Role of real-world evidence in informing cancer care: lessons from colorectal cancer

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ABSTRACT

The term “real-world evidence” (RWE) describes the analysis of data that are collected beyond the context of clinical trials. The use and application of RWE have become increasingly common and relevant, especially in oncology, because there is growing recognition that randomized controlled trials (RCTs) might not be sufficiently representative of the entire patient population that is affected by cancer, and that specific clinical research questions might be best addressed by real-world data. In this brief review, our main aim is to highlight the role of RWE in informing cancer care, particularly focusing on specific examples from colorectal cancer. Our hope is to illustrate the ways in which RWE can complement RCTs in improving the understanding of cancer management and how RWE can facilitate cancer treatment decisions for real-world patients encountered in routine clinical care.

Key Words Real-world evidence, colorectal cancer

INTRODUCTION

In oncology, “real-world evidence” (RWE) refers to evidence derived from the use and analysis of real-world data, which are data obtained outside the context of conventional randomized controlled trials (RCTs)1-2. Real-world data are typically generated based on observations or experiences collated from routine day-to-day clinical practice3. Real-world data are derived from various sources, which can include, but are not limited to, information stored in paper or electronic medical records, pharmacy claims or physician billing databases, retrospective or prospective disease registries, patient-reported outcomes, and mobile or wearable devices3.

The importance of RWE in oncology has been increasing because recognition is growing that RCTs might not always account for the entire patient population affected by a specific cancer. Examples include individuals with significant comorbidities, those living in remote regions, and those belonging to advanced age groups, who frequently do not or cannot participate in clinical trials. Research has shown that, in most RCTs, only 10% of patients with the cancer being studied are represented3. Therefore, whether the findings from those trials can be generalized to the other 90% of the population and whether real-world patients respond to treatments in the same way as clinical trial participants is unclear3. That knowledge gap can potentially be addressed by RWE. Furthermore, RWE studies can analyze the effects of cancer drugs over longer periods of time and examine the associations between cancer and other health conditions in a more pragmatic manner. Pharmaceutical partners and health care payers are both increasingly looking to RWE to inform, respectively, future study designs and funding decisions to ensure that the right drugs are made available to the right patients and that outcomes observed in RCTs are reproduced in the real world4.

In this brief review article, we describe the role of RWE in informing cancer care, particularly drawing on specific examples from the colorectal cancer (CRC) space. In doing so, we hope to illustrate how RWE can offer insights into treatment selection. In addition, we highlight the ways in which RWE complements RCTs in improving our understanding of cancer management and some of the pitfalls that should be recognized when interpreting the results of RWE studies.

DISCUSSION

RWE Can Address Patient Groups Ineligible for Clinical Trials

Standard RCTs usually impose strict inclusion and exclusion criteria in their designs5. That approach is commonly pursued because it results in a more homogenous patient population, which helps to optimize the trial’s internal...
validity and facilitate interpretation of the study findings. Importantly, it can also reduce the costs and resources needed to conduct large multicentre clinical trials. Further, such patient selection minimizes the risk to study participants, because the experimental interventions inherently carry a high potential for unpredictable or serious adverse events. However, careful selection also means that a significant proportion of the patients encountered in routine clinical care are not eligible to participate in RCTs, resulting in their underrepresentation. Groups that are frequently ineligible to enrol in RCTs include patients who are older or frail, those who have significant organ dysfunction, and those who have comorbid illnesses such as heart disease or prior cancers. That situation holds true for many RCTs in CRC.

Oxaliplatin-based chemotherapy remains the mainstay of adjuvant treatment for selected patients with early-stage CRC who are at high risk of disease recurrence. In the MOSAIC trial, 2246 patients with stage II or III colon cancer were randomized to receive either adjuvant fluorouracil–leucovorin (FL) alone or with oxaliplatin (FOLFOX) for 6 months. Because of the superior overall survival associated with FOLFOX, that agent became a standard treatment option (10-year overall survival: 71.7% for FOLFOX vs. 67.1% for FL; hazard ratio: 0.85; \( p = 0.043 \)). Likewise, the X-ACT trial randomized 1987 patients with stage III colon cancer to receive either adjuvant capecitabine or FL. That non-inferiority RCT helped to establish capecitabine as an oral treatment option for patients unsuitable for oxaliplatin-based chemotherapy given that the disease-free survival associated with capecitabine was no worse than that associated with FL (hazard ratio: 0.87; 95% confidence interval: 0.75 to 1.00). Although FOLFOX and capecitabine are both frequently used in older patients with CRC, eligibility criteria in the MOSAIC and X-ACT trials imposed strict age limits, and only patients 18–75 years of age were permitted to participate. Because of those limits, prospective data about the effect of those chemotherapy regimens on outcomes in the advanced age group are lacking. In fact, a subgroup analysis by the MOSAIC investigators suggested that older patients might not benefit from FOLFOX (5-year disease-free survival: 69.1% for FOLFOX vs. 65.8% for FL; hazard ratio: 0.93; 95% confidence interval: 0.65 to 1.35; \( p = 0.71 \)) however, the analysis had been conducted post hoc and was based on a relatively small number of older patients.

Since the publication of those landmark RCTs, a broad spectrum of RWE studies have examined the use and benefit of those adjuvant chemotherapy regimens in groups of patients with CRC who were excluded from the original RCTs. In geriatric oncology, significant efforts have been made to clarify the value of adjuvant chemotherapy in older patients, because strict age cut-offs in most RCTs limit enrolment to individuals less than 70 or 75 years of age. For example, in the RWE study by Ko et al., investigators showed that older patients with stage III colon cancer frequently receive either no adjuvant treatment or capecitabine monotherapy instead of combination FOLFOX chemotherapy solely because of their advanced age. Interestingly, the effects of adjuvant capecitabine and FOLFOX chemotherapy were similar across age bands, with all age groups having comparable side-effect profiles and rates of treatment modifications and discontinuations. Similar observations have emerged from other large population-based RWE studies in Canada, the United States, and Europe, suggesting that the use and choice of adjuvant chemotherapy should not be based on advanced age alone. In fact, another RWE analysis by Raycraft et al. showed that, in significant proportion, deaths in patients with colon cancer are directly related to the colon cancer rather than to competing causes of mortality such as heart disease and stroke. That observation suggests that the cancer deaths might be preventable with appropriate and timely cancer management, including the use of chemotherapy.

Likewise, RCTs frequently limit participation in studies to individuals who are physically fit (for example, having an Eastern Cooperative Oncology Group performance status of 0 or 1) and who have few significant comorbidities, as was the case in the MOSAIC and X-ACT trials. Researchers in RWE studies have therefore also explored the benefit of adjuvant chemotherapy in carefully selected frailer adults, reporting data that indicate an association between receipt of adjuvant chemotherapy and improved outcomes in CRC, even after adjusting for confounders. For instance, in the RWE study by Crosara et al., the authors observed that chemotherapy can still benefit selected patients with poor performance status, with the proviso that dose reductions and close monitoring for toxicities be considered so that the risk for serious adverse events is minimized. Similar RWE about the effects of adjuvant chemotherapy in patients with colon cancer and a high burden of comorbidity is more limited. However, in a retrospective analysis, Haller et al. demonstrated that oxaliplatin-based combination therapies produce comparable outcomes in patients with and without significant comorbidities.

RWE Can Provide Additional Data to Improve Drug Delivery and Drug Effectiveness

“Efficacy” is defined as the extent to which, under ideal circumstances, an intervention produces more benefit than harm; “effectiveness” is defined as the degree to which, under usual circumstances of routine health care practice, an intervention results in more benefit than harm. To that end, cancer drugs that have, in RCTs, been proven to have efficacy might not always result in real-world effectiveness. Because patients in RCTs receive drugs in a controlled and monitored setting, compliance and follow-up are relatively assured. In contrast, because of various barriers, real-world patients might not always be able to access the drugs or might not receive them appropriately. When efficacious drugs are not used with the same intent or to the same degree in routine clinical care as in trials, they cannot be considered effective.

In Canada, evaluation of real-world effectiveness is a particularly relevant issue. The country’s expansive geography poses unique treatment challenges because a significant proportion of the population is dispersed in rural or remote regions that are often a substantial distance from cancer centres. The universal health care system reimburses the cost of all approved cancer drugs, which minimizes out-of-pocket expenses for patients. However, not all patients experience the same level of access to novel therapies because long commutes to and from the cancer hospitals can be logistically or financially prohibitive.
Many patients who initiate therapy are unable to adhere to or complete therapy because monitoring and management of side effects can be difficult when the patients live far from the centres that are equipped to handle acute or serious toxicities.

Because rct s are typically operated and offered at larger tertiary institutions, the delivery of care to patients residing in rural or remote areas might be an unfamiliar exercise. That knowledge gap could be addressed by rwe that provides insights into if and when new therapies are adopted, who adopts them, and whether the resulting experiences with novel drugs are comparable to those in rct s. If geographic disparities in the way that patients with cnc are managed are evident, then rwe can also be leveraged to develop interventions or models of care that narrow the treatment discrepancies.

In the rwe study by Loree et al., median time from diagnosis to oncology consultation was longer for patients living more than 100 km from a treatment centre and for those residing in rural communities. Also, compared with their urban counterparts, the rural-residing patients experienced inferior cnc-specific survival. Urban–rural disparities in cancer care are difficult to study in the context of rct s; rwe such as that from the Loree et al. study highlights a system-level problem that has resulted in the creation of mobile cancer treatment hubs and the expansion of tele-health cancer medicine in specific jurisdictions to narrow the disconnect between urban and rural centres. Those efforts optimize the uptake of new technologies and novel drug therapies, and ensure real-world effectiveness.

Timeliness to therapy has also been a focus of rwe, given the challenges of evaluating timeliness in a prospective fashion and randomizing patients into “early” compared with “late” treatment. Like mosaic and x-act, most rct s mandate that adjuvant chemotherapy be initiated within 8 weeks of surgery, but whether that timeframe is consistently followed in routine clinical practice is unclear. Several rwe studies have investigated the topic. Although results generally showed that, in a clinical context, patients are receiving adjuvant treatment by 8 weeks postoperatively, timeliness is observed to be highly variable, with some patients waiting more than 12 or 16 weeks after surgery. The effect on survival outcomes of delayed receipt of adjuvant chemotherapy remains a matter of debate. Several researchers have described inferior survival among patients who start adjuvant chemotherapy after 8 weeks, but a recent systemic review by Biagi et al. suggested that some benefit persists even though the magnitude of the benefit decreases as the interval between surgery and chemotherapy increases.

RWE Can Assist with Health Technology Assessments and Funding Decisions

Given that administrative and claims data frequently contain time-spanning information, including periods before and after the cnc diagnosis, rwe is also valuable in characterizing the natural history of a specific cancer. Canada is particularly unique in that the universal health care system allows for data capture “from cradle to grave,” meaning that some repositories contain health data spanning a patient’s entire lifetime. One exception is when a patient moves between provinces. Although the universal health care system is federally mandated, it is provincially administered, and so data in the various Canadian jurisdictions are not inherently pooled into a national database. Nonetheless, information from studies using such real-world data are helpful in determining unmet needs and whether and how new drugs can or should be incorporated into existing treatment paradigms. Specific areas that are increasingly incorporating rwe include health technology assessments and unique clinical trial designs.

A major component of any health technology assessment is the cost-effectiveness analysis. Traditionally, the costs used in such economic analyses are based on the prices of branded drugs when they first enter the market. The effect of genericization on the cost-effectiveness or cost–utility of an intervention or drug is unknown because economic analyses are rarely updated using the costs of generic drugs. The rwe study by Cheung et al. helped to underscore the value of economic reassessments. Specifically, those researchers re-examined the co.17 study that initially randomized patients with chemorefractory metastatic cnc to either cetuximab or best supportive care. Investigators applied current-day real-world drug prices into optimized economic models and found that the genericization of cetuximab produced an incremental cost-effectiveness ratio of CAS$261,126 per quality-adjusted life-year gained compared with CAS$299,613 for branded cetuximab. The main conclusion from the study was that failure to revisit economic analyses with the real-world costs of generics could represent a missed opportunity for funding bodies to optimize value-based allocation of health care resources. Leveraging of rwe has also provided a more accurate assessment of the population-based budget impact of introducing novel drugs. For example, an analysis by Ho et al. showed that treatment attrition is high among patients with metastatic cnc and that only a subset of patients actually proceeds from one line of therapy to another. The observation that only 42% of real-world patients reach the third-line setting and are eligible for cetuximab or panitumumab monotherapy can modify the budget impact considerably. The foregoing examples demonstrate the significant role that rwe can play in enhancing the understanding of the economic implications of delivering quality cancer care—insights that have become increasingly important as the financial toxicity of new drugs continues to rise exponentially.

SUMMARY

In closing, the role of rwe is evolving and expanding. Although rct s remain the “gold standard” for evaluating the efficacy of novel interventions in cancer, there is general acceptance that rct s alone might not offer all the answers to relevant clinical or research questions. The important and complementary role that rwe plays with respect to rct s was highlighted in the examples presented here. Using the context of cnc, our article has highlighted some of the common and important uses of rwe, including providing insights about patient groups ineligible for clinical trials, delivering information that can improve real-world drug effectiveness, and offering data that can increase the quality of budget and economic analyses.
CONFLICT OF INTEREST DISCLOSURES

We have read and understood Current Oncology’s policy on disclosing conflicts of interest, and we declare that we have none.

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REFERENCES