Systemic treatment for inoperable pancreatic adenocarcinoma: review and update

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Abstract
There have been many clinical trials conducted to evaluate novel systemic regimens for unresectable pancreatic cancer. However, most of the trial results were negative, and gemcitabine monotherapy has remained the standard systemic treatment for years. A number of molecular targeted agents, including those against epidermal growth factor receptor and vascular endothelial growth factor receptors, have also been tested. In recent years, there have been some breakthroughs in the deadlock: three regimens, namely gemcitabine-erlotinib, FOLFIRINOX, and gemcitabine-nab-paclitaxel, have been shown to prolong the overall survival of patients when compared with gemcitabine monotherapy. In addition, emerging data suggested that the membrane protein human equilibrative nucleotide transporter 1 is a potential biomarker with which to predict the efficacy of gemcitabine. Here we review the literature on the development of systemic agents for pancreatic cancer, discuss the current choices of treatment, and provide future directions on the development of novel agents.

Key words Pancreatic cancer, chemotherapy, biologics, review, literature

Pancreatic ductal adenocarcinoma (pancreatic cancer) is both a prevalent and aggressive malignancy. The cancer ranks as the eighth and ninth leading global cause of cancer-related death in men and women, respectively[1]. In the Asia-Pacific region, the age-standardized incidence reached a plateau after 1985; yet, the incidence continues to rise due to the aging population in the region[2]. For treatment, surgical resection remains the only curative therapeutic modality for early-stage pancreatic cancer. Despite improvements in surgical technique and patient selection as well as the availability of adjuvant chemotherapy, the 5-year survival rate remains low, ranging from 10% to 20%, following curative resection[3,4]. In addition, because of early asymptomatic disease course and delayed presentation, only approximately 20% of patients are amenable to surgery at diagnosis.

Inoperable pancreatic cancer is composed of heterogeneous populations, namely locally advanced and metastatic disease. The prognosis of the two groups was different: the median survival of patients with untreated locally advanced disease was approximately 8 months, whereas untreated patients with metastatic disease had a median survival of 3 to 4 months only[5]. Despite some controversies about the role of radiotherapy or chemoradiotherapy in patients with locally advanced disease, systemic therapy is the most frequently used treatment modality for inoperable pancreatic cancer. For the past 15 years, there have been a large number of clinical trials conducted to test different systemic therapy regimens for inoperable pancreatic cancer. The goal of this paper is to provide an update on the key randomized clinical trial data on systemic agents for inoperable pancreatic cancer. The future directions of development of systemic agents are also discussed.

Gemcitabine Monotherapy

Gemcitabine is a pyrimidine anti-metabolite[6] that exerts a wide spectrum of anti-neoplastic effects on different tumor types. Gemcitabine has conventionally been considered the standard regimen for advanced pancreatic cancer on the basis of the phase III clinical trial reported by Burris et al.[7]. In the study, 128 patients with advanced pancreatic cancer were randomized to receive either gemcitabine, 1,000 mg/m² weekly for 7 courses, followed by 1 week of rest, then days 1, 8, and 15 every 4 weeks, or 5-fluoruracil (5-FU) at the dose 600 mg/m² once weekly. The primary endpoint was clinical benefit rate, which was defined as the improvement in disease-related symptoms including pain, performance status, and weight. The final results showed that patients in the gemcitabine arm...
had higher clinical benefit rate than did those in the 5-FU arm (23.8% vs. 4.6%, \( P = 0.002 \)). There was also a modest improvement in the median overall survival (5.6 months vs. 4.4 months, \( P = 0.002 \)).

**Fixed Dose Rate Infusion of Gemcitabine**

It has been previously postulated that a longer infusion of gemcitabine is associated with a pharmacokinetic advantage\(^7\). Therefore, the approach of fixed dose rate infusion, involving the administration of gemcitabine at a fixed rate over a prolonged period of time, has been studied in the clinical trial setting. Despite the initially encouraging data from a phase II clinical trial\(^8\), a phase III intergroup trial from the United States compared the short infusion of gemcitabine with a fixed dose rate (1,500 mg/m\(^2\) over 150 min weekly for 3 of every 4 weeks). The results showed that the fixed dose was not associated with any remarkable benefit in overall survival when compared with the standard infusion of gemcitabine (6.2 months vs. 4.9 months, \( P = 0.05 \))\(^9\). Therefore, the practice of using a fixed dose rate of gemcitabine has been abandoned by most centers globally.

**Gemcitabine-Based Combinational Chemotherapy**

Following the landmark study by Burris et al.\(^7\), single-agent gemcitabine has been considered the standard regimen and used as the backbone for addition of novel chemotherapeutic agents for treatment of inoperable pancreatic cancer. Over the past 15 years, more than 10 chemotherapeutic agents have been tested in combination with gemcitabine versus single-agent gemcitabine in randomized clinical trials. The results are summarized in Table 1, and the key details are described as below.

**5-FU and its derivatives**

5-FU has been tested in combination with gemcitabine among patients with locally advanced or metastatic pancreatic cancer in a phase III clinical trial (E2297 trial)\(^10\). The dose of 5-FU given in the clinical trial was 600 mg/m\(^2\) per week. Although there was a modest improvement in progression-free survival in the combination of gemcitabine and 5-FU arm (3.4 months vs. 2.2 months, \( P = 0.022 \)), the median overall survival was not different between the two arms (combination arm, 6.7 months vs. gemcitabine arm, 5.4 months; \( P = 0.09 \)).

Capetapibine is a prodrug of 5-FU that undergoes three enzymatic steps to form active 5-FU preferentially in tumor tissues. Two phase III clinical trials have been conducted to test the effects of capetapibine combined with gemcitabine (CapGem). In 2007, Herrmann et al.\(^11\) reported a phase III clinical trial on CapGem for advanced pancreatic cancer. In the clinical trial, patients in the CapGem arm were treated with gemcitabine at the dose 1,000 mg/m\(^2\) on days 1 and 8, together with capetapibine at the dose 650 mg/m\(^2\) twice daily from day 1 to day 14 every 3 weeks, whereas the patients in the control gemcitabine arm were treated with gemcitabine at the dose similar to the landmark study by Burris et al.\(^7\). The proportion of patients with metastatic disease was approximately 80% in each arm. There was no reported significant difference in overall survival between the two groups (CapGem arm, 7.2 months vs. gemcitabine arm, 8.4 months; \( P = 0.2 \)). In 2009, Cunningham et al.\(^12\) reported another phase III clinical trial on CapGem therapy in a larger number of patients. A total of 533 patients have been randomized to the CapGem arm or the gemcitabine arm, and 70% of these patients have metastatic disease. Although this study adopted a high-dose regimen of capetapibine (830 mg/m\(^2\) oral twice daily from day 1 to day 21 every 4 weeks), there was no survival benefit conferred by the addition of capetapibine to the gemcitabine backbone (CapGem arm, 7.1 months vs. gemcitabine arm, 6.2 months; \( P = 0.08 \)).

S1 is another oral 5-FU derivative, which includes three different agents: florafu, gimeracil, and oteracil. S1 is designed to improve the efficacy of 5-FU by adding 5-FU modulators while limiting 5-FU gastrointestinal toxicities\(^15\). The combination of S1 and gemcitabine has recently been evaluated in the phase III GEST trial\(^16\). In the trial, patients with locally advanced or metastatic pancreatic cancer were randomized to S1 (80–120 mg daily from days 1 to 28, every 6 weeks), gemcitabine plus S1 (S1 at 80–120 mg and gemcitabine at 1,000 mg/m\(^2\) on days 1 and 8, every 3 weeks) or gemcitabine monotherapy (1,000 mg/m\(^2\) on days 1, 8 and 15, every 4 weeks). A total of 834 patients have been enrolled. The overall survival of patients in the S1 arm was not inferior to that of patients in the gemcitabine monotherapy arm (S1 arm, 9.7 months vs. gemcitabine arm, 8.8 months; \( P < 0.001 \) for non-inferiority). Nevertheless, the combination of S1 and gemcitabine was not superior to gemcitabine monotherapy (S1 plus gemcitabine, 10.1 months vs. gemcitabine, 8.8 months; \( P = 0.15 \)).

**Platinum and its derivatives**

Cisplatin is a platinum-based compound that inhibits DNA synthesis by forming platinum-DNA adducts\(^16\). There have been a total of four randomized clinical trials conducted to test the combination of cisplatin and gemcitabine (GemCis), namely studies reported by Colucci et al.\(^17\) in 2010, Heinemann et al.\(^18\) in 2006, Colucci et al.\(^19\) in 2002, and Wang et al.\(^20\) in 2002. The most recent study by Colucci et al.\(^17\) recruited the largest number of participants (\( n = 400 \)), which randomized patients with unresectable pancreatic cancer to receive gemcitabine alone or GemCis. The results showed that GemCis did not prolong the median overall survival (GemCis, 7.2 months vs. gemcitabine, 8.3 months; \( P = 0.38 \)) despite a modest improvement in response rate (GemCis, 12.9% vs. gemcitabine, 10.1%; \( P = 0.037 \)). The other three clinical studies, with similar design but with smaller sample sizes, also failed to demonstrate an improvement in the overall survival of patients treated with the GemCis regimen, compared with gemcitabine alone\(^18-20\).

Oxaliplatin is a platinum derivative that, like cisplatin, blocks DNA synthesis\(^17\). There have been two phase III trials to study the combination of oxiliplatin with gemcitabine. Louvet et al.\(^21\) recruited 313 patients with stage IV pancreatic cancer and randomized them to receive treatment with gemcitabine-oxaliplatin combination...
| Authors and reference | Year of publication | Agent(s) Arm | No. of patients | Percentage of patients (%) | Response rate (%) | Median overall survival (months) |
|-----------------------|---------------------|-------------|----------------|---------------------------|-----------------|-------------------------------|
|                       |                     | Locally advanced pancreatic cancer | Metastatic pancreatic cancer |                       |                 |                               |
| **Table 1. Summary on phase III clinical trials on patients with unresectable pancreatic cancer** |
| Berlin et al. [11]    | 2002                | 5-FU GEM + 5-FU GEM 160 | 10.6 | 89.4 | 6.9 | 6.7 |
| Herrmann et al. [12]  | 2007                | Capecitabine GEM + capecitabine GEM 160 | 20.0 | 80.0 | 10.0 | 8.4 |
| Cunningham et al. [13] | 2009            | Capecitabine GEM + capecitabine GEM 267 | 30.0 | 70.0 | 19.1 | 8.2 |
| Colucci et al. [14]   | 2010                | Cisplatin GEM + cisplatin GEM 201 | 12.4 a | 84.6 | 12.9 | 7.2 |
| Herrmann et al. [15]  | 2006                | Cisplatin GEM + cisplatin GEM 98 | 20.0 | 80.0 | 10.2 | 7.5 |
| Colucci et al. [16]   | 2002                | Cisplatin GEM + cisplatin GEM 54 | 19.0 a | 62.0 | 26.4 | 7.0 |
| Wang et al. [17]      | 2002                | Cisplatin GEM + cisplatin GEM 22 | 18.0 a | 68.0 | 11.1 | 7.2 |
| Louvet et al. [18]    | 2005                | Oxaliplatin GEM + oxaliplatin GEM 157 | 30.0 | 70.0 | 28.8 | 8.8 |
| Poplin et al. [19]    | 2009                | Oxaliplatin GEM + oxaliplatin GEM 272 | 10.7 | 89.3 | 9.0 | 5.7 |
| Stathopoulos et al. [20] | 2006         | Irinotecan GEM + irinotecan GEM 60 | 22.0 | 78.0 | 15.0 | 6.4 |
| Rocha Lima et al. [21] | 2004            | Irinotecan GEM + irinotecan GEM 180 | 15.0 b | 82.2 | 16.1 | 6.3 |
| Abou-Alfa et al. [22] | 2006                | Exatecan GEM + exatecan GEM 175 | 21.0 | 79.0 | 6.9 | 6.7 |
| Oettle et al. [23]    | 2005                | Pemetrexed GEM + pemetrexed GEM 283 | 9.9 c | 90.1 | 14.0 | 6.2 |
| Dahan et al. [24]     | 2010                | Leucovorin + 5-FU+ cisplatin (LV5FU2-CDDP) LV5FU2-CDDP then GEM | 102 | 0 | 100 | 19.0 | 6.7 |
|                        |                     | GEM then LV5FU2-CDDP | 100 | 0 | 100 | 22.0 | 8.9 |
| Cantore et al. [25]   | 2003                | 5-FU + leucovorin + epirubicin + carboplatin 5-FU + leucovorin + epirubicin + carboplatin 5-FU + leucovorin + epirubicin + carboplatin GEM 67 | 49.2 | 50.7 | 14.0 | 7.9 |
| Reni et al. [26]      | 2005                | Cisplatin + epirubicin + 5-FU + GEM Cisplatin + epirubicin + 5-FU + GEM Cisplatin + epirubicin + 5-FU + GEM 52 | 28.9 | 81.1 | 38.9 | 5.9 |
| Conroy et al. [27]    | 2011                | FOLFIRINOX GEM 171 | 0 | 100 | 31.6 | 11.1 |
| Von Hoff et al. [28]  | 2013                | Nab-paclitaxel GEM + nab-paclitaxel GEM 431 | 0 | 100 | 23.0 | 8.5 |

*a* Remaining belongs to stage II. *b* Remaining stage is unknown. *c* The given value includes stage III and lower disease. 5-FU, fluorouracil; GEM, gemcitabine; FDR, fixed dose rate.
have been reported with the addition of a chemotherapeutic agent to gemcitabine in patients with metastatic pancreatic cancer. The GemOx regimen includes gemcitabine at 1,000 mg/m² on day 1 with oxaliplatin at 100 mg/m² infused over 120 min on day 2 every 2 weeks. The study demonstrated an improved objective response rate favoring the GemOx combination (GemOx, 26.8% vs. gemcitabine, 7.3%; P = 0.04), but the primary endpoint, median overall survival, was not different between the two arms (GemOx, 9.0 months vs. gemcitabine, 7.1 months; P = 0.13). Another phase III clinical trial conducted by Poplin et al. compared the efficacy of three regimens: GemOx, fixed dose rate infusion of gemcitabine (discussed in section below), and single-agent gemcitabine. No differences in the overall survival or response rates were noted among the arms.

### Taxanes

Paclitaxel is an antimitotic agent that binds to tubulin and causes the development of nonfunctional microtubules. Nanoparticle albumin bound (nab)-paclitaxel is prepared by high-pressure homogenization of paclitaxel in the presence of serum albumin into a nanoparticle colloidal suspension. Nab-paclitaxel has several advantages over paclitaxel[23]. First, the infusion duration is 30 min, which is shorter than the 3-hour infusion time of paclitaxel. Second, there is no need for premedications for hypersensitivity reactions. Third, endogenous albumin transport mechanisms may help nab-paclitaxel to become concentrated in the tumor. Following encouraging phase II/III clinical trial results[24], the combination of gemcitabine and nab-paclitaxel has been compared with gemcitabine in phase III settings. The Metastatic Pancreatic Adenocarcinoma Clinical Trial (IMPACT) was a multinational phase III trial of 861 patients with previously untreated metastatic pancreatic cancer. Subjects were randomized to undergo treatment with nab-paclitaxel at 125 mg/m² followed by gemcitabine at 1,000 mg/m² on days 1, 8, and 15 every 4 weeks, or to be treated with gemcitabine at 1,000 mg/m² once weekly for 7 weeks and then on days 1, 8, and 15 every 4 weeks. The primary endpoint of the study was overall survival. The final results of the study showed that the median overall survival was better in the combination arm than in the single-agent arm (8.5 months vs. 6.7 months, P < 0.001) and that the response rate was also higher in the combination arm (23% vs. 7%, P < 0.001)[25]. Although the rate of life-threatening toxicities was not increased in the combination arm, grade 3 or 4 adverse events were more frequently observed in the combination arm with regard to neutropenia (38% vs. 27%), fatigue (17% vs. 7%), peripheral neuropathy (17% vs. <1%), and diarrhea (6% vs. 1%)[25].

### Other chemotherapeutic agents

Other chemotherapeutic agents such as exatecan, irinotecan, and gemcitabine have been tested in phase III settings to determine if the combination of them with gemcitabine provides extra benefit to patients with unresectable pancreatic cancer[26-28]. All of these studies predominantly recruited patients with metastatic disease, including a small proportion with locally advanced disease, and used overall survival as the primary endpoint. No survival benefits have been reported with the addition of a chemotherapeutic agent to gemcitabine treatment.

### Meta-analyses of clinical trials studying gemcitabine combination treatment

Due to inconclusive results on the benefits of gemcitabine combination therapy in multiple clinical trials, a number of meta-analyses have been conducted to compare the efficacy of gemcitabine combination versus gemcitabine alone (Table 2). Collectively, these analyses show that the gemcitabine combination was associated with a modest benefit in overall survival, with a hazard ratio of 0.9 to 1. Notably, these meta-analyses were conducted before the recent positive data on the gemcitabine-nab-paclitaxel combination became available.

### Non-Gemcitabine Chemotherapy

A number of regimens not based on gemcitabine have been tested clinically. Among these non-gemcitabine regimens, the most notable is the FOLFIRINOX regimen developed by a French group. In 2005, Conroy et al. reported an intensive regimen involving 5-FU, leucovorin, oxaliplatin, and irinotecan (FOLFIRINOX), which had a promising radiologic response rate of up to 39% in a randomized phase II trial as compared with gemcitabine alone. As a result, the phase II trial was expanded to a phase III clinical trial (ACCORD-11), which randomized patients with chemotherapy-naive, metastatic pancreatic cancer to FOLFIRINOX or gemcitabine arm. The primary endpoint was overall survival. The target accrual was 342 patients but the clinical trial was stopped after enrolling 250 patients because a preplanned interim analysis showed that the overall survival was significantly longer in the FOLFIRINOX arm (11.1 months vs. 6.8 months, HR = 0.57, P < 0.001)[29]. The FOLFIRINOX regimen was associated with better response rate (32% vs. 9%, P < 0.001) and better median progression-free survival (6.4 months vs. 3.3 months, P < 0.001) compared with gemcitabine alone. Nevertheless, the improved efficacy of the intensive FOLFIRINOX regimen was at a cost of increased toxicity. Hematologic toxicities, such as neutropenia (45.7% vs. 21.0%, P < 0.001), febrile neutropenia (5.4% vs. 1.2%, P = 0.03), and thrombocytopenia (9.1% vs. 3.6%, P = 0.04), were more noticeable in the FOLFIRINOX arm than in the gemcitabine alone arm. Also, other toxicities including diarrhea (12.7% vs. 1.8%, P < 0.001) and sensory neuropathy (9.0% vs. 0.0%, P < 0.001) were more common in the FOLFIRINOX arm than in the gemcitabine alone arm. The authors concluded that FOLFIRINOX is preferable to gemcitabine in patients with metastatic pancreatic cancer, age younger than 76 years, Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, normal or nearly normal bilirubin level, and no history of cardiac ischemia.

### Molecular Targeted Agents

Although a number of targeted agents have been tested for treatment of pancreatic cancer, most did not demonstrate promising activity to proceed to advanced clinical trial testing (Table 3). At
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present, targeted therapy against epidermal growth factor receptor (EGFR) is the only class of molecular targeted agents tested in the phase III setting. EGFR is overexpressed and implicated in the progression of pancreatic cancer, supporting the therapeutic use of agents targeting EGFR.[31-33] Two anti-EGFR agents, namely erlotinib and cetuximab, have been tested. Erlotinib, a tyrosine kinase inhibitor against EGFR, was tested in combination with gemcitabine in a phase III clinical trial from the National Cancer Institute of Canada[34]. In the study, a total of 569 patients with locally advanced or metastatic pancreatic cancers were randomly assigned to undergo gemcitabine with erlotinib therapy at a dose of 100 mg or 150 mg per day, or gemcitabine and placebo therapy[34]. Although there was no difference in the objective response rate between the two arms, the combination of gemcitabine and erlotinib was associated with a statistically significant improvement in the overall survival (6.2 months vs. 5.9 months, P = 0.038). Regarding the toxicity, this combination was associated with more grade 3 or above toxicities especially diarrhea and skin rash. This clinical trial

Table 2. Summary of meta-analyses on gemcitabine versus its combinations on overall survival of patients with advanced stage pancreatic cancer

| Authors and reference | Year of publication | No. of patients | Arm | Overall survival |
|-----------------------|---------------------|----------------|-----|-----------------|
|                       |                     |                |     | HR/RR/OR (95% CI) | P |
| Sun et al.[56]        | 2012                | 26             | GEM combination vs. GEM | 0.90 (0.82-0.99) | 0.040 |
|                       |                     |                | GEM + fluoropyrimidine vs. GEM | 0.95 (0.77-1.16) | 0.610 |
|                       |                     |                | GEM + camptothecin vs. GEM | 0.97 (0.76-1.25) | 0.840 |
|                       |                     |                | GEM + targeted therapy vs. GEM | 0.85 (0.73-1.00) | 0.050 |
|                       |                     |                | GEM + platinum vs. GEM | 0.91 (0.77-1.09) | 0.300 |
| Ciliberto et al.[57]  | 2013                | 34             | GEM combination vs. GEM | 0.93 (0.85-0.97) | 0.001 |
|                       |                     |                | GEM + fluoropyrimidines vs. GEM | 0.91 (0.84-0.99) | 0.455 |
|                       |                     |                | GEM + others (GEM+PEM, PEGF) vs. GEM | 0.87 (0.63-1.22) | 0.160 |
|                       |                     |                | GEM + platinum vs. GEM | 0.91 (0.82-1.01) | 0.985 |
|                       |                     |                | GEM + biotherapy vs. GEM | 0.94 (0.87-1.01) | 0.534 |
|                       |                     |                | GEM + irinotecan vs. GEM | 1.01 (0.83-1.22) | 0.687 |
| Eltawil et al.[54]    | 2012                | 7              | GEM + molecular targeted agents vs. GEM | 0.94 (0.87-1.01) | 0.090 |
| Hu et al.[54]         | 2011                | 35             | GEM vs. GEMCom | 1.15 | 0.011 |
|                       |                     |                | GEM vs. GEM + fluoropyrimidine | 1.331 (1.081-1.638) | 0.007 |
|                       |                     |                | GEM vs. GEM + platinum | 1.162 (0.981-1.376) | 0.082 |
|                       |                     |                | GEM vs. GEM + oxaliplatin | 1.330 (1.049-1.686) | 0.019 |
|                       |                     |                | GEM vs. GEM + cisplatin | 1.011 (0.794-1.287) | 0.928 |
|                       |                     |                | GEM vs. GEM + camptothecin | 1.029 (0.805-1.315) | 0.822 |
| Xie et al.[60]        | 2010                | 18             | GEM + capecitabine vs. GEM | 0.85 | 0.04 |
|                       |                     |                | GEM + cisplatin vs. GEM | 0.99 | 0.88 |
|                       |                     |                | GEM + 5-FU vs. GEM | 0.95 | 0.46 |
|                       |                     |                | GEM + irinotecan vs. GEM | 1.03 | 0.77 |
|                       |                     |                | GEM + oxaliplatin vs. GEM | 0.80 | 0.001 |
| Heinemann et al.[61]  | 2008                | 15             | GEM combination vs. GEM | 0.91 (0.85-0.97) | 0.004 |
|                       |                     |                | GEM + platinum-based vs. GEM | 0.85 (0.76-0.96) | 0.010 |
|                       |                     |                | GEM + fluoropyrimidine vs. GEM | 0.90 (0.81-0.99) | 0.030 |
|                       |                     |                | GEM + irinotecan/exatecan/pemetrex vs. GEM | 0.99 (0.88-1.10) | NS |
| Banu et al.[62]       | 2007                | 23             | GEM combination vs. GEM | 0.96 | 0.003 |
| Bria et al.[63]       | 2007                | 20             | GEM combination vs. GEM | 0.93 | 0.170 |
|                       |                     |                | GEM + platinum vs. GEM | 0.83 | 0.100 |
| Sultana et al.[64]    | 2007                | 51             | GEM vs. 5-FU | 0.75 (0.42-1.31) | 0.310 |
|                       |                     |                | GEM combination vs. GEM | 0.91 (0.85-0.97) | 0.004 |
|                       |                     |                | GEM + platinum vs. GEM | 0.85 (0.74-0.96) | 0.010 |
|                       |                     |                | GEM + capecitabine vs. GEM | 0.83 (0.72-0.96) | 0.010 |
|                       |                     |                | GEM + irinotecan vs. GEM | 1.01 (0.84-1.22) | NS |
|                       |                     |                | GEM + 5-FU vs. GEM | 0.98 (0.86-1.11) | 0.730 |
| Cunningham et al.[63] | 2009                | 3              | GEM + capecitabine vs. GEM | 0.86 (0.75-0.98) | 0.020 |

GEM, gemcitabine; HR/RR/OR, hazard ratio/relative risk/odds ratio; NS, not significant; vs., versus; PEM, pemetrexed; PEGF, gemcitabine plus 5-fluorouracil, cisplatin and epirubicin.
led to the US Food and Drug Administration’s approval in 2005 of the combination of gemcitabine and erlotinib as a systemic regimen for patients with inoperable pancreatic cancer. On the other hand, cetuximab is a chimeric monoclonal antibody that acts against EGFR on the cellular membrane. The antitumor activity of gemcitabine and cetuximab was initially observed in a phase II trial[35], which led to the commencement of a multicenter phase III clinical trial comparing the gemcitabine-cetuximab regimen with gemcitabine alone[36]. Disappointingly, the combination regimen did not improve the response rate or the overall survival. Other randomized phase II trials failed to demonstrate survival benefit from the combination of cetuximab and chemotherapy[37,38].

Similar to the anti-EGFR approach, the antiangiogenic approach did not appear effective against advanced pancreatic cancer. For example, the antiangiogenic small-molecule axitinib, which targets vascular endothelial growth factor (VEGF) receptor, has been tested in combination with gemcitabine in a randomized phase II clinical trial, but the combination did not demonstrate an improvement in overall survival[39]. Bevacizumab, a monoclonal antibody against VEGF, has been tested in combination with gemcitabine-erlotinib doublet in a phase III clinical trial[40]. In the study, 607 patients were randomly assigned to gemcitabine-erlotinib with or without bevacizumab arm. The addition of bevacizumab did not improve the overall survival (bevacizumab, 7.1 months vs. placebo, 6 months; P = 0.21)[40].

**Second-Line Treatment**

There have been few randomized studies to determine the benefits of second-line therapy. For patients who have been treated previously with gemcitabine as first-line therapy, a randomized trial has assigned patients to receive either FOLFOX, which is a regimen composed of oxaliplatin, 5-FU and folinic acid, or best supportive care alone[41]. However, the trial was stopped prematurely because of poor accrual. Based on 48 patients recruited in the study, there was no significant difference in overall survival between the two groups.
an improvement in the overall survival favoring second-line FOLFOX (4.8 months vs. 2.3 months, \( P = 0.008 \))\(^{[34]}\). Other case series or phase II trials have also indicated potential clinical benefit for second-line chemotherapy following disease progression with first-line gemcitabine\(^{[42-44]}\). On the other hand, for patients who were treated with FOLFIRINOX as the first-line therapy, there were no data on the optimal second-line regimen, but gemcitabine monotherapy appeared to be a reasonable option in view of its relatively good tolerance.

**Systemic Therapy for Inoperable Pancreatic Cancer: Status in 2013**

Despite tremendous effort, a large number of clinical trials failed to demonstrate additional survival benefit in using systemic therapy compared with gemcitabine alone. At present, three novel regimens have succeeded in improving the clinical outcomes and prolonging the overall survival of patients with inoperable pancreatic cancer: the gemcitabine-erlotinib combination\(^{[34]}\), FOLFIRINOX\(^{[30]}\), and the gemcitabine-nab-paclitaxel regimen\(^{[25]}\). Although gemcitabine-erlotinib was associated with a survival benefit in a phase III clinical trial when compared with gemcitabine alone, most clinicians consider the less than 1 month improvement in overall survival too short to be clinically meaningful. In fact, subsequent clinical trials using the gemcitabine-erlotinib doublet as the backbone failed to demonstrate impressive overall survival improvements\(^{[40]}\). Together with the negative results of cetuximab, it remains unclear whether the combination of anti-EGFR treatment and chemotherapy could improve the outcome of pancreatic cancer.

Based on the presented data, FOLFIRINOX was likely the most effective regimen for treatment of inoperable pancreatic cancer. The ACCORD-11 phase III clinical trial was built on the promising results of the phase II trial. The antitumor activity was evidenced by not only a significant improvement in overall survival but also the improved radiologic response rate and progression-free survival. One limitation of the study is its generalizability. More specifically, the trial population was relatively young and fit, with a median age of 61 years, ECOG performance status of 0 or 1, and an absence of jaundice. Although the clinical trial has demonstrated reasonable and manageable toxicity in this population, the toxicity is likely to be more significant and prevalent in patients with less optimal health conditions. Indeed, in real-world practice, FOLFIRINOX is frequently modified to a less aggressive regimen, such as by omitting bolus 5-FU or reducing the dose of oxaliplatin and irinotecan.

The MPACT data in 2013 supported gemcitabine-nab-paclitaxel as another option\(^{[25]}\). As compared with gemcitabine alone, the regimen is associated with consistent benefit in overall survival, response rate, and progression-free survival. Currently, there is no head-to-head comparison of gemcitabine-nab-paclitaxel and FOLFIRINOX, but cross-trial comparison suggested that gemcitabine-nab-paclitaxel was likely a better tolerated regimen. In addition, the MPACT has recruited a small proportion of patients over the age of 75 years or with Karnofsky performance status \( \geq 70 \), further suggesting that the regimen might be better tolerated than the FOLFIRINOX.

**Development of Systemic Therapy: Future Directions**

**Development of novel agents**

After decades of developing cytotoxic agents, it has become evident that the benefit of chemotherapy has reached a plateau. Although gemcitabine is well tolerated, it does not appear to be a good backbone for combination with other chemotherapeutic or molecular-targeted agents. On the other hand, FOLFIRINOX is associated with better antitumor efficacy, but its toxicity profile also renders the regimen difficult to further combine with other cytotoxic chemotherapy. Similar to other solid tumors, further breakthroughs will likely rely on development of targeted agents for the disease\(^{[30,47]}\). Experience from breast and non-small cell lung cancers suggests that success in clinical trials of targeted therapy can only be improved if the agents are applied to carefully selected patients whose tumors are addicted to a known driver gene. Thus, the ideal developmental approach would be to identify key genetic mutations of pancreatic cancer before clinically testing novel agents. To this end, it is important to obtain histologic samples before or along the conduct of clinical trials. Owing to the invasive nature of tumor biopsy, a number of groups are currently studying the use of massive parallel sequencing to study the genome of cancer in plasma samples, which could potentially obviate the need of needle biopsy\(^{[40,46]}\).

**Predictive biomarkers**

Human equilibrative nucleoside transporter 1 (hENT1) is a membrane protein responsible for intracellular transport of gemcitabine. In the adjuvant setting, hENT1 expression in resected tissue is a prognostic marker for overall survival in patients treated with gemcitabine but not in patients treated with 5-FU\(^{[50]}\). Therefore, it has been postulated that the expression of hENT1 could serve as a predictive biomarker for gemcitabine in pancreatic cancer. However, there is currently no data on the role of this marker in predicting tumor response to gemcitabine in patients with inoperable pancreatic cancer. Further studies are required to validate the role of hENT1 in advanced pancreatic cancer before generalized use.

**Patient selection**

Most of the previous clinical trials on novel agents have recruited patients with either metastatic or locally advanced disease. It has become clear that these two populations have different prognoses and distinct responses to chemotherapy. Recent clinical trials have gradually changed from focusing on patients with resectable disease to those with only metastatic disease in order to ensure homogeneous phenotypes and prognosis during the testing of novel agents. This is evidenced by strikingly similar overall survival, approximately 6.8 months, in the MPACT and ACCORD-11 trials, which both recruited only patients with metastatic disease\(^{[30,51]}\). Therefore, it is necessary to divide the population of unresectable pancreatic cancer into locally advanced and metastatic disease.
during testing of novel agents.

Conclusions

The systemic treatment of advanced pancreatic cancer has evolved from gemcitabine monotherapy to a number of active regimens, especially gemcitabine-nab-paclitaxel and FOLFIRINOX. With these advancements, the median overall survival of patients with metastatic pancreatic cancer has improved from 6 months to 11 months. The success on development of novel treatment for pancreatic cancer relies on not only identification of more therapeutic targets but also better patient selection for clinical trials.

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References

[1] Jemal A, Bray F, Center MM, et al. Global cancer statistics. CA Cancer J Clin, 2011;61:69–90.
[2] Lin Y, Tamakoshi A, Wakai K, et al. Descriptive epidemiology of pancreatic cancer in Japan. J Epidemiol, 1998;8:52–59.
[3] Bilimoria KY, Bentrem DJ, Ko CY, et al. Validation of the 6th edition AJCC Pancreatic Cancer Staging System: report from the National Cancer Database. Cancer, 2007;110:738–744.
[4] Neoptolemos JP, Stocken DD, Bassi C, et al. Adjuvant chemotherapy with fluoride or fulmin of anic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial. JAMA, 2010;304:1073–1081.
[5] Oettle H, Post S, Neuhaus P, et al. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. JAMA, 2007;297:267–277.
[6] Hertel LW, Boder GB, Kroin JS, et al. Evaluation of the antitumor activity of gemcitabine (2',2'-difluoro-2'-deoxycytidine). Cancer Res, 1990;50:4417–4422.
[7] Burris HA 3rd, Moore MJ, Andersen J, et al. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. JAMA, 2007;297:267–277.
[8] Grunewald R, Kantarjian H, Du M, et al. Gemcitabine in leukemia: a phase I clinical, plasma, and cellular pharmacology study. J Clin Oncol, 1992;10:406–413.
[9] Tempeko M, Plunkett W, Ruiz Van Haperen V, et al. Randomized phase II comparison of dose-intensive gemcitabine: thirty-minute infusion and fixed dose rate infusion in patients with pancreatic adenocarcinoma. J Clin Oncol, 2003;21:3402–3408.
[10] Poplin E, Feng Y, Berlin J, et al. Phase III, randomized study of gemcitabine and oxaliplatin versus gemcitabine (fixed-dose rate infusion) compared with gemcitabine (30-minute infusion) in patients with pancreatic carcinoma e6201: a trial of the Eastern Cooperative Oncology Group. J Clin Oncol, 2009;27:3778–3785.
[11] Berlin JD, Catalano P, Thomas JP, et al. Phase III study of gemcitabine in combination with fluorouracil versus gemcitabine alone in patients with advanced pancreatic carcinoma: Eastern Cooperative Oncology Group Trial E2297. J Clin Oncol, 2002, 20:3270–3275.
[12] Herrmann R, Bodoky G, Ruhstaller T, et al. Gemcitabine plus capecitabine compared with gemcitabine alone in advanced pancreatic cancer: a randomized, multicenter, phase III trial of the Swiss Group for Clinical Cancer Research and the Central European Cooperative Oncology Group. J Clin Oncol, 2007;25:2212–2217.
[13] Cunningham D, Chau I, Stocken DD, et al. Phase III randomized comparison of gemcitabine versus gemcitabine plus capecitabine in patients with advanced pancreatic cancer. J Clin Oncol, 2009;27:5513–5518.
[14] Saif MW, Syrigos KN, Katritzoglou NA. S-1: a promising new oral fluoropyrimidine derivative. Expert Opin Investig Drugs, 2009;18:335–348.
[15] Ueno H, Ioka T, Ikeda M, et al. Randomized phase III study of gemcitabine plus S-1, S-1 alone, or gemcitabine alone in patients with locally advanced and metastatic pancreatic cancer in Japan and Taiwan: GEST study. J Clin Oncol, 2013;31:1640–1648.
[16] Sanchez SE, Trevino JG. Current adjuvant and targeted therapies for pancreatic adenocarcinoma. Curr Med Chem, 2008;15:1674–1683.
[17] Colucci G, Labianca R, Di Costanzo F, et al. Randomized phase III trial of gemcitabine plus cisplatin compared with single-agent gemcitabine as first-line treatment of patients with advanced pancreatic cancer: the GiP-1 study. J Clin Oncol, 2010;28:1645–1651.
[18] Heinemann V, Quietzsch D, Gieseler F, et al. Randomized phase III trial of gemcitabine plus cisplatin compared with gemcitabine alone in advanced pancreatic cancer. J Clin Oncol, 2006;24:3946–3952.
[19] Colucci G, Giuliani F, Gebbia V, et al. Gemcitabine alone or with cisplatin for the treatment of patients with locally advanced and/or metastatic pancreatic carcinoma: a prospective, randomized phase III study of the Gruppo Oncologia dell’italia meridionale. Cancer, 2002;94:902–910.
[20] Wang X, Ni Q, Jin M, et al. Gemcitabine or gemcitabine plus cisplatin for in 42 patients with locally advanced or metastatic pancreatic cancer. Zhonghua Zhong Liu Za Zhi, 2002,24:404–407. [in Chinese]
[21] Surveillance, Epidemiology, and End Results (SEER) Program. SEER Stat Database: Incidence—SEER 18 Regs Research Data + Hruuciane Katrina Impacted Louisiana Cases, Nov 2011 Sub (1973–2009 varying)—Linked To County Attributes–Total U.S. 1969–2010 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch. Released April 2012. Available at: http://seer.cancer.gov/data/metadata.html.
[22] Louvet C, Labianca R, Hammel P, et al. Gemcitabine in combination with oxaliplatin compared with gemcitabine alone in locally
advanced or metastatic pancreatic cancer: results of a GERCOR and GISCAD phase III trial. J Clin Oncol, 2005;23:3509–3516.

[23] Yared JA, Tkaczuk KH. Update on taxane development: new analogs and new formulations. Drug Des Devel Ther, 2012;6:371–384.

[24] Von Hoff DD, Ramanathan RK, Borad MJ, et al. Gemcitabine plus nab-paclitaxel is an active regimen in patients with advanced pancreatic cancer: a phase I/II trial. J Clin Oncol, 2011;29:4548–4554.

[25] Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med, 2013;369:1691–1703.

[26] Stathopoulos GP, Syrigos K, Aravantinos G, et al. A multicenter phase III trial comparing irinotecan-gemcitabine (IG) with gemcitabine (G) monotherapy as first-line treatment in patients with locally advanced or metastatic pancreatic cancer. Br J Cancer, 2006;95:587–592.

[27] Abou-Alfa GK, Letourneau R, Harker G, et al. Randomized phase III study of exatecan and gemcitabine compared with gemcitabine alone in untreated advanced pancreatic cancer. J Clin Oncol, 2006;24:4441–4447.

[28] Oettle H, Richards D, Ramanathan RK, et al. A phase III trial of pemetrexed plus gemcitabine versus gemcitabine in patients with advanced pancreatic cancer: a randomized, multicentre, phase II trial. Lancet Oncol, 2008;9:39–44.

[29] Kindler HL, Ioka T, Richel DJ, et al. Axitinib plus gemcitabine versus placebo plus gemcitabine in patients with advanced pancreatic adenocarcinoma: a double-blind randomised phase 3 study. Lancet Oncol, 2011;12:256–262.

[30] Van Cutsem E, Vervenne WL, Bennouna J, et al. Phase III trial of bevacizumab in combination with gemcitabine and erlotinib in patients with metastatic pancreatic cancer. J Clin Oncol, 2009;27:2231–2237.

[31] Neoptolemos J, Greenhalf W, Ghaneh P, et al. HENT1 tumor levels predict survival of pancreatic ductal adenocarcinoma patients who received adjuvant gemcitabine and adjuvant 5FU on the
Therapy for unresectable pancreatic carcinoma

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ESPAC trials. J Clin Oncol, 2013;31 suppl:abstr 4006.

[51] Von Hoff DD, Ervin TJ, Arena FP, et al. Results of a randomized phase III trial (MPACT) of weekly nab-paclitaxel plus gemcitabine versus gemcitabine alone for patients with metastatic adenocarcinoma of the pancreas with PET and CA19-9 correlates. J Clin Oncol, 2013;31 suppl:abstr 4005.

[52] Rocha Lima CM, Green MR, Rotche R, et al. Irinotecan plus gemcitabine results in no survival advantage compared with gemcitabine monotherapy in patients with locally advanced or metastatic pancreatic cancer despite increased tumor response rate. J Clin Oncol, 2004;22:3776–3783.

[53] Dahan L, Bonnétain F, Ychou M, et al. Combination 5-fluorouracil, folic acid and cisplatin (LV5FU2-CDDP) followed by gemcitabine or the reverse sequence in metastatic pancreatic cancer: final results of a randomised strategic phase III trial (FFCD 0301). Gut, 2010;59:1527–1534.

[54] Cantore M, Fiorentini G, Luppi G, et al. Randomised trial of gemcitabine versus flec regimen given intra-arterially for patients with unresectable pancreatic cancer. J Exp Clin Cancer Res, 2003;22:51–57.

[55] Reni M, Cordio S, Milandri C, et al. Gemcitabine versus cisplatin, epirubicin, fluorouracil, and gemcitabine in advanced pancreatic cancer: a randomised controlled multicentre phase III trial. Lancet Oncol, 2005;6:369–376.

[56] Sun C, Ansari D, Andersson R, et al. Does gemcitabine-based combination therapy improve the prognosis of unresectable pancreatic cancer? World J Gastroenterol, 2012;18:4944–4958.

[57] Ciliberto D, Bottà C, Correale P, et al. Role of gemcitabine-based combination therapy in the management of advanced pancreatic cancer: a meta-analysis of randomised trials. Eur J Cancer, 2013;49:593–603.

[58] Etawil KM, Renfrew PD, Molinari M. Meta-analysis of phase III randomized trials of molecular targeted therapies for advanced pancreatic cancer. HPB (Oxford), 2012;14:260–268.

[59] Hu J, Zhao G, Wang HX, et al. A meta-analysis of gemcitabine containing chemotherapy for locally advanced and metastatic pancreatic adenocarcinoma. J Hematol Oncol, 2011;4:11.

[60] Xie DR, Yang Q, Chen DL, et al. Gemcitabine-based cytotoxic doublets chemotherapy for advanced pancreatic cancer: updated subgroup meta-analyses of overall survival. Jpn J Clin Oncol, 2010;40:432–441.

[61] Heinemann V, Boeck S, Hinke A, et al. Meta-analysis of randomized trials: evaluation of benefit from gemcitabine-based combination chemotherapy applied in advanced pancreatic cancer. BMC Cancer, 2008;8:82.

[62] Banu E, Banu A, Fodor A, et al. Meta-analysis of randomised trials comparing gemcitabine-based doublets versus gemcitabine alone in patients with advanced and metastatic pancreatic cancer. Drugs Aging, 2007;24:865–879.

[63] Bria E, Milella M, Gelibter A, et al. Gemcitabine-based combinations for inoperable pancreatic cancer: have we made real progress? A meta-analysis of 20 phase 3 trials. Cancer, 2007;110:525–533.

[64] Sultana A, Smith CT, Cunningham D, et al. Meta-analyses of chemotherapy for locally advanced and metastatic pancreatic cancer. J Clin Oncol, 2007;25:2607–2615.

[65] Moore MJ, Hamm J, Danczy J, et al. Comparison of gemcitabine versus the matrix metalloproteinase inhibitor BAY 12-9566 in patients with advanced or metastatic adenocarcinoma of the pancreas: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol, 2003;21:3296–3302.

[66] Van Cutsem E, van de Velde H, Karasek P, et al. Phase III trial of gemcitabine plus tipifarnib compared with gemcitabine plus placebo in advanced pancreatic cancer. J Clin Oncol, 2004;22:1430–1438.

[67] Sandlerowicz AM, Johnson JR, Sridhara R, et al. Erlotinib/gemcitabine for first-line treatment of locally advanced or metastatic adenocarcinoma of the pancreas. Oncology (Williston Park), 2007;21:1696–1706; discussion 1706–1699, 1712, 1715.

[68] Kindler HL, Niedzwiecki D, Hollis D, et al. Gemcitabine plus bevacizumab compared with gemcitabine plus placebo in patients with advanced pancreatic cancer: phase III trial of the Cancer and Leukemia Group B (CALGB 80303). J Clin Oncol, 2010;28:3617–3622.

[69] Ko AH, Venook AP, Bergsland EK, et al. A phase II study of bevacizumab plus erlotinib for gemcitabine-refractory metastatic pancreatic cancer. Cancer Chemother Pharmacol, 2010;66:1051–1057.