Perspective

The generalizability paradox within palliative care clinical trials

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Abstract: We are increasingly recognizing that personalized advanced and chronic illness care requires meticulous assessment and management of supportive care needs across the entire disease trajectory. This requires drawing clinical decisions from a research evidence base that is presumably generalizable to a heterogeneous patient population, often with poor performance status, multi-morbidity, and a large symptom distress profile. As sometimes this is not the case, how do we improve evidence generation that can be consistently applied to all patients with advanced disease?

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The evidence base establishing the efficacy of palliative care interventions has grown remarkably over the last decade. Several key pivotal clinical trials, adopting the methodologic rigor of randomized prospective studies that dominate other medical disciplines, have demonstrated the value of palliative care services across multiple domains of care. These recent successes parallel a remarkable growth in the clinical infrastructure for delivering hospital-based palliative care, ultimately ensuring an adequate effector arm for the innovations and discoveries from research. Recent recognition of the importance of palliative care from others, including the American Society of Clinical Oncology (1), serves to emphasize the imperative of continuing to build this knowledge base so that we can improve outcomes through both primary and consultative care delivery. In this effort, and as palliative care grows as an evidence based field, we must recognize several inherent challenges within the design, conduct, and analysis of palliative care clinical research and its application to clinical practice.

Conducting palliative care clinical trials that will significantly impact the way we improve the experience of patients with serious illness is difficult. Some may forget that until recently we were having a broad discourse regarding the ethics of conducting intervention studies in vulnerable and dying patients. The consensus from these debates was that this type of research is indeed ethical and valuable (2), the challenge is now to design and conduct studies that match the needs of our patients. Difficulties of running palliative care clinical trials have been well described (3); largely centering on issues of recruitment, attrition, compliance, and subject burden. Correctly, much of the focus on overcoming barriers to palliative care research has concentrated on the importance of efficient patient accrual and feasibility of completing protocol interventions to achieve adequate power for analysis and answering the scientific question at the heart of the study. Too often however, the larger questions of implementation and generalizability are left unanswered by the study results. A classic example comes from a familiar landmark randomized clinical trial in palliative care.

Imagine an intervention that could extend the overall survival of patients with advanced cancer at a magnitude replicated by no other when added to the proven standard of care. Remarkably, this intervention has no known risks or side effects, adds little to the cost of overall care, and improves patient quality of life. But a major caveat exists. This intervention is only available at less than one-third of National Cancer Institute-designed cancer centers

and approximately 10% of community cancer centers (4). Neither the Food and Drug Administration (FDA), the pharmaceutical industry, nor the Centers of Medicare and Medicaid Services (CMS) can impact this shortage immediately or meaningfully. Yet, this is arguably the most dramatic evidence of the potential benefits of a palliative care intervention that has been demonstrated to date. The natural question is why and how this intervention came to be in short supply and what can be done to mitigate this situation and similar situations in the future.

Many readers will have guessed that we are referring to the groundbreaking demonstration of a potential survival benefit from the introduction of early palliative care services added to usual oncology care in advanced lung cancer. However, what has perhaps been underappreciated is that the applicability of this study, performed at a specialized academic cancer center, stands limited to the minority of practice settings nationally where there is sufficient infrastructure to implement an outpatient, co-management program between thoracic oncology and consultative palliative care. This major limitation of the study by Temel *et al*. has spawned policy-level discussions on the achievable avenues for integrating palliative care into usual oncology care, especially when solutions often cannot mimic those used in the clinical trial (5). In addition, this study has raised questions regarding whether this data can and should be applied to all advanced cancer settings, or should be restricted to patients with lung cancer (1).

Issues of generalizability from clinical trial data to clinical practice are certainly not unique to palliative care. Oncology has various examples of discordant findings (6,7), which have further inspired both a movement towards "practical" clinical trial designs (8) and increased utilization of comparative effectiveness research (9). Of note, whereas clinical trial data can be often compared to population-based registries in oncology to validate applicability, there remains a formidable lack of such infrastructure in palliative care. Though this is changing from efforts like our Carolinas Consortium for Palliative Care (10) and the Palliative Care Research Cooperative Group (11), chronicling the experiences of large, multi-site cohorts of patients receiving palliative care represents an important, but not immediately achievable, national goal.

Yennurajalingam *et al*. (12) recently addressed the question of generalizability of clinical trial data for fatigue related palliative care interventions. They compared demographics, disease characteristics, and fatigue severity between two populations at a single academic medical center, MD Anderson in Houston. The first cohort consisted of patients enrolled in one of 5 therapeutic clinical trials for cancer-related fatigue. The second cohort consisted of consecutive patients seen in the outpatient oncology palliative care clinic. To assess how these two cohorts differ, the investigators compared over 300 patients in the former group to over 1,200 in the latter. To establish similar cohorts, patients in the outpatient palliative care clinic with an Edmonton Symptom Assessment Scale (ESAS) fatigue severity score of ≥4 and adequate mental status (as measured by the Memorial Delirium Assessment Scale or Mini Mental Status Examination) were included for analysis.

Perhaps not surprisingly, notable differences between the two cohorts were seen, including the baseline demographics. Whereas the cancer-related fatigue clinical trial cohort (CCT) was majority female (62%) with the most frequent diagnosis of breast cancer followed by lung cancer; the outpatient palliative care (OPC) group consisted mostly of men (52%) with the most frequent diagnosis of lung cancer followed by gastrointestinal cancer. Both groups had similar frequencies of cancer types not fitting within the usual dominant categories; this was recorded as "other" and found 20% and 23% in the OPC and CCT cohorts, respectively.

Though fatigue scores were similar between the two groups, baseline symptom distress profiles for non-fatigue symptoms differed significantly significantly. Using ESAS to perform a discipline-standard symptom inventory, the investigators found important statistical and clinical differences among severity of pain, nausea, anxiety, drowsiness, appetite, overall well-being, dyspnea, sleep, and overall ESAS score. Though some symptoms had small differences, others like pain, anxiety, and overall ESAS score reflected magnitudes of difference known to be clinically meaningful (13). Moreover, the overall survival between both cohorts was striking. Whereas those entered into a clinical trial had an overall survival of almost 18 months, the OPC group shared a survival less than 4 months. Overall, the CCT cohort shared lower symptom distress burden for non-fatigue symptoms and dramatically longer overall survival. The differences in patient demographic, symptoms and prognosis raises an immediate question: can the data from the trials be applied in the outpatient palliative care clinic among patients with similar levels of fatigue? Despite the discrepancies in patient population characteristics, the sparse clinical trial data on management of fatigue might be expected to compel clinicians to generalize these findings to usual care settings. Clearly, the benefits of the interventions

seen in the trial may not apply in the average patient seen in the outpatient setting where the causes of fatigue, exacerbating factors, and potential for toxicity from the intervention may be very different.

The differences among patients in fatigue related trials and the average patient seen in the outpatient clinic highlighted by the group from M.D. Anderson suggests that both the application of trial data in the clinic and the process for further evidence development in palliative care must be re-examined. In an increasingly challenging funding environment, where governmental and foundational support is shrinking for investigator-initiated clinical trials and limited industry sponsorship is provided for the off-patent interventions common to palliative care; highly-generalizable findings that can be translated into routine clinical care are needed.

Three key factors that may ultimately affect the generalizability of a study can and should be addressed during clinical trial design. First, patient eligibility should be as broad as possible and designed to match the characteristics of patients in the general target population for the intervention. Second, the setting for delivery of the intervention and follow-up should duplicate the setting where the results are expected to be implemented to the extent possible, with recognition and recording of special features of the trial setting that may be related to clinical impact of the intervention. Third, selective patient accrual on the basis of patient interest in the study and physician referral should be anticipated, planned for in terms of recruitment of key subsets of patients and recording of potential confounding demographic or disease specific differences, and reported and considered in analysis and presentation of results.

It is well understood that both patient interest in direct benefit and physician recommendation can influence clinical trial participation (14). Though there is no proven generalizable benefit to participation in a clinical trial, potential for direct benefit is a strong incentive that may contribute to difference between patients who participate in trials and those with similar conditions who do not (15). Additionally, the issue of physician influence is quite important. Physicians may feel hesitant to offer or discuss a potential supportive care clinical trial with patients who have worse performance status or prognosis. They may also hold incorrect assumptions regarding dual enrollment, such as for patients with refractory, advanced disease who wish to pursue cancer-directed Phase I or II options and who are candidates for a supportive care trial, eventually influencing the case mix included in the study.

Palliative care clinical trial inclusion and exclusion criteria should reflect an *a priori* approach to including a heterogeneous population. For example, we have shown that the majority of patients seen in consultative palliative care settings have an approximate Karnofsky Performance Status of 40-60%, reflecting significant need for assistant with activities of daily living (16). The prevalence of patients with such poor status, but who still pursue regular, non-hospice, clinical care and who may have interests in clinical trial participation, should compel palliative care trial designs to include those with ECOG PS of 3 and even 4. In addition, we must further expand our methods to include community-based clinical studies, home-based clinical trials, and collaborative clinical trial networks that support accrual of all populations. This requires non-traditional thinking in expanding the infrastructure of where clinical trials are performed, from within the walls of our medical centers to now including the communities in which our patients live and work.

Currently, clinicians in palliative care must use caution in interpretation of the literature, asking: do these results apply to my specific patient? When an intervention is applied outside of the context in which it was well studied, ideally we should be collecting data to expand our knowledge base and help address questions of generalizability for the future. Ultimately, without a concerted effort to address the generalizability issues of palliative care clinical trials, we run the risk of performing high-profile, resource-intensive clinical studies that are never translated into benefits for the patients we saw clinic or neither approach will bring us closer to our goal of providing patient-centered, comprehensive palliative care to all with serious and advanced illness. Innovation and creative thinking must go beyond designing the interventions we aim to test, and extend to the realm of ensuring generalizability of results. Without this, we will never solve the paradox between research discoveries and clinical implementation in this field.

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