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Original article

Molecular profiling in Italian patients with advanced non-small-cell lung cancer: An observational prospective study

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ABSTRACT

Objectives: Molecular profiling of advanced non-small-cell lung cancer (NSCLC) is recommended according to European and Italian guidelines. However, molecular routine assessment remains still heterogeneous. This observational study aimed to take a picture of the real clinical practice in molecular testing and therapeutic choices in advanced Italian NSCLCs.

Materials and methods: This study prospectively enrolled newly diagnosed advanced or recurrent NSCLCs referred to 38 Italian centres, from November 2014 to November 2015. Information regarding molecular profiling and treatment choices were collected. Description of patients' outcome included overall survival (OS), progression-free survival in first (PFS1) and second-line (PFS2).

Results and conclusion: Among 1787 patients enrolled, 1388 (78%) performed at least one molecular analysis during the history of disease: 76% were tested for *EGFR*, 53% for *ALK*, 27% for *KRAS*, 16% for *ROS1*, 14% for *BRAF*, 5% for *HER2*, 4% for *MET* and 1% for *FGFR*. The remaining 399 patients (22.3%) did not receive any molecular test. Among patients receiving at least one molecular analysis, 583 (42%) presented a molecular alteration. Considering *EGFR* mutated and/or *ALK* rearranged patients (402), for which target agents were routinely reimbursed at time of study in Italy, the 86% received a personalized treatment as first and/or second line: the 90% (286) of *EGFR* mutants received an *EGFR* tyrosine kinase inhibitor, mostly gefitinib (41.1%) or afatinib (36.4%) while 74% (62) of *ALK* translocated patients received an *ALK* inhibitor, mostly crizotinib (64%). Median OS was 9.34 months (95% CI 8.62–10.0), median PFS1 was 4.61 months (95%CI 4.31–4.84) and median PFS2 was 2.76 months (95%CI 2.57–3.19).

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In the Italian clinical practice, routine molecular assessment was largely applied in NSCLC patients, according to national guidelines, but a low level of *ALK* test was reached. Most of *EGFR* mutants an *ALK* rearranged patients received a personalized treatment as first and/or second line.

1. Introduction

More than 41.000 lung cancer new diagnoses are expected in Italy each year, representing 11% of all cancer diagnosis [1]. Non-small-cell Lung Cancer (NSCLC) accounts 83% of lung cancers, and more than 50% of cases are diagnosed at advanced stage, when systemic treatment with palliative intention is the only available therapeutic approach [2]. The deeper and deeper knowledge about the biological mechanisms underlying cancer cells transformation and proliferation has allowed molecular target identification and specific inhibitors development, moving to a more personalized therapy. In particular, for Epidermal Growth Factor Receptor (*EGFR*) mutated and Anaplastic Lymphoma Kinase (*ALK*) rearranged cases, treatment strategy has substantially changed in the last few years [3].

In Europe, three different *EGFR* tyrosine kinase inhibitors (TKIs) (gefitinib, erlotinib and afatinib) have been approved in first-line for *EGFR* mutated patients, and the *ALK*-inhibitor crizotinib is the standard care for *ALK* rearranged cases [4–7]. Recently, osimertinib has been approved for patients presenting the *EGFR T790M* mutation and experiencing disease progression after a previous treatment with an *EGFR* TKI [8], while ceritinib (with also a positive opinion for an initial authorization of alectinib) has been approved in *ALK* rearranged patients progressing after crizotinib [9,10]. According to the European Society of Medical Oncology (ESMO) recommendations, *EGFR* and *ALK* analysis are recommended in all advanced non-squamous lung carcinoma and in advanced squamous carcinoma presenting a minimal or remote smoking history. Routine testing for other biomarkers is not currently recommended [11]. The Italian Association of Medical Oncology (Associazione Italiana di Oncologia Medica, AIOM) and the Italian Society of Pathology and Cytodiagnostic (Società Italiana di Anatomia Patologica e Citologia diagnostica, SIAPEC) produced similar indications, also reported in the national lung cancer diagnosis and treatment guidelines [12]. The molecular landscape is still constantly evolving and the knowledge about molecular alteration incidence is increasing. Because of the upcoming availability of new interesting results about other targeted agents (for instance, crizotinib in *ROS1* amplifications [13], dabrafenib or vemurafenib for *BRAF* mutations [14,15], trastuzumab, afatinib or dacomitinib for *HER-2* mutations [16,17]), it could be soon necessary to routinely perform further molecular tests as *ROS1*, *HER-2*, *BRAF* and others. Some experiences of multicentric networks providing a routinely molecular assessment in advanced NSCLC are already ongoing. The French National Cancer Institute (INCa) founded a national program for the systematic analysis of a molecular panel in advanced NSCLC patients diagnosed in more than 20 different oncologic centres in France [18–20]. The Lung Cancer Consortium represents a multicentric program in the United States with the same objective and other similar initiatives are ongoing across the world [21]. In Italy, no national program exists and no data or registries are available about the diffusion of molecular assessment in advanced NSCLC patients. Clinical practice remains still heterogeneous in terms of selection of patient, timing of requests, execution modality and molecular test application. This prospective observational study enrolled patients with advanced or recurrent NSCLC referring to Italian Oncological Centers in a one-year period, in order to explore the clinical practice about molecular assessing and treatments choices in this population and to have a real life situation in this specific context for dialogue with stakeholders.

2. Materials and methods

2.1. Patients and Italian "drug arsenal"

The study prospectively enrolled consecutive advanced or recurrent NSCLC patients referred to 38 Italian oncological centres from November 2014 to November 2015. Patients had a cytological or histological diagnosis of advanced NSCLC, staged according to the 7th edition TNM of the American Joint Committee on Cancer [22]. They underwent to diagnostic procedures, molecular evaluations and treatments choices according to the local practice and national guidelines. In the 2013 and 2015 AIOM guidelines edition the *EGFR* mutation and the *ALK* rearrangement assessments were strongly recommended in advanced NSCLC according to histological (adenocarcinoma, large cell carcinoma, mixed carcinoma with adenocarcinoma and not otherwise specified – NOS – carcinoma) or clinical features (young, never-smoker patients) [23,24]. Other molecular assessments were not recommended outside clinical trials.

When the study was performed, erlotinib and gefitinib were already approved for *EGFR* mutated patients, while afatinib became available few months later the accrual starting. Crizotinib was reimbursed only in second-line setting for *ALK* rearranged patients, while ceritinib, alectinib and osimertinib were available only within clinical trials. Patients with other molecular alterations received specific target drugs only within clinical trials or off-label administration. Otherwise, they underwent standard "not targeted" treatments. Nivolumab became available at the end of the accrual period only for pre-treated advanced squamous carcinoma, while the combination of nintedanib and docetaxel was not reimbursed.

This study was approved by the ethical committee of each oncologic centre involved. All patients gave written informed consent before inclusion in the study.

2.2. Data collection

The following data were collected: age, gender, ethnicity, family history of cancer, smoking status, second-hand smoke or toxic agents exposure, TNM stage according to the 7th edition of the American Joint Committee on Cancer [22], type of biological sample available for diagnosis, pathological diagnosis according to the 2011 International Association for the Study of Lung Cancer/European Respiratory Society classification [25], date of advanced or recurrent NSCLC diagnosis and molecular assessment during the history disease focusing mostly on eight genes: *EGFR*, *KRAS*, *BRAF*, *ALK*, *ROS1*, *MET*, *HER-2* and *FGFR*. The following data about oncologic treatment were collected: oncologic systemic treatments (up to the second-line), best response, date of disease progression, date of death or date of last follow-up assessment. The radiological assessments were evaluated by each investigator peripherally, without a central review.

All data were collected in a web platform called "Genomicitalia", adopting the more validated open source technologies (PHP, HTML5, CSS3) and human-machine interaction (HMI) methodologies. The web platform used well-validated technologies, as MySQL and Jquery, and the Model View Controller method to guarantee centralized security checks assuring the integrity and the quality of collected data. The San Luigi Hospital had full access to all the data as coordinator centre.

2.3. Molecular assessment

The molecular assessments were performed during the history of