Mitigation of gastrointestinal side effects among patients receiving NALIRIFOX for metastatic pancreatic ductal adenocarcinoma

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KEY LEARNINGS

Proactive management of GI AEs may help to reduce their impact and allow patients with mPDAC who are receiving NALIRIFOX to remain on the treatment for as long as possible, which may lead to improved survival outcomes.

BACKGROUND

- Oncology nurses play a pivotal role in assessing and managing the side effects of chemotherapy.
- Based on the results of NAPOLI 3 (NCT04083235), liposomal irinotecan + 5-flurouracil/leucovorin + oxaliplatin (NALIRIFOX) is approved by the US Food and Drug Administration for the first-line treatment of adults (no upper age limit) with metastatic pancreatic ductal adenocarcinoma (mPDAC).[1,2]
- Diarrhea is a known dose-limiting adverse event (AE) associated with irinotecan-based chemotherapy.[2,3]
- However, analysis of gastrointestinal (GI) AE management in NAPOLI 3 has not yet been reported.

OBJECTIVE

- To describe GI AEs and the management strategies used to treat chemotherapy-induced diarrhea among patients enrolled in NAPOLI 3 who received NALIRIFOX at centers in North America.

CONCLUSIONS

- A high proportion of patients receiving NALIRIFOX in NAPOLI 3 experience diarrhea, a common AE associated with irinotecan-based therapy.
- Oncology nurses support patients with mPDAC at every phase of their treatment journey.
- Assessing the signs and symptoms of chemotherapy-induced diarrhea, providing accurate and timely patient education and consulting with the medical team regarding appropriate prevention and treatment may reduce complications and optimize survival outcomes for patients.

METHODS

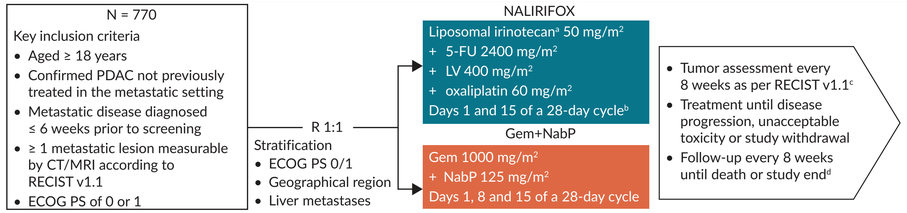
Study design

- NAPOLI 3 was a randomized, open-label, phase 3 study conducted at 187 sites in 18 countries worldwide.[1]
- Patients (N = 770) with confirmed untreated mPDAC were randomized 1:1 to receive NALIRIFOX or nab-paclitaxel plus gemcitabine (Figure 1).
- Pharmacological management of diarrhea according to institutional or international guidelines was permitted but not mandated, and initiation was recommended following the first episode of poorly formed stools or the earliest onset of more frequent than normal bowel movements.
- Prophylactic and therapeutic use of atropine was recommended for the management of diarrhea occurring owing to cholinergic syndrome, and loperamide as the first-line pharmacological therapy for treatment-induced diarrhea.

Analysis

- In this *post hoc*, exploratory analysis, the occurrence of GI AEs and use of anti-diarrhea medications were examined across the overall survival (OS) subgroups (≤ 12.0 months and > 12.0 months) of patients who received NALIRIFOX in North America.
- The use of atropine as prophylaxis or treatment was evaluated according to the following (non-exclusive) definitions:
  - Prophylaxis was defined as atropine initiated on the day of (or 1 day prior to) NALIRIFOX initiation, or within 2 days (either side) of NALIRIFOX initiation with a stated indication of "prophylaxis" or similar text.
  - Treatment was defined as atropine received in response to diarrhea.
- The use of loperamide and other anti-diarrhea medications was not defined as prophylaxis or treatment owing to limitations of differentiating between the intended purpose and implementation of prescribed oral medications.
- Data were examined descriptively; no statistical testing was performed.

Figure 1. NAPOLI 3 study design



[a]Dose expressed as irinotecan free-base equivalent. [b]Administered sequentially as a continuous infusion over 46 hours (dose delays and oxaliplatin discontinuation were permitted). [c]Until progressive disease. [d]The study was complete once all patients had discontinued the study treatment or ≥ 543 OS events had occurred.
5-FU, 5-fluorouracil; CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; Gem, gemcitabine; LV, leucovorin; MRI, magnetic resonance imaging; NabP, nab-paclitaxel; OS, overall survival; PDAC, pancreatic ductal adenocarcinoma; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors.

RESULTS

Patients

- Of the 120 patients in North America randomized to receive NALIRIFOX in NAPOLI 3 (intention-to-treat population), 65 (54.2%) and 55 (45.8%) had an OS of ≤ 12.0 months and > 12.0 months, respectively (Table 1).
- Generally, in the longer OS subgroup, a higher proportion of patients were female and had an Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0 than the shorter OS subgroup (Table 1).

Diarrheal AEs

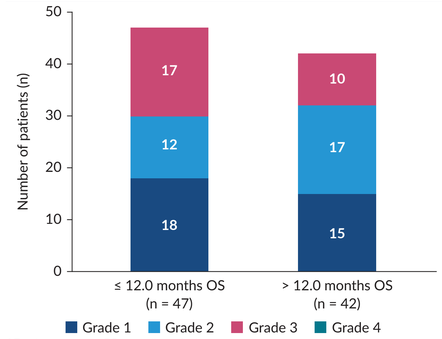
- Among patients in North America who received NALIRIFOX in NAPOLI 3 (n = 112, safety population), diarrhea occurred in 47/57 patients (82.5%) and 42/55 patients (76.4%) in the ≤ 12.0 months and > 12.0 months OS subgroups, respectively (Figure 2).
- The occurrence of grade 3 diarrhea was highest in the ≤ 12.0 months OS subgroup, in which 17 of the 47 patients (36.2%) experienced grade 3 diarrhea (Figure 2).
- A similar proportion of patients in the ≤ 12.0 months OS subgroup and the > 12 months OS subgroup experienced at least one event of acute diarrhea (17/57 [29.8%] and 17/55 [30.9%], respectively).
- Numerically more patients in the ≤ 12.0 months OS subgroup had delayed diarrhea (30/57 [52.6%]) than those in the > 12 months OS subgroup (25/55 [45.5%]).

Table 1. Patient demographics and disease characteristics

Patient characteristics	≤ 12.0 months OS (n = 65)	> 12.0 months OS (n = 55)
Age, years		
Median (IQR)	65.0 (60.0–71.0)	65.0 (53.5–69.0)
Sex, n (%)		
Female	24 (36.9)	25 (45.5)
Race, n (%)		
White	56 (86.2)	43 (78.2)
ECOG PS score, n (%)		
0	20 (30.8)	26 (47.3)
1	45 (69.2)	29 (52.7)
Liver metastases in eCRF, n (%)		
Yes	56 (86.2)	38 (69.1)
Number of metastatic sites, n (%)		
1	21 (32.3)	13 (23.6)
2	24 (36.9)	15 (27.3)
≥ 3	20 (30.8)	27 (49.1)

ECOG PS, Eastern Cooperative Oncology Group performance status; eCRF, electronic case report form; IQR, interquartile range; OS, overall survival.

Figure 2. Occurrence and summary of diarrheal AEs



AE, adverse event; OS, overall survival.

Anti-diarrhea medication use

- Overall, in patients with diarrhea (n = 89), atropine, loperamide and other anti-diarrhea medications were received (as treatment or prophylaxis) by 71.9% (n = 64), 75.3% (n = 67) and 13.5% (n = 12) of patients, respectively (Table 2).
- Atropine was used for prophylaxis in 59.5% of patients in the > 12 months OS subgroup and 53.2% of patients in the ≤ 12 months OS subgroup, and as treatment in 31.0% and 38.3% of the subgroups, respectively.

Table 2. Anti-diarrhea medication use

	≤ 12.0 months OS (n = 47)	> 12.0 months OS (n = 42)
Patients who received atropine,[a] n (%)	32 (68.1)	32 (76.2)
Patients who received loperamide, n (%)	37 (78.7)	30 (71.4)
Patients who received other anti-diarrhea medication,[b] n (%)	5 (10.6)	7 (16.7)

[a]Includes atropine alone and atropine + diphenoxylate combinations. [b]Includes bismuth subsalicylate, cholestyramine, hyoscyamine sulfate, opium alkaloids total, other anti-diarrheals, papaver somniferum, papaver somniferum tincture and racecadotril.
OS, overall survival.

Abbreviations 5-FU, 5-fluorouracil; AE, adverse event; CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; eCRF, electronic case report form; Gem, gemcitabine; GI, gastrointestinal; IQR, interquartile range; LV, leucovorin; mPDAC, metastatic pancreatic ductal adenocarcinoma; MRI, magnetic resonance imaging; NabP, nab-paclitaxel; NALIRIFOX, liposomal irinotecan + 5-flurouracil/leucovorin + oxaliplatin; OS, overall survival; PDAC, pancreatic ductal adenocarcinoma; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors.

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