Comparing Trial and Real-world Adjuvant Oxaliplatin Delivery in Patients With Stage III Colon Cancer Using a Longitudinal Cumulative Dose

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IMPORTANCE Delivery of adjuvant chemotherapy can differ substantially between trial and real-world populations. Adherence metrics like relative dose intensity (RDI) cannot capture the timing of modifications and mask differences in the total amount of chemotherapy received.

OBJECTIVE To compare oxaliplatin delivery between MOSAIC trial participants and patients treated in the US Oncology Network with stage III colon cancer using a longitudinal cumulative dose (LCD).

DESIGN, SETTING, AND PARTICIPANTS This cohort study used secondary data from the MOSAIC trial, an international randomized clinical trial (concluded in 2004), and electronic health records from US Oncology (2009-2018), a network of community oncology practices in the US. It included participants in MOSAIC with stage III colon cancer who were randomized to receive treatment with oxaliplatin and fluorouracil/leucovorin (n = 663) and US Oncology patients with stage III colon cancer who were treated with a modified FOLFOX-6 regimen (n = 2523).

EXPOSURES Oxaliplatin and fluorouracil/leucovorin.

OUTCOMES AND MEASURES We evaluated RDI and LCD over time and at the end of treatment in the MOSAIC and US Oncology populations. We used bootstrapping to estimate 95% confidence bands for LCD differences between the populations.

RESULTS The 663 MOSAIC participants (296 women [44.7%]) and 2523 US Oncology patients (1245 women [49.4%]) were generally similar with respect to demographic characteristics. Median RDI was lower in US Oncology (80% in MOSAIC vs 70% in US Oncology). The LCD also suggested differences in the total amount of oxaliplatin received between populations; the final median LCD in US Oncology was 10.2% lower than in MOSAIC, equivalent to receiving 1.2 fewer treatment cycles less of oxaliplatin. This difference only began 133 days into treatment and persisted after accounting for covariates, likely in terms of more frequent oxaliplatin treatment discontinuation in US Oncology patients than their MOSAIC counterparts.

CONCLUSIONS AND RELEVANCE The study results suggest that real-world patients in community practice in the US treated with modified FOLFOX 6 received less oxaliplatin than their historical counterparts in the MOSAIC trial, with differences manifesting late in the treatment course. The LCD allowed us to identify the amount and extent of these differences, the timing of which was unclear when using RDI alone.

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Adjuvant chemotherapy is a complex process. Most infusion-based chemotherapeutic regimens involve giving set dosages of agents for several cycles at set intervals. Toxic effects are associated with deviations from a prescribed treatment schedule; however, monitoring of adherence in trials and protocol-defined dose modifications can be associated with fewer deviations and, in turn, treatment delivery closer to the standard than real-world delivery. In these cases, benefits estimated from trials may not apply to real-world populations.

To characterize deviations, trials routinely report metrics calculated at the end of follow-up, including the proportion who experienced a dose reduction of an agent by 15% or more, missed doses, or completed all infusion cycles.[1,2] Chemotherapy trials also calculate relative dose intensity (RDI; ratio of received daily dose to standard daily dose).[3] These measures characterize behavior but obscure timings of dose reductions, delays, and discontinuations.

We previously proposed a new metric, longitudinal cumulative dose (LCD),[4] describing chemotherapy delivery during the treatment course. Unlike RDI, LCD is calculated and compared throughout treatment. We previously used LCD to examine oxaliplatin and fluorouracil delivery within the MOSAIC trial.[1] In this article, we compared LCD and RDI as metrics, characterizing differences in oxaliplatin delivery between MOSAIC and real-world patients with stage III colon cancer treated within the US Oncology Network, a network of community oncology practices.

Key Points

Question Does comparing trial and real-world population chemotherapy delivery using a longitudinal cumulative dose (LCD) provide additional information vs comparing delivery with relative dose intensity?

Findings In this cohort study comparing oxaliplatin delivery in 663 patients in the MOSAIC trial and 2523 real-world patients with stage III colon cancer treated within the US Oncology Network, median LCD differed by 1.2 total doses, with these differences between groups emerging 133 days after initiating chemotherapy.

Meaning The study results suggest that characterizing treatment delivery longitudinally with LCD can provide additional insight into the differences between trial and real-world patients beyond relative dose intensity.

Methods

Trial Population

A total of 663 patients with stage III colon cancer randomized to receive treatment with oxaliplatin with fluorouracil and leucovorin (FOLFOX, specifically FOLFOX4) that received at least 1 chemotherapy treatment cycle in MOSAIC.[1] Individual-level data were accessed via ClinicalStudyDataRequest.com, a data-sharing platform providing trial data access.[5] The study was deemed exempt from review by the UNC Chapel Hill institutional review board, with informed consent waived because of the use of deidentified data.

Real-world Population

A total of 2523 patients with stage III colon cancer treated with FOLFOX were identified in Ontada/the US Oncology Network's electronic health record (iKnowMed) database from 2009 to 2018, which includes oncology-focused medical record data for more than 400 community oncology practice sites in the US, capturing nearly 750 000 patients annually.[6] We restricted the study sample to patients who met trial eligibility criteria and were receiving treatment with modified FOFOLX 6 (mFOFOLX6). Patients with no reported laboratory values within 365 days before FOLFOX treatment initiation were assumed to be trial eligible, with the exception of performance status.

Longitudinal Cumulative Dose

The LCD quantifies the proportion of the final chemotherapy dose received by a point. At each point t through the end of follow-up at time T, LCD for a patient equals[4]

$$\frac{\sum_{t=0}^{Tt} Dose\ of\ drug}{Final\ standard\ dose\ of\ the\ drug} * 100\%.$$

For 12-cycle chemotherapy agents infused every 14 days, a patient with no dose reductions or delays has an LCD of 8.3% on days 1 to 14, 16.7% on days 15 to 28, and reaches an LCD of 100% on day 154. If the patient experiences a permanent dose reduction by half after the initial dose, they have an LCD of 8.3% for days 0 to 13, and after 12 cycles their LCD will be 54.2%. Population-level LCD summary statistics can be calculated and compared.

Statistical Analyses

First, we calculated oxaliplatin RDIs in SAS (SAS Institute). Next, we calculated medians and 25th and 75th percentiles of oxaliplatin LCD in the MOSAIC and US Oncology populations through 250 days (approximately when the last patient received their 12th dose of FOLFOX) after initial infusion and plotted these values. We calculated daily differences between medians of the LCD curves in the 2 populations. Nonparametric bootstrap methods[7] (2500 samples) estimated 95% confidence intervals and confidence bands for all statistics. Weight-based standardization[8] assessed whether standardizing MOSAIC to reflect the age, sex, cancer substage, and body mass index of US Oncology reduced LCD differences.

Results

The **Table** presents characteristics of the populations, including age, sex, cancer substage, and performance status (Karnofsky performance status[9] for MOSAIC, Eastern Cooperative Oncology Group performance status score for US Oncology). Median RDI was higher among participants in MOSAIC at 80% (95% CI, 78%-82%) compared with those in US Oncology at 70% (95% CI, 69%-71%), with a median RDI difference of 10% (95% CI, 7.8%-12.2%). An RDI of more than 70% is a marker of improved colon cancer survival.[10]

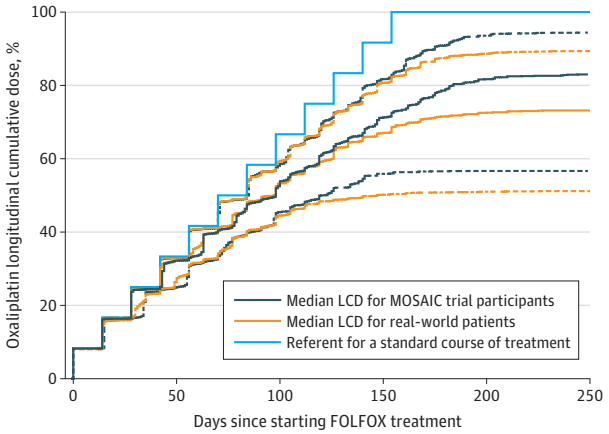
Using LCD, we identified when oxaliplatin delivery differences manifested (**Figure 1**). While medians and 25th and 75th

Table. Characteristics of the MOSAIC Participants With Stage III Colon Cancer Randomized to FOLFOX and Trial-Eligible US Oncology Patients With Stage III Colon Cancer

Variable	No. (%)	
	MOSAIC population	US Oncology
No.	663	2523
Male sex	367 (55.3)	1278 (50.6)
Female sex	296 (44.7)	1245 (49.4)
Age, y		
18-34	23 (3.5)	64 (2.5)
35-44	42 (6.3)	196 (7.8)
45-54	131 (19.8)	613 (24.3)
55-64	232 (35.0)	780 (30.9)
65-75	235 (35.4)	870 (34.5)
Overall mean (SD)	58.9 (10.5)	58.4 (10.7)
Cancer substage		
IIIA	45 (6.8)	389 (15.4)
IIIB	393 (59.3)	1620 (64.2)
IIIC	225 (33.9)	514 (20.4)
KPS		
≤70	186 (28.1)	NA
80-90	377 (56.9)	NA
100	100 (15.1)	NA
ECOG score		
0	NA	1042 (41.3)
1	NA	1410 (55.9)
2	NA	71 (2.8)
Oxaliplatin RDI		
Median (IQR), %	80 (65-92)	70 (56-82)
Median difference, % (95% CI)	1 [Reference]	10 (7.8-12.2)

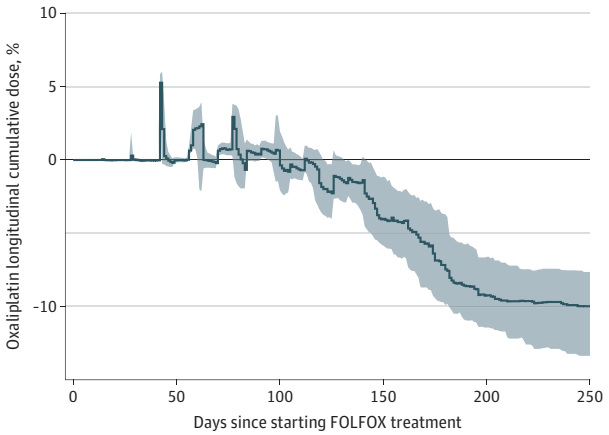
Abbreviations: ECOG, Eastern Cooperative Oncology Group; KPS, Karnofsky performance status; MOSAIC, Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer; NA, not applicable; RDI, relative dose intensity.

Figure 1. Summary of Population Oxaliplatin Longitudinal Cumulative Dose (LCD) for MOSAIC Trial Participants and Real-world Patients



The dark blue line is the median LCD for MOSAIC trial participants, while the upper and lower dashed black lines are the 75th and 25th percentiles, respectively. The orange line is the median LCD for real-world patients, with the upper and lower dashed gray lines again corresponding to the 75th and 25th percentiles. The bright blue line provides a referent for a standard course of treatment.

Figure 2. Difference in Median Longitudinal Cumulative Dose (LCD) Between MOSAIC Trial Participants and Real-world Patients Over Time



The solid line represents the difference between the median LCD in real-world patients and the median LCD in trial participants ($LCD_{USOncology}$-LCD_{MOSAIC}), with the gray areas representing the 2.5th and 97.5th percentiles of that difference from 2500 bootstraps.

percentiles of oxaliplatin LCD overlapped across the MOSAIC and US Oncology populations through 133 days (19 weeks), median LCD differences afterwards were outside of the confidence bands (α = .05) (**Figure 2**). This timing was also visible when examining 95% confidence bands for median LCDs in each group (eFigure 1 in the Supplement). At day 250 (ie, the end of follow-up), the median LCD was 10.2 percentage points (95% CI, 7.7-13.4) lower among US Oncology patients than MOSAIC participants, translating to the median US Oncology patient receiving 1.2 (95% CI, 0.9-1.6) fewer treatment cycles of standard oxaliplatin compared with the median MOSAIC participant. Standardizing MOSAIC's covariate distribution to US Oncology's had little impact on LCD (eFigure 2 in the Supplement), suggesting differences were not explained by age, sex, cancer substage, or body mass index.

Discussion

The LCD showed that MOSAIC participants and US Oncology patients had similar oxaliplatin delivery until differences emerged after 133 days, something that RDI could not identify. At the end of follow-up, these differences translated to US Oncology patients receiving 1.2 fewer treatment cycles of oxaliplatin than their MOSAIC counterparts. While the clinical effect of LCD differences is unclear,[4] these findings raise concerns about extrapolation of benefits estimated in MOSAIC to real-world patients.

There are many explanations for discrepancies in oxaliplatin LCD, given that LCD differences were not reduced by standardization. Reductions, delays, and discontinuation all lower LCD and occur more often in real-world than in trial settings because of the willingness and need for oncologists and patients to deviate from protocols.[11] That the median LCD for US Oncology patients plateaued earlier than for the MOSAIC participants suggests that discontinuation rather than dose reduction may be associated with the LCD gap. Because MOSAIC

enrolled Europeans before 2000, regional and temporal trends may have been associated with treatment delivery, with emerging evidence of adverse effect irreversibility creating more cautious clinicians over time. Financial toxic effects are another cause of chemotherapy cessation in the real world[12,13] that is associated with lower LCD later in treatment.

Our findings are particularly interesting given the IDEA trial's findings of only a 0.4% difference in 5-year survival for 12-cycle vs 6-cycle adjuvant chemotherapy regimens.[14] As differences in median LCD did not manifest until after 133 days of treatment, 6-cycle regimens (which ideally finish at 84 days) may result in more similar trial and real-world LCDs and RDIs. Characterizing the delivery of 6-cycle regimens in trial and real-world populations in the US will require additional study.

Limitations

This demonstrative work was limited to estimating quantitative differences in LCD in a straightforward setting with little exploration of censoring or LCD's clinical affects. Exploring the clinical relevance of the associations of these differences with specific end points is also important given IDEA's findings. If outcome differences are meaningful, quantifying them would be an essential step in exploring the use of real-world data as a valid external comparison for single-arm trials and establishing meaningful thresholds for LCD adherence. Finally, developing methods that account or adjust LCD for early mortality or loss to follow-up in data sources with complete and accurate ascertainment of death and censoring events is warranted.

Conclusions

The LCD is a measure of treatment delivery that is continuously updated throughout the therapeutic course. Using it, we identified that differences in oxaliplatin delivery between trial and real-world patients manifested after 133 days. Whatever the reason for these differences, developing new metrics to understand associations with patient outcomes is critical.

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Concept and design: Webster-Clark, Keil, Boyd, Sanoff, Westreich, Lund.
Acquisition, analysis, or interpretation of data: Webster-Clark, Robert, Frytak, Boyd, Stürmer, Lund.
Drafting of the manuscript: Webster-Clark, Keil.
Critical revision of the manuscript for important intellectual content: Webster-Clark, Robert, Frytak, Boyd, Stürmer, Sanoff, Westreich, Lund.
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Supervision: Keil, Boyd, Westreich, Lund.
Other - methodological oversight: Westreich.

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