Lung cancer management: leaving behind the 'one-fits-all' concept for a personalized approach

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Q What are the main differences between the various types of non-small-cell lung cancer?

The difference between various subtypes of non-small-cell lung cancer (NSCLC) is a morphological definition. Sometimes diagnosis can be difficult and the pathologist is required to perform special immunohistochemistry stains that will help differentiate different histologies such as adenocarcinoma, squamous cell carcinoma and others. In this regard, it is important to reaffirm that the diagnosis of large-cell carcinoma must be made with a tumor-resected specimen and not through fine-needle aspiration biopsy. In the past, all NSCLC patients were treated similarly (using platinum-based therapy); however, over the last years histological subtype is crucial for defining the therapy to be used [1–3]. To date, histology is a 'rudimentary' predictive biomarker; the discoveries of driven mutations and other molecular phenotypes in these histological subtypes of NSCLC are helping us to individualize therapy nowadays. For now, medical oncologists and pathologists must make all efforts to define the correct histological subtype in each patient.

Q How do clinicians detect, diagnose & stage NSCLC?

Currently, there is no generally accepted screening test for lung cancer. Several lung cancer screening methods have been studied including tests of sputum (mucus brought up from the lungs by coughing), chest x-rays and spiral (helical) CT scans. To date, there is an international effort for lung cancer screening in those patients who have a high risk of developing lung cancer. The International Early Lung Cancer Action Program (I-ELCAP) is a

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group of 48 institutions in nine countries, dedicated to studying the benefits associated with early detection of lung cancer by CT screening, and the best practices for using it. Nonetheless, this month, the American Lung Association (ALA) recommended low-dose CT screening for current or former smokers with at least 30 pack-years, aged 55–74 years. As per ALA, low-dose CT should be recommended for screening in those individuals who meet the National Lung Screening Trial (NLST) criteria: current or former smokers aged 55–74 years with a smoking history of at least 30 pack-years and no history of lung cancer. On the other hand, the US Preventive Services Task Force has not recommended screening for lung cancer despite the results from the National Cancer Institute's NLST published in the *New England Journal of Medicine* in August 2011 [4]; that study showed that screening high-risk individuals with CT scan reduced lung cancer deaths by 20.0% compared with chest x-rays.

However, approximately 20% of all NSCLC cases are seen in never smokers. For them, there are not methods approved for screening. The diagnosis of NSCLC can be reached via several methods: a surgical resection of the tumor or a biopsy. The latter could be carried out via bronchoscopy, or ultrasound- or CT-guided biopsy. In addition, cytology specimen from the endobronchial field (airway) or from pleural effusion (if malignant) or other suspicious lesion can yield the diagnosis. The staging of a patient with lung cancer is carried out by radiological studies. These could be carried out by CT or PET or a combined modality of these two known as CT–PET. Depending on tumor size, location of lymph nodes, the presence or not of satellite lesions and their location, clinicians are able to define the staging that is crucial for therapeutic decisions and prognosis. Early-stage lung cancers (I and II) are suitable for surgical resection. Usually, stage IIIA and IIIB are treated with combined modality of treatment (chemotherapy plus radiation therapy) and stage IV disease is treated with systemic therapy.

Q Why is the prognosis for NSCLC so poor?

The prognosis of NSCLC is poor because, first, most of the patients are diagnosed at late stages (IIIB and IV). Second, with the exceptions of few mutations, the genome of lung cancer is complex and does not show an abnormality that is overexpressed and that may become a potential target for therapeutic development. In different studies, approximately 40% of NSCLCs have been found to have mutations, and therapy development and clinical trials are ongoing; however, for most of the cases, no driven mutations have been identified yet.

Q What is currently the most successful treatment for lung cancer?

The most successful therapy for lung cancer and specifically NSCLC has been the discovery of a driven mutation in the EGF receptor (EGFR). This mutation in the EGFR has been effectively targeted by tyrosine kinase inhibitors (TKIs) such as erlotinib and gefitinib. These two agents exert their effect on the intracellular domain of this receptor [5–10]. Conversely, a monoclonal antibody known as cetuximab blocks the extracellular domain of the receptor, avoiding the interaction between the EGF ligand and its receptor, and thus inhibiting intracellular signaling downstream [11]. Moreover, a vaccine against the EGF ligand has been developed with encouraging results [12–16]. Other biological agents have also been developed, but if we consider the number of patients who can benefit from all these agents, certainly it has been EGFR TKIs that have been the agents with major success in lung cancer treatment over the last 10 years. These agents have indications in first-, second- and third-line of treatment. It is worth noting that their toxicity profile is superior to conventional cytotoxic chemotherapy.

Q What are the most promising treatments presently in clinical trials?

With the discovery of the EGFR pathway and its crucial role in tumorigenesis as well as the development of an effective targeted therapy (e.g., TKIs), many clinical trials are investigating other pathways in NSCLC.

To date, we have a better understanding of many intracellular pathways and the crosstalk among them that sometimes calls for resistance to therapy. There is tremendous interest in targeting angiogenesis and other relevant signaling pathways such as PTEN, mTOR, PI3K, Ras, MAPK and MEK. An area of active research is how to restore sensitivity to EGFR TKIs once the patient has developed resistance to them. At least in part, mechanisms of resistance to TKIs, such as *de novo* T790M mutation and overexpression of c-Met, have emerged [17,18]. Clinical trials are underway targeting these pathways to make the tumor cells susceptible to TKIs again [19]. The list of novel targeted agents in early development is large.

Q Why is immunotherapy for lung cancer such an appealing option?

As we know, conventional systemic chemotherapy is palliative, and even with the novel targeted agents the survival advantage is modest. Immunotherapy research in NSCLC has shown it to be feasible, safe and effective in recent years [20–27]. Because of that, there are several Phase III clinical trials ongoing to look into survival advantage in early-stage lung cancer (after resection) as well as late stage. Also, novel vaccines have shown a favorable toxicity profile and the question here is to use this modality either in combination with chemotherapy or after chemotherapy and sustain the responses obtained. Although Phase II clinical data from many vaccines look promising, we must wait for the results of the ongoing confirmatory trials.

Q How close are we to seeing vaccines for NSCLC in the clinical setting?

Three vaccines are in the first stages of clinical trials [101–103]: belagenpumatucel-L, MAGE-A3 and BLP-25. If one of these vaccines proves to offer survival advantage in the Phase III trials, the day to see a vaccine routinely used in clinical practice is not too far away.

Q What do we know about biomarkers for NSCLC? What is the prognostic & predictive value of the markers already identified?

This is a broad topic in thoracic oncology. At least two mutations have proved to be of clinical significance and tests must be ordered anytime we see a never-smoker patient (regardless of the histology) or a nonsquamous cell histology. Thus, providing another reason as to why it is so important to define the correct diagnosis. Many researchers will argue that every patient, regardless of the histology, should be tested if we are moving into personalized medicine. Nonetheless, many studies have clearly identified those groups that should be tested. Mutation in the EGFR is a prognostic marker for survival and a predictive biomarker for response to TKIs (e.g., erlotinib and gefitinib) [6]; the presence of *EML4/ALK* translocation is a predictive biomarker for response to an ALK inhibitor recently approved by the US FDA known as crizotinib [28,29]. These two genetic abnormalities are recognized by the National Comprehensive Cancer Network in its treatment algorithm guidelines. There are many other biomarkers, such as *ERCC1*, *RRM1* and *BRCA1* (DNA repair genes), thymidilate synthase, β-tubulin and others, which are waiting for large, confirmatory clinical trials [30–37].

Q How does a clinician decide whether to offer a patient maintenance or switch maintenance therapy versus close observation?

The best clinical parameter to decide if a patient qualifies for palliative chemotherapy or any therapy for lung cancer is the performance status. Once the decision to treat is made, the second parameter is what was the response attained during the first four to six cycles of chemotherapy. For those patients who attained a clinical benefit (meaning stable diseases, partial remission [at least 30% tumor reduction] or complete remission [tumor disappear]), there are three drugs approved by the FDA and EMA: bevacizumab (the ECOG 4599 trial), pemetrexed (the JMEN study and, recently, the PARAMOUNT trial) and erlotinib (the SATURN trial) [3,38–40]. All these trials have met their primary end point. The ECOG 4599, JMEN and

SATURN trials showed an overall survival advantage. The PARAMOUNT trial met its primary end point (progression-free survival), and overall survival was recently presented at the annual meeting of the American Society of Clinical Oncology (ASCO) in Chicago, IL, USA this past June. The results were positive for overall survival. The PARAMOUNT trial, which was recently published in *Lancet Oncology* by Paz-Ares and colleagues, responded to the niche left by the JMEN trial. In the JMEN study, nonsquamous NSCLC patients received four cycles of nonpemetrexed-based chemotherapy doublet followed by either placebo versus pemetrexed [38]. This is a classic example of switch maintenance as none of the patients received pemetrexed initially. As pemetrexed is well tolerated and has a favorable toxicity profile, clinicians ask themselves: is pemetrexed also effective as continuation maintenance if used upfront? This was the question answered by the PARAMOUNT trial [39]. Thus, pemetrexed could become a standard maintenance (either continuous or switch) therapy soon. Some clinicians prefer to use switch maintenance if the patient only attains stable disease during the initial four to six cycles of therapy. In this sense, this is practically moving second-line therapy immediately upfront. Many clinicians will opt for continuation maintenance if clinical response was seen at the initial therapy. In my personal opinion, I think that we should exhaust as much as we can from any specific treatment while the patient is not showing progression of disease and is tolerating the therapy well. Thus, we can expand our armamentarium for our patients for as long as we can.

In terms of observation, I personally disagree with it as all studies now using continuation or switch maintenance have shown either survival or progression-free survival advantage. Furthermore, studies have also shown that at least 30% of patients, who were not chosen to receive maintenance therapy, never receive second-line therapy [41–43]. So, by using maintenance therapy, the number of patients who will see a second- or third-line therapy will significantly increase.

Q Are we still learning about the pathways involved in NSCLC? What does this mean for drug development?

Even with the case of the EGFR pathway – the most studied tumorigenesis mechanism in NSCLC in recent years – we still do not have the entire picture of how this important receptor interacts with others and which are the crosstalks that bring resistance. So, yes, we are constantly learning, but we are far away from deciphering the complexity of the lung cancer genome.

Q What are your hopes for the future of treatment for NSCLC? What advances would you like to see in the next 5 years?

The hope for NSCLC treatment has never been so positive than at this present time. However, we need to understand that more resources are needed to foster clinical investigations in order to move forward in this field.

The most needed information in thoracic oncology is to define who really needs to be treated or not after surgical resection in order to develop a strong prognostic biomarker. Research in this direction is underway; hence, we will avoid the delivery of unnecessary cytotoxic therapies to patients. Another area eagerly awaiting for us is immunotherapy. Immunotherapy has already proven to be effective in solid tumors such as prostate cancer and melanoma. Thus, it will be great to have a vaccine that may consolidate surgery by boosting the patient's immune system. Although many TKIs with antiangiogenic properties have been developed and studied in the clinic, bevacizumab remains the only approved and effective drug. In this regard, we need to continue looking for predictive biomarkers that can help us to sort out which patients will benefit from this anti-VEGF agent as well as the others that have not found their niche yet.

Finally, we are continuing to move towards personalized medicine. Now we have to research further in areas in which we have already found partial success. For example, there are differences between EGFR mutations of the same *EGF* gene in terms of how they will response to TKIs.

Thus, patients whose tumors harbor the EGFR mutation should receive TKIs as frontline. The question for the future is: can we individualize the personalized therapy further?

As research in lung cancer continues its steady progress, more questions emerge. These questions are the fuel for all us researchers to continue our battle against cancer, and hopefully to find the cure one day.

Financial & competing interests disclosure

E Santos is a member of the Speaker Bureau for Genentech, Lilly US Oncology, Pfizer and Bristol-Myers Squibb. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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