A Comprehensive Review of Methods to Measure Oral Oncolytic Dose Intensity Using Retrospective Data

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ABSTRACT

BACKGROUND: Understanding the real-world use of oral oncolytics is essential to assess drug effectiveness. Retrospective analyses using medical and pharmacy claims data allow observation of drug use patterns and health outcomes. However, studies of medication adherence to oral oncolytics may not be sufficient in characterizing exposure because they typically measure refill frequency, not the administered dose or dose changes. Patients who appear fully adherent by traditional measures may be receiving different doses and experiencing differing effectiveness. Relative dose intensity (RDI) is a measure that has been used for intravenous drugs to capture the amount of a particular chemotherapeutic agent administered per unit of time (dose intensity), expressed as the fraction of the amount recommended in evidence-based guidelines. Such a measure would be useful for real-world studies of comparative effectiveness to characterize patient exposure to oral oncolytics.

OBJECTIVE: To identify studies that used administrative claims data to measure real-world oral oncolytic dose intensity, RDI, or similar constructs.

METHODS: Two health sciences librarians conducted a literature search (PubMed, January 1, 1809–February 6, 2018) including terms in each of the following concept areas: oncology drugs, dosage, and retrospective data sources. At least 2 reviewers scanned each title and abstract of publications retrieved from PubMed. Abstracts that indicated the study reported dose or related concepts and oral oncolytics using retrospective data sources were marked for full-text review. During full-text review, papers were excluded if they did not study oral oncolytics (i.e., only described intravenous chemotherapy); if they did not report drug dosage; or if the study was not retrospective. Resulting studies were included for full-text data extraction.

RESULTS: Of the 1,640 publications returned from the search, 41 were marked for full-text review. Full-text review established that 17 studies addressed a concept related to dose of oral oncolytics using retrospective data. Twenty-four studies were excluded: 11 did not measure dose; 9 did not study oral oncolytics; and 4 were not retrospective studies. Among the 17 articles marked for extraction, 5 articles reported dose intensity or RDI using medical records or electronic health record (EHR) data.

CONCLUSIONS: This study reveals not only the need for a claims-based measure of dose intensity for oral oncolytics, but also provides a basis for the development of such a measure based on previous EHR-based studies. While several claims data studies have characterized oral oncolytic dosing and duration, we found that no studies combined these dimensions into a single measure such as dose intensity. Methods using EHR data may be translatable to a claims data study. Future research is needed to develop and validate such measures.

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What is already known about this subject

- Characterizing real-world use of oral oncolytics is essential to assess drug effectiveness.
- Many oral oncolytics are distributed through pharmacies, which results in administrative claims data for reimbursement and allows for utilization studies of retrospective medical and pharmacy claims data.

What this study adds

- While many retrospective studies characterize treatments patterns or adherence (using refill data), few address medication dosage.
- This study illustrates a need for measures and methods that use retrospective claims data to capture dose intensity of oral oncolytics.
- Studies identifying dose intensity using medical records may serve as a basis for future methods development.

Oral medications are increasingly used for cancer treatment. Because these drugs are often dispensed in the pharmacy, prescription refill data can be used to understand their real-world use, which is essential to assess drug effectiveness. Retrospective analyses using administrative medical and pharmacy claims data from public and private payers allow observation of drug use patterns and health outcomes and are commonly used for outcomes research. Because oral oncolytics are used for some long-term treatments, studies of medication adherence have appeared in the literature to characterize this use.¹ The term “adherence” refers to the agreement between patients and providers about what medication is chosen, as well as the dosage and frequency.^{1,2}

Real-world studies of medication adherence that use prescription refill data from administrative pharmacy claims typically report measures such as medication possession ratio (MPR), which measures the number of doses dispensed over the entire refill period.¹⁻³ This measure has been used extensively to characterize whether patients are adherent to their chronic conditions medications. While understanding patient adherence (i.e., whether patients took their medications as prescribed) is an important concept,⁴ typically used adherence measures do not consider administered dose of medications or titrations that may occur. Persistence, or the duration of therapy, is also important in assessing oral oncolytic therapy,

FIGURE 1 PRISMA Diagram to Illustrate Study Inclusion for Literature Review

PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

since it allows examination of overall time on treatment as opposed to a proportion of prescriptions filled over time. Dosing may be more individualized in the oncology setting, and traditional measures of adherence are not sufficient to assess exposure because they do not capture dose or dose adjustments that are commonly employed.

Dose intensity is a measure that has been used to capture the amount of a particular chemotherapeutic agent administered per unit of time and is associated with patient outcomes, including survival.^{5,6} Relative dose intensity (RDI) expresses dose intensity as the fraction of the amount recommended, that is, the dose administered relative to the standard dose indicated in a protocol or in evidence-based guidelines.⁷ This measure is used commonly in the literature assessing intravenous chemotherapy safety and efficacy.⁸ Measures such as dose intensity or RDI would be useful to measure the dimensions of medication frequency, dose, and duration using claims data, but it is unclear whether claims-based dose intensity or RDI measures have been used to analyze oral oncolytic use.

The primary objective of our review was to identify studies that used pharmacy claims data to measure real-world oral oncolytic dose intensity, RDI, or similar constructs. Our secondary objective was to describe studies whose methods could be modified to assess dose intensity, RDI, or similar constructs.

Methods

Literature Search Strategy

Two health sciences librarians (EFG and GB) conducted literature searches using the PubMed database (January 1, 1809–February 6, 2018). The search strategies included terms in each of the following concept areas: oncolytics, dosage, and claims data (including other retrospective data such as medical

records and registries). In a pilot search to test the scope of available literature, the claims category was narrowed to include just 1 subject heading and 1 keyword related to administrative claims. Three reviewers (JDR, JFS, and JAT) independently scanned the resulting publications returned from the PubMed pilot search (n = 165) and assessed each title for its relevance to the study question. Then, 1 team member (JDR) reviewed the 165 abstracts to assess agreement. The full text of several abstracts that appeared likely to address the study question was used to adjust the methods and keywords for the full search. See the Appendix (available in online article) for the full PubMed search strategy. Study selection, analysis, and reporting were conducted in accordance with PRISMA guidelines.⁹

Eligibility

We included retrospective studies that reported dosing patterns, dose changes, starting dose, RDI, or dose intensity of oral oncolytic drug therapy. Eligible studies needed to report drug dose as one of their measures. Publications were excluded if they (a) were not studies of human subjects; (b) were clinical studies of safety or efficacy; (c) did not use a retrospective data source (e.g., administrative claims, electronic health record (EHR) data, or medical records); (d) did not address medication dose in study measures; or (e) did not reference oral oncolytics.

Search Strategy and Extraction

The study team used a multistep process to select papers for full-text review. At least 2 reviewers (JDR, JFS, or JAT) independently scanned the resulting publication title and abstracts returned from the PubMed full search using Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia) to determine eligibility using the criteria previously

TABLE 1 Characteristics of Retrospective Studies Examining Dose, Dose Intensity, or RDI of Oral Oncolytics

Author	Country	Data Source	Cancer Type	Drugs Studied	Dose Characterization	Study Outcomes
Bendaly et al., 2017 ¹⁹	United States	Medical records obtained from oncologists associated with Cardinal Health Specialty Solutions	Small cell lung cancer	Ceritinib	Dose reductions	Treatments, dosing patterns, and early outcomes
Castellano et al., 2013 ²⁴	Spain	Medical records at Hospital del Mar in Barcelona and Hospital Universitario 12 de Octubre in Madrid, Spain	Renal cell carcinoma	Sunitinib, sorafenib	RDI, discontinuation, interruption, or dose change	Treatment patterns
Choueiri et al., 2010 ¹²	United States	Renal Clinical Research Information System at Beth Israel Deaconess Medical Center and Dana-Farber Cancer Institute, Boston, MA	Renal cell carcinoma	Sunitinib, sorafenib, bevacizumab	Dose interruption, reduction, or increase	Safety and treatment patterns
Darkow et al., 2007 ²⁰	United States	Electronic pharmacy, enrollment data, and medical claims from a U.S. managed care provider	Chronic myeloid leukemia	Imatinib	Treatment interruption and medication nonadherence (MPR)	Health care costs
Gelderblom et al., 2017 ²⁵	Australia, Greece, Israel, Italy, the Netherlands and the United Kingdom	Multicountry, multicenter, retrospective chart review	Soft tissue sarcomas	Pazopanib	RDI, mean starting dose, percentage of patients with dose reductions, treatment duration	Treatment patterns, effectiveness, and adverse events
Hess et al., 2013 ¹⁰	United States	SDI Health, now part of IMS Health, Plymouth Meeting, PA	Renal cell carcinoma	Sunitinib, sorafenib, temsirolimus	Treatment patterns, duration of therapy, dosing patterns, and treatment changes; percentage of prescriptions unfilled, escalated, maintained, and reduced	Treatment patterns and dosing
Lafeuille et al., 2014 ²¹	United States	Truven Health Analytics MarketScan Commercial Claims and Encounters and Medicare Supplemental Dataset (December 2010-August 2012) and Symphony Health Solutions ProMetis Lx (June 2009-March 2013).	Prostate cancer	Abiraterone	Adherence patterns (MPR), daily dose	Utilization and adherence
Latremouille-Viau et al., 2017 ²²	United States	Two large U.S. administrative claims databases	Chronic myeloid leukemia	Dasatinib, nilotinib	Dose decrease or increase, treatment discontinuation, treatment switch, adherence	Treatment patterns, adherence to TKI therapy, HRU, and health care cost
Lu et al., 2017 ¹⁵	Taiwan	NHI research database (NHIRD) and diagnosis of HCC from the Taiwan Cancer Registry	Hepatocellular carcinoma	Sorafenib	Treatment discontinuation, initial dose, time to discontinuation	Prescription patterns and treatment outcomes
MacLean et al., 2016 ¹¹	United States	Specialty Pharmacy Data Mart, and IMS-managed database	Renal cell carcinoma	Axitinib, pazopanib	Discontinuation, dose increase, dose decrease, and/or both	Patient characteristics, treatment patterns, dosing, treatment line, duration of therapy
Mitra et al., 2012 ¹⁶	United States, Japan, United Kingdom, Germany	Medical records	Chronic myeloid leukemia	Imatinib, dasatinib, nilotinib	Dose escalation, highest daily dose, reason for discontinuation	Treatment patterns, choice of drugs, clinical outcomes, adverse events
Pal et al., 2016 ¹⁷	United States	Medical records	Renal cell carcinoma	Everolimus, axitinib	Dose escalation, dose de-escalation	Dosing patterns and drug costs
Porta et al., 2014 ²⁶	France, Ireland, Italy, Spain, United Kingdom	Medical records from multiple European countries	Renal cell carcinoma	Sunitinib	Dose reductions, interruptions, discontinuation, dose intensity, RDI	Adverse events, treatment modifications, dose intensity, overall survival

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TABLE 1 Characteristics of Retrospective Studies Examining Dose, Dose Intensity, or RDI of Oral Oncolytics (*continued*)

Author	Country	Data Source	Cancer Type	Drugs Studied	Dose Characterization	Study Outcomes
Saleh et al., 2014 ¹³	United States	EMR and patient management system (OASIS) integrated with the billing system of Georgia Cancer Specialists	Chronic myeloid leukemia	Imatinib	Treatment patterns, dose increase, decrease, discontinuation, and switch rates	Treatment patterns, including dose increase, dose decrease, discontinuation, and switch, the monitoring rate, and treatment response
Schnadig et al., 2014 ²³	United States	EMR of 17 McKesson Specialty Health/U.S. Oncology Network practices	Renal cell carcinoma	Sunitinib	Dose intensity, frequency of dose reductions, dose delays, schedule changes, discontinuations	Frequency of dose reductions, dose delays, schedule changes, discontinuations, toxicities, and outcomes
Shingina et al., 2013 ¹⁸	Canada	A retrospective chart review of 99 patients referred to the clinic at BC Cancer Agency	Hepatocellular carcinoma	Sorafenib	Dose reductions, time to dose reduction, duration of treatment, discontinuation	Effectiveness and tolerance
Stenehjem et al., 2014 ¹⁴	United States	Electronic data warehouse for the University of Utah Health Care, which includes Huntsman Cancer Institute	Chronic myeloid leukemia	Imatinib	Dose escalation, reductions, discontinuation	Treatment patterns and monitoring adverse events

EMR=electronic medical record; HCC=hepatocellular carcinoma; HRU=health care resource utilization; MPR=medication possession ratio; NHIRD=National Health Insurance Research Database; RDI=relative dose intensity; TKI=tyrosine kinase inhibitor.

described. Tags were added to papers that contained 1 or more of the following concepts: dose change, starting dose, adherence, persistence, duration, discontinuation, treatment pattern, RDI, and dose intensity. Conflicts arising during title and abstract review were resolved by 2 reviewers (JDR and JFS). Papers that appeared to include the concepts of dose intensity, RDI, dose, and/or duration were retained for full-text review.

During full-text review (JFS and JDR), additional papers were excluded that did not meet the previously described inclusion criteria. Figure 1 displays the PRISMA diagram for identification of eligible studies included in our review.⁹ After identifying eligible studies, the following data elements were extracted from each full-text publication: author, year, country, data source, cancer type, drugs studied, dose characterization (e.g., dose intensity and RDI) and primary study outcomes.

Results

Description of Literature

A total of 1,640 abstracts were screened, of which 41 were selected for full-text review. Full-text review established that 17 studies were eligible for extraction (Table 1). Twenty-four studies were excluded during full-text review because they did not measure dose (n=11), did not study oral oncolytics (n=9), or were not retrospective studies (n=4). Among the 17 articles included in our review, 11 were conducted in the United States, 5 were conducted outside the United States, and 1 was conducted

across multiple countries including the United States. The most common cancers studied were renal cell carcinoma (RCC; n=7) and chronic myeloid leukemia (CML; n=4; Table 1).

Summary of Literature

Studies Reporting Dose Using Administrative Claims Data Sources. Of 5 studies that used administrative claims, 2 focused specifically on drug dose and concepts related to dose. Hess et al. (2013) studied real-world use of targeted therapies for RCC in U.S. claims data and reported starting dose, duration of therapy, and whether patients continued, switched, or added therapies over time.¹⁰ MacLean et al. (2016) also published a study of real-world treatment of RCC and reported duration of therapy, daily dose, and whether the dose was modified after therapy initiation as separate measures.¹¹

Studies Reporting Dose Using EHR and Other Medical Record Data Sources. Eight EHR or medical record studies reported dose and related concepts but did not specifically report dose intensity or RDI. Choueiri et al. (2010) performed a medical record review from 2 oncology centers in the United States and described initial doses of sunitinib and sorafenib for RCC, as well as subsequent dose changes but not dose intensity.¹² Saleh et al. (2014) used electronic medical record (EMR) data to study treatment patterns and outcomes for CML patients using imatinib and reported starting dose.¹³ Stenehjem et al. (2014) used retrospective EHR review methods

to study first-line imatinib for CML treatment, reporting dose modifications in relation to the initial dose.¹⁴ Lu et al. (2017) used the National Health Insurance Research Database of Taiwan to analyze prescription patterns of sorafenib in patients with advanced hepatocellular carcinoma.¹⁵ They described variation in initial starting dose and subsequent modifications. Their related analyses looked at predictors of standard initial dose and whether standard initial dose was an independent predictor of overall survival, adjusting for covariates. Mitra et al. (2012) performed medical record abstraction and reported characteristics and treatment patterns of patients with CML using imatinib and either dasatinib or nilotinib, as well as the characteristics of their physicians.¹⁶ Starting daily dose of each drug, dose escalation, highest daily dose, and treatment duration were reported. Pal et al. (2016) also conducted a medical record review of patients with RCC using axitinib or everolimus after discontinuation of a tyrosine kinase inhibitor.¹⁷ Their study mainly focused on costs but also reported whether patients' initiation dose was with the recommended dose and whether dose adjustments were made. Shingina et al. (2013) used a chart review to assess sorafenib use in RCC patients, reporting initial dose, treatment duration, and outcomes.¹⁸ Bendaly et al. (2017) used a chart review process to characterize treatments and dosing patterns of ceritinib for small-cell lung cancer, reporting starting dose and subsequent dose reductions along with reports of adverse events, progression-free survival, and clinical response.¹⁹

Studies of Adherence and/or Persistence and Dose. Our search returned 3 adherence studies that also mentioned dose (and were therefore eligible for inclusion in our study). Darkow et al. (2007) studied nonadherence to imatinib and treatment interruptions and associated health care costs using health care claims data.²⁰ This study assessed MPR as the measure of adherence using medication refills and addressed imatinib starting dose as a potential characteristic associated with adherence. Lafeuille et al. (2014) studied adherence patterns of patients using abiraterone acetate and concomitant prednisone using claims data, reporting MPR and mean daily dose per patient.²¹ Latremouille-Viau et al. (2017) used claims data to describe treatment patterns and adherence for CML patients using dasatinib or nilotinib.²² Dose increases or decreases, as compared with the initial dose, were identified. Average daily dose was reported, as well as whether doses were lower or higher than recommended.

Studies Specifically Reporting Dose Intensity and/or RDI. Schnadig et al. (2014) used EMR data from U.S. oncology practices in their study of first-line sunitinib treatment for RCC.²³ Dose intensity was one of their main study outcomes, in addition to dose reductions, delays, discontinuation, and other treatment patterns. The authors did not provide a formula to calculate dose intensity. It was likely a variable available in their

data source. Three chart review studies reported dose intensity or RDI. Castellano et al. (2013) performed a medical record review for patients treated with sunitinib and sorafenib for RCC at Spanish hospitals.²⁴ They calculated RDI as the actual average daily dose of drug divided by the optimal or recommended dose found in the prescribing information. Gelderblom et al. (2017) used a multicountry, multicenter chart review approach to study the use of pazopanib for treatment of advanced soft tissue sarcoma.²⁵ This study did report RDI as a ratio of the mean daily dose as compared with the recommended starting dose, with the purpose of assessing treatment patterns, effectiveness, and adverse events. Porta et al. (2014) conducted a cohort study among several European countries and used medical records to assess dose intensity of sunitinib for treatment of RCC.²⁶ They calculated dose intensity as the actual daily dose divided by the optimal or recommended daily dose.

During full-text review, we identified a number of studies that, while not meeting the criteria for full-text review, did provide a basis for future methods work in this area. Three studies used retrospective data sources such as EHR data to calculate RDI, although they did not study oral drugs.²⁷⁻²⁹ Jonasch et al. (2016) used medical records to characterize RCC treatment patterns and reported whether patients had dose adjustments but did not report the dose itself.³⁰ Tan et al. (2015) reported efficacy and safety of sunitinib in a single-center study and was specifically focused on dosing strategies.³¹ These 2 studies would contribute to understanding individualized dosing of these treatments.

Discussion

We aimed to identify methods using pharmacy claims data to measure dose intensity, RDI, or similar constructs for studies of oral oncolytics in real-world practice. While there were a number of claims-based studies that reported dose, none characterized dose with a measure such as dose intensity or RDI. We found 17 studies that assessed dose, dose intensity, or RDI of oral oncolytics using any retrospective data source (administrative claims, EHR, or other medical record review). One study specifically mentioned that there are limited data on RDI from observational studies for RCC.²⁴ One study using EHR data specifically reported dose intensity and several chart review studies described RDI.²³⁻²⁶ While we aimed to specifically identify claims-based methods, these EHR and chart reviews are useful for future methods development and may be applicable to future methods studies using claims data.

While some of the studies we found characterized treatment patterns, many aimed to associate treatment patterns with tolerability, safety, and survival outcomes.³² When comparing oral oncolytic treatment outcomes using administrative claims data, it is critical to understand whether patients were adherent to their therapy, as well as initial dose and dose changes resulting from tolerability, adverse events, or progression. A

measure of dose intensity or RDI would capture individualized dose changes that would enhance characterization of exposure and its association with outcomes. Engle et al. (2018) discussed the issue of reduced RDI as a potential source of bias in clinical trials because patients enrolled in cancer clinical trials may not achieve dose intensity specified in the trial, and efficacy and/or adverse effects associated with a particular dose may be underestimated.⁸ Claims-based studies may be subject to similar bias that could be reduced with better measures of dose and dose changes.

Pharmacy claims data are often used for understanding factors associated with adherence to oral oncolytics for long-term treatment and subsequent outcomes; however, traditional adherence studies commonly focus on refill frequency and not the dose of the medication. Including dose intensity measures to adherence studies that focus on refills, especially those that consider factors related to adherence or adherence improvement,^{33,34} could potentially reveal whether dose changes also occurred when adherence increased or decreased. In studies that link adherence to outcomes, measures that include dose or duration at a particular dose may lead to better estimates of drug effectiveness. Several studies did not calculate dose intensity but reported data about dose that appeared to allow for such a calculation, relative to the recommended or starting dose. For example, Lafeuille et al. reported MPR and mean daily dose per patient but not relative to guidelines or recommended dosing in a single metric such as RDI.²¹ Latremouille-Viau et al. reported average daily dose, as well as whether it was lower or higher than recommended.²² Darkow et al. examined whether the imatinib starting dose was a potential characteristic associated with adherence. This association was significant in their base analysis, which suggests that a measure of dose intensity would be warranted in this setting.²⁰

A measure of RDI necessitates the comparison with a planned dose, which is unobservable in claims data, but as suggested by several of the papers found in our search, treatment guidelines may be used. Alternatively, assuming the prescriber calculated the optimal and appropriate dose for a given patient, the initial starting dose could also be considered as a denominator value. Three chart review studies reported RDI and used the following 2 approaches: (1) divide the actual average daily dose of drug by the optimal or recommended dose found in the prescribing information^{24,26} or (2) report RDI as a ratio of the mean daily dose as compared with the recommended starting dose.²⁵ It appears that the elements needed to perform the calculation of dose intensity and RDI are available in claims data (i.e., dose and duration), in addition to the recommended dose found in guidelines or labeling. A methods study using claims data could confirm this as a possible approach. Validation using EHR data would further strengthen such a measure.

Two studies are particularly helpful for future methods development.^{8,35} Amlani et al. (2016) compared adherence

measures using administrative data versus medical record data and found a number of differences.³⁵ The authors enriched the claims data with EMRs to identify patients with intentional treatment delays or inappropriate treatment delays. The results from this study show that 84% of the treatment delays were intentional, and if only administrative data would have been used, these patients would have been incorrectly assessed. This highlights the importance of considering individualized dosing and using methods that can detect dose changes. It will be important to discern the differences between a claims-based or EHR-based measure of RDI and what limitations may exist for claims-based studies.

Engle et al. described 4 related measures of dose intensity for clinical trial analysis that could be tested in claims data or EHR-linked claims data.⁸ Adjusted dose intensity captured provider- or protocol-specified dose reductions as total milligrams per cycle. Planned dose intensity was calculated using the trial protocol dose per day and cycle duration. Patient-specific dose intensity was the actual amount of medication taken by the patient as measured by pill counts or patient diaries. The RDI was then calculated by dividing the patient-specific dose intensity by the planned dose intensity and multiplying by 100. This incorporates the concept of patient medication adherence as well because it measures not only the planned dose, but the actual dose that was reported as consumed by the patient.⁸ Engle's method could be translated to a retrospective claims analysis with several considerations: The planned DI and provider-specified dose reductions are unknown unless observed in EHR-linked data, but as previously mentioned, guidelines or labeling could serve as a reference for comparison (e.g., National Comprehensive Cancer Network, American Society of Clinical Oncology, or European Society for Medical Oncology). The patient-specific dose intensity could easily be captured using pharmacy claims with several potential limitations. As is the case with all retrospective studies using claims data, one can only observe prescriptions that are actually filled. Primary nonadherence, prescriptions that are never filled by patients, is not observable and would potentially bias measures of dose intensity.

Implications

Understanding the real-world use of oral oncolytics, used increasingly for cancer treatment, is essential to assess real-world drug effectiveness and comparative effectiveness. Retrospective analyses using medical and pharmacy claims data allow observation of dose, drug utilization patterns, and health outcomes over time frames longer than most clinical trials in larger and broader real-world populations. It appears that enhanced measures of oral oncolytic use may be helpful. Patients may receive individualized dose changes, and these changes in drug exposure could lead to changes in observed effectiveness. Patients who exhibit similar "adherence" by traditional measures of refill frequency may be using different doses of drugs; therefore, they may experience different therapeutic benefits. Measures of refill

frequency, so commonly used for measuring adherence, are not sufficient to capture exposure because they do not consider continuous time on therapy or dose changes. Future methods research should work toward creating measures that capture medication starting dose, changes in dose over time, and daily exposure and discontinuation (already reflected in traditional adherence measures). These measures would not only enhance characterization of adherence or treatment patterns, but would be valuable for comparative effectiveness studies. Enriched data sources such as administrative claims linked to EHR data would allow better characterization of observed dose changes because it would allow assessment of individualized dosing, disease progression, and other clinical factors. These data would provide an ideal setting for methods validation.

Limitations

We did not include references from other sources, such as Embase, which could be viewed as a limitation. We decided to exclude these references because of the resources available to review the references and the sheer volume of references retrieved in Embase. The full search (as described in the Methods section) performed in Embase retrieved 5,958 citations, after removing duplicates that already appeared in the PubMed search. We felt that the PubMed search, returning over 1,600 citations, while perhaps not including every retrospective study of oral oncolytics, would likely provide a good representation of the methods currently in use by researchers.

Conclusions

Our literature review revealed that there is a need for enhanced measures of oral oncolytic use that include adherence and dose for use in retrospective studies. EHR-linked claims data would allow development and validation of more comprehensive measures. A measure of dose intensity or RDI for oral oncolytics would provide a valuable measure for future oncology outcomes research studies.

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DISCLOSURES

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APPENDIX PubMed Search Strategy

The search was run via www.pubmed.gov and retrieved documents between January 1, 1809, and February 6, 2018.

("antineoplastic agents"[Mesh] OR "antineoplastic agents"[Pharmacological Action] OR "neoplasms/drug therapy"[Mesh] OR "antineoplastic protocols"[Mesh] OR "cytostatic agents"[Mesh] OR "alkylating agents"[Mesh] OR "alkylating agents"[Pharmacological Action] OR chemotherapy[tiab] OR chemotherapeutic*[tiab] OR cytostatic*[tiab] OR anticancer[tiab] OR oncolytic*[tiab] OR oncologic[tiab] OR oncologics[tiab] OR antineoplastic*[tiab] OR antitumor[tiab] OR antitumour[tiab] OR tyrosine kinase inhibitor*[tiab] OR alkylating agent*[tiab] OR angiogenesis inhibitor*[tiab] OR anticarcinogenic*[tiab] OR antimetabolite*[tiab] OR antimitotic*[tiab] OR angiogenesis antagonist*[tiab] OR monoclonal antibodies[tiab] OR monoclonal antibody[tiab])

AND

("dose-response relationship, drug"[Mesh] OR "drug administration schedule"[Mesh] OR "drug dosage calculations"[Mesh] OR "maximum tolerated dose"[Mesh] OR "no-observed-adverse-effect level"[Mesh] OR "drug evaluation"[Mesh] OR "drug tolerance"[Mesh] OR dosage measur*[tiab] OR dose measur*[tiab] OR initial dose[tiab] OR initial dosage[tiab] OR initial dosing[tiab] OR starting dose[tiab] OR starting dosage[tiab] OR dose intensity[tiab] OR dosing intensity[tiab] OR dosage intensity[tiab] OR dose pattern*[tiab] OR dosage pattern*[tiab] OR dosing pattern*[tiab] OR dosing change*[tiab] OR dose change*[tiab] OR dosage change*[tiab] OR treatment pattern*[tiab] OR dose cycle[tiab] OR dosage cycle[tiab] OR dosing cycle[tiab] OR metronomic dosing[tiab] OR metronomic dosage[tiab] OR metronomic dose[tiab] OR treatment regimen*[tiab] OR dose adjustment*[tiab] OR dosage adjustment*[tiab] OR dosing adjustment*[tiab] OR dose modification*[tiab] OR dosage modification*[tiab] OR dosing modification*[tiab] OR dose delay*[tiab] OR dosing delay*[tiab] OR dose reduction*[tiab] OR dosage reduction*[tiab] OR dosing reduction*[tiab] OR prescribing pattern*[tiab] OR drug holiday*[tiab] OR drug tolerability[tiab] OR patient tolerability[tiab] OR treatment duration[tiab] OR drug tolerance[tiab])

AND

("medical records"[Mesh] OR "drug utilization review"[Mesh] OR "Registries"[Mesh] OR claims[tiab] OR electronic health record*[tiab] OR medical record*[tiab] OR chart review*[tiab] OR administrative data*[tiab] OR claim data*[tiab] OR drug utilization review*[tiab] OR drug utilisation review*[tiab] OR record review*[tiab] OR registry[tiab] OR registries[tiab])