J Bras Pneumol. 2019;45(3):e20190139
http://dx.doi.org/10.1590/1806-3713/e20190139

The importance of molecular characterization in lung cancer

Gilberto de Castro Junior[1,2,a], Guilherme Harada[2,b], Evandro Sobroza de Mello[3,c]

Lung cancer is the second leading cause of cancer and the most common cause of death from cancer worldwide.[1] In the initial diagnostic workup of lung cancer, it is essential to recognize the fact that it is a highly heterogeneous disease. Precise molecular characterization is key to improving understanding of the tumor pathogenesis, to determining the prognosis, and to defining an individualized treatment plan based on predictive biomarkers. Therefore, since 2010, the Association for Molecular Pathology, the College of American Pathologists, and the International Association for the Study of Lung Cancer have collaborated to review the main evidence in molecular analysis and its implications. The most recent guideline, issued in 2018, includes many relevant recommendations and advocates for testing all patients with nonsquamous non-small cell lung cancer (NSCLC) for *EGFR* activating mutations, *ALK* rearrangements, and *ROS1* rearrangements; if adequate material is available, another group of genes—including *BRAF*, *MET*, *RET*, *ERBB2* (*HER2*), and *KRAS*—should be included in an expanded panel.[2] In addition, samples should be tested for predictive biomarkers of response to immune checkpoint inhibitors targeting the programmed death 1/programmed death-ligand 1 (PD-L1) pathway, such as PD-L1 expression in the tumor and inflammatory cells, and the tumor mutational burden should be also determined.

The importance of molecular characterization of NSCLC has been demonstrated in many trials,[3,4] which has had a major impact on clinical practice. Patients in whom the tumors have targetable oncogenic drivers and who have access to matched therapies have been shown to have better response rates, longer progression-free survival, and better quality of life scores than do unselected patients treated with traditional chemotherapy.[3,4] In fact, the Lung Cancer Mutation Consortium analyzed tumors from 1,007 patients with NSCLC and demonstrated absolute gains in overall survival in the patients in whom an oncogenic driver was identified in biopsy samples and who were treated with matched targeted therapies in comparison with those who did not receive genotype-directed therapies (3.5 years vs. 2.4 years, hazard ratio = 0.69; p = 0.006).[5] Another key advance that must be mentioned is related to the superiority of pembrolizumab, an anti-programmed death 1 antibody, in terms of overall survival rates, in comparison with platinum-based chemotherapy, in NSCLC patients with a tumor proportion score for PD-L1 ≥ 50%.[6] Therefore, the identification of these predictive biomarkers is a critical step in the treatment decision-making process for patients with NSCLC.

In the current issue of the JBP, Oliveira et al.[7] describe the frequency of EGFR mutations, ALK rearrangements, and PD-L1 expression in tumor samples evaluated at a surgical pathology laboratory in northeastern Brazil. Using a sensitive, next-generation sequencing technique, the authors found the frequency of EGFR activating mutations to be 22%. Using immunohistochemistry with the D5F3 clone, they detected ALK expression in 10.4% of the samples, and immunohistochemistry with the SP263 clone revealed a surprisingly low (50.9%) rate of PD-L1 positivity. In comparison with other studies conducted in Brazil, the EGFR mutation rate was similar,[8] whereas the level of ALK expression was higher.[9] Selection bias (due to geographic limitations and small sample sizes) could explain those discrepancies. Larger samples evaluated in multicenter studies would be more informative. Regarding PD-L1 expression, the high proportion of tumors testing negative for PD-L1 (49.5%) is remarkable in comparison with the 30% rate observed in the KEYNOTE-189 trial.[10] In one recent study conducted in Brazil, 61.39% of the 1,018 tumors evaluated (with clone 22C3) tested negative for PD-L1 expression,[11] suggesting that the epidemiology of this biomarker could be different among patients in Brazil.

Brazil faces many challenges in terms of broadening access to molecular pathology diagnosis and health technology in general. In addition to the delayed NSCLC diagnosis, a low proportion of patients have access to the recommended molecular testing.[8] Only half of all patients with advanced NSCLC who are diagnosed with lung adenocarcinoma are tested for EGFR activating mutations, and even fewer are tested in the public health care system. Data regarding ALK rearrangements and PD-L1 expression are scarce. All of that has direct impacts on overall survival rates, which differ between patients treated in the public sector and those treated in the private sector,[12] the median overall survival among patients with stage IV adenocarcinoma being 14.2 months for those who underwent molecular testing compared with 8.5 months for those who did not.

Among the barriers to access to molecular testing and matched targeted therapies in Brazil are the continental dimensions of and widespread internal social inequalities within the country, as well as preanalytical issues, such

1. Serviço de Oncologia Clínica, Instituto do Câncer do Estado de São Paulo, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.
2. Centro de Oncologia, Hospital Sírio-Libanês, São Paulo (SP) Brasil.
3. Laboratório de Anatomia Patológica, Instituto do Câncer do Estado de São Paulo, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.
a. http://orcid.org/0000-0001-8765-3044; b. http://orcid.org/0000-0003-4012-3251; c. http://orcid.org/0000-0002-4383-2910

as the poor quality of formalin at many hospitals and inappropriate handling of small tissue samples in pathology laboratories. Access to the latest health technologies is restricted to a few centers, which compromises prevention, diagnosis, and treatment. There is a considerable delay in the approval of new therapies and in the activation of clinical trials by regulatory agencies, making it even more difficult to broaden access to new technologies. Ways to overcome some of the aforementioned obstacles include international collaboration, the creation of larger databases, and education (of physicians and patients), as well as the fostering of positive dialogues among medical societies, pharmaceutical companies, and advocacy groups.[13]

In daily clinical practice, precision oncology, in which pathological and molecular data, such as those related to prognostic and predictive biomarkers, are incorporated into the decision-making process, can identify the best candidates for some molecular-targeted therapies. Therefore, describing the molecular profile of patients with NSCLC in Brazil is essential to broadening access to therapies that are more safe and effective.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424. https://doi.org/10.3322/caac.21492
2. Lindeman NI, Cagle PT, Aisner DL, Arcila ME, Beasley MB, Bernicker EH, et al. Updated Molecular Testing Guideline for the Selection of Lung Cancer Patients for Treatment With Targeted Tyrosine Kinase Inhibitors: Guideline From the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology. J Thorac Oncol. 2018;13(3):323-358. https://doi.org/10.1016/j.jtho.2017.12.001
3. Mok TS, Wu YL, Thongprasert S, Yang CH, Chu DT, Saijo N, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med. 2009;361(10):947-57. https://doi.org/10.1056/NEJMoa0810699
4. Soria JC, Tan DSW, Chiari R, Wu YL, Paz-Ares L, Wolf J, et al. First-line ceritinib versus platinum-based chemotherapy in advanced ALK-rearranged non-small-cell lung cancer (ASCEND-4): a randomised, open-label, phase 3 study. Lancet. 2017;389(10072):917-929. https://doi.org/10.1016/S0140-6736(17)30123-X
5. Kris MG, Johnson BE, Berry LD, Kwiatkowski DJ, Iafrate AJ, Wistuba II, et al. Using multiplexed assays of oncogenic drivers in lung cancers to select targeted drugs. JAMA. 2014;311(19):1998-2006. https://doi.org/10.1001/jama.2014.3741
6. Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. N Engl J Med. 2016;375(19):1823-1833. https://doi.org/10.1056/NEJMoa1606774
7. Oliveira ACSM, Alves da Silva AV, Alves M, Cronemberger E, Carneiro BA, Melo JC, et al. Molecular profile of non-small cell lung cancer in northeastern Brazil. J Bras Pneumol. 2019;45(3):e20180181.
8. Araujo LH, Baldotto C, Castro G Jr, Katz A, Ferreira CG, Mathias C, et al. Lung cancer in Brazil. J Bras Pneumol. 2018;44(1):55-64. https://doi.org/10.1590/s1806-37562017000000135
9. Gomes JR, Amarante MPF, D'Alpino RDA, Moreira RB, Sousa TTS, Lino ADR, et al. Mutation profile in non-small cell lung cancer: Analysis of a Brazilian population. J Clin Oncol. 2015;33(15 suppl):e19115.
10. Gandhi L, Rodríguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, et al. Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. N Engl J Med. 2018;378(22):2078-2092. https://doi.org/10.1056/NEJMoa1801005
11. Gelatti AC, Moura F, Gaiger AMF, Macedo MP, Lopes LF, Zaffaroni F, et al. Lower prevalence of PD-L1 expression in advanced non-small lung cancer in Brazil. Journal of Clinical Oncology. 2018;36(15 suppl):e21140. https://doi.org/10.1200/JCO.2018.36.15_suppl.e21140
12. Cronemberger E, Baldotto C, Marinho F, De Marchi P, Araujo LH, Franke F, et al. P3.01-12 EGFR Mutation and Targeted Therapies: Difficulties and Disparities in Access to NSCLC Treatment in Brazil. J Thorac Oncol. 2018;13(10 Suppl):S871-S872. https://doi.org/10.1016/j.jtho.2018.08.1572
13. Santos M, Coudry RA, Ferreira CG, Stefani S, Cunha IW, Zalis MG, et al. Increasing access to next-generation sequencing in oncology for Brazil. Lancet Oncol. 2019;20(1):20-23. https://doi.org/10.1016/S1470-2045(18)30822-2