Increasing efficiency of FOLFIRINOX administration in patients with pancreatic cancer

The Dutch NVMO Committee for Sustainability and Efficiency has formulated recommendations to increase the efficiency of administering FOLFIRINOX in patients with pancreatic cancer. The goal is to make the treatment more patient-friendly, less time-toxic and more cost-effective while reducing use of resources and thus environmental impact.

Background

FOLFIRINOX has been used for over 10 years as a first-line treatment for unresectable or metastatic pancreatic cancer [1,2]. This treatment consists of a combination of 5-fluorouracil (5FU) with folinic acid, irinotecan, and oxaliplatin and is administered biweekly [1,3]. The regimen also includes dexamethasone, granisetron, and atropine as co-medications to reduce chemotherapy side effects. For persistent nausea, metoclopramide and/or olanzapine are effective [1,4]. The current FOLFIRINOX regimen is based on the phase-1 efficacy and safety study first presented in 2000 [3]. Subsequent phase-2 and -3 studies adopted the recommended dosages, infusion durations, volumes, and overall administration schedule from the phase-1 studies [2,3,5]. Despite new insights, the regimen has seen little to no optimization since its inception [8-11,15-18]. This article provides recommendations for a more efficient FOLFIRINOX regimen.

Premedication

Dexamethasone and granisetron, typically administered intravenously, can be given orally instead [1,4]. Oral administration enhances patient participation and reduces costs and environmental impact. Oral premedication should be taken at least one hour before chemotherapy starts. Given their relatively long half-lives, patients could take dexamethasone and granisetron in the morning before traveling to the hospital [1,6,7]. The ASCO guidelines do not specify the exact 5HT3-receptor antagonist, allowing ondansetron to be used instead of granisetron [7,8]. Dexamethasone's oral dose recommendations vary between 8 and 20 mg per day [4,6,8]. We prefer 8 mg. Atropine administration to prevent acute cholinergic syndrome from irinotecan remains subcutaneous (Table).

Reducing Infusion Duration

The most significant time savings can be achieved by accelerating folinic acid administration. Currently, folinic acid (400mg/m2 in 100ml NaCl 0.9%) is administered over two hours [1]. With a maximum infusion rate of 160mg/min, this can be reduced to 15-20 minutes (Table 2) [9]. Additionally, oxaliplatin can be administered simultaneously with irinotecan, saving 1.5 hours (Table 2) [10-12]. This requires preparing irinotecan in 5% glucose instead of NaCl 0.9% due to oxaliplatin's reactivity with chloride ions in NaCl infusion fluid [11,12]. Irinotecan remains stable for 28 days in both NaCl 0.9% and 5% glucose at room temperature [13]. This change therefore does not affect stability.

Lastly, after irinotecan has been fully infused, folinic acid can be administered concurrently with the remaining oxaliplatin using the shortened infusion time (Table 1) [10-12]. Again, this requires preparing folinic acid in 5% glucose, which does not affect stability [14]. The revised regimen (Table 1) uses two infusion lines with a glucose primary infusion. Oxaliplatin is connected to the first line and irinotecan followed by folinic acid to the second. Before oxaliplatin administration, the line is flushed with 50ml 5% glucose according to the standard flush schedule (300-600ml/hour) [10,16]. Irinotecan and folinic acid are compatible if they come into contact for a short duration (up to about 3 minutes). With a short folinic acid infusion duration, the pump is set to 999ml/hour, flushing the line within 3 minutes, making an additional flush step unnecessary [15,16].

5FU Bolus: Valuable or Redundant?

For 5FU in the "classic" FOLFIRINOX regimen for metastatic pancreatic cancer, a bolus (400mg/m2) is administered before a prolonged infusion over 46-48 hours (2400mg/m2) [1]. Since the bolus has been omitted in the adjuvant setting (modified FOLFIRINOX), its value and whether it could be combined with the prolonged infusion (400+2400=2800mg/m2 over 46-48 hours) are debated. Our recommendation not to combine the bolus with the prolonged infusion for metastatic pancreatic cancer is twofold. The bolus disrupts RNA function, while the prolonged infusion at lower concentrations disrupts DNA synthesis, meaning they work through different mechanisms [17]. Additionally, the cytotoxic effect of 5FU is time-dependent rather than dose-dependent [17]. Therefore, combining the two doses (2800mg/m2 over 46-48 hours) is undesirable as the bolus's added value would be lost.

Table 1: FOLFIRINOX Regimen Based on the Recommendations

Time	Medication	Dose	Administration	Duration
-01:00	Dexamethasone	8mg	oral	NA
-01:00	Granisetron	2mg	oral	NA
00:00	Atropine	0.25mg	subcutaneous	NA
00:00	Glucose 5%	50ml	IV flush	NA
00:05	Oxaliplatin (500 ml Glucose 5%)	85mg/m2	IV (line 1)*	120 minutes
00:05	Irinotecan (250 ml Glucose 5%)	180mg/m2	IV (line 2)	90 minutes
01:40	Folinic acid (250 ml Glucose 5%)	400mg/m2	IV (line 2)	20 minutes
02:00	5-FU	400mg/m2	IV (line 2)	10-15 minutes
02:15	5-FU	2400mg/m2	Elastomer pump	46 hours

*Line 1 must be flushed with 50ml glucose 5% (300-600ml/hour) at the start of 5-FU bolus (2:05). This flushes the line and prevents contact between oxaliplatin and NaCl 0.9% from the 5-FU.

Extrapolating the Recommendations

These recommendations for a more efficient FOLFIRINOX regimen can be applied to other 5FU-containing regimens, including modified FOLFIRINOX, FLOT, FOLFIRI, FOLFOX, and FOLFOXIRI.

Key Messages

- Dexamethasone and granisetron can be administered orally.
- The infusion duration of folinic acid can be shortened from 120 to 15-20 minutes.
- Irinotecan and folinic acid can be administered sequentially (in 5% glucose) simultaneously with oxaliplatin.
- The 5FU bolus should be retained due to conflicting data and the different mechanisms of action compared to prolonged 5FU infusion.

Table 2: Time Savings with the FOLFIRINOX Regimen

Medication	**Administration**	**Time saved per per Administration**	**Time saved per Patient***
Dexamethasone	Oral instead of IV	5 minutes	1 hour
Granisetron	Oral instead of IV	5 minutes	1 hour
Oxaliplatin	Concurrent with irinotecan	n/a**	n/a
Irinotecan	Concurrent with oxaliplatin	90 minutes**	18 hours
Folinic acid	Concurrent with oxaliplatin	120 minutes***	24 hours
Flushing	Only flush before oxaliplatin	40 minutes****	8 hours
Total Time Savings		**260 minutes**	**52 hours**

*Based on a patient undergoing 12 cycles.
**90 minutes saved by concurrent administration with oxaliplatin.
***120 minutes saved by reducing to 15 minutes, allowing concurrent administration with oxaliplatin.

****Includes 50ml NaCl 0.9% flush (30 minutes) and glucose 5% flush after oxaliplatin (10 minutes).

About the Authors:

The committee “sustainability and efficiency” of the Dutch Society of Medical Oncology (NVMO) was initiated in 2022. Their remit is to demonstrate that it is possible to increase both the sustainability as well as the efficiency of medical oncology care. The committee consists of medical oncologists and hospital pharmacists. They regularly publish specific guidelines and suggestions for daily practice based on both published literature and daily experience. All published guidelines are freely accessible at “https:www.nvmo.org/duurzaam-en-doelmatigheid/”.

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