EDITORIAL

The Role of Real-World Evidence to Support Treatment Choices in Malignant Pleural Mesothelioma

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In this issue of *JTO Clinical and Research Reports*, Kerrigan et al.[1] report outcomes from patients diagnosed with having malignant pleural mesothelioma (MPM) who received at least one line of pemetrexed-based chemotherapy. They describe the prescribing patterns with specific interest in the following: the platinum analog used in combination with pemetrexed as first-line treatment (no difference observed between cisplatin and carboplatin); whether maintenance pemetrexed prolongs survival (also not observed); and finally, in patients who received subsequent lines of therapy, whether immunotherapy was more efficacious than chemotherapy (no statistically significant difference found here either).

Although these three findings do not substantively alter current views of managing MPM, one can consider how the research platform used by Kerrigan et al.[1] can appraise and inform treatment paradigms.

Real-world evidence (RWE) is gaining importance and credence in the medical literature. RWE reports outcomes from treatments or technologies in the clinical management of a disease, derived from single- or multi-institution chart review projects, specific RWE platforms, disease-specific registries, or health care administrative data. There are inherent constraints to applying the results of prospective controlled clinical trials, with very specific eligibility criteria, to general practice. RWE can consider clinical outcomes for unselected populations or selected subgroups of interest, potentially more applicable to everyday clinical decision-making, ultimately providing pragmatic support in the clinic, both in understanding efficacy and safety. RWE may provide supportive data in areas where there is a paucity of clinical trial data or in rare conditions. Increasingly, RWE may be incorporated into regulatory submissions to support approval of new treatments and can provide valuable information on health system utilization of treatments or services.[2]

Nevertheless, there are well-recognized limitations of RWE.[2] Foremost is that selection for interventions in routine practice raises the potential for bias, although it may not be feasible to adjust for confounding variables in interpreting outcomes owing to the lack of control data. There is also a basic issue about the quality of the data used for analysis. Each source of RWE will have its own benefits and challenges. Disease registries and health care administrative data have the benefit of including data on large numbers of patients, with minimal effort, as data already exist and are being used in research as a secondary objective. The obvious challenge is that the data were not created with research in mind, and therefore are often missing key components that are important to accurately answer a given research question. Single-center chart reviews can be time consuming to undertake and are often limited by small patient numbers. Nevertheless, there is an ability to collect and analyze significant patient-level detail specific to the research question at hand. Multicenter collaborations can achieve more meaningful patient numbers and help generate more robust RWE.

With the emergence of electronic health records, the ability to curate RWE from patient charts has become more feasible. Standards are now described for the level of quality in RWE. For example, the Observational Medical Outcomes Partnership Common Data Model is designed to provide a standardized level of quality

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observational data using standardized vocabularies that enhance analysis and can lead to generation of reliable reports and evidence.[3] Similarly, in RWE evidence research in cancer, minimal Common Oncology Data Elements has been developed by the American Society of Clinical Oncology (ASCO) to provide a standardized set of cancer data points that can allow patient-level research and information to be curated from electronic health records.[4] Finally, the Clinical Data Interchange Standards Consortium is a global nonprofit organization that collaborates with groups such as the U.S. Food and Drug Administration and the European Medicines Agency to develop data standards for clinical research.[5]

The Real-World Evidence Alliance is a U.S.-based group of private companies that specialize in RWE and data analytics in health, seeking to engage with the U.S. Food and Drug Administration and the U.S. Congress to enhance the use of RWE to support regulatory decision-making.[6] Flatiron, a part of the RWE Alliance, is a health technology company founded in 2012 that specifically works to develop oncology RWE and claims to have patient-level data from more than 3 million patients with cancer in the United States from more than 280 cancer centers. Deidentified patient data are pulled from the electronic medical records by trained data abstractors, with as little as 30-day recency.[7] Most of the contributing centers are community cancer centers, who are perhaps less likely to participate in the same number of randomized controlled trials (RCTs) as major academic centers, and therefore able to provide a better picture of routine oncology practice in large parts of the United States.

The use of the Flatiron database by Kerrigan et al.[1] showcases some of the strengths and weaknesses of the Flatiron platform. They were able to report relatively current information on 787 patients with MPM who were treated with platinum-based chemotherapy, a significant feat in a rare disease. Nevertheless, despite propensity matching, they lack significant high-quality data regarding confounding factors that may bias their results. Stage of disease is notably missing from their analysis, and several time-varying factors are included dating back to 180 days before the start of treatment. This is a significant duration of time for a disease with a median overall survival (OS), in their analysis, of approximately 1 year. Mortality data in Flatiron Health come from a composite variable, trading currency for the reliability of population-based Vital Statistics.[7]

The dataset for the study of Kerrigan et al.[1] covered the period from January 2011 to July 2019. The study findings support the recommendations made in the ASCO guideline for treatment of MPM that was published in 2018.[8] The ASCO guideline was based on a comprehensive review that focused on the results of systematic reviews, meta-analyses, RCTs, and prospective and retrospective comparative observational studies published between 1990 and 2016, with greater weight given to those recommendations supported by higher levels of scientific evidence. In this instance, RWE lends support to an evidence-based practice guideline, providing reassurance that the guideline recommendations are relevant to day-to-day management in the clinic.

Nevertheless, treatment of MPM has changed dramatically in the past few years. The MAPS study was published in 2016 and revealed an OS advantage when bevacizumab was added to platinum/pemetrexed chemotherapy.[9] The uptake of this regimen has been quite variable, perhaps owing to the modest OS benefit observed, the cost of the drug, the lack of regulatory drug approval for the indication, and numerous prior negative studies investigating angiogenesis as a target in MPM. Other angiogenesis agents have been studied,[10] but this approach has been overtaken by the emergence of immunotherapy strategies.

Most notable has been the landmark CheckMate 743 study, which reported an improvement in survival outcomes for ipilimumab/nivolumab compared with platinum/pemetrexed as first-line treatment of MPM.[11] Aside from a 4-month advantage in median OS, there was a 14% increase in survival rates at 2 years. Nevertheless, updated analyses have questioned whether the OS advantage is limited to the nonepithelioid population and whether programmed death-ligand 1 (PD-L1) expression may play a predictive role.[12]

In the second-line setting, Professor Dean Fennell in 2021 presented or published the results of two important studies, the topic of one of the main questions asked by the RWE data presented by Kerrigan et al.[1] First, the CONFIRM study randomized patients with advanced MPM, previously treated with platinum-based chemotherapy, to either nivolumab or placebo and revealed a significantly prolonged OS with nivolumab.[13] Second, Professor Fennell reported the VIM study of vinorelbine plus active supportive care versus active supportive care alone and concluded that (despite prolongation of progression-free survival, but not OS) this could be considered an appropriate off-label use of chemotherapy.[14]

Another strategy of interest is combining chemotherapy with immunotherapy. The DREAM trial, a phase 2 study of cisplatin/pemetrexed plus durvalumab, revealed significant activity for the combination with no apparent differential effect based on the histologic subtype of mesothelioma.[15] Eagerly awaited are the results of phase 3 trials assessing this strategy, such as the Canadian Cancer Trials Group IND.227 trial

comparing platinum/pemetrexed with platinum/pemetrexed plus pembrolizumab (ClinicalTrials.gov: NCT02784171).

So where does RWE fit in the face of randomized data recently published and presented in the MPM field? It would be interesting to see whether Kerrigan et al.,[1] or other groups, could provide RWE in MPM since the start of the immunotherapy era. Would such data help to answer questions about the role of ipilimumab and nivolumab in a nonepithelioid population, or would having individual patient data, including PD-L1 status, help further to define which patients with MPM benefit from immunotherapy and which patients should still receive chemotherapy upfront? If results of the pending phase 3 trials of chemotherapy plus immunotherapy are positive, there will then be interest in trying to determine an optimal sequence for these different agents and regimens.

At the very least, RWE would indicate how clinicians have viewed data from trials of immunotherapy, enumerating the treatment regimens being used in routine practice. RWE could help define preferences for subsequent lines of treatment, including efficacy of platinum/pemetrexed as second-line therapy after dual immunotherapy, or indeed third-line treatment options if drugs such as vinorelbine and gemcitabine still have clinical utility.

In conclusion, the article by Kerrigan et al.[1] reveals the strengths and weaknesses of RWE, by validating practices and demonstrating care in these patients to be in line with current guidelines, but in this case not being able to cast extra light on questions that remain open despite RCTs. Although RWE will not replace the hierarchical position held by meta-analyses and RCTs in the levels of scientific evidence, when collected robustly using often agreed standards such as the Observational Medical Outcomes Partnership, minimal Common Oncology Data Elements, or Clinical Data Interchange Standards Consortium, RWE can complement and provide additional insight, and such research should be commended and encouraged.

CRediT Authorship Contribution Statement

Paul Wheatley-Price: Conceptualization, Writing - original draft.

Sara Moore: Writing - review and editing.

Christopher Lee: Writing - review and editing.

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