Real-world outcomes associated with liposomal irinotecan dose reductions in metastatic pancreatic ductal adenocarcinoma

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Aim: This study sought to understand the association between liposomal irinotecan dose reductions (DRs) and clinical outcomes among patients with metastatic pancreatic ductal adenocarcinoma. **Materials & methods:** A retrospective study of adult patients with metastatic pancreatic ductal adenocarcinoma treated with liposomal irinotecan in the Flatiron Health database was conducted to assess treatment and clinical outcomes. **Results:** DRs occurred in 28.4% of the 320 patients in the study. Patients with DRs had longer overall survival (7.7 [95% CI: 6.2–10.2]) vs 3.6 [3.2–4.1] months) and time to discontinuation (4.2 [3.0–4.9] vs 1.4 [1.0–1.5] months) than patients without DRs. Results were consistent in a validation analysis requiring three cycles of treatment. **Conclusion:** Liposomal irinotecan DRs were associated with improved clinical outcomes compared with patients without DRs.

Lay abstract: Liposomal irinotecan + 5-fluorouracil/leucovorin is an approved treatment regimen for patients with metastatic pancreatic cancer following progression after gemcitabine-based therapy. Patients may not be able to tolerate the recommended full dosage of liposomal irinotecan due to toxicities and their physicians may choose to reduce the dosage in order to continue treatment. The authors examined 320 patients treated with liposomal irinotecan-based regimens. About a quarter of the patients had their dose reduced. The data suggest that dose reductions were an effective strategy to keep patients on treatment and improve clinical outcomes.

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Keywords: dose reduction • dose–response relationship • duration of treatment • electronic health records • liposomal irinotecan • pancreatic ductal adenocarcinoma • retrospective studies • treatment outcome

Pancreatic cancer comprises approximately 3% of all cancer diagnoses in the USA with 57,600 estimated new cases in 2020 [1,2]. Despite ranking eleventh for cancer incidence, pancreatic cancer was predicted to result in 47,050 cancer-related deaths in the USA in 2020 [2]. Without timely innovation in treatment, pancreatic cancer is projected to rapidly become the second-leading cause of cancer-related deaths in the USA [3].

The lack of specific early symptoms combined with the aggressive nature of the disease mean that most cases of pancreatic cancer are advanced and metastatic at diagnosis, when surgical resection is no longer a viable option [4,5]. Pancreatic cancer has a very poor prognosis; in the USA, the 5-year survival rate for all stages of the disease combined is 9% [1,5]. Median survival time from pancreatic cancer diagnosis for patients with metastatic disease ranges from 2.8–5.7 months [6]. The majority of pancreatic cancers are adenocarcinomas, with pancreatic ductal adenocarcinoma (PDAC) being the most common type (80% of all cases) [7]. PDAC tumors are characterized by extensive stromal tissue, creating a microenvironment that promotes tumor growth [8], increases resistance to radiation and chemotherapy [9] and forms a barrier to drug delivery [10].

Advances in the medical treatment of unresectable metastatic disease have been achieved in the last decade. In 2015, liposomal irinotecan (ONIVYDE[®], Ipsen, MA, USA; historical names include nal-IRI, MM-398 and

PEP02) in combination with 5-fluorouracil and leucovorin (5-FU/LV) was approved for the treatment of patients with metastatic PDAC (mPDAC) after disease progression following gemcitabine-based therapy [11]. This intravenous liposomal formulation of irinotecan, a topoisomerase I inhibitor prodrug, prolongs circulation and increases plasma half-life [12].

In the international, open-label, randomized, Phase III NAPOLI-1 trial, combination therapy with liposomal irinotecan + 5-FU/LV was associated with increased median overall survival (OS) and progression-free survival (PFS) compared with 5-FU/LV alone in patients with mPDAC who had received prior gemcitabine-based therapy (OS: 6.2 months [95% CI: 4.8–8.4] vs 4.2 months [95% CI: 3.3–5.3]; PFS: 3.1 months [95% CI: 2.7–4.2] vs 1.5 months [95% CI: 1.4–1.8]) [13].

The recommended dose of liposomal irinotecan is 70 mg/m² free base, administered as part of the liposomal irinotecan + 5-FU/LV regimen [11]. However, *post hoc* analyses of data from NAPOLI-1 suggest that dose reductions or delays to manage toxicities do not have an adverse impact on outcomes [14]. This finding is supported by data from two small-scale, real-world studies: dose reductions were not associated with decreases in OS or PFS in retrospective real-world studies in patients with advanced PDAC in the USA (n = 56) and Austria (n = 52) [15,16]. There is a need to understand further the impact of liposomal irinotecan dose modification on clinical outcomes to help guide clinicians when making individualized treatment decisions in their clinical practice.

The aim of this real-world study was to assess the association between reducing the dose of liposomal irinotecan treatment (as part of the liposomal irinotecan + 5-FU/LV regimen) and clinical outcomes in a large population of patients with mPDAC in the USA in comparison with patients who did not have their dose reduced.

Materials & methods

Data source

This retrospective observational analysis used patient data from the Flatiron Health database. This is a longitudinal, demographically and geographically diverse nationwide US electronic health record (EHR)-derived de-identified database. Patient-level data included structured and unstructured data curated via technology-enabled abstraction. For this analysis, data were collected in July 2019 and included patient follow-up until 30 June 2019. As of July 2019, the database included data from over 280 cancer clinics (~800 sites of care) and more than 2.2 million active US patients with cancer [17]. Approximately 80% of the patients with data in the Flatiron Health database were treated in community settings, the remainder receiving therapy in academic settings. To protect patients' confidentiality, data were de-identified and provisions were put in place to prevent re-identification.

Study population

Patients included in the study were at least 18 years of age and had been diagnosed with pancreatic cancer using diagnostic codes 157.xx and C25.xx from the International Classification of Diseases and Related Health Problems, 9th and 10th revisions, Clinical Modification [18]. In addition, they had pathology consistent with PDAC and evidence of stage IV or progressive/recurrent disease on or after 1 January 2014. Patients were also required to have at least two documented clinical visits on or after 1 January 2014 and to have received liposomal irinotecan-based treatment. The index date for each patient was defined as the date on which they started the initial liposomal irinotecan-containing treatment regimen in the metastatic setting. The follow-up period was defined as the time from the index date until the patient died or the date of their last activity (clinical visit or documented administration), whichever occurred first. The final cohort comprised patients receiving weight-based starting doses of liposomal irinotecan of 70 ± 5 mg/m².

To assess patients who had prolonged treatment of liposomal irinotecan, a validation analysis was performed. These patients had similar inclusion criteria as the main cohort; however, they were required to receive at least three cycles of liposomal irinotecan and remain on treatment for at least 4 weeks. They were treated with liposomal irinotecan-based regimens between November 2015 and October 2019 and were categorized into two starting dose groups, 70 and <65 mg/m², to capture patients with low-initial doses.

Lines of therapy

Lines of therapy were derived by applying oncologist-defined rules to the treatments they received after or up to 14 days before the diagnosis of metastatic disease. Treatments discontinued less than 28 days after their initiation were not considered to be distinct lines of therapy in the Flatiron Health database. The addition of a new therapy after 28 days was considered to be the start of a subsequent regimen unless 5-FU was substituted for capecitabine or vice versa, LV was substituted for levoleucovorin or vice versa, LV or levoleucovorin was added, or protein-bound

paclitaxel was added to a gemcitabine regimen (or vice versa) within 90 days from the start of the line of treatment. These were operational rules informed by clinical input and were applied to the data *post hoc*. Based on these rules, first-line treatment in the metastatic setting in this analysis may not necessarily have been the first-line treatment received clinically.

Data collection

Demographic and clinical characteristics were documented at the index date. These comprised the most recent height, weight, Eastern Cooperative Oncology Group (ECOG) performance status score, serum albumin levels, neutrophil count and lymphocyte count within 30 days before initiation of liposomal irinotecan therapy. The characteristics of liposomal irinotecan treatment collected comprised the following: 6-week cumulative dose (i.e., total dose of liposomal irinotecan in mg/m^2), frequency, timing, presence of dose reductions (defined as a difference of $\geq 7 \text{ mg}/\text{m}^2$ lower than the starting dose) and length of therapy (defined as the number of days between the date of initiation and the last date of the last treatment cycle). No censoring was applied to the liposomal irinotecan treatment data. Use of supportive medication during treatment with liposomal irinotecan was recorded; supportive medication was defined as a documented administration or non-cancelled order of granulocyte colony-stimulating factor, antiemetics or saline.

Treatment outcomes

Treatment outcomes comprised treatment duration, dose reduction, cumulative dose, real-world OS (rwOS), real-world time to treatment discontinuation (rwTTD) and the occurrence of prespecified real-world adverse effects (rwAEs) during treatment. The rwTTD was defined as the time from treatment initiation to treatment discontinuation (the end of a line of therapy was defined as the last noncancelled order or administration of a component present in the regimen that occurred between the database defined start and end dates) for any reason. Patients were considered to have discontinued therapy if they met any of the following criteria: had a subsequent line of therapy; had a date of death if no subsequent line of therapy was observed; or had a gap of more than 120 days between the last administration or non-cancelled order of the line and the last visit or medication administration, if there was no subsequent line of therapy. As rwTTD utilizes censoring of patients, it is considered a separate outcome from treatment duration. Neutropenia, thrombocytopenia, anemia, fatigue, nausea, neuropathy and diarrhea comprised the rwAEs and were identified directly from EHRs using codes from the International Classification of Diseases and Related Health Problems, 9th and 10th revisions, Clinical Modification [18]. The treatment outcomes were considered ‘real world’ to emphasize that this is not a clinical trial setting and may have some biases and limitations due to the nature of real-world data. When laboratory values were available, patients were stratified by grade based on the National Cancer Institute Common Terminology Criteria for Adverse Events grading system [19]. If a patient had multiple different grades during treatment, all were recorded independently.

Statistical analysis

Data on demographic and clinical characteristics, treatment duration, dose reduction, cumulative dose and rwAEs were analyzed with descriptive statistics. Kaplan–Meier methods were used to estimate the median rwOS and rwTTD from treatment initiation. For the rwOS analyses, the 15th day of the month of death was assigned as the death date; for patients who did not die during the study, data were censored at their last visit or the date of the last treatment administration. Time-dependent Cox proportional hazards models were used to estimate the differences in rwOS and rwTTD between subgroups of patients who had or had not had their dose of liposomal irinotecan reduced during treatment (dose reduction was the time-dependent covariate analyzed). The impact of baseline characteristics or prognostic variables was not examined in this analysis. Statistical analyses were performed using SAS statistical software, version 9.4 (SAS Institute Inc., NC, USA).

Results

Demographic & clinical characteristics

In total, 320 patients with mPDAC in whom liposomal irinotecan treatment had been initiated at the recommended dose ($70 \pm 5 \text{ mg}/\text{m}^2$) were included in the analysis. At the start of treatment in the metastatic setting, patients had a median age of 68 years (interquartile range [IQR]: 62–73 years) and 51.9% were men (Table 1). A total of 57.8% of patients had been diagnosed initially with stage IV disease and 56.9% had ECOG performance status scores of 0 or 1 (Table 2). Additional clinical characteristics of included patients are reported in Supplementary Table 1. Most patients (93.1%) were treated in the community setting.

Table 1. Patient demographic characteristics in the main cohort.

Characteristic	Overall population		Dose reduced		Dose not reduced	
	n	%	n	%	n	%
Total	320	100.00	91	100.00	229	100.00
Age at index (years) [†]						
– ≤65	128	40.00	30	32.97	98	42.79
– ≥66	192	60.00	61	67.03	131	57.21
Median (Q1–Q3), years	68.0 (62.0–73.0)		70.0 (63.0–73.0)		67.0 (61.0–73.0)	
Sex						
– Male	166	51.88	47	51.65	119	51.97
Smoking status						
– History of smoking	175	54.69	39	42.86	136	59.39
– No history of smoking	145	45.31	52	57.14	93	40.61
Race						
– Asian	6	1.88	2	2.20	4	1.75
– White	233	72.81	71	78.02	162	70.74
– Other race/missing	81	25.31	18	19.78	63	27.51

[†]In the Flatiron Health database the recording of patient age is capped at 85 years to protect patient confidentiality.

Q: Quartile.

In the validation analysis, a total of 348 patients received treatment for at least three cycles. Of these patients, 220 (63%) initiated treatment at the indicated dose (70 mg/m²), while 128 (37%) initiated treatment at low dose (<65 mg/m²). This cohort had a median age of 69 years (IQR: 62.5–75 years) and 52.6% were men (Table 3). A total of 188 (54%) of patients had been diagnosed initially with stage IV disease, 209 (60%) had ECOG performance scores of 0 or 1 and 48 (13.8%) had an ECOG score of 2+ at treatment initiation (Table 4). The community setting was the most common treatment setting among patients (94%) and 33.3% of patients had two or more prior lines of treatment (Table 4). Additional clinical characteristics for the included patient populations are included in Supplementary Table 2.

Liposomal irinotecan treatment

Liposomal irinotecan was most commonly initiated as a second-line treatment in the metastatic setting (49.1% of patients); 15.3% of individuals received liposomal irinotecan as a first-line treatment and 35.6% as a third- or later-line treatment. A total of 59 patients (18.44%) received only one dose of liposomal irinotecan. Similarly, for the patients included in the validation analysis, liposomal irinotecan was most commonly initiated as a second-line treatment in the metastatic setting (51.7% of patients); 14.9% of patients received liposomal irinotecan as a first-line treatment and 33.3% as a third- or later-line treatment.

The dose of liposomal irinotecan was reduced for 91 patients (28.4%) during liposomal irinotecan + 5-FU/LV treatment, with a median initial reduction of 16.5 mg/m². The median time from initiation of treatment to reduction of the dose was 36 days (IQR: 22–63 days); for 53 of the 91 patients (58.2%), the dose was reduced within 6 weeks of starting treatment. Compared with patients whose dose was not reduced, those with dose reduction were older (median age 67 vs 70 years, respectively) and greater proportions had been diagnosed *de novo* with metastatic disease (45.1 vs 62.9%, respectively) and were being treated with liposomal irinotecan as part of a third or later line of therapy (29.7 vs 38.0%, respectively). In the validation analysis, dose reductions were experienced by 83 (38%) patients initiating treatment at 70 mg/m² and 26 (20%) patients initiating at <65 mg/m². The median time from initiation of treatment to dose reduction was 5.4 weeks (IQR: 3.4–9.1 weeks) and 5.1 weeks (IQR: 3.1–10.1 weeks) for those in the 70 and <65 mg/m² cohort, respectively.

The overall population was treated continuously with liposomal irinotecan for a median of 6.1 weeks (IQR: 2.1–17.3 weeks) and the mean cumulative dose during the first 6 weeks was 178.3 mg/m² (standard deviation [SD]: 72.3), which was lower than the expected 210 mg/m² for three cycles of liposomal irinotecan treatment. Compared with patients whose dose was not reduced, those with a reduced dose had a longer median continuous treatment duration (15.3 [IQR: 6.1–28.1] weeks vs 4.3 [2.0–12.0] weeks, respectively) but a similar mean cumulative dose during the first 6 weeks (187.1 [SD: 54.3] vs 174.8 [SD: 78.1] mg/m², respectively). The difference in treatment

Table 2. Clinical characteristics of patients in the overall population of the main cohort.

Characteristic	n	%
Total	320	100.00
Tumor location		
– Head	166	51.88
– Other	154	48.13
Stage at diagnosis		
– IV	185	57.81
– Other	135	42.19
ECOG score		
– 0	48	15.00
– 1	134	41.88
– 2+	54	16.88
– Missing/unknown	84	26.25
Baseline albumin, g/l		
– <40	237	74.06
– ≥40	60	18.75
– Unknown	23	7.19
Practice type		
– Academic	22	6.88
– Community	298	93.13
Treated with prior irinotecan in metastatic setting		
– Yes	78	24.38
– No	242	75.63
Treated with 5-FU at any time before index date		
– Yes	139	43.44
– No	181	56.56
Treated with gemcitabine at any time before index date		
– Yes	296	92.50
– No	24	7.50
Treated with oxaliplatin at any time before index date		
– Yes	133	41.56
– No	187	58.44
Treated with paclitaxel protein-bound at any time before index date		
– Yes	274	85.63
– No	46	14.37
Previous lines of therapy		
– 0	49	15.31
– 1	157	49.06
– ≥2	114	35.63
Surgery type before index date		
– Distal pancreatectomy	15	4.69
– Total pancreatectomy	1	0.31
– Whipple	64	20.00
– No surgery	240	75.00

Data for additional clinical characteristics are reported in [Supplementary Table 1](#).
5-FU: 5-fluorouracil; ECOG: Eastern Cooperative Oncology Group.

duration persisted in the validation analysis. Among patients initiating treatment at 70 mg/m², the median duration of continuous liposomal irinotecan treatment was 12.6 weeks (IQR: 6.3–23.0 weeks). In patients with a dose reduction the median duration of treatment was 19.0 weeks (IQR: 10.3–29.4 weeks), while the median duration of treatment was 10.3 weeks (IQR: 6.1–18.1 weeks) for those without a dose reduction. Among patients initiating

Table 3. Patient demographic characteristics in the validation analysis.

Characteristic	Overall population		Initial dose 70 mg/m ²				Initial dose <65 mg/m ²			
			Dose reduced		Dose not reduced		Dose reduced		Dose not reduced	
	n	%	n	%	n	%	n	%	n	%
Total	348	100.00	83	100.00	137	100.00	26	100.00	102	100.00
Age at index (years) [†]										
– ≤65	123	35.34	28	33.73	59	43.07	7	26.92	29	28.43
– ≥66	225	64.66	55	66.27	78	56.93	19	73.08	73	71.57
– Median (Q1–Q3), years	69.0 (62.5–75.0)		69.0 (63.0–73.0)		67.0 (61.0–73.0)		70.5 (64.0–76.0)		71.5 (64.0–78.0)	
Sex										
– Male	183	52.59	44	53.01	71	51.82	15	57.69	53	51.96
Smoking status										
– History of smoking	180	51.72	39	46.99	81	59.12	11	42.31	49	48.04
– No history of smoking	168	48.28	44	53.01	56	40.88	15	57.69	53	51.96
Race										
– Asian	6	1.72	2	2.41	2	1.46	1	3.85	1	0.98
– White	262	75.29	61	73.49	95	69.34	21	80.77	85	83.33
– Other race/missing	80	22.99	20	24.10	40	29.20	4	15.38	16	15.69

[†] In the Flatiron Health database the recording of patient age is capped at 85 years to protect patient confidentiality.

Q: Quartile.

treatment at <65 mg/m², the median duration of continuous liposomal irinotecan treatment was 9.1 weeks (IQR: 6.1–18.0 weeks). For patients who received a dose reduction the median duration of treatment was 16.1 weeks (IQR: 8.1–24.1 weeks), compared with a median duration of treatment of 8.6 weeks (IQR: 6.1–13.9 weeks) for those without a dose reduction.

Supportive medication

A total of 44.4% of patients in the main cohort received a growth factor during treatment (49/91 patients with and 93/229 patients without dose reduction); the granulocyte colony-stimulating factor most commonly administered was pegfilgrastim (38.1% of individuals). Most patients (98.4%) received at least one antiemetic during treatment and 71.6% received saline solution. Supportive medication data was not collected for the validation analysis.

Clinical outcomes

Median rwOS was 4.3 months (95% CI: 3.9–5.5) for the main cohort. Median rwOS was 7.7 months (95% CI: 6.2–10.2) for patients whose liposomal irinotecan dose was reduced and 3.6 months (95% CI: 3.2–4.1) for those whose dose was not reduced (hazard ratio [HR]: 0.67 [95% CI: 0.49–0.91]) (Figure 1). After adjusting for the time to dose reduction, mortality decreased by 33% among patients whose dose was reduced compared with those whose dose was not reduced. Additionally, ECOG performance score and serum albumin were independent predictors of rwOS in univariate and multivariable analyses. rwOS decreased by line of therapy; Patients treated in first line (1L) had a median rwOS of 5.3 months (95% CI: 3.6–7.7), those treated in second line (2L), 4.7 months (95% CI: 3.5–6.2) and patients treated in third line or later (3L+), 4.1 months (95% CI: 3.2–5.8). Median rwOS followed the same trend for patients with no dose reduction as in the overall cohort with reduced survival by line of therapy, 1L: 4.1 months (95% CI: 2.2–11.5), 2L: 3.7 months (95% CI: 3.0–5.0) and 3L+: 3.4 months (95% CI: 2.6–4.1). The opposite trend in median rwOS by line of therapy was observed for patients whose dose was reduced, 5.6 months (95% CI: 3.5–8.1), 8.1 months (95% CI: 4.2–14.5) and 10.1 months (95% CI: 6.4–11.5) for patients treated in 1L, 2L and 3L+, respectively, though these estimates are limited by small sample sizes.

For the main cohort the median rwTTD was 1.9 months (95% CI: 1.4–2.4). Patients whose dose was reduced had a longer median rwTTD than those without dose reduction (4.2 months [95% CI: 3.0–4.9] vs 1.4 months [95% CI: 1.0–1.5]; HR 0.95 [95% CI: 0.68–1.33]) (Figure 2). After adjusting for the time to dose reduction, there was a 5% decrease in rwTTD (i.e., treatment duration increased) among patients whose dose was reduced compared with those whose dose was not reduced. In both univariate and multivariable analyses baseline ECOG performance score and serum albumin were significant predictors of rwTTD.

Table 4. Clinical characteristics of patients in the validation analysis.

Characteristic	Overall population		Initial dose 70 mg/m ²				Initial dose <65 mg/m ²			
			Dose reduced		Dose not reduced		Dose reduced		Dose not reduced	
	n	%	n	%	n	%	n	%	n	%
Total	348	100.00	83	100.00	137	100.00	26	100.00	102	100.00
Tumor location										
– Head	178	51.15	46	55.42	72	52.55	11	42.31	49	48.04
– Other	170	48.85	37	44.58	65	47.45	15	57.69	53	51.96
Stage at diagnosis										
– IV	188	54.02	41	49.40	79	57.66	15	57.69	53	51.96
– Other	160	45.98	42	50.60	58	42.34	11	42.31	49	48.04
ECOG score										
– 0	64	18.39	12	14.46	24	17.52	8	30.77	20	19.61
– 1	145	41.67	35	42.17	60	43.80	6	23.08	44	43.14
– 2+	48	13.79	9	10.84	19	13.87	4	15.38	16	15.69
– Missing/unknown	91	26.15	27	32.53	34	24.82	8	30.77	22	21.57
Baseline albumin, g/l										
– <40	247	70.98	62	74.70	95	69.34	22	84.62	68	66.67
– ≥40	73	20.98	16	19.28	33	24.09	1	3.85	23	22.55
– Unknown	28	8.05	5	6.02	9	6.57	3	11.54	11	10.78
Practice type										
– Academic	21	6.03	8	9.64	5	3.65	1	3.85	7	6.86
– Community	327	93.97	75	90.36	132	96.35	25	96.15	95	93.14
Treated with prior irinotecan in metastatic setting										
– Yes	71	20.40	14	16.87	33	24.09	4	15.38	20	19.61
– No	277	79.60	69	83.13	104	75.91	22	84.62	82	80.39
Treated with 5-FU at any time before index date										
– Yes	143	41.09	32	38.55	53	38.69	12	46.15	46	45.10
– No	205	58.91	51	61.45	84	61.31	14	53.85	56	54.90
Treated with gemcitabine at any time before index date										
– Yes	317	91.09	77	92.77	125	91.24	23	88.46	92	90.20
– No	31	8.91	6	7.23	12	8.76	3	11.54	10	9.80
Previous lines of therapy										
– 0	52	14.94	15	18.07	21	15.33	6	23.08	10	9.80
– 1	180	51.72	44	53.01	72	52.55	9	34.62	55	53.92
– ≥2	116	33.33	24	28.92	44	32.12	11	42.31	37	36.27
Surgery type before index date										
– Distal pancreatectomy	19	5.46	4	4.82	8	5.84	2	7.69	5	4.90
– Total pancreatectomy	2	0.57	0	0.00	1	0.73	0	0.00	1	0.98
– Whipple	76	21.84	20	24.10	27	19.71	5	19.23	24	23.53
– No surgery	251	72.13	59	71.08	101	73.72	19	73.08	72	70.59

Data for additional clinical characteristics are reported in [Supplementary Table 2](#).
5-FU: 5-fluorouracil; ECOG: Eastern Cooperative Oncology Group.

For the validation analysis, median rwOS was 6.6 months (95% CI: 6.1–7.7) for the overall population, 7.2 months (95% CI: 6.2–8.1) for patients receiving an initial dose of 70 mg/m² and 6.2 months (95% CI: 5.0–7.4) for patients receiving <65 mg/m². Among those receiving 70 mg/m², patients with a dose reduction had a longer median rwOS of 8.9 months (95% CI: 7.3–10.8) compared with patients without a dose reduction who had a median rwOS of 6.0 months (95% CI: 4.8–7.2); HR: 0.78 (95% CI: 0.56–1.09) ([Supplementary Figure 1](#)). In patients initiating at <65 mg/m², those with a dose reduction had a longer rwOS compared with those without a dose reduction; 7.7 months (95% CI: 5.0–14.9) and 6.0 months (95% CI: 4.7–7.2), respectively; HR 0.93 (95% CI: 0.55–1.56) ([Supplementary Figure 2](#)). Median rwOS for patients who initiated at 70 mg/m² followed a similar

Figure 1. Real-world overall survival from the start of treatment with liposomal irinotecan in combination with 5-fluorouracil and leucovorin in the main cohort. Data are for patients whose dose of liposomal irinotecan was or was not reduced during treatment. The 15th day of the month of death was assigned as the death date; for patients who did not die during the study, data were censored at their last visit or the date of the last treatment administration. The hazard ratio is from a Cox proportional hazards model.

trend as the main cohort by line of therapy, with less separation between 2L and 3L+: 1L: 7.7 months (95% CI: 4.7–13.2), 2L: 6.6 months (95% CI: 5.3–8.3) and 3L+: 6.6 months (95% CI: 5.1–9.2). Patients who received <65 mg/m² experienced a wider range of outcomes by line: 12.9 months (95% CI: 6.8–not reached), 7.3 months (95% CI: 6.0–8.4) and 4.7 months (95% CI: 3.8–5.6) for patients treated in 1L, 2L and 3L+, respectively.

Real-world adverse effects

Hematological laboratory abnormalities, treatment-associated symptomology and other rwAEs experienced in the main cohort are summarized in Tables 5 & 6. Neutropenia, thrombocytopenia and anemia occurred at grades 3 or 4 in 10.9, 3.8 and 14.1% of patients, respectively, in the overall population (Table 5). The proportions of patients experiencing these laboratory abnormalities at grades 3 or 4 were greater among individuals whose dose was reduced than in those without dose reduction (respectively: neutropenia, 18.7 vs 7.9%; thrombocytopenia, 4.4 vs 3.5%; anemia, 23.1 vs 10.5%). Of the 91 patients whose dose was reduced, 77 (84.6%) experienced a hematological abnormality of any grade before the first dose reduction.

Diarrhea, fatigue, nausea and neuropathy were reported in 11.9, 8.1, 15.3 and 3.1% of patients, respectively, in the overall population (Table 5). Greater proportions of patients whose dose was reduced experienced these rwAEs

Figure 2. Real-world time to treatment discontinuation from the start of treatment with liposomal irinotecan in combination with 5-fluorouracil and leucovorin in the main cohort. Data are for patients whose dose of liposomal irinotecan was or was not reduced during treatment. The hazard ratio is from a Cox proportional hazards model.

Table 5. Real-world adverse effects during treatment in the main cohort.

Adverse event	Overall population (%), (n = 320)	Dose reduced (%), (n = 91)	Dose not reduced (%), (n = 229)
Laboratory abnormality			
– Neutropenia [†]	10.9	18.7	7.9
– Thrombocytopenia [†]	3.8	4.4	3.5
– Anemia [‡]	14.1	23.1	10.5
Other symptomatology			
– Diarrhea	11.9	16.5	10.0
– Fatigue	8.1	14.3	5.7
– Nausea	15.3	27.5	10.5
– Neuropathy	3.1	5.5	2.2

[†] Grades 3 or 4.
[‡] Grade 3.

Table 6. Hematological laboratory abnormalities encountered during treatment by grade of severity in the main cohort.

Laboratory abnormality	Overall population (%), (n = 320)	Dose reduced (%), (n = 91)	Dose not reduced (%), (n = 229)
Neutropenia (neutrophil count)			
– Any (<LLN)	70 (21.9)	26 (28.6)	44 (19.2)
– Grade 1 or 2 (<LLN– 1.0×10^9 /l)	57 (17.8)	23 (25.3)	34 (14.9)
– Grade 3 or 4 (< 1.0×10^9 /l)	35 (10.9)	17 (18.7)	18 (7.9)
Thrombocytopenia (platelet count)			
– Any (<LLN)	119 (37.2)	43 (47.3)	76 (33.2)
– Grade 1 or 2 (<LLN– 50.0×10^9 /l)	117 (36.6)	43 (47.3)	74 (32.3)
– Grade 3 or 4 (< 50.0×10^9 /l)	12 (3.8)	4 (4.4)	8 (3.5)
Anemia (hemoglobin)			
– Any (<LLN)	276 (86.3)	83 (91.2)	193 (84.3)
– Grade 1 or 2 (<LLN–8.0 g/dl)	274 (85.6)	82 (90.1)	192 (83.8)
– Grade 3 (<8.0 g/dl)	45 (14.1)	21 (23.1)	24 (10.5)

LLN: Lower limit of normal.

than of patients whose dose was not reduced (respectively: diarrhea, 16.5 vs 10.0%; fatigue, 14.3 vs 5.7%; nausea, 27.5 vs 10.5%; neuropathy, 5.5 vs 2.2%). The validation analysis did not assess rWAEs.

Discussion

This retrospective, observational analysis of data from a demographically and geographically diverse US EHR database examined the association between dose reduction and the effectiveness of treatment with liposomal irinotecan (as part of a liposomal irinotecan + 5-FU/LV regimen) in patients with mPDAC.

Almost 30% of patients in the current study had their dose of liposomal irinotecan reduced during treatment, with approximately half of the dose reductions occurring in the first 6 weeks of treatment. Patients whose dose was reduced had a longer median continuous treatment duration and a similar mean cumulative dose during the first 6 weeks than those without dose reductions. Consistency was observed with rates of dose reduction in the validation analysis (38% of patients with 70 mg/m² initial dose and 20% of patients with <65 mg/m² initial dose) and the proportion of dose reductions occurring within the first 6 weeks of treatment were very similar (51.8 and 53.9% for the two groups, respectively). Patients in the validation analysis whose dose was reduced had a longer median continuous treatment duration and a smaller mean cumulative dose during the first 6 weeks than those without dose reductions. The proportion of patients with dose reductions was generally consistent with that in other real-world studies of liposomal irinotecan + 5-FU/LV therapy in patients with pancreatic cancer (dose reductions were reported in 32 [15], 27 [16], 23 [20] and 39% [21] of patients and dose reductions and/or delays in 50% [22] of patients).

Results of the current analyses indicated that patients in the main cohort with dose reductions experienced longer rwOS and a 5% decrease in rwTTD compared with those without dose reductions. Patients in the validation analysis with dose reductions, regardless of starting dose, experienced longer rwOS compared with those without dose reductions. These findings echo those of a US-based retrospective chart review in 56 patients with advanced pancreatic cancer receiving a liposomal irinotecan + 5-FU/LV regimen, in which a significantly longer median PFS was recorded in patients with liposomal irinotecan dose reduction than in those without dose reduction (5.4 vs 2.6 months, respectively; $p = 0.035$); OS was numerically longer in patients with dose reduction than in those without it, but the difference was not statistically significant (7.1 vs 4.5 months, respectively; $p = 0.1226$) [15]. Although a clinical benefit was not associated with dose reduction, similar findings were reported in a retrospective study of 52 patients with advanced pancreatic cancer who had received liposomal irinotecan + 5-FU/LV at a single center in Austria; no significant differences were observed in OS or PFS between patients with or without liposomal irinotecan dose reductions, supporting the suggestion that dose reductions do not have a negative impact on clinical outcomes and is an appropriate strategy to manage toxicity without affecting efficacy [16]. To our knowledge, no other studies have examined the real-world impact of dose reductions on clinical outcomes.

Furthermore, reductions in liposomal irinotecan dose were reported in 33% of patients in the Phase III NAPOLI-1 study [13]; this proportion is similar to that found in the present study. Despite inherent differences between

clinical trials and real-world studies, OS in the overall study population in the present analysis was consistent with that reported in NAPOLI-1 (4.2 months [95% CI: 3.3–5.3] vs 6.2 months [95% CI: 4.8–8.4], respectively) [13]. Similarly, the impact of dose reduction was consistent with real-world findings; *post hoc* analyses of NAPOLI-1 data determined a median OS of 9.4 and 8.4 months in patients who required tolerability-guided dose reduction or delay, respectively [14]. The present real-world study confirms the safety profile of liposomal irinotecan + 5-FU/LV seen in clinical trials. However, documented rates of rAEs reported in the present study may well be lower than the true values because symptomatic adverse effects may be under-reported in EHR databases, for example, if the clinician does not enter the reported symptoms in the designated structured data field of the EHR.

Dose reductions of liposomal irinotecan in the clinical setting may be an effective way to manage tolerability and adverse event challenges in patients with a clinical response to therapy. In the main cohort of the current study, 84.6% of patients whose dose was reduced experienced a hematological laboratory abnormality of any grade before dose reduction. Although most of the observed dose reductions were likely related to the incidence of adverse effects, it is not possible to confirm this based on the current study design. Adverse effects were identified as the most frequent reason for liposomal irinotecan dose reduction in previous real-world studies of liposomal irinotecan + 5-FU/LV therapy in patients with pancreatic cancer [15,16,22].

Several factors may be responsible for the disparity in clinical outcomes observed between patients with and without dose reductions. We consider it likely that the increased treatment time in patients with dose reductions (main cohort: 15.3 vs 4.3 weeks months in those without dose reduction; validation analysis: 19.0 weeks in those with dose reduction and initial dose of 70 mg/m² vs 10.3 weeks in those without dose reduction and initial dose of 70 mg/m²; 16.1 weeks in those with dose reduction and initial dose of <65 mg/m² vs 8.6 weeks in those without dose reduction and initial dose of <65 mg/m²) resulted in a therapeutic benefit that ultimately influenced survival outcomes. It is possible that the reduction in dose, especially if aimed at managing tolerability, facilitated the extended treatment time. However, this interpretation should be considered with caution; patients receiving treatment for longer may simply have had more prospect of requiring dose reduction. Likewise, patients who were deriving benefit but experiencing AEs may be more likely to dose reduce than those without treatment benefit, who may choose to discontinue therapy. We do not consider it likely that the difference between groups in mean dose intensity of liposomal irinotecan during the first 6 weeks of treatment (main cohort: 187.1 vs 174.8 mg/m²) was a significant factor because the difference was not statistically significant and because both values were below the expected dose for three cycles (210 mg/m²). However, in the validation analysis, mean dose intensity in those with a dose reduction and initial dose of either 70 or <65 mg/m² was lower than the respective cohorts without a dose reduction. Differences in baseline demographics and clinical characteristics between patients in the dose reduction and no dose reduction groups may have influenced our findings in both the main cohort and the validation analysis: patients with dose reductions were generally older than those without dose reductions and greater proportions had been diagnosed *de novo* with metastatic disease and were being treated with liposomal irinotecan as part of a third or later line of therapy. However, notably, advanced age and stage of disease may have been expected to be associated with a worse prognosis [5]. Additionally, patients with less intensive or shorter metastatic treatment regimens prior to liposomal irinotecan may be indicative of a predisposition to worse outcomes.

Despite some advances in recent years in the treatment of patients with pancreatic cancer, the prognosis has remained stubbornly poor [1,5]. Furthering our understanding of how to maximize the clinical benefits of treatments already available, in this case the impact of liposomal irinotecan dose reductions, may go some way to addressing the significant unmet need among this group of patients.

Limitations

Several limitations inherent in the analysis of observational retrospective data should be considered when interpreting the results of this study. These include random allocation and bias in the frequency and availability of data (e.g., systematic differences across patients in terms of missing data or the frequency of data collection), which cannot be controlled for completely with statistical methods, including the time-to-event analyses presented here. Moreover, the causal relationships between dose reduction and extended treatment duration cannot be ascertained because this was not a randomized trial. Because the study inclusion criteria required patients to have received a minimum of one dose of liposomal irinotecan, some patients who were categorized as without dose reduction, in fact, simply discontinued or died before receiving a second dose. Also, information is not available on the reasons for dose reductions which limit interpretation of these findings. Another limitation is that some of the outcomes are measures of treatment duration rather than disease response; treatment duration can be a surrogate measure of many

outcomes, including disease response, patient tolerance, patient preference, travel, or additional events outside of disease response. The following additional limitations are specific to the Flatiron Health database. The recording of patient age is capped at 85 years to protect patient confidentiality; this may have affected the summary statistics for age and precluded analysis of clinical outcomes according to age. The number of prior treatment lines may have been underestimated in the analysis because treatments discontinued less than 28 days after their initiation are not considered to be distinct lines of therapy in the database. Local therapy, such as palliative radiation, is not captured in the database. Healthcare encounters outside of specific facilities or networks may have been missed causing underestimations. Finally, because most of the patients in the analysis had been treated at community clinics, the results may not be generalizable to other settings.

Conclusion

In this retrospective, real-world study of patients with mPDAC who had received liposomal irinotecan + 5-FU/LV in the USA, a reduction in the dose of liposomal irinotecan did not result in a decrease in clinical effectiveness. In fact, compared with patients without dose reductions, individuals whose dose was reduced had longer median rwOS and median rwTTD. The relationship between dose reductions and clinical outcomes appears to be independent of starting dose, as comparisons between those with and without dose reductions were consistent across cohorts with different initial dose amounts. Future prospective studies are required to characterize further the association between liposomal irinotecan dosing and clinical outcomes.

Summary points

- There is a need to understand further the impact of liposomal irinotecan dose modification on clinical outcomes in patients with metastatic pancreatic ductal adenocarcinoma to help guide clinicians when making individualized treatment decisions in their clinical practice.
- Of 320 patients included in the main cohort, 28.4% had a reduction in liposomal irinotecan dose during treatment; median time from therapy initiation to dose reduction was 36 days (interquartile range [IQR]: 22–63 days).
- Of 348 patients receiving treatment for at least three cycles and included in the validation analysis, 31.3% had a reduction in liposomal irinotecan dose during treatment; median time from therapy initiation to dose reduction was 5.4 weeks (IQR: 3.4–9.1 weeks) for patients starting at 70 mg/m² and 5.1 weeks (IQR: 3.1–10.1 weeks) for patients starting at <65 mg/m².
- In the main cohort, patients with dose reductions had a longer median continuous treatment duration (15.3 weeks [IQR: 6.1–28.1] vs 4.3 weeks [IQR: 2.0–12.0]), longer median real-world overall survival (7.7 months [95% CI: 6.2–10.2] vs 3.6 months [95% CI: 3.2–4.1]) and longer median real-world time to treatment discontinuation (4.2 months [95% CI: 3.0–4.9] versus 1.4 months [95% CI: 1.0–1.5]) than individuals without dose reductions.
- Among patients starting at a dose of 70 mg/m² in the validation analysis, patients with dose reductions had a longer median continuous treatment duration (19.0 weeks [IQR: 10.3–29.4] vs 10.3 weeks [IQR: 6.1–18.1]) and longer median real-world overall survival (8.9 months [95% CI: 7.3–10.8] vs 6.0 months [95% CI: 4.8–7.2]) than individuals without dose reductions.
- Among patients starting at a dose of <65 mg/m² in the validation analysis, patients with dose reductions had a longer median continuous treatment duration (16.1 weeks [IQR: 8.1–24.1] vs 8.6 weeks [IQR: 6.1–13.9]) and longer median real-world overall survival (7.7 months [95% CI: 5.0–14.9] vs 6.0 months [95% CI: 4.7–7.2]) than individuals without dose reductions.
- A higher proportion of patients with dose reductions than without dose reductions experienced grade 3 and/or 4 real-world adverse events.
- In this retrospective, real-world study of patients with metastatic pancreatic ductal adenocarcinoma who had received liposomal irinotecan + 5-fluorouracil and leucovorin in the USA, a reduction in the dose of liposomal irinotecan did not result in a decrease in clinical effectiveness, showing similar results to previously published data.
- The relationship between dose reductions and clinical outcomes appears to be independent of starting dose, as comparisons between those with and without dose reductions were consistent across cohorts with different initial dose amounts.
- Future prospective studies are required to characterize further the association between liposomal irinotecan dosing and clinical outcomes.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/fon-2020-0902

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