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'Considering the totality of evidence: Combining real-world data with clinical trial results to better inform decision-making

Clinical trials are the key mechanism for testing efficacy of cancer therapy. While results from clinical trials have high internal validity, generalizability is limited due to strict criteria for inclusion and exclusion (i.e., eligibility criteria).[1] Indeed, eligibility criteria are designed to protect the safety of trial participants by excluding those expected to have low efficacy or high toxicity from the treatment under investigation. However, if overly restrictive, eligibility criteria can also result in narrow populations that do not reflect the general population treated in routine practice. Recent analyses of cancer clinical trial data have shown that eligibility criteria have become increasingly restrictive, ranging from 16 to 32 exclusion criteria per trial, over time.[2,3] Therefore, it is not surprising that <5% of US adult patients with cancer participate in clinical trials, and those who do are often younger and healthier than patients seen in clinical practice.[4-9] These differences raise serious concern that the "efficacy" of cancer therapies reported in published clinical trials provides incomplete evidence of their "effectiveness" when administered to patients in routine care.

Oncologists treating patients with cancer know that patients routinely ask: "is chemotherapy effective for patients like me?". The challenge has been what to tell the patient. In this issue of *Pharmacoepidemiology and Drug Safety*, Cramer–van der Welle and colleagues address this knowledge gap for clinicians caring for patients with Small Cell Lung Cancer (SCLC).[10] SCLC is a rare and aggressive form of lung cancer, characterized by rapid proliferation, early development of metastases, and limited life expectancy (e.g., median survival of 10 months), even when treated with standard platinum-based systemic therapy.[11,12] In this cleverly-designed study, authors used Dutch cancer registry data from 568 patients with SCLC treated at seven large hospitals to calculate the 'efficacy-effectiveness (EE) factor' – the ratio of each 'real-world' patient's observed overall survival (i.e., effectiveness) to the pooled median survival for clinical trial patients receiving the same treatment (i.e., efficacy). As such, the EE factor and its magnitude (relative to 1.0) indicate whether, and to what extent, there are differences in overall survival for SCLC patients in routine practice versus the pivotal clinical trial.

There are two main findings worth emphasis. First, the survival of patients with SCLC treated in the real-world was 20% shorter than for patients included in trials (median EE factor, 0.79, $p < 0.001$ relative to 1.0). Notably, this corresponded to an absolute difference in median OS of approximately 2 months. Second, the lower survival observed in the real-world may be driven by certain vulnerable subpopulations underrepresented in the clinical trials: the elderly and those with poor Eastern Cooperative Oncology Group Performance Status (ECOG PS) (i.e., the classification of a patient's well-being based on level of function). For example, among patients aged >65 years, and ECOG PS >2 (unable to carry out work activities, or worse), EE factors were 0.72 and 0.62, respectively, indicating even larger survival disparities for these patient subgroups.

The investigators should be applauded on these important findings, which help clinicians to better inform patients with SCLC of expected treatment outcomes in real world settings. These data are particularly useful for clinicians in the oncology community, who are often left to extrapolate data from clinical trials to patients seen in everyday practice who may not have met the entry criteria for the trial. Further, the analysis is highly relevant given the recent emphasis placed on data collected outside of clinical trials to support regulatory decision making, now mandated by the 21st Century Cures Act.[13]

However, the study by Cramer – van der Welle and colleagues also leaves several important questions unanswered – why does an efficacy-effectiveness gap exist, does it persist in the era of novel anti-cancer therapy (e.g., immunotherapy), and are novel approaches needed to more efficiently and accurately integrate clinical trial and real-world data? In our opinion, the primary mechanism of the gap is that trial participants differ substantially from those treated in routine practice. For example, it is well established in the oncology community that patients with "poor-prognosis" – the elderly (>65), those with poor performance status (ECOG PS >2), organ dysfunction (liver or kidney injury), or brain metastases – are commonly excluded in pivotal clinical trials of chemotherapy, despite such patients representing up to 50% of all patients with advanced cancer, including SCLC.[14-18] While Cramer – van der Welle et al. confirm inferior survival outcomes in some of these subgroups, without adjustment for differences in patient characteristics in their comparison of real-world and clinical trial outcomes, the extent to which the efficacy-effectiveness gap is attributable to differences in these characteristics versus other factors is unknown. Differences in the delivery of care in a clinical trial versus routine care may also contribute to the efficacy-effectiveness gap. For some cancer types and treatment modalities, adherence to treatment is likely to be higher in the trial setting due to the close monitoring of toxicity, improved access to trial coordinators and schedulers, etc. Different patterns of adherence to therapy can impact the population-level benefits and harms of a given treatment, and in turn serve as a further driver of the efficacy-effectiveness gap. In some settings, differences in treatment delivery may be thought of as different "versions" of the treatment, which may hinder direct comparisons of their impact.[19]

Further, the results from this analysis, which was limited to patients treated with chemotherapy, cannot be generalized to patients treated with immunotherapy in combination with chemotherapy – the current standard of care in combination for SCLC.[20,21] Among immunotherapy-treated patients, the magnitude of the disparity between clinical trial- and real-world- populations is expected to be even more pronounced. In contrast to chemotherapy, immunotherapy is an appealing option for older and frailer patients. First, it offers the potential for long-term benefit in a small subset of patients.[22] Second, it is associated with a favorable toxicity profile.[23] Third, it is not metabolized by the liver or kidney and thus can be administered in patients with organ dysfunction.[24] We and others have shown rapid uptake of immunotherapy in poor-prognosis patients who may not live long enough to derive benefit from any anti-cancer therapy, termed 'desperation oncology' in the lay press.[25-30] Thus, it is highly plausible that immunotherapy use in older and more frail patients in routine care may fail to produce the benefits seen in the pivotal clinical trials of immunotherapy in SCLC.

To facilitate comparisons of real-world and clinical trial data, a variety of analytic approaches can be considered to more accurately estimate the efficacy-effectiveness gap and pinpoint the specific causes of this gap. As noted above, differences in the distribution of patient characteristics between patients treated in trials and those seen in routine practice are expected to be a key driver of differences in outcomes. To quantify the proportion of the efficacy-effectiveness gap attributable to specific patient characteristics such as age or ECOG PS, the distribution of survival times observed for real-world patients can be adjusted, for instance via weighting, to produce the counterfactual survival distribution that would have been observed had real-world patients resembled clinical trial participants. As noted by Cramer – van der Welle et al., individual patient data from clinical trials are typically not available for reanalysis. Therefore, weighting of the distribution of survival times observed in real-world patients can be used to harmonize the distribution of patient characteristics based on reported means from clinical trial results using methods such as matching adjusted indirect comparison.[31] Alternatively, methods for recreating individual patient-level survival data from published Kaplan–Meier curves[32] can be used followed by direct comparison of real-world and trial outcomes using survival regression methods to estimate the magnitude of the "trial" effect. The residual difference in survival between trial and clinical practice patients, after adjusting for patient characteristics, represents the portion of the efficacy-effectiveness gap that cannot be explained by these patient characteristics.[33]

In addition to methods that address differences in patient characteristics, appropriate methods are needed to address differences in data quality and completeness between trials and real-world data collected via electronic health records (EHR) and other healthcare databases such as claims. Key data elements such as ECOG PS may not always be recorded in real-world data or, when recorded, may not be recorded with the same consistency observed in trials. Methods that address missing and error-prone covariates are needed to address these data quality issues. Additionally, outcome measures may be missing from EHR data due to patient attrition from the healthcare system or lack of systematic assessment (e.g., to ascertain disease progression). Systematic lack of capture of mortality data leads to overestimation of patient survival for real-world data[34] potentially leading to underestimation of the efficacy-effectiveness gap. This is less of a concern in contexts with high mortality rates such as the current study of SCLC where death was observed for all but seven patients. However, in settings with longer survival where many patients are censored this can lead to substantially biased survival estimates. Careful consideration of when to censor patients who may no longer be under observation in EHR data is needed to avoid this bias.[35]

While clinical trials should remain the gold standard for assessing treatment efficacy, clinical trial design has not kept pace with evolving patient populations, with the result that treatment effectiveness is often unknown for broader populations. As highlighted by Cramer – van der Welle and colleagues, positive results from pivotal clinical trials of SCLC therapy may not translate into improved outcomes for many patients treated in everyday practice. Supplementing clinical trial results with appropriately designed post-marketing studies of real-world populations has the potential to close the evidentiary gap which exists in oncology between clinical research and practice, providing evidence to support informed decision making for the broad population of patients seen in routine clinical practice, particularly those underrepresented in clinical trials.

CONFLICT OF INTEREST

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