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Translating Hispanic Genomic Factors in Lung Cancer Into Clinical Practice: EGFR Testing for Improved Outcomes

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1. Introduction

Lung cancer is the leading cause of cancer-related death in the United States. Incidence and mortality of lung cancer vary according to racial/ethnic groups. Interestingly, Hispanics in the United States are less likely to be diagnosed with lung cancer when compared to non-Hispanic whites (1). These differences in incidence and outcomes may be attributed to a complexity of factors, including a genetic component (2, 3). The value of personalized medicine is increasing, as there is growing evidence that genetic characteristics in tumors related to race and ethnicity produce varied outcomes and responses to therapies (4-6). Advanced lung cancer patients with mutations in the epidermal growth factor receptor (EGFR) have a markedly improved response rate to tyrosine kinase inhibitors (TKIs) such as erlotinib and gefitinib. Results from a multi-center, single-arm, open-label clinical study showed a median progression-free survival (PFS) rate of 10.9 months for patients treated with gefitinib as compared to a median PFS rate of 7.4 months for patients treated with platinum based chemotherapy (7). A similar study found that patients treated with erlotinib had an objective response rate (ORR) of 65% and a median overall survival (OS) of 22.9 as compared to an ORR of 16% and a median OS of 19.5 for patients treated with platinum based chemotherapies (8). Recently EGFR mutations have been reported in higher rates among Hispanic patients (9). Given the improved outcomes provided by targeted therapy for EGFR mutations, the need for easily accessible and uniform EGFR testing is apparent. Yet barriers persist for EGFR testing in lung cancer patients, particularly with Hispanic patients. The Hispanic population in the United States is projected to be the third fastest growing group, with a projected increase of 115% by the year 2060 (10). Historically, Hispanics and other racial/ethnic minorities have experienced significant disparities in access to healthcare and health outcomes (11). As the United States becomes increasingly diverse, it is imperative to gain a more comprehensive understanding of genetic variations in tumors from all racial and ethnic populations. We summarize what is known in the current literature on EGFR mutation testing for lung cancer patients and subsequently discuss the implications for improving clinical practice.

2. Arguments

2.1. Genomics and EGFR

EGFR mutations in non-small cell lung cancer (NSCLC) have been identified in approximately 15% of the adenocarcinoma patients in the United States (12). The identification of these mutations has ushered in a new era of personalized medicine, offering the possibility of improved outcomes from treatment (13, 14). EGFR TKI treatments, such as erlotinib or gefitinib, are most effective when used with patients with EGFR mutations. While the standard of care for NSCLC has traditionally consisted of platinum-based chemotherapies such as carboplatin or cisplatin, TKIs are a more effective course of treatment in individuals with EGFR mutations, with a clear benefit in response and progression-free survival (12). For this reason, the American society of clinical oncology recommended that "patients with advanced NSCLC who are being considered for first-line therapy with an EGFR TKI (patients who have not previously received chemotherapy or an EGFR TKI) should have their tumor tested for EGFR

mutations to determine whether an EGFR TKI or chemotherapy is the appropriate first line therapy" (12). In 2013, the FDA approved erlotinib (Tarceva) as a first-line treatment for patients with metastatic NSCLC with EGFR mutations (8) and subsequently approved gefitinib (IRESSA) (7) in 2015. The national comprehensive cancer network (NCCN) clinical practice guidelines have recommended the use of erlotinib and gefitinob for advanced NSCLC patients with appropriate mutations, demonstrating the importance of EGFR testing. Systematic testing for the EGFR mutations in NSCLC patients is essential to identifying the most appropriate course of first line therapy (15).

2.2. EGFR Mutations and Hispanics

Utilization of EGFR TKIs has highlighted ethnic/racial differences among patients with NSCLC (16). Higher frequency of EGFR mutations have been observed in Hispanics and east-Asian patients as compared to non-Hispanic white patients, while Black patients have a lower or similar mutation when compared to non-Hispanic whites (17). Similarly, frequency of EGFR mutations in Asian-Indian patients is comparable to those of non-Hispanic white patients (18). These variations likely result from genetic differences as opposed to lifestyle choices alone (17). Improved survival rates of US Hispanic patients with lung cancer compared with other ethnicities have been attributed to the higher frequency of EGFR mutations and lower frequency of smoke exposure among Hispanics (19). While there is a relationship between race/ethnicity and EGFR mutation status (20), recent research suggests that this relationship has greater complexity. McQuitty et al. (3) cite findings in which no significant differences were found in the frequency of certain biomarkers (KRAS, MET, BRAF, mTOR, STAT3, JAK2, PIK3CA, AKT1 through AKT3 and PTEN) in lung adenocarcinomas in Hispanics compared with non-Hispanics and Ibrahim (21) suggests that observed differences in race/ethnicity and outcomes in NSCLC may be attributed to differential access to care.

Treatment guidelines require prioritization of EGFR testing over other molecular predictive tests for all NSCLC patients, regardless of race, sex and other clinical factors (22), yet it is vital to understand the importance of EGFR testing within Hispanic populations. The lower incidence of lung cancer in Hispanics, coupled with the higher incidence of EGFR mutation fosters improved survival rates. Racial and ethnic minorities are less likely than White patients to receive stage appropriate cancer care (23) and early identification of the best targeted therapies is especially important for these populations. Initiatives such as the affordable care act (ACA) have improved access to health care for many low-income adults, but Hispanics have the highest uninsured rates in the United States and are less likely to acquire health insurance when compared with other racial/ethnic groups (24). Constraints in access to high quality health care services result in particularly deleterious outcomes in a cancer context. For example, Hispanic patients were less likely to be treated at a NCI-designated comprehensive cancer center (NCICCC) when compared to non-Hispanic white patients due to issues with access, such as distance from the NCICCC and insurance status. Failure to utilize a NCICCC reflects a disparity in care as lung patient cancers treated at non-NCICCC facilities have poorer outcomes when compared to lung cancer patients who are treated at NCICCCs (25). Additionally, delays in treatment can also adversely influence cancer outcomes. Weksler et al. (26) found that Hispanic lung cancer patients presented with more advanced disease at the time of resection, as compared to white and black patients. Given these disparities, it is particularly important to conduct EGFR testing especially among patients of Hispanic origin, to determine the most appropriate first line of treatment for NSCLC.

2.3. Barriers to EFGR Mutation Testing

EGFR mutation testing guides treatment decisions for targeted therapy, potentially improving lung cancer outcomes. Despite the benefits, there are noted barriers to EGFR mutation testing including access to testing, technical testing issues such as poor quality biopsies, providers' unfamiliarity with recommended guidelines and lack of education of radiologists and other non-oncologists (27).

Testing factors such as specimen collection, processing time, sample size and testing labs often complicate the process. In some cases, patient specimens do not have optimal quality and/or sufficient quantity of tissue for testing (28-30). The testing process presents time constraints, which may be detrimental for patients with advanced lung disease. Once the tissue sample is collected, results may not be available for up to two weeks (31) based on the guidelines set forth for recommended turn- around- time from the laboratory, however some labs take even longer. Clinicians may choose to administer cancer treatment rather than wait for EGFR test results so as not to delay care for a late stage or metastatic patient (15).

Patients' and providers' attitudes and knowledge concerning genetic testing shape their perceptions of the potential benefits and disadvantages of genetic testing. Patients often cannot discern between germ line genetic testing for hereditary cancers and genetic testing for somatic mutations (32). Gray et al. (33) found that many patients had misunderstandings about biomarker/genetic testing and expressed a reluctance to participate. Similarly, Rose et al. (34) found that patient' misconceptions about biomarker testing in lung cancer combined with concerns about employment and/or racial and ethnic discrimination, served as impediments to testing.

In some cases, oncologists also require improved education. Chen et al. (27) conducted focus groups with oncologists and found overwhelming support for mutation testing and genomic targeted therapy. However, oncologists demonstrated gaps in knowledge and understanding of the guidelines concerning mutation testing for NSCLC that likely resulted from a lack of understanding and less

experience treating NCSLC patients. Oncologists also identified several barriers to prescribing targeted therapy including insufficient tissue samples, costs of conducting the test, wait times for test results, cost and identification of additional mutations. Understanding oncologists' perceptions of barriers provides helpful insight into the factors that may influence oncologists' decision-making and subsequent implementation of genomic based therapies. Successful widespread implementation of EGFR testing requires both an acknowledgement and response to the perceived barriers for both patients and physicians.

3. Conclusions

3.1. Addressing Barriers: Education and Clinical Communication

Taken together, these findings demonstrate the importance of educating both patients and physicians about EGFR and other key biomarkers (ALK, BRAF, etc.), particularly when care is provided outside of an NCICCC. Oncologists who do not routinely treat NSCLC patients may be unsure of mutation testing guidelines, interpretation of test results, or protocol for ordering mutation testing at their institution/practice setting. In these instances, institutions or regional networks could provide training that directly addresses oncologists' education needs, including clarification of mutation testing guidelines for first and subsequent lines of treatment, as well as guidance for ordering tests and interpreting results.

Clinical communication between oncologists and their patients also plays a critical role in effectively conveying the benefit of EGFR mutation testing. Oncologists and their clinical teams should provide clear, cogent explanations of biomarker testing and related risks and benefits that are easily understandable for patients. Discussions concerning biomarker testing should be culturally tailored, addressing any concerns that Hispanic patients might have regarding privacy, discrimination or psychological harm. Oncologists should also set realistic expectations for patients when discussing testing turn- around- time and treatment options upon return of the results, taking care to update patients in the interim. Community-level interventions are also essential for educating certain Hispanic patients, especially immigrant and low socioeconomic status patients. As referenced above, failure to receive care at an NCICCC represents a clear disparity for Hispanic patients. Educational interventions that address biomarker testing, as well as the importance of consulting a nearby NCICCC (regardless of distance or insurance status), may increase the likelihood that Hispanics patients would be open to seeking care at an NCICCC. Education and clinical communication are essential when addressing perceived barriers that might adversely affect clinical decision-making concerning EGFR mutation testing and genomic targeted therapies.

Identifying EGFR status plays a pivotal role in determining the most appropriate course of first line treatment and increases the chances for improved rates of overall survival for Hispanic patients. Improving physician and patient education, as well as clinical communication processes, are important steps in addressing barriers to systematic implementation of testing for key biomarkers. Future economic studies could reveal important information about the cost/benefit of providing TKIs to all Hispanic lung cancer patients and forgoing biomarker testing, in light of recent evidence showing improved outcomes.

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Footnote

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