Guideline Concordance With Durvalumab in Unresectable Stage III Non-Small Cell Lung Cancer: A Single Center Veterans Hospital Experience

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Background: Durvalumab is recommended by national guidelines for patients with unresectable stage III non-small cell lung cancer (NSCLC) following concurrent chemoradiation therapy (CRT). Nonadherence to guidelines is associated with adverse outcomes. We studied the adherence and identified barriers to durvalumab usage at the Birmingham Veterans Affairs Medical Center (VAMC) Oncology Clinic in Alabama.

Methods: Using retrospective analysis, we assessed the use of consolidative durvalumab among veterans at Birmingham VAMC. The health records of all veterans with stage III unresectable NSCLC from October 2017 to August 2019 were reviewed. Data collected included demographics, barriers to CRT initiation and completion, durvalumab usage, and reasons for not prescribing durvalumab.

Results: In our data review, 34 patients were found to have stage III unresectable NSCLC. Twenty (58.8%) of those 34 initiated CRT, but only 16 (47.1%) completed CRT treatment and 7 (20.6%) underwent further treatment with durvalumab. Of the 14 patients who did not initiate CRT, the most common reasons were poor performance status and/or the presence of comorbidities. Of the evaluable cohort of 34, 11 (32.4%) patients with stage III NSCLC received durvalumab. Of the 9 eligible patients who did not receive durvalumab, the most common reasons cited were toxicities experienced during or following CRT (11.8%).

Conclusions: Just one-third of patients were eligible to receive durvalumab at Birmingham VAMC. This was likely due to the difference between clinical trial and real-world patient populations. Interventions to address socioeconomic and system level barriers to improve our center's delivery of lung cancer treatment are planned.

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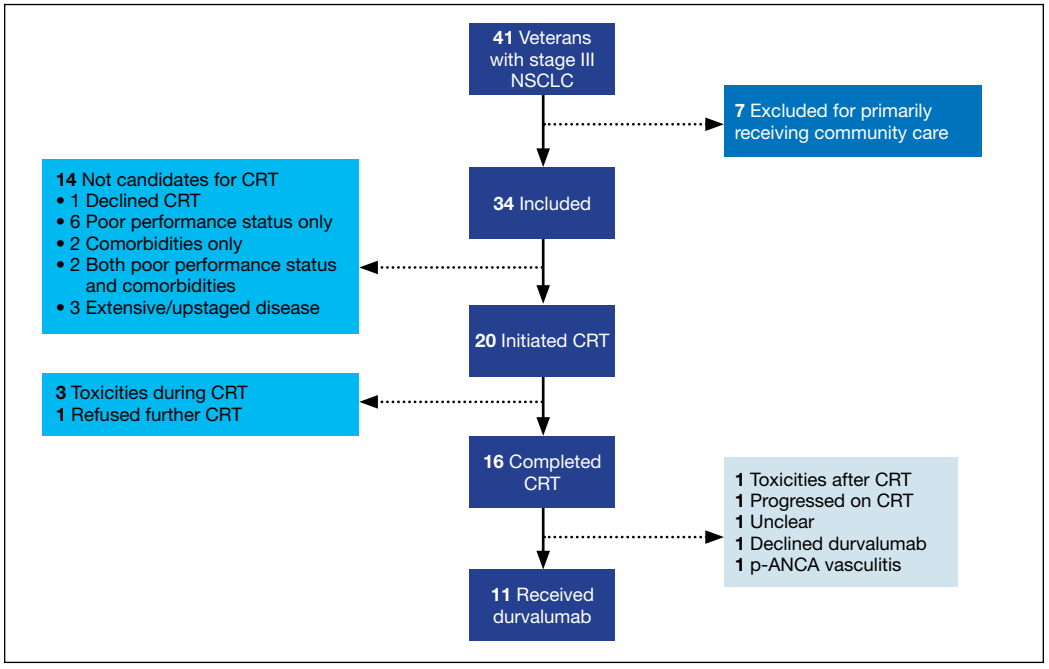
The US Food and Drug Administration (FDA) approved the use of durvalumab for patients with unresectable stage III non-small cell lung cancer (NSCLC) whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy (CRT).[1] After 2 randomized phase 3 studies in 2017 and 2018 showed significant progression-free and overall survival respectively,[2,3] durvalumab became a category 1 recommendation for the above indication per National Comprehensive Cancer Network (NCCN) guidelines.[4] Adherence to guidelines have been shown to improve patient survival across several cancer types.[5-7] However, guideline adherence rates have been variable across health institutions. Therefore, further study is warranted to evaluate nonadherent practices with the goal of improving the quality of cancer care delivery.[8,9]

Stage III NSCLC is associated with poor survival rates.[10] Concurrent CRT remains the standard of care in patients with good performance status based on clinical trial populations.[4] Lung cancer remains a disease of the elderly, with a median age at diagnosis of 70 years.[11] Discrepancies in the treatment of lung cancer in older adults can vary widely due to a lack of evidence surrounding the treatment in those who have comorbidities and poor performance status, widening the gap between clinical trial and real-world populations.[11]

A recent review by Passaro and colleagues revealed that at least 11 pivotal randomized controlled trials have shown the activity of immune checkpoint inhibitors (ICI) in locally advanced and metastatic lung cancer. However, these studies have mostly excluded patients with a performance status of the Eastern Cooperative Oncology Group (ECOG) level ≥ 2.[11]

Durvalumab is one of many new therapies to enter clinical practice to demonstrate survival benefit, but its use among veterans with stage III NSCLC in adherence with National Comprehensive Cancer Network (NCCN) guidelines was not robust at the Birmingham Veterans Affairs Medical Center (VAMC) in Alabama. Therefore, we decided to study the level of adherence and to identify

FIGURE Study Population of Veterans With Stage III NSCLC From October 2017 to August 2019 at Birmingham VAMC



Abbreviations: CRT, chemoradiation therapy; NSCLC, non-small cell lung cancer; p-ANCA, perinuclear anti-neutrophil cytoplasmic antibodies; VAMC, US Department of Veterans Affairs Medical Center.

barriers to conformity to the category 1 NCCN recommendations.

METHODS

The Birmingham VAMC Outpatient Oncology Clinic billing data identified all individuals diagnosed with lung cancer treated between October 2017 and August 2019. Patients who did not have NSCLC that was stage III and unresectable were excluded from our study. Patients who did not receive a majority of their treatment at US Department of Veterans Affairs (VA) facilities were excluded as well. Each patient's demographic, functional level, and tumor characteristics during the treatment planning phase and follow-up visits were obtained. Two investigators who evaluated health care provider documentation using the VA Computerized Patient Record System (CPRS) conducted chart reviews.

The primary outcomes were the proportion of patients who received concurrent CRT and the proportion who received durvalumab consolidation. Our chart review also categorized reasons for nonreceipt of concurrent CRT and subsequent durvalumab. Documented reasons for guideline discordancy were generated empirically and broadly. We noted if documentation was unclear and included reasons for why a veteran was not a candidate for CRT, the presence of toxicities associated with CRT, and a patient's refusal for therapy despite medical advice. Descriptive data were analyzed for all clinical or demographic characteristics and outcomes.

This was considered an internal quality improvement initiative. As such, Birmingham VAMC did not require institutional review board approval for the study. The facility is accredited by the American College of Surgeons Commission on Cancer.

RESULTS

A total of 41 veterans with stage III NSCLC were identified to have established care in the Birmingham VAMC Oncology Clinic between October 2017 and August 2019. Of these, 7 received the majority of their treatment from community-based non-VA facilities and 14 were not candidates for CRT and were excluded from this study.

The mean (SD) age of study participants was 70.0 (8.4) years (range, 57 to 92 years). Most of the study veterans (33; 97.1%) were

TABLE Baseline Characteristics (N = 34)

Characteristics	Results
Age, mean (SD) [range], y	70.0 (8.4) [57-92]
Male gender, No. (%)	33 (97.1)
Race, No. (%)	
White	14 (41.2)
Black	20 (58.8)
NSCLC stage III, No. (%)	
A	18 (52.9)
B	13 (38.2)
C	3 (8.8)
Pathologic subtype, No. (%)	
Adenocarcinoma	12 (35.3)
Squamous	19 (55.9)
Other/unclear/unknown	3 (8.8)
ECOG score, No. (%)	
0 - 1	18 (52.9)
≥ 2	11 (32.4)
Unclear from documentation	5 (14.7)
Concurrent CRT Initiated, No. (%)	20 (58.8)
Durvalumab received, No. (%)	11 (32.4)

Abbreviations: CRT, chemoradiation therapy; ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung cancer.

male and 20 (58.8%) were African American (Table). Eighteen (53%) of study participants had clinical stage IIIa NSCLC; 19 (56%) showed a squamous subtype of NSCLC. A majority (53%) of the veterans studied were evaluated to be functionally fit with an ECOG status of 0 to 1, although documentation of ECOG status was lacking in 5 (14.7%) patients in the initial treatment planning visit records. It was unclear if performance status had been reevaluated and changes noted over the course of concurrent CRT.

CRT Patients

The relative distribution of veterans who underwent CRT for stage III NSCLC plus the reasons they did not receive guideline-based treatment with durvalumab is shown in the Figure. Fourteen patients (41%) were inappropriate candidates for CRT; the most common reason for this was their poor performance status upon initial evaluation and 3 patients (8.8%) in the study had extensive disease or were upstaged upon follow-up clinic visit.

Twenty (59%) veterans in the study initiated CRT. However, only 16 (47.1%) completed CRT. Those who dropped out of CRT did so because of toxicities that included various cytopenia, gastrointestinal toxicities due to radiation and/or chemotherapy, or failure to thrive.

Durvalumab Treatment

After initiation of CRT, 9 (26.5%) patients did not go on to receive durvalumab. Three patients (8.8%) suffered toxicities during CRT. One study patient was found to have a severe respiratory infection requiring intensive care unit admission. Another study patient was found to have a new sternal lesion on follow-up positron emission tomography. One declined because of a history of severe antineutrophil cytoplasmic antibodies vasculitis, which made durvalumab use unsafe. Three patients (8.8%) declined treatment with CRT or durvalumab because of personal preference. Documentation was unclear as to why durvalumab was prescribed to one patient who had completed CRT.

DISCUSSION

NCCN guidelines on the use of durvalumab in NSCLC are based on the phase 3 PACIFIC placebo-controlled randomized clinical trial. This trial, which included only patients with documented performance status of ECOG 0 or 1, reported that grade 3 or 4 events occurred in 30.5% of patients randomized to consolidative durvalumab. Treatment was discontinued in 15.4% of patients due to adverse events.[3]

Our study examined consolidation therapy with durvalumab in patients with unresectable stage III NSCLC with an ECOG performance status of 0 to 1 who had not progressed after 2 or more cycles of definitive concurrent CRT.[4] Patients with previous exposure to immunotherapy, a history of immunodeficiency, active infection, unresolved toxicity from CRT, autoimmune disease, and patients who received sequential CRT were excluded.[2] Surprisingly, the adherence rate to guidelines was close to 100% with appropriate documentation and justification of CRT initiation and durvalumab use. Five (14.7%) of veterans with unresectable stage III NSCLC did not have clear

documentation of ECOG status on initial visit and only 1 veteran who completed CRT did not have clear documentation as to why durvalumab was not provided. Unfortunately, 23 (68.6%) veterans in the study were unable to receive durvalumab, a potentially disease-modifying drug; nearly one-third (10) of veterans were deemed poor candidates for concurrent CRT despite the fact that 52.9% (18) of veterans in the study had a documented ECOG of 0 or 1 on initial evaluation.

Clinical Trials vs Real World

The heterogeneity between anticipated study populations, those who were able to receive durvalumab in the PACIFIC trial, compared with our observed real-world veteran population, likely stems from the lack of information about how comorbidity and fitness can affect the choice of therapeutic intervention in patients with lung cancer.[12] In addition, older adults who participated in randomized controlled trials (RCTs) are not representative of the average older adult who presents to medical oncology clinics, making the application of guideline concordant care difficult.[13]

Similar real-world observations parallel to our analyses have confirmed, complemented and/or refuted findings of RCTs, and have helped impact the treatment of multiple acute and chronic conditions including influenza, cardiovascular disease, and diabetes.[14]

A component of socioeconomic barriers and access to supportive care played roles in the decisions of certain patients who chose not to undergo concurrent CRT despite medical advice. These 2 obstacles also affected the decision making for some in the study when considering the use of durvalumab (administered by a 60-minute IV infusion every 2 weeks for 1 year) per recommended guidelines.[1] These hurdles need further study in the context of their effect on quality of life and the difficulties generated by various social determinants of health.

Limitations

Study limitations included the biased and confounding factors previously described about retrospective and nonrandomized observational studies that are controlled for during RCTs.[15] Electronic health record data may have been incorrectly collected resulting in missing or wrong data points that affect the validity of our conclusion. Recall bias with regard to documentation by health care providers describing reasons why CRT or durvalumab were not initiated or the patient's ability to recall previous treatments and report ECOG status or toxicities also may have impacted our findings. Comorbidities and poor performance status, frequently occurring among veterans, negatively impact cancer treatment decisions and may result in a detection bias. For example, tobacco use, cardiovascular disease, including heart failure, and chronic obstructive pulmonary disease, are notoriously higher in the US veteran population when compared with civilian cohorts.[16-18] Also, veterans with poorly controlled depression and posttraumatic stress disorder resulting in functional impairment are a factor.[19] Steps were taken to address some of these biases by performing repeat checks of tabulated data and employing 2 independent reviewers to evaluate all relevant clinical documentation, compare results, and reach a consensus.

CONCLUSIONS

This retrospective analysis of adherence to category 1 NCCN guidelines for durvalumab use among patients at the Birmingham VAMC Oncology Clinic reinforced our practice and identified minor deficiencies in documentation that would impact future clinical visits. More importantly, it depicted the massive disparity in treatment candidacy among Birmingham veterans compared with clinical trial populations. Efforts will be made to address factors impacting a veteran's candidacy for CRT and explore other variables such as socioeconomic barriers to treatment. Multiple complementary tools to assess patients' frailty, such as the Charlson Comorbidity Index (CCI), are now being used for a variety of disorders including cancers. More robust data and standardization are needed to validate the use of these assessments in predicting response to immune checkpoint inhibitors.

Immune checkpoint inhibitors are currently being evaluated in stage III NSCLC studies and may be implemented as routine practice in the future.[12] It is important to

distinguish fit from frail veterans with lung cancer for treatment selection. We would like to see the expansion of the eligibility criteria for clinical trials to include patients with a performance status of ECOG 2 in order for results to be truly generalizable to the real-world population. Our hope is that such work will improve not only the quality of lung cancer care, but also the quality of care across multiple tumor types.

Author disclosures

The authors report no actual or potential conflicts of interest with regard to this article.

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