

EDITORIAL

Population-Based Outcomes in NSCLC

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See the Note section for the author's affiliation.

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A nihilistic approach to the treatment of non-small cell lung cancer (NSCLC) has characterized the predominant attitude of physicians as well as patients during most of my professional career. This attitude has persisted despite therapeutics that have demonstrated efficacy in terms both of quality and quantity of life since at least the early 1990s (1). The level of benefit and the trade-off in terms of toxicity has improved remarkably in the past 25 years. During this time, we have seen several key developments. The first has been the development of very effective antiemetic therapies with 5HT3 serotonin blockade, neurokinin 1 antagonists, and other agents that have made “traditional” platinum-based therapies more tolerable and have moved the site of treatment from the inpatient to the outpatient setting. Second, the reemergence of histology as a predictive marker for therapeutics (pemetrexed and bevacizumab) has resulted in a higher likelihood and duration of benefit from cytotoxic treatments. Third, the discovery of specific activating mutations responsive to tyrosine kinase inhibitors (interestingly, a result of clinical observation rather than laboratory discovery) and the widespread availability of genetic testing have allowed for the introduction of agents with the potential to benefit 80–90% of the patients undergoing therapy. Most recently, the introduction of immunotherapeutics has completely altered the landscape of therapy with the rapid introduction of four new agents in a variety of settings and combinations in NSCLC that substantially improve outcomes with acceptable levels of toxicity.

In this issue of the Journal, Maguire et al. provide a snapshot of clinical practice on a population basis just prior to the immunotherapy era in the California population (2). Although one can argue that the results are already obsolete with the rapid changes that have occurred since 2015, there are important aspects of this analysis that cannot be ignored. In terms of the results of treatment, the paper, for the most part, validates and extends prior work based on Surveillance, Epidemiology, and End Results (SEER)-Medicare data that was inherently restricted to a population age of older than 65 years (3). Most important, despite the substantial progress in the management of NSCLC that occurred prior to the immunotherapy era, a bare majority

of patients with advanced NSCLC received the benefits of these advances. Although at least some of this can be attributed to patients presenting with severely impaired performance status and/or severe comorbidity, a depressingly large proportion of this gap between research and practice appears as the result of socioeconomic factors in the United States. However, the tendency toward undertreatment transcends national boundaries and health-care systems and has been seen in a similar study from Canada (4). Therefore, one needs to recognize that nihilistic views regarding treatment of this disease also play an important role in whether patients receive treatment.

An additional facet that needs to be considered is expertise. This is a somewhat taboo topic and runs counter to the goal of community-based care. However, there is consistent evidence that treatment in specialized centers is advantageous. Specifically, as demonstrated in the current paper as well as in other analyses, treatment in academic centers and more specifically, the National Cancer Institute–designated cancer centers, results in better outcomes (5). This is disappointing given the widespread availability and apparent use of guidelines (eg, by the American Society of Clinical Oncology or the National Comprehensive Cancer Network). Why does this occur? Partly a consequence of knowledge regarding the current standard of care but also a lack of the familiarity with complications and management of complications that can come only with experience.

Although most of the results of this analysis are consistent with the known benefits and outcomes of treatment of NSCLC, the lack of benefit from multiagent chemotherapy for squamous cell disease is unexpected. The data reported are insufficient to allow for firm conclusions and are in conflict with essentially all clinical trial data. Although squamous cell carcinoma patients may have an overall inferior prognosis, the relative benefits of cisplatin-based chemotherapy treatments are similar for squamous and nonsquamous subtypes (6–9). The result also conflicts with other population-based analyses from employing SEER-Medicare data, which did not identify differences between squamous and nonsquamous disease (3). Squamous cell carcinoma is a biologically distinct entity from

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the nonsquamous subtypes (which are themselves extraordinarily heterogeneous) (10). To date, no drug target has been validated in this disease despite numerous attempts, most notably through the Lung Master Protocol, SWOG S1400, a collaborative effort by the National Clinical Trials Network, industry, the Food and Drug Administration, and private organizations (Friends of the [National Institutes of Health] NIH) to find such drugs (11).

There are several areas of this report that require context and demonstrate the limitations of this type of analysis. One example is that the authors are critical of the relatively limited uptake of bevacizumab by oncologists despite a superior outcome in a randomized trial. It is important to recognize the bevacizumab-eligible population as an inherently better group of patients. The results of the control arm (carboplatin/paclitaxel) of the Eastern Cooperative Oncology Group (ECOG) 4599 trial (the study that led to the approval of bevacizumab for NSCLC) were markedly superior (overall survival 10.3 months vs 8.1 months) to a similarly treated arm on the prior ECOG trial (E1594), which did not have the restrictions on eligibility (no squamous carcinoma, anticoagulation, hemoptysis, central nervous system disease) (12,13). Furthermore, subsequent analyses of the ECOG trial indicated that there was no benefit from the addition of bevacizumab to chemotherapy in the elderly (defined as age >70 years) (14). These factors, coupled with the withdrawal of approval in metastatic breast cancer, likely accounts for the paucity of use of this drug (15).

Overall, the results of this study provide a snapshot of practice that confirms the results of clinical trials but demonstrates how socioeconomic features and physician attitudes strongly influence how these developments are applied. Overcoming these barriers is likely to remain an important challenge.

Note

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