Practical Application of Real-World Evidence in Developing Cancer Therapies

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One substantial limitation of randomized clinical trials (RCTs) relates to the stringent eligibility criteria that are typically used. As a result, only a small percentage of patients who face the disease under study are considered for RCT participation. Not surprisingly, this highly selected trial population often does not accurately reflect the patient population requiring treatment.¹ Whereas this selectivity facilitates the interpretation of results by diminishing confounders, such as comorbid medical disease, concomitant medication interactions, and organ dysfunction, it also limits the generalizability of RCT results. Consequently, clinicians commonly treat patients who do not meet the entry criteria for the RCT of the most efficacious therapy. Physicians must therefore interpret and extrapolate existing data and use their discretion and judgment in making treatment decisions for individual patients. Medical training facilitates these analyses and, at the same time, there is tremendous subjectivity and discretion around many of these decision points.

Traditionally, retrospective analyses have helped to fill the void of guidance on how to apply RCT results more broadly. These endeavors are labor intensive, require extensive manual chart review, and are slow to come to fruition. Fortunately, the development of technology to analyze big data sets and the increasing use of electronic medical records (EMRs) present a novel paradigm for collecting, aggregating, and analyzing data from a broad group of patients. Such data could be quickly captured and harnessed to generate real-world evidence (RWE) that, in turn, might help guide decision making in more patients. Although the tremendous potential of this approach is frequently discussed, common definitions, best practices, and the validity of outcome measures for RWE have not yet been established.^{2,3} The US Food and Drug Administration has embraced the potential role of RWE in drug development and issued a framework for its Real-World Evidence Program to evaluate the potential use of RWE to support new indication approvals of drugs.⁴

It is in this context that Stewart et al⁵ present a large analysis of real-world end points around the use of immunotherapy in non-small-cell lung cancer. Recently, use of immunotherapy has transformed the landscape of therapeutic options in non-small-cell lung cancer⁶⁻¹³ and yet little guidance exists beyond the landmark clinical trials. Whereas some retrospective studies have expanded our understanding of

the activity of these agents in patients who are typically excluded from RCTs,¹⁴ much remains unknown and ripe for study.

As reported by Stewart et al⁵ in the article that accompanies this editorial, six discrete health care organizations were able to implement a common protocol for data extraction and assessment of real-world end points. Of importance, this team successfully surmounted barriers to multi-institutional collaborations by creating standard definitions for data elements and pooling data from different electronic sources in a consistent format. Not surprisingly, the authors found that certain data elements were more accessible than others. For example, dates of treatment were usually available through claims data; however, survival status and date of death availability varied tremendously depending on the information source. Furthermore, progression-based end points required substantial extraction of text from unstructured data fields in EMRs.

Despite these challenges and limitations, RWE was remarkably consistent with previously reported RCTs, thus providing an initial validation of this process for certain end points. Specifically, overall survival data identified in patient cohorts from the RWE process were consistent with those from published trials of these agents. In addition, substantial data were generated on the efficacy of treatment in patient populations that are not substantially reflected in clinical trials. Time to progression and progression-free survival end points were more challenging and complete data were not available from all organizations, depending on which underlying data source was used.

In addition to the established use of retrospective data or RWE in providing postapproval safety data, there is clearly a role for the use of RWE to augment available RCT data.¹⁵ There will never be RCTs to address all variables that arise in routine clinical care, and some important questions are not suited to randomization. Conceivably, RWE could be used to provide data on patients other than those who are typically included in RCTs and to identify groups of patients who derive more or less of the efficacy of a particular intervention. Such work could also spark hypotheses for the next iteration of prospective studies and provide large and

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robust historical control groups for single-arm phase II trials, particularly in less-common disease states.

It is crucial, however, that, as advances in computing technology generate RWE with increasing rapidity and abundance, clinicians and researchers remain vigilant in validating the output and providing contextualization of these analyses. Data are only available for drugs that are already in routine use, and the decision-making process remains beyond our current data capture ability. By the time RWE is available, a clinician has already evaluated a patient, considered many patient-specific factors that are often poorly captured in our EMR platforms, discussed options with the patient, and used this information to make a treatment decision.

Studies such as that presented by Stewart et al begin to define and validate a robust tool in the arsenal of retrospective research. Using such protocols will help iterate advances and refinements of existing treatments more rapidly. The automation of this process must continue with our technology partners and must exploit our nascent understanding of these big data analyses in the design and development of EMRs and cancer registries that facilitate research, where possible. Only by implementing standardized systems and definitions for data entry, extraction, and analysis will the potential of RWE to expand oncology research by learning from the treatment of each and every patient be fulfilled.

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