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Real-world evidence on first- and second-line palliative chemotherapy in advanced pancreatic cancer

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Abstract

In spite of recent diagnostic and therapeutic advances, the prognosis of pancreatic ductal adenocarcinoma (PDAC) remains very poor. As most patients are not amenable to curative intent treatments, optimized palliative management is highly needed. One key question is to what extent promising results produced by randomized controlled trials (RCTs) correspond to clinically meaningful outcomes in patients treated outside the strict frames of a clinical trial. To answer such questions, real-world evidence is necessary. The present paper reviews and discusses the current literature on first- and second-line palliative chemotherapy in PDAC. Notably, a growing number of studies report that the outcomes of the two predominant first-line multidrug regimens, *i.e.* gemcitabine plus nab-paclitaxel (GnP) and folfinirix (FFX), is similar in RCTs and real-life populations. Outcomes of second-line therapy following failure of first-line regimens are still dismal, and considerable uncertainty of the optimal management remains. Additional RCTs and real-world evidence studies focusing on the optimal treatment sequence, such as FFX followed by GnP or vice versa, are urgently needed. Finally, the review highlights the need for prognostic and predictive biomarkers to inform clinical decision making and enable personalized management in advanced PDAC.

Key Words: Pancreatic cancer; Palliative therapy; Cancer chemotherapy; Gemcitabine; Paclitaxel, nano albumin-bound; Folfinirix

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Core Tip: This review summarizes and interprets published real-world evidence of the effectiveness and safety of treatment strategies in advanced pancreatic cancer. The real-world outcomes of first-line chemotherapy regimens such as folfinirinox and gemcitabine/ nab-paclitaxel are thoroughly reviewed. The results of randomized controlled trials (RCTs) exploring the regimens seem to be largely generalizable in a real-world context. On second-line options, *i.e.* salvage chemotherapy following failure of first-line therapy, significant uncertainties remain. Additional RCTs and real-world evidence studies addressing current and novel regimens, and the optimal sequence of these, are needed.

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INTRODUCTION

Over the past decades, mortality has decreased for many types of cancer. One exception is pancreatic cancer (pancreatic ductal adenocarcinoma, PDAC), which is soon expected to overtake breast cancer as the second most common cause of cancer-related death[1]. The majority of PDAC patients still present with either locally advanced or metastasized disease, and hence are considered beyond curative potential. For those individuals, as well as for those resected patients who suffer from relapses, palliative systemic therapy and/or radiotherapy are the only treatment options available.

Historically, palliative treatment of PDAC was limited mostly to regimens based on 5-fluorouracil (5-FU), usually with modest results at best. In that setting, 5-FU treatment was more or less experimental, but evidence from a randomized trial in 1996 showed that palliative chemotherapy in PDAC improved median overall survival (mOS) as well as quality of life compared with the best supportive care only[2]. The year after, gemcitabine replaced 5-FU as the gold standard in this clinical scenario based on the results of another randomized trial with prolonged mOS in favor of gemcitabine[3].

For a period of almost 15 years thereafter, many attempts to further improve the treatment in the setting of palliative PDAC were made by adding various cytotoxic drugs and monoclonal antibodies to gemcitabine, often resulting in increased toxicity without any significant survival benefit for patients[4-10]. A first breakthrough came in 2011, when a randomized controlled trial (RCT) showed a significant and clinically meaningful survival benefit over gemcitabine with the triplet combination chemotherapy known as Folfinirinox (FFX, 11.1 mo *vs* 6.8 mo for gemcitabine monotherapy)[11]. The survival advantage occurred at the expense of considerably increased hematological and non-hematological toxicity in the intervention group. Another transformative RCT introduced the combination of gemcitabine and nano-albumin-bound paclitaxel (GnP). The regimen produced a smaller effect on overall survival (8.5 mo *vs* 6.8 mo for gemcitabine monotherapy). Nonetheless, it also resulted in increased toxicity, especially myelosuppression and chemotherapy-induced peripheral neuropathy[12]. The finding of more than tripled objective response ratio for the intervention group compared with gemcitabine (roughly 30% *vs* 10%) in both trials indicated a substantial antitumoral effect with the use of those combination regimens. Conversely, the treatment response duration of first-line therapy was usually short, and the RCT-population typically included highly selected patients with lower comorbidity and frailty compared with real-life patients. Whether survival and toxicity data from trials are generalizable to patients treated in routine clinical practice is unclear.

Regarding second-line treatment in PDAC, evidence is scarce. Empirical chemotherapy has been used in highly selected patients, and is usually reserved for very fit or young patients who responded to first-line treatment. Most often, gemcitabine and 5-FU have been used either as monotherapy or in combination with either oxaliplatin or irinotecan. In one of the few RCTs conducted, Oettle *et al* [13]

compared the combination of folinic acid and fluorouracil (FF) in a 42-day cycle with FF in combination with oxaliplatin (OFF). The latter regimen gave significantly longer median progression-free survival (mPFS) and mOS, even though the absolute increase in months was rather small (mPFS 2.0 mo *vs* 2.9 mo, and mOS 3.3 mo *vs* 5.9 mo for FF and OFF, respectively). The occurrence of low-grade neuropathy was more than five times higher (38% of patients) in the OFF group. In contrast, the PANCREOX RCT, which compared the commonly used regimens of 5-FU/leucovorin infusion (5-FU/LV) and modified FOLFOX6 (mFOLFOX6) did not show any advantage with the addition of oxaliplatin[14]. There was no significant difference in the primary mPFS endpoint (3.1 mo *vs* 2.9 mo for mFOLFOX6 and FU/LV). The mOS favored 5-FU/LV (9.9 mo *vs* 6.1 mo for mFOLFOX6). Furthermore, substantial toxicity was observed in the mFOLFOX6-arm, with grade 3-4 adverse events affecting a majority (63%) of participants[14]. A more recent RCT[15] explored the role of 5-FU/LV and liposomal irinotecan in the second-line setting. The combination showed a small survival benefit over 5-FU/LV alone (6.1 *vs* 4.2 mo). However, the 5-FU/LV and liposomal irinotecan combination has not gained widespread traction in countries such as Canada and Sweden because regulatory authorities and health technology assessment bodies have considered the treatment to be not economically justifiable[16-18].

As the results of RCTs may be difficult to interpret and properly implement as standard healthcare, it is essential to complement the basis of knowledge with real-world evidence. The aim of this review was to summarize and assess available studies reporting real-world evidence in support of first- and second-line palliative chemotherapy in advanced PDAC. In first-line therapy, the focus was restricted to the two most established multidrug regimens, *i.e.* FFX and GnP. For second-line therapy, where the evidence on the optimal regimen is weak, no restriction in terms of regimen was applied.

LITERATURE SEARCH

PubMed was searched on December 19, 2020 for studies with titles containing the phrases “pancreatic cancer” and “real world”. All results were assessed for potential relevance. Only studies of human pancreatic cancer in the palliative setting and written in English were selected for possible inclusion in this review. Additional requirements for inclusion were information related to chemotherapy (FFX and/or GnP in the first-line setting, or any regimen in the second-line setting); survival [(overall survival (OS) data were required, progression-free survival (PFS) data were optional, and surrogate markers for OS were not accepted); real-world study population, and study type (retrospective or prospective cohort trials). RCTs, published study protocols, case studies, and meeting abstracts were not included. Studies reporting data on several treatment regimens were included as long as either FFX or GnP was among them, and specific survival data and treatment intention for the regimens were clearly distinguishable and compatible with the criteria mentioned above. Included studies are presented in a structured way with key data in tables sorted by topic and year of publication.

RESULTS

The PubMed query on first-line therapy returned 87 publications. Following careful review with regard to the inclusion criteria and scope of this review, 14 articles were selected, four with data on GnP (Table 1), one reporting FFX data (Table 2), eight that compared FFX and GnP (Table 3), and one covering several first-line treatments. The PubMed search of second-line setting returned 17 articles of which 15 were potentially relevant. The articles were subclassified according to which first-line treatment (FFX or GnP) had been administered (Tables 4 and 5). In addition to the above mentioned articles, several papers that did not focus on a specific first- or second-line regimen, and/or described the treatment pattern in general terms, were identified and will be discussed in the relevant section of this review.

First-line GnP combination chemotherapy

Studies evaluating the effect of GnP in the real-world setting are listed in chronological order in Table 1. One study prospectively evaluated the efficacy of the regimen in younger (< 70 years) *vs* older (> 70 years) patients and found no significant between-

Table 1 Real-world studies of gemcitabine/nab-paclitaxel in the first-line setting[19-23]

Ref.	Location	Study design	Stage M1	n	Regimen	mOS in mo	Subgroup analysis	mPFS in mo	Remarks
Prager <i>et al</i> [19], 2021	Austria	Prospective cohort	100%	317	GnP	10.6/10.2	Age < 70/> 70	5.6/5.5	No difference in frequent toxicities
Blomstrand <i>et al</i> [20, 21], 2019/2020	Sweden	Retrospective cohort	71%	75	GnP	10.9	Alb < 3 g/L, age < 65 with shorter survival	5.2	Less hematotoxicity than MPACT
Ostwal <i>et al</i> [22], 2018	India	Retrospective cohort	83%	78	GnP	11.6		5.6	Grade III-IV toxicity 35%
Quinton <i>et al</i> [23], 2018	United Kingdom	Retrospective cohort	100%	74		8.4		-	Hematotoxicity similar to MPACT

GnP: Gemcitabine/Nab-paclitaxel; M1: Metastatic disease; mOS: Median overall survival; mPFS: Median progression-free survival.

Table 2 Real-world studies of Folfirinox in the first-line setting[24]

Ref.	Location	Study design	n	M1	Regimen	mOS in mo	mPFS in mo	Remarks
Cavanna <i>et al</i> [24], 2019	Italy	Retrospective cohort	50	74%	FFX/mFFX	10.1	5.6	mFFX sign less toxicity

FFX: Folfirinox; M1: metastatic disease; mFFX: Modified Folfirinox; mOS: Median overall survival; mPFS: Median progression-free survival.

group differences of either mOS (10.6 mo and 10.2 mo) or adverse events[19]. Real-world survival outcomes were superior to those observed in the phase III MPACT trial [12]. The authors suggested that the difference could be explained by a larger fraction of patients proceeding to second-line treatment, 47.4%-56.2% in the real-world studies compared with 38% in the MPACT study[12]. It is also noteworthy that the proportion of patients with performance status (PS) 0 or 1 or corresponding Karnofsky score was somewhat higher than in the MPACT trial. Another study retrospectively evaluated the benefit of GnP in advanced PDAC and found an mOS of 10.9 mo in the entire cohort, and an mOS of 17.1 mo in the locally advanced group[20]. Hematological toxicity was less frequent than in the MPACT study. In the same cohort, multivariate analysis found that low albumin (< 36 g/L) and age (< 65) were significant predictors of worse survival[21].

An additional study found comparable survival outcomes with the use of non-cremophore-based paclitaxel and gemcitabine, with an mOS of 11.6 mo and an mPFS of 5.6 mo[22]. In this retrospective cohort, the majority of patients had metastatic disease (83%) and PS 1 (80%). Grade III-IV toxicity was reported in 36% of patients, with hematological toxicity as the most frequent type of adverse event. In another retrospective cohort analysis where all patients had metastatic disease, mOS was 8.4 mo[23]. Most patients were in PS 1 (66%) at the time of treatment initiation. Similar frequencies of hematological toxicity were seen, with grade III-IV neutropenia being the most frequently reported adverse event (35% of patients).

First-line FFX combination chemotherapy

Studies evaluating the effectiveness of FFX in the real-world setting are listed in chronological order in Table 2. One study evaluated FFX treatment in a retrospective cohort and reported an mPFS of 5.6 mo and an mOS of 10.1 mo[24]. The first 18 consecutive patients received full-dose FFX and the following 32 cases received dose-reduced modified FFX (mFFX), resulting in significantly lower toxicity with fewer hematological and non-hematological side-effects.

First-line FFX vs GnP

Studies comparing the real-world effectiveness of FFX and GnP are listed in chronological order in Table 3. One retrospective cohort study of first-line treatment of patients with metastatic PDAC reported an mOS of 12.7 mo with FFX and 10.2 mo with GnP[25]. Tumor marker serum CA-19-9 and neutrophil-lymphocyte-ratio (NLR) were associated with survival. Authors intended to analyze patients aged above 70 years separately but this group was too small. Hematological toxicity was evenly distributed between the two treatments. Of interest, neuropathy was only reported in

Table 3 Real-world studies comparing Folfirinox and Gemcitabine/Nab-paclitaxel in the first-line setting[25-32]

Ref.	Location	Study design	n	M1	Regimen	mOS in mo, P value	Prognostic factors	mPFS in mo, P value	Remarks
Franco <i>et al</i> [25], 2020	Spain	Retrospective cohort	119	50%	FFX 59; GnP 60	FFX 12.7; GnP 10.2; $P = 0.912$	Ca19-9, NLR	-	Toxicity data not reported
Wang <i>et al</i> [26], 2019	Canada	Retrospective cohort	225	58%	FFX 92; GnP 87; Gem 46	FFX 14.1; GnP 10.5; Gem 4.2	-	FFX 8.4; GnP 8.5; Gem 3.7	Sign more hematotoxicity in FFX
Pusceddu <i>et al</i> [27], 2019	-	Review	3813	NA	FFX 1690; GnP 2123	1.15 longer for FFX. $P = 0.03$	-	-	GnP more neurotoxicity and anemia. FFX more neutropenia
Chiorean <i>et al</i> [28], 2019	-	Review	> 6915	NA	FFX > 3556; GnP > 3359	FFX 15.9; GnP 14.4	-	FFX 11.7; GnP 8.5	FFX more neutropenia, GnP more neuropathy
Papneja <i>et al</i> [29], 2019	Canada	Retrospective cohort	119	77%	FFX 86; GnP 33	FFX 9.0; GnP 9.0	S-Alb, male sex, 2 nd line therapy	FFX 6.0; GnP 4.0	Grade 1-2 thromboembolism, mucositis and neuropathy sign more in FFX. Among grade 3-4 toxicity only fatigue sign more in GnP group
Kordes <i>et al</i> [32], 2019	Sweden	Retrospective cohort	595	-	FFX 31; GnP 66; Gem 185	FFX 9.9; GnP 9.8; Gem 6.6	-	-	No sign differences in toxicity comparing FFX <i>vs</i> GnP
Cartwright <i>et al</i> [30], 2018	United States	Retrospective cohort	486	100%	FFX 159; GnP 255; Gem 72	FFX 11.4; GnP 9.8; Gem 4.4	-	-	No sign differences in toxicity comparing FFX <i>vs</i> GnP
Kim <i>et al</i> [31], 2018	United States	Retrospective cohort	654	100%	FFX 317; GnP 337	FFX 13.8; GnP 12.1; $P = 0.96$	Age	-	Less toxicity in GnP group

FFX: Folfirinox; Gem: Gemcitabine; GnP: Gemcitabine/Nab-paclitaxel; M1: Metastatic disease; mOS: Median overall survival; mPFS: Median progression-free survival; NA: Not applicable; NLR: Neutrophil-leucocyte ratio; s-Alb: Serum albumin.

two patients receiving FFX. A study that compared the real-world effectiveness of FFX, GnP and gemcitabine reported OS durations of 14.1, 10.5 and 4.2 mo for the three treatments, respectively[26]. FFX treated patients were significantly younger and had better PS, and OS was significantly longer in both FFX- and GnP-treated patients compared with gemcitabine. The majority of patients had metastatic disease (68%). For the subgroups with localized disease, median OS had not been reached at the time of publication. The occurrence of neutropenia, febrile neutropenia, and neuropathy was significantly more frequent in FFX treated patients. In a review article, slightly longer survival (an additional 1.2 mo) was noted in favor of FFX over GnP. Despite the numerical difference, the overall adjusted risk of death was similar regardless of the regimen administered[27]. Neurotoxicity and anemia were seen more frequently in GnP-treated patients; neutropenia was more often associated with FFX treatment. In another review, a similar, non-significant, survival benefit was seen for FFX, with a reported OS of 15.9 mo *vs* 14.4 mo for GnP[28]. PFS was 11.7 mo with FFX and 8.5 mo for GnP. Toxicity data were not consistently reported in the studies, but neutropenia was more often associated with FFX than with GnP. The opposite was observed for neuropathy. In a retrospective study that largely focused on metastatic PDAC patients (77%), equivalent survival for FFX and GnP was reported (OS 9.0 mo for both regimens, $P = 0.88$). However, PFS was slightly longer with FFX, although the difference was not statistically significant (6.0 mo for FFX *vs* 4.0 mo for GnP, $P = 0.38$) [29]. There were no significant differences in the frequencies of severe toxicity between the two regimens. Another retrospective study reported OS of 11.4, 9.8 and 4.4 mo for FFX, GnP and gemcitabine monotherapy, respectively. Again, the differences were not significant[30]. Patients receiving GnP were significantly older and had worse PS. Toxicities were evenly distributed between the treatment groups. No significant prognostic factors were found in multivariate analysis, except for PS 2+, which was associated with worse survival. In another Celgene-funded real-world retrospective cohort study, there was a slight, non-significant, trend that favored FFX over GnP, with an OS of 13.8 mo compared with 12.1 mo[31]. All patients had metastatic disease. Common side-effects such as nausea, vomiting, diarrhea and mucositis were less

Table 4 Real-world studies of second-line therapy following failure of Folfirinox[36-44]

Ref.	n	M1	2L regimen	mPFS in mo	mOS in mo	Remarks	AE
Portal <i>et al</i> [36], 2015	57	100%	GnP	5.1	8.8	Prospective cohort	38% grade 3-4 toxicity
Mita <i>et al</i> [37], 2019	30	80%	GnP	3.8	7.6	Phase II	70% grade 3-4 toxicity
Tsang <i>et al</i> [38], 2019	159	67%	GnP 78; Gem 81	-	5.8; 4.6	Population-based, three Canadian provinces	-
Zhang <i>et al</i> [39], 2018	60	73%; 75%; 73%	GnP 30; Gem 8; BSC 22	3.6; 2.5	5.7; 3.8	Single center	More grade 3-4 fatigue in Gem
Nguyen <i>et al</i> [40], 2017	30	77%	GnP	3.7	12.4	Single center	Grade 3-4 thrombocytopenia (33%), anemia (23%), nausea (17%)
Bertocchi <i>et al</i> [41], 2015	23	100%	GnP	3.0	5.0	Single center	-
Zhang <i>et al</i> [42], 2015	28	82%	GnP	3.0	5.7	Single center	Grade 3-4, anemia (25%), thrombocytopenia (25%), neutropenia (18%)
Caparello <i>et al</i> [44], 2016	71	-	GnP	2.5	6.2	Single center	-
Rissy <i>et al</i> [43], 2017	12	100%	GnP	4.9	-	Single-center	No grade 3-4 toxicity reported

BSC: Best supportive care; Gem: Gemcitabine; GnP: Gemcitabine/Nab-paclitaxel; M1: metastatic disease; mOS: Median overall survival; mPFS: Median progression-free survival.

Table 5 Real-world studies of second-line treatment with Folfirinox following failure of gemcitabine/nab-paclitaxel or single-agent gemcitabine[46-51]

Ref.	n	M1	1L regimen	2L regimen	mPFS in mo	mOS in mo	Remarks
Sawada <i>et al</i> [46], 2020	104	100%	GnP	Modified; FFX	3.9	7.0	Bolus 5-FU omitted. 55% grade 3-4 toxicity
Matsumoto <i>et al</i> [47], 2020	23	83%	GnP	FFX 12; mFFX 11	5.3; 4.3	6.9; 12.8	No sign difference in toxicity between FFX/mFFX
Assaf <i>et al</i> [50], 2011	27	100%	Gem	FFX	3.0	8.5	56% grade 3-4 neutropenia
Kobayashi <i>et al</i> [48], 2017	18	100%	Gem	FFX	2.8	9.8	Phase I/II. 83% grade 3-4 toxicity
Kim <i>et al</i> [51], 2018	39	82%	Gem	Attenuated; FFX	3.8	8.5	Oxaliplatin: 65 mg/m ² . 41% grade 3-4 neutropenia
Chung <i>et al</i> [49], 2018	48	79%	Gem	Reduced irinotecan and oxaliplatin; FFX	5.8	9.0	Phase III irinotecan: 120 mg/m ² ; Oxaliplatin: 60 mg/m ² ; 65% grade 3-4 neutropenia

5-FU: Fluorouracil infusion; FFX: Folfirinox; Gem: Gemcitabine; GnP: Gemcitabine/Nab-paclitaxel; M1: Metastatic disease; mFFX: Modified Folfirinox; mOS: Median overall survival; mPFS: Median progression-free survival.

frequent in the GnP group. A Swedish retrospective study comparing palliative first-line treatment in a PDAC patient cohort that included 31 FFX, 66 GnP, and 185 gemcitabine patients reported OS of 9.9, 9.8 and 6.6 mo, respectively[32]. Patient characteristics, including age and PS, varied substantially among the three groups. No significant differences in grade 3 or higher toxicities were reported between FFX and GnP.

Second-line real-world studies

Second-line treatment in PDAC: Despite advancements in the first-line treatment of advanced PDAC, most patients progress and succumb to the disease. To date, three phase III randomized clinical trials have been reported in the second-line treatment space[13-15] and are thoroughly described above under the background heading.

These three trials compared 5-FU alone *vs* 5-FU/oxaliplatin doublets[13,14] or 5-FU *vs* nal-irinothecan *vs* 5-FU/nal-irinothecan doublet[15], and were all conducted after the patients progressed on gemcitabine-based chemotherapy as first-line treatment for advanced PDAC. However, the contemporary first-line standard treatment includes FFX or GnP combinations for patients with good PS[11,12]. There are no randomized clinical trial data for second-line treatment specifically after failure on FFX and GnP. Second-line treatment of advanced pancreatic cancer is largely driven by the chemotherapy regimen administered in the first-line setting. In a large real-world study that examined the outcome of 167 patients with advanced PDAC using several treatment regimens, the mOS from start of second-line therapy (OS2) was 5.2 mo, and plasma albumin, serum CA-19-9, and performance status were identified as key prognostic factors[33].

Second-line treatment after first-line FFX: In the real world, such patients are usually treated with GnP combination or gemcitabine monotherapy. The initial supportive evidence for use of GnP after first-line use of FFX in advanced pancreatic cancer was published in the form of case reports[34,35]. Subsequently, a prospective multicenter cohort study of 57 patients treated with GnP after FFX failure reported an mPFS of 5.1 mo and an OS2 of 8.8 mo[36]. It is noteworthy that just over half of the patients who received FFX for advanced pancreatic cancer in the frontline setting were eligible to receive salvage therapy with GnP in this cohort study. The objective response rate was 17.5%, while the disease control rate was 58.0%. From the start of first-line chemotherapy, the median OS was 18.0 mo. Grade 3-4 toxicities were observed in 40.0% of patients, of which neutropenia and neuropathy were the two most common. Recently, a phase II study of 30 patients reported in this setting described an mPFS of 3.8 mo and an OS2 of 7.6 mo[37]. The corresponding figures from the start of first-line chemotherapy were 9.3 and 14.2 mo, respectively. The overall response rate was 13.3% and the disease control rate was 46.7%. Grade 3-4 toxicities were reported in 70.0% patients, the most common being neutropenia and neuropathy. Furthermore, several real-world studies have been reported to support the use of GnP as second-line treatment. A large population-based Canadian study compared the real-world data of 368 patients with advanced PDAC treated with first-line FFX across two provinces with differential access to second-line treatment[38]. Of these, 159 patients (43.2%) received second-line treatment that was equally allocated as GnP (49.1%) and single-agent gemcitabine (50.9%). In a secondary analysis, the mOS counted from the initiation of second-line chemotherapy (OS2) was slightly longer for GnP compared with (5.8 mo *vs* 4.6 mo, $P = 0.01$).

Another Canadian study included 60 patients with advanced PDAC who received FFX as the first-line treatment[39]. Of these, 30 patients (50.0%) were treated with GnP, 8 (13.3%) with gemcitabine alone, and 22 patients (37.7%) received optimal supportive care. The mPFS (3.6 mo *vs* 2.5 mo, $P = 0.03$), and OS2 (5.7 mo *vs* 3.8 mo, $P = 0.03$) were longer in patients who received GnP compared with gemcitabine (Table 4). Other real-world studies have reported similar PFS and OS2 with the use of GnP after failure of FFX[40-44]. Furthermore, a recently published systematic review that included 16 studies reported a higher overall response rate (14.4% *vs* 8.4%, $P = 0.038$), disease control rate (53.5% *vs* 30.2%, $P < 0.001$), PFS (3.6 mo *vs* 2.5 mo, $P = 0.030$), and OS2 (5.7 mo *vs* 3.8 mo, $P = 0.030$) with GnP than with gemcitabine monotherapy[45]. Similar grade 3/4 event rates were reported in the prespecified analysis (22.9% *vs* 34.6%, $P = 0.415$). Overall, GnP appears to be a reasonable second-line treatment after FFX and patients considered unfit for GnP may benefit from gemcitabine monotherapy, while those with a poor performance status should be offered the best supportive care.

Second-line treatment after first-line GnP: In the absence of a head-to-head comparison of FFX and GnP in advanced PDAC, a substantial proportion of patients are treated with GnP in the first-line setting. Several chemotherapy regimens using a combination of fluoropyrimidines with irinotecan and/or oxaliplatin have been used in the real-world as salvage, second-line therapy of such patients. It is intuitive to consider FFX in this setting. A recent retrospective analysis of 104 patients treated with modified FFX (*i.e.* intravenous oxaliplatin 85 mg/m², intravenous irinotecan 150 mg/m², and continuous infusion of 5-fluorouracil 2400 mg/m² for 46 h without bolus infusion) in that setting reported an objective response rate of 10.6% and a disease control rate of 56.7%[46]. The median PFS and OS2 were 3.9 mo and 7.0 mo, respectively. Grade 3-4 adverse events were reported in 54.8% patients and included hematological toxicities and peripheral sensory neuropathy. A smaller study of 23 patients who received standard FFX ($n = 12$) and modified FFX ($n = 11$) reported a median PFS of 5.3 mo and an OS of 6.9 mo in patients who received standard dosages.

The corresponding numbers for those receiving modified FFX were 4.3 and 12.8 mo, respectively[47]. The observed differences in survival between the FFX and mFFX groups were not statistically significant.

Other real-world studies have reported the effectiveness of either the standard or modified FFX regimen after failure of single-agent gemcitabine as first-line therapy[48-51]. The studies, which adopted several modifications of the original FFX regimen, reported a PFS of 2.8-5.8 mo and OS2 of 8.5-9.8 mo (Table 2). Overall, limited data from real-world studies supports the use of modified FFX after failure of GnP. However, it is an intensive chemotherapy regimen and a high rate of grade 3-4 adverse events has been reported in above-mentioned studies, primarily hematological events and peripheral neuropathy. Patient selection remains paramount for electing to use such a regimen.

A real-world study of 52 patients with gemcitabine-refractory advanced PDAC reported that nano-liposomal irinotecan with FF was associated with a median PFS of 3.8 mo and OS2 of 6.8 mo[52]. The figures closely mirror the outcome reported from the phase III NAPOLI-1 study[15]. Capecitabine combined with oxaliplatin has also been used in this setting, and several studies have reported a PFS of around 3 mo and OS2 of approximately 6 mo[53-55]. The median PFS and OS with single-agent capecitabine in 41 patients who failed first-line therapy were reported to be 1.5 mo and 4.3 mo, respectively[56].

Therefore, in patients considered unfit for FFX as second-line treatment, a doublet chemotherapy with fluoropyrimidine and oxaliplatin or nano-liposomal irinotecan is reasonable, while monotherapy with capecitabine may be considered for those with borderline performance status. There are no clinical trials that have compared the efficacy of oxaliplatin with irinotecan in this setting. However, a meta-analysis reported that the combination of a fluoropyrimidine plus irinotecan significantly improved both PFS and OS2, while the oxaliplatin combination modestly improved PFS but not OS2[57]. The modest benefit with these regimens should be balanced with the associated adverse events, and best supportive care should be considered a viable option for patients with poor general condition.

Targeted therapy and immunotherapy

As survival is still short, even when the most effective modern combinations of cytotoxic drugs are administered to patients with good performance status, it is tempting to look for alternatives such as targeted therapies or immune checkpoint inhibitors for the treatment of advanced PDAC. While the major breakthrough is yet to come, some recent findings may have the potential to become game-changing treatments of at least some types of PDAC in the future.

Approximately one in every five patients with advanced PDAC harbors a germline or somatic mutation in the DNA damage repair pathway[58]. There are limited data to suggest that Poly (ADP-ribose) polymerase (PARP) inhibitors may be effective in such patients. For example, a retrospective analysis of patients with previously treated PDAC (median prior therapies = 2) harboring a mutation in the DNA damage repair pathway reported an objective response rate of 23%, PFS of 7.6 mo and OS of 16.5 mo with olaparib[59]. Another report of 30 patients with BRCA1/2 mutations and no available standard treatment options reported disease control rate of 31% and an objective response rate of 4% with olaparib[60]. The role of immunotherapy in advanced PDAC is still evolving. However, a low prevalence (< 2%) of deficient mismatch repair suggests a limited role of immune check point inhibitors in this setting, at least with the currently available drugs[61,62].

CONCLUSION

Pancreatic cancer not amenable to surgical resection remains one of the most difficult challenges for medical oncologists around the globe. Despite improved diagnostic imaging tools, most cases are detected at a stage where cure or long-term survival are not achievable. Nevertheless, there is reason for cautious optimism. Large RCTs over the last decade have introduced first-line FFX and GnP regimens as the current standard of care, which has significantly changed the treatment landscape. Although extrapolation of the outcomes observed in highly selected RCT populations should be done with great care, combined evidence from real-world studies across different countries and health care systems indicates that the regimens are effective and reasonably safe in the real-world setting. In several of the real-world evidence public-

ations, FFX was associated with a slightly better median OS than GnP, but selection bias was probable. Thus, it is possible that the differences observed might be the result of less fit patients being prescribed GnP rather than FFX. A sufficiently large head-to-head RCT comparing first-line FFX and GnP would potentially resolve these issues, but such a study is unlikely to occur.

In terms of second-line therapies, there are still considerable gaps in our knowledge. The few available RCTs provide only limited guidance, and it is difficult to translate their results into real-life practice. Notably, none of the published RCTs addresses whether the sequence of FFX followed by GnP or GnP followed by FFX is the most feasible or beneficial approach. Still, those sequences are often advocated by expert guidelines, and several real-world experience studies support that strategy. The extrapolation of RCTs into the real world is, at least in theory, even more complex in the second-line setting because patients at that point in their disease trajectory are likely to be frailer than patients eligible for first-line therapy.

The accumulating real-world evidence presented in this review points to some key conclusions. Several multidrug regimens show promising potency and acceptable toxicity in the first-line scenario, and to a somewhat lesser extent, the second-line setting. Outcomes reported in RCTs seem to be relatively consistent when the respective regimens are administered in real-life patients. Larger and/or pooled real-world studies are needed to further explore prognostic and predictive parameters such as serum albumin, serum CA-19-9, NLR and other novel biomarkers. Regarding second-line chemotherapy, the RCTs and real-world studies published to date are not fully aligned, and the key question regarding the optimal sequence of regimens remains uncertain. While most patients in this situation have very short expected survival, the identification of reliable clinical and biochemical biomarkers could be very helpful to inform treatment decision making.

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