Standard versus Modified FOLFIRINOX Protocols in Patients with Metastatic Pancreatic Carcinoma: Efficacy versus Toxicity

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Abstract:

Background: FOLFIRINOX revolutionized the management of patients with metastatic pancreatic adenocarcinoma (MPA). However, studies have shown severe toxicity profile leading to its limitation as a standard of care protocol.

Aim: Comparison between standard and modified FOLFIRINOX in terms of response rate (RR) and toxicity profile among patients with MPA.

Methods: We reviewed the medical records of 34 patients diagnosed with MPA, they were divided into two groups: standard FOLFIRINOX or modified FOLFIRINOX in the first line setting.

Results: We observed no statistically significant differences in terms of response rate between the two treatment arms 30% in the standard arm and 28.6 % in the modified arm respectively. the toxicity profile was slightly better in the modified arm, namely, dose reductions14.2% vs 40 % favoring modified arm, treatment delay 28.5 % vs 50 % in the standard arm and toxicity mandating hospitalization 21.4 % vs 30 % also favoring modified arm, however this didn't reach statistically significant difference.

Conclusion: Modified FOLFIRINOX presents comparable activity compared to standard FOLFIRINOX in MPA in terms of response rate and toxicity profile favoring the modified protocol.

Keywords: FOLFIRINOX, metastatic, pancreas adenocarcinoma.

Received: 26 February 2024
Accepted: 3 March 2024

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Background:

Metastatic pancreatic adenocarcinoma (MPA) is one of the worst prognosis malignancies with an estimated 5-year overall survival rate of 3.7% [1,2]. Gemcitabine based combination chemotherapy was the gold standard option in treating metastatic disease demonstrating slight overall survival (OS) advantage over gemcitabine alone [3].

The ACCORD 11/PRODIGE 4 trial came out in the year 2013 with a revolution in the management of MPA demonstrating a median OS of 11.1 vs 6.8 months favoring FOLFIRINOX protocol over gemcitabine alone together with better median progression free survival of 6.4 versus 3.3 months respectively and a better objective response rate of 31.6 and 9.4 respectively [4].

Unfortunately, the appealing outcome of the FOLFIRINOX protocol came with the expense of toxicity. High rates of grades III-IV neutropenia (45%), vomiting (14%), fatigue (23%) and diarrhea (12%) were reported and forced practitioners to select the protocol for fit and young patients [5-7].

Because of toxicity profile of FOLFIRINOX, studies have evaluated a less toxic regimen with same efficacy; and hence came out the attenuated form of modified FOLFIRNOX.

Studies have also addressed the activity and toxicity of the modified FOLFIRINOX protocol with similar survival outcome to those of the original ACCORD 11/PRODIGE 4 trial and more tolerable toxicity profile [8-12]

Hence, we conducted a retrospective analysis at our center to compare standard and modified FOLFIRINOX in terms of response rate and toxicity profile among patients with MPA.

Methods:

We conducted a retrospective study, performed in Kasr El Ainy Oncology Center, Cairo University. Data was extracted from electronic medical records; we enrolled 34 records for patients with MPA who were indicated for first line treatment with FOLFIRINOX. Data was collected from January 2023 till June 2023. The patients were divided into 2 groups, one received the full dose of the FOLFIRINOX protocol and the other received the Modified dose of the same protocol. and the study was approved by our Ethical committee.

Inclusion criteria:

- Age range is between 18-70 years
- Pathologically confirmed MPA treated with FOLFIRINOX protocol whether standard or modified dose
- Patients should be able to at least receive one complete cycle of whether standard or modified protocol as we cannot evaluate efficacy and toxicity on an incomplete cycle

Exclusion criteria:

- Patients with previous malignancy elsewhere as not to confound the validity of endpoints
- Major medical or psychological illness, which would interfere with treatment
- ECOG PS 3-4

Treatment:

Chemotherapy protocol was delivered as shown in (table 1) via intravenous (IV) port, inserted during 2 days of admission, cycles were repeated every 14 days.

Standard FOLFIRINOX consisted of Irinotecan 180 mg /m^2 infused over 90 minutes, folinic acid 400 mg/ m^2 IV infusion over 30 minutes, oxaliplatin 85 mg/m^2 IV infusion over 120 minutes,5-Fluorouracil 400 mg/m^2 IV bolus and 2400 mg/m^2 continuous IV infusion over 46 hours.

Modified FOLFIRINOX consisted of Irinotecan 135 mg /m^2 infused over 90 minutes, folinic acid 400 mg/m^2 IV infusion over 30 minutes, oxaliplatin 50 mg/m^2 IV infusion over 120 minutes,5-Fluorouracil 2400 mg/m^2 continuous IV infusion over 46 hours.

Table 1: treatment protocol for each study group.

Drug	Standard FOLFIRINOX	Modified FOLFIRINOX
Irinotecan (infusion over 90 minutes)	180 mg/m^2	135 mg/m^2
Oxaliplatin (Infusion over 120 minutes)	85 mg/m^2	50 mg/m^2
5-Fluorouracil	Bolus: 400 mg/m^2 Continuous infusion: 2,400 mg/m^2	Continuous infusion: 2,400 mg/m^2
Folinic Acid (infusion over 30 minutes)	400 mg/m^2	400 mg/m^2

Procedures:

Objective response rate was assessed using RECIST 1.1 criteria. Response rate was extracted from the original radiological reports, assessment of response was performed on the 3rd cycle with comparative Computed Tomography (CT).

Acute toxicity and compliance to the therapy was evaluated based on the Common Terminology Criteria for Adverse Events version 4.0.

Results:

We identified 51patients with MPA treated with first line FOLFIRINOX. Sixteen patients were excluded as per exclusion criteria while one patient had concomitant malignancy.

The median age was 59 years old. Most patients were males. ECOG 0-1 constituted most patients with only 15 % having ECOG 2. About 47 % of tumors were in the head of pancreas and nearly all the patients had only one metastatic site. Patients were divided into two groups as shown in (table 2).

Table 2: Demographical and clinical features of the study population

Characteristics	Standard FOLFIRINOX (N=20)	Modified FOLFIRINOX (N=14)	P
Age	56 (50.7-60.0)	62 (57-69.2)	0.001
Sex			0.69
Male	11 (55.0)	7 (50.0)	
Female	9 (45.0)	7(50.0)	
ECOG			0.40
0	10 (50)	5 (36)	
1	6 (30)	7 (50)	
2	4 (20)	2(14)	
Tumor site			0.683
Head/neck	10 (50.0)	6 (42.8)	
Body/tail	10 (50 .0)	8 (57.2)	
Number of metastatic sites			0.28
1	9 (45)	7 (50)	
2	11 (55)	7 (50)	

Patients treated with standard FOLFIRINOX had a higher objective response rate of 30% compared to modified FOLFIRINOX with a rate of 28.6%, although this difference was not statistically significant (p=0.930) (table 3). There were no statistically significant variations in toxicity between the two treatment groups. In the standard arm, there was a higher incidence of grades 3-4 febrile neutropenia (25%) compared to the other arm (14%) without statistically significant difference. Dose reductions and treatment delays were much higher in the standard protocol (40 % vs 14.2%) and (50% vs 28.5%) respectively. toxicities mandating hospitalization were also higher in the standard arm (30% vs 21.4%), none of these differences were statistically significant. (table 4)

Table 3: Radiological response to treatment

Variable (RECIST 1.1)	Standard FOLFIRINOX N (%)	Modified FOLFIRINOX N (%)	P
Objective Response (complete + partial response)	6 (30)	4 (28.6)	0.930
Complete response	0 (0)	0 (0)	
Partial response	6 (30)	4 (28.6)	
Stable disease	10 (50)	7 (50)	
Progressive disease	4 (20)	3 (21.4)	

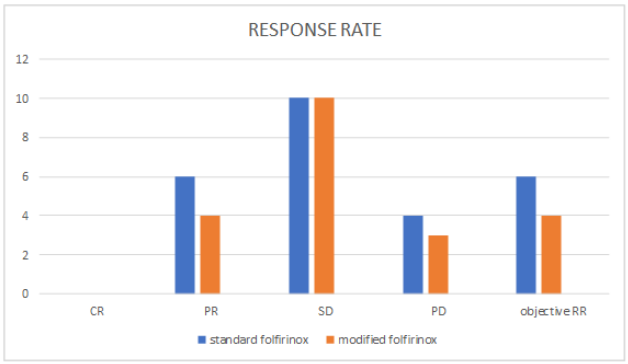
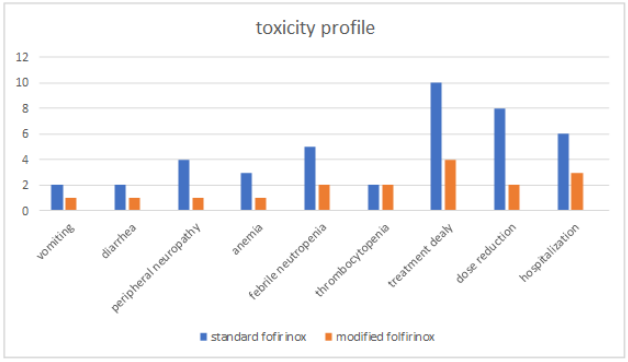


Table 4: Toxicity profile of regular and attenuated FOLFIRINOX

Event	Standard FOLFIRINOX N=20 (%)	Modified FOLFIRINOX N=14 (%)	P
G3-4 toxicity	7 (35)	4 (28.5)	0.694
Vomiting	2 (10)	1 (7.1)	0.772
Diarrhea	2 (10)	1 (7.1)	0.772
Peripheral neuropathy	4 (20)	1 (7.1)	0.302
Anemia	3 (15)	1 (7.1)	0.487
Febrile neutropenia	5 (25)	2 (14.2)	0.449
thrombocytopenia	2 (10)	2 (14.2)	0.712
Treatment delay	10 (50)	4 (28.5)	0.216
Dose reduction	8 (40)	2 (14.2)	0.109
Hospitalization	6 (30)	3 (21.4)	0.581



Discussion:

Many randomized trials have demonstrated that superiority of FOLFIRINOX as the standard treatment for patients with MPA. young patients with good performance are the best fit for this protocol although high rate of toxicity was described even in this group specially neutropenia.

In our study, there was no difference in RR between the two different arms. the standard protocol was numerically better than the modified one 30% vs 28.6 % respectively. The first trial testing modified FOLFIRINOX in MPA was conducted in the year 2016, they enrolled patients diagnosed with locally advanced pancreatic adenocarcinoma or metastatic disease with lower doses of irinotecan 135 mg/m^2 and bolus fluorouracil of 300 mg/m^2. The RR in this cohort was 35%. [8] Ueno et al. conducted another phase II study testing different doses of irinotecan 150 mg /m^2 and no 5-FU bolus in 69 MPA patients. The objective RR was 37.7% [9].

Similarly, Li et al. tested another reduced dose of both oxaliplatin 50 mg/m^2 instead of 85 mg/m^2 and irinotecan 135 mg/m^2 instead of 180 mg/m^2 and omission of bolus fluorouracil in 62 patients with MPA. The overall RR was 32.5 % [10]. these outcomes were consistent with ones found in the ACCORD 11 - PRODIGE 4 trial with RR of 31.6 % in the standard FOLFIRINOX arm.

Decreased RR has been shown to occur only after reducing the dose intensity of FOLFIRINOX agents to more than 30 % of the original doses [13]. In our study we sticked to dose reductions less than 30 % as not to interfere with RR except for omitting the 5-FU bolus. This is consistent with a prospective and retrospective trials of FOLFIRINOX in MPA [12,14,15]. Also, in colorectal cancer, omitting bolus 5-FU has been associated with better toxicity while maintaining same efficacy [16,17].

Also, in borderline resectable disease, FOLFIRINOX given as neoadjuvant was without the 5-FU bolus component [18]. all these data suggest giving FOLFIRINOX without the bolus 5-FU.

In our study the irinotecan dose was 135mg/m^2. In previous studies the irinotecan dose in the modified protocol ranged from 135-165 mg/m^2 [8,9,10,12,14,19]. Irinotecan has been associated with significant increase of nausea, vomiting and diarrhea when combined with oxaliplatin and 5-FU. When the dose is reduced from 180 mg/m^2 to 165 mg/m^2, the prevalence of severe vomiting in grade 3-4 was significantly lower than that found in the ACCORD 11/PRODIGE 4 trial (3.6% versus 14.5% respectively) [20].

In our study, we reduced the dose of irinotecan to 135 mg/m^2 so as not to interfere with the efficacy and to lower the risk of toxicity as vomiting, diarrhea, and neutropenia.

The overall RR in our study was more or less similar to the previously described in the preceding studies [4,6,8].

The main purpose of using the modified FOLFIRINOX is lowering toxicity.in our study, all the

treatment related toxicity was numerically better in the modified arm, especially the dose reductions, treatment delays and toxicity mandating hospitalization. Unfortunately, we couldn't demonstrate statistically significant benefit favoring the modified protocol. We believe that this is because of the relatively small size of the population examined and the retrospective data of our study. Patients treated with modified protocol were relatively older than those of the standard one. Also, we used prophylactic growth colony stimulating factor (G-CSF) for majority of patients treated with the standard protocol and some of the modified one and this might have biased the analysis, thus the rates of G3-4 neutropenia in the two arms were much lower than the described in the ACCORD 11/PRODIGE 4 study.

Conclusion:

We concluded that modified FOLFIRINOX demonstrated same activity as standard protocol in terms of RR with numerically better toxicity profile putting into considerations the bias stated before. We believe that modified FOLFIRINOX should replace the standard protocol at least for old comorbid patients who cannot withstand the toxicity of the standard protocol.

Abbreviations

MPA: metastatic pancreatic adenocarcinoma
RR: response rate
OS: overall survival
G-CSF: growth colony stimulating factor
IV: intravenous

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