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MINIREVIEWS

Dilemma of first line regimens in metastatic pancreatic adenocarcinoma

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Abstract

Pancreatic cancer is one of the deadliest cancers, ranking fourth among cancer-related deaths. Despite all the major molecular advances and treatment breakthroughs, mainly targeted therapies, the cornerstone treatment of metastatic pancreatic cancer (mPC) remains cytotoxic chemotherapy. In 2016, more than 40 years after the introduction of gemcitabine in the management of mPC, the best choice for first-line treatment has not yet been fully elucidated. Two main strategies have been adopted to enhance treatment efficacy. The first strategy is based on combining non-cross resistant drugs, while the second option includes the development of newer generations of chemotherapy. More recently, two new regimens, FOLFIRINOX and gemcitabine/nab-paclitaxel (GNP), have both been shown to improve overall survival in comparison with gemcitabine alone, at the cost of increased toxicity. Therefore, the best choice for first line therapy is a matter of debate. For some authors, FOLFIRINOX should be the first choice in patients with an Eastern Cooperative Oncology Group score (0-1) given its lower hazard ratio. However, others do not share this opinion. In this paper, we review the main comparison points between FOLFIRINOX and GNP. We analyze the two pivotal trials to determine the similarities and differences in study design. In addition, we compare the toxicity profile of the two regimens as well as the impact on quality of life. Finally, we present studies revealing real life experiences and review the advantages and disadvantages of possible second-line therapies including their cost effectiveness.

Key words: Review; Metastatic pancreatic cancer; FOLFIRINOX; Gemcitabine/nab-paclitaxel; Pivotal trials

Core tip: This paper is a mini-review that compares the design of the two pivotal trials studying the role of FOLFIRINOX and gemcitabine/nab-Paclitaxel in the management of metastatic pancreatic cancer. It also

analyzes the effects these regimens have on toxicity profile, quality of life, real life experiences, choice of second-line therapy and cost.

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INTRODUCTION

Adenocarcinoma of the pancreas is one of the most aggressive human cancers, ranking fourth among cancer related deaths[1]. Recent biomolecular progress has led to a better comprehension of pancreatic carcinogenesis; however, the revolutionary targeted and immune therapies have not shown any significant results[2]. Subsequently, cytotoxic drugs remain the backbone of treatment for metastatic pancreatic cancer (mPC). Gemcitabine has been the standard of care in mPC since 1996, providing a limited survival of six months due to the intrinsic capacity of cancer cells and the surrounding microenvironment to resist cytotoxicity[3-5]. More aggressive regimens were developed to overcome these resistance mechanisms. The combination of non-cross resistant agents, GTX (gemcitabine, docetaxel and capecitabine) and PEFG (cisplatin, epirubicin, fluorouracil and gemcitabine), enhanced tumor shrinkage by acting on different stages of cell cycle and bypassing mechanisms of drug resistance[6-8].

In 2011, French investigators from the Groupe Tumeurs Digestives of Unicancer and the PRODIGE Intergroup published the results of a phase Ⅱ/Ⅲ trial that revealed a clinically significant survival benefit and better quality of life for a regimen combining 5-FU/leucovorin, oxaliplatin and irinotecan (FOLFIRINOX) at the expense of increased toxicity[9]. Another option is nab-paclitaxel, which is a second generation chemotherapy agent that exploits the ability of albumin to deliver the hydrophobic molecule, paclitaxel, to targeted tissues. Nab-paclitaxel was combined with gemcitabine in the multinational MPACT phase Ⅲ trial and added an OS benefit of 2.6 mo compared to single agent Gemcitabine[10,11]. Table 1 summarizes the efficacy of the FOLFIRINOX and gemcitabine/nab-paclitaxel (GNP) as published in the pivotal studies of ACCORD/PRODIGE and MPACT trials, respectively.

The best choice for first-line therapy is a matter of debate. The National Comprehensive Cancer Network (NCCN) panel considers FOLFIRINOX as the first choice for *Eastern Cooperative Oncology Group (*ECOG) 0-1 patients given its lower HR for death, whereas nab-paclitaxel should be reserved for ECOG 2 patients (NCCN 2016). Conversely, ASCO and ESMO consider both regimens as acceptable treatment options for ECOG 0-1 patients[12,13]. Indirect comparisons using the ESMO magnitude of clinical benefit scale show a higher score for the FOLFIRINOX regimen when compared to GNP (5/5 *vs* 2/5, with a higher score indicating a better regimen in terms of survival benefit and quality of life)[14]. In addition, a Bayesian meta-analysis comparing multiple systemic protocols in advanced pancreatic cancer showed a trend toward better survival with FOLFIRINOX compared to GNP[15]. In view of this debate, we conducted this review to discuss the main comparison points between FOLFIRINOX and GNP, including the design of the two pivotal trials, toxicity profiles, quality of life, real life experiences, choice of second-line therapy and cost effectiveness.

TRIAL DESIGN: PRODIGE *VS* MPACT

The PRODIGE and MPACT trials were both randomized controlled trials (RCTs) based on an intent to treat principle and included 342 and 861 patients with mPC, respectively. Both trials had nearly the same tumor characteristics[9,16]. Additionally, the median age (61 years for both trials) and sex ratio (1.6 for PRODIGE and 1.3 for MPACT) were nearly identical. However, the French trial included only patients less than 76 years old with good performance status based on the ECOG evaluation system (ECOG 0-1). In contrast, the MPACT trial did not specify an age limit (age ranged from 27 to 86 years) and included patients with intermediate performance status based on the KPS system (KPS < 90 in nearly 42% of patients). In addition, the PRODIGE trial only included patients from French centers while the MPACT trial was a multinational study including patients from North America (63%), Australia (14%), and Eastern (15%) and Western Europe (9%). In addition, patients in the Gemcitabine arm of the PRODIGE trial received only 6 mo of therapy even if they were not progressing (17%), nearly half of whom did not continue. While some authors do not consider these differences important given that the survival curves of the gemcitabine arm in the two trials are "superimposable", others do not share this opinion. In fact, Gemcitabine is a well-known drug that is tolerated in the elderly population, even in intermediate health systems such as that of Eastern Europe. The same is not true when a new drug such as nab-paclitaxel is added to gemcitabine. In fact, the forest plot in the MPACT study clearly shows an effect of age and country on hazard ratio. In the same sense, Tehfe *et al*[17] published an analysis of patients from Canada (a subgroup of the MPACT trial) and showed an OS equal to 11.9 mo in the GNP arm compared to 7.1 mo in the gemcitabine arm with a hazard ratio of 0.76. However, this subgroup analysis included only 63 patients and was underpowered to detect a statistically significant result.

Table 1 Comparison of the pivotal studies approving FOLFIRINOX and gemcitabine/nab-paclitaxel in metastatic pancreatic cancer

		ACCORD/PRODIGE trial (FOLFIRINOX)[9]	MPACT trial (GNP)[10]
Study characteristics	Duration	December 2005-October 2009	May 2009-April 2012
	Location	France	Multinational
	Number of patients	342	861
	Study design	Phase 2-3	Phase 3
	Control arm	Gemcitabine	Gemcitabine
Patient and tumor characteristics	Median age	61 years	62 years
	Sex distribution	Male (62%)	Male (57%)
	ECOG	PS 0 (37.4%)	KPS 100 (16%)
		PS 1 (61.9%)	KPS 80-90 (77%)
		PS 2 (0.6%)	KPS 60-70 (7%)
	Tumor stage	Metastatic	Metastatic
	Metastatic sites	Liver (87.6%)	Liver (85%)
		Lung (19.4%)	Lung (35%)
		Peritoneum (19.4%)	Peritoneum (4%)
	Tumor location	Head (39.2%)	Head (44%)
Response	ORR (%)	31.6	23
	PR (%)	31	23
	SD (%)	38.6	27
	DCR (%)	70.2	48
	PFS (mo)	6.4	5.5
	OS (mo)	11.1	8.5
	1-yr OS (%)	48.4	35
Safety (Grade 3-4 toxicities)	Neutropenia	45.7	38
	Febrile neutropenia	5.4	3
	Thrombocytopenia	9.1	13
	Anemia	7.8	13
	Fatigue	23.6	17
	Peripheral neuropathy	9	17
	Diarrhea	12.7	6
Side effects	Toxic death	0.6	4
	Alopecia	11.2	50
	G-CSF use	42.5	26

DCR: Disease control rate; GNP: Gemcitabine/nab-paclitaxel; PR: Partial response; ORR: Overall response rate; OS: Overall survival; SD: Stable disease.

TOXICITY AND QUALITY OF LIFE

The toxicity profile of a chemotherapy regimen is a major contributor in its adoption. Based on the two trials, hematologic toxicity is in favor of the FOLFIRINOX regimen and includes a lower incidence of neutropenia (45% *vs* 38%) (although the use of G-CSF was more common), anemia (7.8% *vs* 13%), and thrombocytopenia (9.1% *vs* 13%). The remaining toxicities are listed in Table 1[9,16]. Peripheral neuropathy attributed to Nab-paclitaxel is a particular debilitating toxicity; grade 3 peripheral neuropathy was encountered in 17% of the patients but improved to grade 1 toxicity or less in a median of 29 d[10]. Real-life studies with a closer follow-up of patients showed fewer side effects compared to those reported in the clinical trials[18]. Chemotherapy-induced hair loss is often a major determinant of the treatment regimen selected and was more commonly encountered in the GNP regimen (50% *vs* 11.2%)[9,16].

Overall, FOLFIRINOX remarkably improved global health status, emotional functioning and many of the symptoms of mPC, such as pain and anorexia (although FOLFIRINOX did not relieve diarrhea), in the first two months of treatment. It also showed significantly increased time to physical or cognitive deterioration[19]. On the other hand, quality of life was not assessed in the MPACT trial. In contrast, GNP showed significant improvement in quality-adjusted survival in comparison to gemcitabine alone using the Quality-Adjusted Time Without Symptoms or Toxicities (Q-TWiST) methodology, despite the limitations of the Q-TWiST analysis and the lack of prospective quality of life data from the MPACT trial[8].

Because significant toxicity was not uncommon, more tolerable treatment regimens were created by modifying the administration or drug dosing schedule. In the modified FOLFIRINOX regimens, either the 5-fluorouracil bolus was omitted or the dose of irinotecan was reduced. Stein *et al*[20] published solid data in a prospective study, enrolling both locally advanced and mPC patients who received a modified FOLFIRINOX regimen including a 25% dose reduction in 5-FU or irinotecan. These modifications successfully maintained the efficacy of the drugs while significantly decreasing the toxicity profile (decreased neutropenia, vomiting and fatigue). Additional exploratory analyses of the MPACT trial showed that patients who had dose delays or reductions (71% and 41%, respectively) had better outcomes[8]. These practical changes are capable of modifying the tolerance profile of the drugs while preserving efficacy. Tables 2 and 3 compare the

Table 2 Comparison of the FOLFIRINOX and modified FOLFIRINOX trials

		ACCORD/PRODIGE trial (FOLFIRINOX)[9]	Stein *et al*[20] Modified FOLFIRINOX	Mahaseth *et al*[21] (Modified FOLFIRINOX)	Ghorani *et al*[22] (Modified FOLFIRINOX)
Study design	Location	France	United States	United States	United Kingdom
	Number of patients	342	44	36	18
	Study design	Phase 2-3 Prospective	Phase 2 Prospective	Phase 2 Prospective	Retrospective
	Dosing		25% reduction in bolus 5-FU and irinotecan doses	No 5-FU bolus	No 5-FU bolus and 25% reduction in irinotecan doses
Patient and tumor characteristics	Median age	61 years	62	63	60
	Sex distribution	Male (62%)	Male (56.8%)	Male (56.8%)	Male (44.6%)
	ECOG	PS 0 (37.4%) PS 1 (61.9%) PS 2 (0.6%)	PS 0 (46%) PS 1 (54%)	PS 0 (22%) PS 1 (76%) PS 2 (1%)	PS 0 (56.6%) PS 1 (44.4%)
	Tumor stage	Metastatic	Metastatic	Metastatic	Locally advanced and metastatic
	Metastatic sites	Liver (87.6%) Lung (19.4%) Peritoneum (19.4%)	Liver (54.1%) Lung (32.4%) Peritoneum (37.8%)		
	Tumor location	Head (39.2%)	Head (54.8%)	NA	Head (566%)
Response	ORR (%)	31.6	35.1	30	47
	PR (%)	31	35.1	NA	47
	SD (%)	38.6	51.5	NA	23
	DCR (%)	70.2	86.6	NA	80
	PFS (mo)	6.4	6.1	8.5	7.2
	OS (mo)	11.1	10.2	9	9.3
	1-yr OS (%)	48.4	38	NA	NA
Safety (grade 3-4 toxicities)	Neutropenia	45.7	12.2	3	0
	Febrile N.	5.4	4.1	0	5.6
	Thrombocytopenia	9.1	9.5	4	0
	Anemia	7.8	5.4		0
	Fatigue	23.6	12.2	13	5.6
	Peripheral neuropathy	9	2.7	4	0
	Diarrhea	12.7	16.2	13	16.7
	Toxic death	0.6	0	0	0
Additional information			Pegfilgastrim on each cycle	Pegfilgastrim on each cycle	Pegfilgastrim on each cycle

DCR: Disease control rate; PR: Partial response; ORR: Overall response rate; OS: Overall survival; SD: Stable disease.

classical to the modified form of FOLFIRINOX and GNP respectively[20-23].

CHOICE OF SECOND-LINE

The optimal treatment sequence dictates the choice of first-line treatment for mPC. In fact, in the PRODIGE trial, only 47% of the patients were fit enough to receive second-line therapy while only 12.5% of patients received a second-line therapy after initially receiving a gemcitabine-based combination, yet the median OS was limited to 4.4 mo among those receiving second-line treatments. On the other hand, in the MPACT trial, 40% of the patients received additional therapy after GNP[24]. According to these data, similar numbers of patients were able to receive second-line therapy after either FOLFIRINOX or GNP.

Data on the administration of GNP after FOLFIRINOX failure in the literature is limited to a few retrospective studies with conflicting data. The AGEO trial, a prospective multicenter study, evaluated the use of GNP in the second-line setting after FOLFIRINOX failure. The disease control rate was 58% with a 17.5% overall response rate and OS of 8.8 mo. Twelve patients (21%) had an ECOG of 2, and 40% had grade 3-4 toxicities without any treatment-related deaths[25]. In another retrospective study by Zhang *et al*[26], 28 patients treated with the same regimen showed less satisfactory results, with an OS of 23 wk.

Small retrospective studies assessed the efficacy of FOLFIRINOX in the second line setting with a modest improvement in OS, but none evaluated its efficacy after GNP[27,28]. In fact, the only data available is from the exploratory analyses of the second line treatment of the MPACT trial, where FOLFIRINOX (despite demonstrating interesting data) was only administered to 18 patients (10.5% of the whole population), calling the use of this treatment sequence into question[16].

Consequently, definitive recommendations concerning the optimal sequence of therapy cannot be made. The prospective data from the AGEO trial makes GNP a better and more plausible option as a second-line option after FOLFIRINOX administration. However, large RCTs are needed to create newer guidelines.

Table 3 Comparison of the gemcitabine/nab-paclitaxel and modified gemcitabine/nab-paclitaxel trials

		MPACT trial[10] (GNP)	Krishna *et al*[23] (Modified GNP)
Study design	Location	International	United States
	Number of patients	861	49
	Dosing		Omission of Day 7 doses
	Study design	Phase 3	Retrospective
Patient and tumor characteristics	Median age (yr)	62	65
	Sex distribution	Male (57%)	Male (57%)
	Tumor stage	Metastatic	Metastatic
	Metastatic sites	Liver (85%)	Liver (57%)
		Lung (35%)	Lung (27%)
		Peritoneum (4%)	Peritoneum (43%)
	Tumor Location	Head (44%)	Head (51%)
	PFS (mo)	5.5	4.8
	OS (mo)	8.5	11.1
Safety (Grade 3-4 toxicities)	Neutropenia	38	10
	Thrombocytopenia	13	4
	Anemia	13	15
	Fatigue	17	6
	Peripheral neuropathy	17	2
	Diarrhea	6	0

GNP: Gemcitabine/nab-paclitaxel; OS: Overall survival; PFS: Progression free survival.

COST-EFFECTIVENESS

In addition to weighing efficacy and safety, oncologists must evaluate financial considerations to choose the optimal chemotherapy regimen. In fact, the NCCN shows a tendency toward incorporating the financial burden of cancer drugs into its decision-making strategy. Cost-effectiveness of each regimen is largely dependent on the societal willingness-to-pay (WTP) threshold set by each country. For instance, setting the WTP in Canada at $130000 makes the FOLFIRINOX regimen the optimal strategy in mPC. However, decreasing the limit to $80000 renders Gemcitabine monotherapy the only possible therapeutic choice[29]. Similarly, the increased WTP threshold in Greece rendered the GNP protocol a potential option in the treatment of patients with mPC[30].

Both FOLFIRINOX and GNP showed consistent cost-effectiveness and cost-utility with superior survival efficacy in independent analytical studies[31,32]. However, it is not until recently that the values of each regimen were compared. The value of the different regimens in mPC was compared based on Medicare rates, which take into consideration the cost and administration of the drug, hospitalization and management of associated adverse events. The monthly costs of FOLFIRINOX and GNP were $7234 and $12221 respectively. However, the cost of the overall treatment based on progression free survival in each protocol was estimated at $46289 and $67216. FOLFIRINOX seemingly exhibits higher cost-effectiveness than GNP according to these results. However, it is worth mentioning that the cost of the FOLFIRINOX regimen is mainly due to its toxicity profile. Dosing modifications could limit the incidence of serious side effects and thus further increase the cost-effectiveness of this protocol (Monthly cost of FOLFIRINOX is $763 versus $9008 for the GNP protocol). Consequently, in September 2015, the National Institute for Health and Care Excellence recommended against the use of GNP in patients with mPC due to the limited benefits in comparison to the cost of the drug. An alternative cheaper option that might be considered is modified GNP (which is yet to be validated), which has an overall treatment cost of $36226[33].

CONCLUSION

Overall, both FOLFIRINOX and GNP result in better overall survival and quality of life. In the absence of direct comparison, the treatment choice for patients with mPC is determined by physical toxicity and financial cost, both of which favor the FOLFIRINOX regimen. Further studies should aim to evaluate the modified schedules and dosing of both regimens in multinational RCTs and search for biomarkers that predict response to treatment[34]. In addition, the choice of first-line therapy in the future may not be limited to these two regimens, as newly developed drugs/therapeutic strategies should be tested in clinical trials to find more efficacious options for patients with good performance status.

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