Gemcitabine as second-line chemotherapy after FOLFIRINOX failure in advanced pancreatic cancer showed a median OS period of 3.7 months, a median PFS period of 2.1 months, and a disease control rate of 40 % [67]. Evaluation of gemcitabine efficacy after the FOLFIRINOX regimen in patients with advanced pancreatic adenocarcinoma also found an ORR of 11 % and a clinical benefit of 44 %, regardless of their previous response to the first-line treatment [68].

8.2.2. Gemcitabine-based treatment

Although guidelines recommend gemcitabine-based regimens after FOLFIRINOX failure, the evidence is significantly limited [35,69]. In the randomized phase III GEMPAX UNICANCER study, paclitaxel plus gemcitabine failed to demonstrate an OS benefit over gemcitabine monotherapy (6.4 vs. 5.9 months) [70]. The randomized phase III CT-4006 study, which compared cationic liposomes embedded with paclitaxel plus gemcitabine versus gemcitabine monotherapy, had completed patient accrual and the results are expected to come out soon [71].

8.3. Recommendations

- In patients with preserved PS (ECOG PS 0–1) without relevant comorbidities, proposing second-line treatment with a 5-FU- or

Table 1
Landmark ongoing clinical trials for pancreatic cancer.

Trial ID	Date of start	Trial stage	Phase	N	Stage of disease	Line of treatment	Therapeutic intervention	Strategy
NCT04935359 [87]	June 23, 2021	Recruiting	III	490	Metastatic	1	NIS793 + gemcitabine + nab-paclitaxel vs placebo + gemcitabine + nab-paclitaxel	Blockade of transforming growth factor β (TGFβ)
NCT03816163 [88]	January 25, 2019	Recruiting	II	369	Metastatic, claudin-18.2-positive	1	Zolbetuximab + gemcitabine + nab-paclitaxel vs gemcitabine + nab-paclitaxel	Targeting claudin-18 isoform 2 (CLDN18.2)
NCT05254171 [89]	February 24, 2022	Recruiting	II/III	150	Metastatic	1	SBP-101 + gemcitabine + nab-paclitaxel vs placebo + gemcitabine + nab-paclitaxel	A small molecule polyamine metabolic inhibitor
NCT03310632	October 16, 2017	Active, not recruiting	I/II	52	Metastatic	1	Antroquinonol + gemcitabine + nab-paclitaxel	A cyclohexenone compound purified from an extract of Antrodia camphorata
NCT05026905	August 30, 2021	Recruiting	II	86	Metastatic	1	S-1 + leucovorin + gemcitabine + nab-paclitaxel vs oxaliplatin (GASL) + gemcitabine + nab-paclitaxel (GAP)	Combination with other chemotherapeutic agents
NCT04338763	April 8, 2020	Recruiting	I	48	Advanced	1	RP72 monotherapy vs RP72 + gemcitabine	Blockade of CXCR1 and CXCR2
NCT04659603	December 9, 2020	Recruiting	II	94	Advanced, CEACAM5-positive	2 or 3	Tusamitamab monotherapy vs. Tusamitamab + gemcitabine	Blockade of CEACAM5
NCT05512377 [90]	August 23, 2022	Recruiting	II	155	Advanced	Any	BI 907828	Inhibiting the interaction between p53 and MDM2
NCT04185883 [91]	December 4, 2019	Recruiting	Ib/II	1143	Advanced, *KRAS G12C* mutation	Any	Sotorasib + trametinib + panitumumab vs sotorasib + AMG 404 vs sotorasib + RMC-4630 vs sotorasib + afatinib vs sotorasib + panitumumab ± FOLFIRI vs sotorasib + atezolizumab vs sotorasib + carboplatin, pemetrexed, docetaxel, paclitaxel, pembrolizumab vs sotorasib monotherapy vs sotorasib + palbociclib vs sotorasib + everolimus vs sotorasib + pembrolizumab vs sotorasib + MVASI® (bevacizumab-awwb) + FOLFIRI or FOLFOX vs sotorasib + TNO155 vs sotorasib + BI 1701963	*KRAS G12C* inhibitor
NCT05737706	February 21, 2023	Recruiting	I/II	304	Advanced, *KRAS G12D* mutation	Any	MRTX1133	*KRAS G12D* inhibitor
NCT05242822	February 16, 2022	Recruiting	I	120	Advanced, FGFR2 and/or FGFR3 gene alterations	Any	KIN-3248	Pan-fibroblast growth factor receptor inhibitor

ID, identification; N = number.

gemcitabine-based treatment is reasonable, depending on the first-line chemotherapy used.
- Within 5-FU-based regimens, any residual toxicities of the first-line treatment can lead to the choice of another chemotherapy regimen.

9. Treatment beyond second-line regimens

Currently, there is no standard chemotherapy regimen for patients with metastatic adenocarcinoma after disease progression on nal-IRI plus 5-FU/LV. Patients are encouraged to participate in clinical trials if their performance is good (see below). Palliative and hospice care is important for unfit patients.

With advancements in NGS technology, several pancreatic cancers harbor various genetic alterations. The number of druggable alterations in the modern pharmaceutical industry is increasing because of high-throughput drug screening. Moreover, the price of NGS has dropped rapidly and has become more affordable for the general population, compared with that from 5 years ago. For a disease with unsatisfactory treatment results, it is worthwhile to have cancer tissue sequenced either in newly diagnosed or chemotherapy-failed patients with advanced pancreatic cancer (see below).

In recent years, immunotherapy has become an important part of the anticancer therapies for several types of cancers. Although several trials using single immune checkpoint inhibitors (ICIs) have failed to demonstrate efficacy in patients with pancreatic cancer, there is a trend toward testing the efficacy of combination therapy with ICIs and chemotherapy in clinical trials (see below). Cell therapy, another type of immunotherapy, is gaining increasing attention for pancreatic cancer, which has a poor prognosis (see below).

9.1. Recommendations

- In addition to hospice care, fit patients should be encouraged to participate in clinical trials after disease progression on nal-IRI plus 5-FU/LV.
- NGS, immunotherapy, and other emerging reports may provide treatment choices for certain populations.

9.2. NGS, targeted therapy, and immune therapy

9.2.1. NGS

NGS is a powerful technology used in cancer studies and clinical practice. In pancreatic cancer, NGS may help guide treatment. Most pancreatic carcinomas (>80 %) result from sporadic mutations that randomly occur. Only a small percentage (<10 %) are attributed to inherited germline mutations. Certain germline mutations in genes are associated with varying levels of increased risk for pancreatic carcinoma. Familial pancreatic cancers, defined as cases which at least two first-degree relatives have pancreatic cancer, represent only 5–10 % of all pancreatic cancer cases. *BRCA2* mutations are the most common

Table 2
Non-genetically engineered immune cell therapy in pancreatic cancer.

	N	Cell	Other modality	Disease	Outcome
Stift A et al. (2003) [92]	9	DC + tumor lysate		Metastatic	No responder
Bauer C et al. (2011) [93]	12	DC + tumor lysate	Gem ± Oxa	Inoperable	PR in 1, SD in 2
Rong Y et al. (2012) [94]	7	DC + MUC1 peptide	95	Inoperable	No responder
Koido S et al. (2014) [95]	11	DC + WT-1 peptide	Gem	Metastatic	SD in 6
Chung MJ et al. (2014) [96]	20	CIK		Metastatic refractory to Gem	SD in 4 Median PFS 11.0 weeks Median OS 26.6 weeks
Jian N et al. (2017) [97]	4 11 25	None DC + CIK DC + CIK	S-1 None S-1	Inoperable	SD in 2 (S-1), 5 (doublet), and 20 (triplet) 6M-PFS: 0 % (S-1), 9.09 % (doublet), 41.6 % (triplet) 6M-OS: 25 % (S-1), 18.2 % (doublet), 62.2 % (triplet)
Lin M et al. (2017) [98]	37 30	NK, allogeneic None	IRE IRE	Inoperable	CR in 3 (IRE), 5 (doublet) PR in 8 (IRE), 12 (doublet) SD in 7 (IRE), 10 (doublet)
Lin M et al. (2020) [99]	30 32	Vγ9Vδ2, allogeneic None	IRE IRE	Locally advanced	Median PFS (month): 11 (doublet), 8.5 (IRE) Median OS (month): 14.5 (doublet), 11 (IRE)
Aoki T et al. (2017) [100]	28 20	Vγ9Vδ2, autologous None	Gem Gem	Curatively resected	Median RFS (month): 26 (both)

Abbreviations: CIK, cytokine-induced killer cell; CR, complete response; DC, dendritic cell; Gem, gemcitabine; IRE, irreversible electroporation therapy; N, number; NK, natural killer cell; OS, overall survival; Oxa, oxaliplatin; PFS, progression-free survival; PR, partial response; RFS, recurrence-free survival; SD, stable disease.

inherited disorders in familial pancreatic cancer. Other familial syndromes associated with pancreatic cancer include hereditary pancreatitis, hereditary nonpolyposis colorectal cancer, hereditary breast and ovarian cancers, Peutz–Jeghers syndrome, ataxia telangiectasia, familial atypical multiple mole melanoma syndrome, and Li–Fraumeni syndrome.

9.2.2. Targeted therapy

Although targeted therapies have shown significant success in the treatment of various types of cancers, their effectiveness in pancreatic cancer is limited [40,72]. Despite the identification of *KRAS* oncogene in the 1960s, *KRAS* was thought to be "undruggable." In 2013, the Shokat laboratory revealed a novel switch II pocket that directly inhibited the activated *KRAS* isozyme caused by the *G12C* mutation. In the combined population of phases I and II, 38 patients received sotorasib, and the confirmed ORR was 21 % [73]. The median PFS and OS periods were 4.0 months (95 % CI, 2.8–5.6) and 6.9 months (95 % CI, 5.0–9.1), respectively.

Some driver alterations have been identified in 5.4 % of patients with wild-type *KRAS*, including fusion of neuregulin 1 (*NRG1*) [74], fibroblast growth factor receptor 2 [75], neurotrophin tyrosine kinase receptor 3, and ROS proto-oncogene 1 (*ROS1*). Good responses to entrectinib and larotrectinib therapy in patients with pancreatic cancer with *NTRK* and *ROS1* fusions have been reported [76–78], although they occur in a remarkably low percentage of cases, approximately 0.34 % [72].

Another promising subgroup for targeted therapy in pancreatic cancer, accounting for up to 24 % of patients, are those with defects in DNA damage response mechanisms, including germline or somatic mutations in *BRCA1/2* and *PALB2* or a mutational signature indicative of "BRCAness." Several studies are currently investigating the use of poly-(ADP-ribose)-polymerase inhibitors as monotherapy or in combination with chemotherapy in patients with pancreatic cancer with DNA damage response defects. Regarding maintenance therapy, olaparib was approved based on the phase III POLO study, with olaparib having significantly better PFS than the placebo (HR, 0.53; 95 % CI, 0.35–0.82; $P = 0.004$) in patients with germline *BRCA1/BRCA2* mutation who had not progressed during first-line platinum-based chemotherapy at least 16 weeks [79].

9.2.3. Immunotherapy

ICIs have revolutionized the treatment of various cancers but have shown limited effectiveness in pancreatic cancer owing to their poor immunogenicity and immunosuppressive tumor microenvironment. Combination approaches involving ICIs, chemotherapy, vaccines, radiation, and cytokine antagonists have been explored in clinical studies. Pembrolizumab has received FDA approval for the treatment of microsatellite instability high (MSI-H) cancers [80]. However, the prevalence of MSI-H in pancreatic cancer is approximately <1 % [81].

9.3. Clinical trials for metastatic pancreatic cancer

Participation in a clinical trial for metastatic pancreatic cancer may offer patients the opportunity to access new treatments that are not yet available to the public. By volunteering for a clinical trial, patients can help themselves and others face the disease. Patients should be aware of the possible risks and uncertainties associated with clinical trials. Patients may not benefit from new treatments or may experience serious adverse effects. Patients may also have to follow strict protocols and procedures that affect their daily lives. Clinical trials for pancreatic cancer are listed on clinicaltrials.gov ([Table 1].

9.4. Cell therapy

Autologous non-genetically engineered immune cell therapy is well-tolerated but has limited clinical antitumor activity when used alone [Table 2]. The additional benefits of a combination of standard therapies in palliative or adjuvant settings still need confirmation in randomized trials. However, the efficacy of tumor-infiltrating lymphocytes in the treatment of pancreatic cancer remains unclear. Chimeric antigen receptor-modified T-cell therapy with cell surface targets remains under investigation [82–86]. Therefore, additional data are required to clarify the safety and efficacy of genetically engineered cell therapies for pancreatic cancer.

9.5. Recommendations

- Maintenance of olaparib is an option for germline *BRCA1/BRCA2* mutations, especially for patients who prefer chemotherapy holidays.

- Currently, there is no standard treatment beyond second-line regimens, and enrollment in clinical trials is recommended.
- NGS testing may be considered for the potential detection of druggable mutations, despite their rarity. Genetic counseling should be considered in patients with familial pancreatic cancer.
- ICIs are not recommended for routine use alone or in combination with standard treatments for pancreatic cancer, except in patients with MSI-H.
- Cell therapy using autologous immune cells may be optional in patients with pancreatic cancer with stage IV or refractory stage I–III disease under the regulation of the "Regulations Governing the Application or Use of Specific Medical Techniques or Examinations, or Medical Devices" in Taiwan.

10. Conclusion

This review provides an overview of the medical treatment for pancreatic cancer, covering various disease stages and therapeutic approaches. It emphasizes the importance of patient selection and initial assessment. Postoperative adjuvant chemotherapy is recommended for resectable diseases, whereas neoadjuvant therapy is recommended for borderline resectable diseases. Induction chemotherapy and concurrent chemoradiotherapy have been used to treat locally advanced tumors.

Systemic therapies are pivotal for improving patient outcomes in metastatic diseases. It incorporates data from international and Taiwan-specific studies to guide first- and second-line treatment choices. Additionally, it explores treatment options beyond second-line treatment and highlights the potential role of NGS in identifying targeted immunotherapies. Furthermore, novel treatments, including clinical trials and cell therapy, offer promising avenues for future advancements in pancreatic cancer management.

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Data availability statement

This manuscript utilizes publicly accessible data from previously published studies, so no supplementary data is accessible for distribution.

Declaration of competing interest

None

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