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COMMENT

Personalizing medicine – strategies for implementing the evaluation of ALK rearrangement in non-small-cell lung cancer in Portugal☆

Personalizando a medicina – estratégias para implementar a avaliação do rearranjo do *ALK* no carcinoma do pulmão de não pequenas células em Portugal

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In 2008, in Portugal there were about 3300 new cases of lung cancer and almost the same number of deaths for this pathology.[1]

Improvement in NSCLC survival has been modest in the past 2 decades. From the early 1990s, there have been changes in the treatment of advanced NSCLC, including the introduction of new chemotherapy (CT) agents and regimens,[2] increasing use of salvage CT,[3,4] and the development of molecularly targeted therapies, specially the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs).[5] Tailoring treatment for every NSCLC patient has become the goal in terms of balancing clinical benefit against toxicity ratio.

We are still a long way from understanding the puzzle of genetic driver alterations in NSCLC. There are questions about the molecular characterization of lung cancer leading to the identification of different molecular alterations, such as *EGFR* mutations or *anaplastic lymphoma kinase* (*ALK*) translocations, and to subsets of lung cancer disease with a distinct natural history and response to treatment, together with the growing number of treatment options. How can we match the right patient population to the best treatment option? How much is society able to pay for the implementation of methods for molecular characterization of lung cancer disease? How can we improve the cost-effectiveness of these methods? Is society able to shoulder the burden of

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these new molecular diagnostic methods and new therapeutic drugs, even if they are at some level cost-effective? Will there ever be sufficient evidence to meet the challenge of cost containment?

Testing patients with advanced or metastatic NSCLC for *EGFR* mutation status may help doctors to determine those who are most likely to respond to EGFR TK inhibitors, tailoring therapy at diagnosis. In Portugal, we conducted a retrospective analysis of three major centers of the north of the country (Centro Hospitalar de V. N. Gaia, Instituto Português de Oncologia – Centro do Porto, Hospital de S. João), from July 2006 to January 2011 [personal data]. We studied 621 patients, with a mean age of 65 years (20–89 years-old), 30% of whom were female. The tumours were 64% adenocarcinoma and 21% squamous cell carcinoma. In the NSCLC population there was an *EGFR* mutation in 14.3% (17.5% with adenocarcinoma and 9.5% with squamous cell carcinoma), of which there was 6.3% in exon 19 (43.8% of mutated patients, mp), 5.3% in exon 21 (37.1% of mp), 1.7% in exon 20 (12.4% of mp) and 1.0% in exon 18 (6.7% of mp).

The work began 5 years ago in two major centers with the selection of some patients based on clinical characteristics. After perceived the notion of the role of the EGFR TK inhibitors in first-line treatment for advanced or metastatic NSCLC, these centers and *a posteriori* the third one began the analysis of all possible newly diagnosed patients. Meanwhile, there were discussions in national scientific forums, involving key opinion leaders and some cooperative groups such as the Portuguese Lung Cancer Study Group, about the need for *EGFR* mutation analysis. These meetings played a vital role in making everyone think about the following: how much lung cancer tissue is needed, how to optimize the circuit from harvesting of tissue to mutation analysis, how long should (could) we wait from harvest to analysis, what pathologists and geneticists need to give to those who treat patients.

ALK rearrangement (*ALK*+) was identified in NSCLC as an inversion in chromosome 2p with or without interstitial deletion, inv(2)(p21p23), resulting in the *echinoderm microtubule-associated protein-like 4* (*EML4*)-*ALK* fusion product.[6] This fusion oncogene, which represents one of the newest molecular targets in NSCLC, has a role as the key driver of lung tumorigenesis in a subset of patients[6,7] and can be effectively blocked by small-molecule inhibitors that target ALK. *EML4-ALK* is uncommon, occurring in 2–7% of all NSCLC.[8,9] It is more prevalent in patients who have never smoked or who have a history of light smoking and in patients with adenocarcinomas.[7,10,11] In the selected populations, the prevalence could be about 20–30% of patients with EML4-ALK mutations.[12] Nevertheless, sex, age and smoking status were not solid variables related with *ALK*-rearranged NSCLC.[13]

At present there is no standard method for detecting *EML4-ALK* mutations and various molecular techniques can be used. Fluorescent *in situ* hybridization (FISH) is the most common method currently used and also for enrolment in a clinical trial, although it is expensive and not routinely available. The standardization of all preanalytical variables, including tissue handling, fixation and processing, and the choice of anti-ALK antibodies are essential when using FISH.[14]

Crizotinib (PF-02341066, Pfizer) is an oral ATP competitive selective inhibitor of the ALK and MET TKs inhibiting tyrosine phosphorylation of activated ALK at nanomolar concentrations.[15,16] The first phase I trial published, evaluated 82 patients with ALK-rearranged advanced NSCLC who had received multiple previous therapies.[8] At a mean treatment duration of 6.4 months, the overall response rate was an impressive 57% with a rate of stable disease of 33%. The estimated probability of 6-month progression-free survival was 72%, with no median for the study reach. The drug resulted in grade 1 or 2 (mild) gastrointestinal side effects.

In an unselected NSCLC population, only around 4% have *ALK* rearrangements, and this small proportion of ALK+ lung cancer patients is a major limitation for access to the related drug, crizotinib. How we can identify this group of patients and which ALK testing method should be employed is a major issue for discussion and research.

It is possible to define three groups of tumors which do not harbor *ALK* rearrangements at all and could be excluded from *ALK* screening: those tumors with activating *EGFR* mutations, those in patients that showed an objective response to previous EGFR TK inhibitors treatments, and eventually tumors without TTF-1 expression.[17] But this strategy will only select patients after knowing the result of the *EGFR* mutation test or the evaluation of a response to the EGFR TK inhibitors, in this way losing at least 5–7 working days (for the first hypothesis) or 1–3 months (for the second group). In relation to TTF-1 expression, this marker is only negative in a minority of cases, and so its relevance to selection of *ALK*+ patients is marginal.

For Portugal, the initial step will be to involve some of the major centers, for instance in a selected population (stage IV adenocarcinoma NSCLC who never smoked or were light smokers). The goals will be to evaluate and optimize the circuits needed from harvest to the implementation of the test and how the clinicians obtain the result. At the same time, some national meetings will be necessary to discuss the importance of ALK, the test of its mutation and the value of crizotinib for *ALK*+ patients. After these initial stages, probably two or three major centers will decide to do the *ALK* mutation test on all new NSCLC patients, to learn more about the real incidence of the *ALK* mutation in the Portuguese NSCLC population. These phases will also allow us to request crizotinib for patients with *ALK*+ and so acquire experience with this drug.

At the end of the day, every clinician who treats NSCLC will need to characterize the tumor histologically and, particularly at the level of some molecular targets. These characteristics will influence the choice of the drugs, taking into account the drug related adverse events and of course survival rates. This is personalizing medicine.

References

1. GLOBOCAN 2008 (IARC). http://globocan.iarc.fr/factsheets/populations/factsheet.asp?uno=620 (date last accessed 11 July 2011).
2. Bunn PJ, Kelly k. New chemotherapeutic agents prolong survival and improve quality of life in non-small cell lung cancer: a review of the literature and future directions. Clin Cancer Res. 1998;4:1087–100.

3. Fossella F, De Vore R, Kerr R, Crawford J, Natale R, Dunphy F, et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens, The TAX 320 Non-Small Cell Lung Cancer Study Group. J Clin Oncol. 2000;18:2354–62.
4. Shepherd F, Dancey J, Ramlau R, Mattson K, Gralla R, O'Rourke M, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol. 2000;18:2095–103.
5. Giaccone G. Epidermal growth factor receptor inhibitors in the treatment of non-small-cell lung cancer. J Clin Oncol. 2005;23:3235–42.
6. Soda M, Choi YL, Enomoto M, Takada S, Yamashita Y, Ishikawa S, et al. Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. Nature. 2007;448:561–6.
7. Soda M, Takada S, Takeuchi K, Choi YL, Enomoto M, Ueno T, et al. A mouse model for EML4-ALK positive lung cancer. Proc Natl Acad Sci USA. 2008;105:19893–7.
8. Kwak EL, Bang YJ, Camidge DR, Shaw AT, Solomon B, Maki RG, et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. N Engl J Med. 2010; 363:1693-1703, Erratum in: N Engl J Med. 2011; 364(6):588.
9. Kris MG, Johnson BE, Kwiatkowski DJ, Iafrate AJ, Wistuba II, Aronson SL, et al. Identification of driver mutations in tumor specimens from 1,000 patients with lung adenocarcinoma, The NCI's Lung Cancer Mutation Consortium (LCMC). J Clin Oncol. 2011; Suppl.:29 [abstr CRA7506].
10. Perner S, Wagner PL, Demichelis F, Mehra R, Lafargue CJ, Moss BJ, et al. EML4-ALK fusion lung cancer: a rare acquired event. Neoplasia. 2008;10:298–302.
11. Wong DW, Leung EL, So KK, Tam IY, Sihoe AD, Cheng LC, et al. The EML4-ALK fusion gene is involved in various histologic types of lung cancers from nonsmokers with wild-type EGFR and KRAS. Cancer. 2009;115:1723–33.
12. Shaw AT, Yeap BY, Mino-Kenudson M, Digumarthy SR, Costa DB, Heist RS, et al. Clinical features and outcome of patients with non-small-cell lung cancer who harbor EML4-ALK. J Clin Oncol. 2009;27:4247–53.
13. Paik JH, Choe G, Kim H, Choe JY, Lee HJ, Lee CT, et al. Screening of anaplastic lymphoma kinase rearrangement by immunohistochemistry in non-small cell lung cancer, correlation with fluorescence in situ hybridization. J Thorac Oncol. 2011;6:466–72.
14. Hicks DG, Tubbs RR. Assessment of the HER2 status in breast cancer by fluorescence in situ hybridization: a technical review with interpretative guidelines. Hum Pathol. 2005;36:250–61.
15. McDermott U, Iafrate AJ, Gray NS, Shioda T, Classon M, Maheswaran S, et al. Genomic alterations of anaplastic lymphoma kinase may sensitize tumors to anaplastic lymphoma kinase inhibitors. Cancer Res. 2008;68: 3389–95.
16. Christensen JG, Zou HY, Arango ME, Li Q, Lee JH, McDonnell SR, et al. Cytoreductive antitumor activity of PF-2341066, a novel inhibitor of anaplastic lymphoma kinase and c-Met, in experimental models of anaplastic large-cell lymphoma. Mol Cancer Ther. 2007;6:3314–22.
17. Koh Y, Kim DW, Kim TM, Lee SH, Jeon YK, Chung DH, et al. Clinicopathologic characteristics and outcomes of patients with anaplastic lymphoma kinase-positive advanced pulmonary adenocarcinoma, suggestion for an effective screening strategy for these tumors. J Thorac Oncol. 2011;6:905–12.