



New discoveries in lung cancer biology: paving the road of personalized medicine

“Discoveries of novel mutations and carcinogenic pathways, immunoregulation and better diagnostic tools have contributed to recent advances in NSCLC. In the years to come, the future of lung cancer treatment and outcomes will look more promising than ever.”

In the first issue of *Therapy* 2011, we have dedicated our best effort to provide the latest information in non-small-cell lung cancer (NSCLC), as well as how advances in molecular medicine are being used to improve both response rate and survival in lung cancer patients. The usefulness and crucial role that molecular medicine plays in medical oncology has recently been recognized. For many decades, lung cancer was considered:

- A dismal disease with no chances for a meaningful survival
- A disease that carries a heterogeneous phenotype making it difficult to target
- A disease that represents a challenge for early diagnosis
- An entity that escapes the immunosurveillance of the host

Fortunately, advances in molecular biology and immunology have begun to decipher important tumorigenesis mechanisms that will allow us to customize our therapeutic armamentarium to individuals who carry specific molecular phenotypes. Therefore, we will be able to target patients' tumors more effectively and, thus, obtain a better quality of response than what we have seen in the past. We expect that this personalized approach will also improve survival and decrease side effects from therapies in lung cancer patients.

Several Phase III clinical trials have resulted in fruitful results in the NSCLC field in recent years. These studies have not only changed clinical practices, but have also increased our therapeutic armamentarium against lung cancer. Clinical trials, such as JMBD (cisplatin/pemetrexed vs cisplatin/gemcitabine plus a preplanned analysis by histology) [1], pemetrexed maintenance trial after clinical benefit from conventional cytotoxic therapy [2], Iressa Pan-Asia Study (IPASS; gefitinib vs carboplatin/paclitaxel with

a preplanned analysis by EGF receptor mutation) [3], and Sequential Tarceva in Unresectable NSCLC (SATURN) trial (erlotinib as maintenance, or 'immediate second-line' or sequential after clinical benefit from conventional chemotherapy) [4], have established new guidelines in the treatment of lung cancer. However, the progress needs to continue.

Novel data regarding the use of irreversible tyrosine kinase inhibitors (TKIs) presented at the 35th European Society of Medical Oncology (ESMO) meeting is outlined in this issue by Bordoni [5]. The mechanism of action of reversible TKIs such as gefitinib and erlotinib is not fully understood, and several questions remain to be answered. For our patients on TKI therapy, it is crucial to know the outcome if patients exposed to gefitinib or erlotinib are challenged with an irreversible TKI, what will follow after patients acquire resistance to the TKI, and how to monitor acquired mutations and the toxicity profile of these novel agents. Bordoni thoroughly reviews and discusses the potential role of afatinib (also known as BIBW 2992), an irreversible EGF receptor (EGFR)/Her2 neu TKI [5]. Results from the LUX-Lung trial program including LUX-Lung 1 (presented at ESMO in October 2010) and LUX-Lung 2 are discussed, as well as ongoing clinical trials such as LUX-Lung 3 and 5. Afatinib appears to be effective not only in EGFR-mutated tumors, but also in those who overexpress Her2 neu [5].

Neoadjuvant chemotherapy for early-stage and locally advanced NSCLC is under investigation. The interest in exploring these clinical settings without jeopardizing patients' safety has been fueled by several factors, including a better toxicity profile and efficacy attained from this new generation of chemotherapy and targeted agents, better supportive care and more precise methods of radiotherapy delivery. Jafri and Mills extensively review this controversial topic, and



Edgardo S Santos

University of Miami Leonard M Miller
School of Medicine, Sylvester
Comprehensive Cancer Center,
1475 NW 12th Avenue, D8-4, Miami,
FL 33136, USA
Tel.: +1 305 243 3286
Fax: +1 305 243 3289
esantos2@med.miami.edu

provide the actual data from several randomized clinical trials, as well as meta-analyses [6]. They also explore whether to offer chemotherapy alone or in combination with radiation therapy as a neoadjuvant depending on the nodal status of the mediastinum. Although there is no clear-cut evidence to make one or the other modality the standard of care, the article exemplifies the need for more research in this controversial area.

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In the metastatic setting, the success of the IPASS has served as a platform to explore other possibilities of exploiting the EGFR pathway in NSCLC [3]. EGFR TKIs have revolutionized the management of NSCLC, especially in those patients whose tumors harbor an *EGFR* mutation [3,4,7-9]. These mutations are more commonly seen in never smokers and the adenocarcinoma histologic subtype. Many Phase III trials have established TKIs as the preferred therapy for patients with *EGFR* mutant tumors. However, it was not until the recent ESMO meeting in Milan, Italy, where Zhou *et al.* presented the final results of the OPTIMAL (CTONG 0802) trial in which all randomized patients had an activating *EGFR* mutation [9]. This trial was statistically significant in favor of erlotinib versus carboplatin/gemcitabine combination for progression-free survival (13.1 vs 4.6 months, respectively); data on overall survival are not yet available. Thus, this therapy has become the standard of care and first-line therapy for those patients whose tumors harbor this abnormality. Consequently, there is tremendous interest in improving the results already obtained with TKIs. What about combining these targeted agents with conventional chemotherapy or radiation therapy in a ‘selected’ population? This has been addressed in this issue by Bastos and Lilenbaum, who point out the disappointing results obtained when TKIs have been combined with chemotherapy in an unselected group of lung cancer patients [10]. Nonetheless, cetuximab, a monoclonal antibody against EGFR, has resulted in promising and interesting results in Phase II trials when combined with radiation therapy [11]. This monoclonal antibody has also demonstrated some mixed responses in combination with chemotherapy. A Phase II trial

from the Southwest Oncology Group (SWOG) combined two biologic agents, cetuximab and bevacizumab, with carboplatin/paclitaxel, followed by maintenance therapy with cetuximab/bevacizumab [12]. SWOG 0536 met its primary end point and, thus, a Phase III trial, SWOG 0819, is on active accrual.

In 2009, maintenance therapy emerged once again in the NSCLC therapeutic scene; this time with well-designed studies and positive results. The concept and use of different modalities of maintenance therapy have been reviewed by Lebovic *et al.* [13]. The arrival of targeted agents such as erlotinib and cytotoxic agents with better toxicity profiles (with the use of adequate prophylaxis), such as pemetrexed, has resulted in overall survival advantage when used as maintenance therapy [2,4]. Other biological agents with an acceptable toxicity profile, such as bevacizumab and cetuximab, have also been tested in the context of maintenance therapy [14,15]. However, these drugs have not been studied in placebo-controlled trials. As clinicians, we are looking to control patients’ disease, obtaining a ‘good’ initial response, or a durable and truly stable disease. Therefore, we believe that we may impact the quality of life of patients with advanced NSCLC, and perhaps we can increase the number of patients who may take second-line therapy, providing that their progression is accompanied with fewer symptoms and a lower impact on the patient’s performance status. The article by Lebovic *et al.* helps to clarify the dilemma between maintenance, sequential or immediate second-line therapy versus the ‘watch-and-wait’ approach that has dominated the field of clinical intervention in the last 40 years in terms of NSCLC treatment [13]. The goal of maintenance therapy is to preserve the initial response attained with a first-line therapy without significantly affecting the patient’s quality of life and performance status. In other words, put the disease in a chronic state for as long as possible. Lebovic *et al.* provide a description of two different types of maintenance approach. Whether pemetrexed should be included in combination with platinum-based therapy upfront and continued as a maintenance therapy or if another agent should be used as the maintenance therapy remains to be answered in the context of a clinical trial.

Another mechanism for the treatment of lung cancer that has been studied in the last decade is the development of vaccines. To date, we know that NSCLC is also suitable for targeting by this approach. The progress in this field has been

more cumbersome for researchers owing to the intense work required to elaborate the vaccines, as well as the cost of manufacturing these compounds. In a very comprehensive article, Holt *et al.* explain the different mechanisms used to activate the host's immune system, either by using antigen-specific or a nonspecific driven immune reaction against NSCLC cells [16]. As a result of encouraging outcomes seen in Phase II clinical trials, several Phase III, multinational, randomized clinical trials are currently investigating certain vaccines that may impact survival in NSCLC [17–19]. Holt *et al.* present a close-up picture of the MAGE-A3 as Adjuvant Non-Small-Cell Lung Cancer Immunotherapy (MAGRIT) trial, as well as the scientific platform that spurred the sponsor into launching a major Phase III worldwide trial [16]. This Phase III trial is examining the effect of MAGE-A3, a promising protein that is expressed in 50% of NSCLC. This study is actively recruiting worldwide in the adjuvant setting. The importance of adjuvant therapy is dependent on the poor survival of NSCLC patients, even in the early stages. Therefore, there is a desperate need to improve the results that a simple surgical resection approach can offer. Adjuvant chemotherapy is considered standard of care for patients with pathological stage II–IIIA, while stage IB is still controversial, and is currently the subject of investigation. Therefore, vaccination is a potential strategy to support these efforts in the adjuvant setting; other trials are examining the usefulness of vaccination in advanced stages (e.g., the Stimulating Targeted Antigenic Responses to NSCLC [START] and Survival, Tumor-free, Overall, and Progression-free [STOP] trials). The latter trial has an innovative concept: instead of stimulating the immune system via tumor antigen, it aims to counteract the immunoregulatory effect of tumor-derived TGF- β 2. The study name represents the expected end points (tumor-free, overall and progression-free survival) of this international, multicenter, randomized, double-blind study involving up to 700 individuals with advanced-stage NSCLC.

Finally, as mitigated by Ku and de Lima Lopes Jr, NSCLC was originally believed to be a homogenous disease and, hence, it was uniformly treated with cytotoxic chemotherapy, usually with the same chemotherapy regimen [20]. Today, NSCLC is recognized as being composed of distinct molecular subtypes, corresponding to specific clinical phenotypes. In 2007, a new mutation, *EML4-ALK*, was discovered in NSCLC [21]. Patients whose tumors carry this mutation do not respond to conventional chemotherapies and commercially available TKIs; therefore, it is imperative that we understand when and who should be tested for this rare mutation.

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In summary, this issue of *Therapy* examines the actual state-of-the-art management of NSCLC as well as ongoing research in the area. Beyond the use of novel combinations of cytotoxic agents, this issue focuses on a novel concept in oncology: customizing therapy. The molecular profile of the patient's tumor is one of the key elements that will help us to deliver personalized medicine. Discoveries of novel mutations and carcinogenic pathways, immunoregulation and better diagnostic tools have contributed to recent advances in NSCLC. In the years to come, the future of lung cancer treatment and outcomes will look more promising than ever.

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