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Non-small cell lung cancer: the challenges of the next decade

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With about 1.5 million new cases per year, lung carcinoma is the most frequent cancer in the world; it is also the first killer in adult patients, accounting for more than a fifth of deaths from cancer (Ferley et al., 2008). It is partly preventable with smoking cessation and it is slowly decreasing in the developed countries because of the many campaigns against tobacco addiction developed in the last decades but this is not the case in developing countries. In addition, we are observing a growing amount of lung cancer in females and in the never smoker population which may represent a significant amount of lung tumors in some series (Ferley et al., 2008). Since multiple pathways implicated in the development of lung tumors can now be better identified, several new therapeutic options may now be offered to patients. Nevertheless, the heterogeneity of non-small cell lung cancer (NSCLC) make it a particularly complex and unpredictable disease at presentation. A large number of new molecular targets are reported every year that may potentially be of interest for drug development. However, only very few targeted agents have reached the registration step up to now. There are several reasons for these frequent failures. They include (i) not predominant alterations of pathways, (ii) multiplicity of potentially predominant alterations, (iii) lack of specificity of targeted molecules, (iv) suboptimal strategies of registration, often related to an excessive speed in the design and launch of clinical trials mostly focused on registration requirements.

Thousands of teams are working on these issues worldwide but the processes of publication are not flexible. They are generally slow when any signal, positive or negative, should be published as soon as it is discovered.

That is the reason why on-line journals with the fastest review process must be developed in order to ensure a large divulgation of the most recent biological and clinical data.

Frontiers in Thoracic Oncology wants to offer this opportunity to the many fundamental and translational researchers who work on thoracic tumors and particularly NSCLC, the most frequent thoracic malignancy.

The major fields to be considered for NSCLC in the next decade include prevention, diagnostic procedures, surgery, radiotherapy, chemotherapy, targeted agents and vaccines, and the strategic management of each lung cancer patient at different stages of the disease.

Prevention is a key issue for the control of cancer. Smoking cessation in the world would prevent the majority of lung tumors. Nevertheless, up to 30% of lung cancer are diagnosed in never smokers in the developed countries and a lot remains to be explored to identify other potential agents responsible for the development of adenocarcinoma in particular.

Chemoprevention in patients at high risk of development of lung cancer is another research area that has so far not been fully exploited, especially in view of the explosion of knowledge about the molecular abnormalities that have been identified in this disease. Large randomized studies performed in the 1980s and 1990s have been substantially negative, but they were mainly based on weak epidemiological assumptions rather than biological evidence.

Diagnostics have considerably evolved in the last 20 years and positron emission tomography (PET) scan, endobronchial ultrasound (EBUS), and transesophageal ultrasound (EUS) are now part of an accurate preoperative assessment of potentially operable patients in most referral centers. But diagnostics also include the molecular profile of each tumor. An explosion of new targets have been observed in the last decade, several of which having already led to the development of new targeted agents (EGFR, ELM4–ALK in particular). More than half patients with lung adenocarcinoma have a single driver mutation according to the Lung Cancer Mutation Consortium (The National Lung Screening Trial Research Team, 2011). An extensive molecular profile of each tumor is becoming a standard in the most experienced centers. Proteomics are still in their early development era but they might play a major role in the very near future.

On an other hand, the role of low-dose CT scan for early detection of lung cancer will probably increase in the next future since the National Cancer Screening Trial recently reported a benefit of three yearly CT scans compared to chest-X-rays in a selected population at risk (Kris et al., 2011). Abnormalities in the tissues surrounding the tumor may potentially allow identifying those micro-nodules (<1 cm) most likely to be malignant.

SURGERY

Technological advances, personal experience, and knowledge generated from clinical trials continue to improve our understanding on the possibilities offered by surgery for staging and surgical management of patients with lung carcinoma.

There have been significant advances in evaluating the role of surgery as part of multimodality management in patients with potentially resectable primary tumors and mediastinal lymph node involvement. Data from the recently published IASLC staging classification suggest that patients with single level N2 disease have the same survival as patients with multi-level N1 disease, and this has led to the questioning of the rationale of excluding all patients with N2 disease from surgery (Rusch et al., 2007). Moreover clinical trials of induction chemotherapy in patients with N2 disease suggest similar outcomes in survival between operable patients randomized to surgery or further radiotherapy (Shepherd et al., 1998; Johnstone et al., 2002; van Meerbeeck et al., 2007; Albain et al., 2009).

Lung sparing will probably be one of the priorities of lung cancer management in the future. Most organs have already benefited

from partial preservation in the management of cancer. The option for patients with limited lung function have included bronchoplastic and angioplastic sleeve resections and, when this is suitable, sublobar resection (in particular segmentectomy), where as much as possible of the normal lung is preserved. Limits of economic dissection and preventive treatment of preserved lung tissues are still investigational at the moment.

Extensive surgery for some T4 tumors is another area of potential improvement and debate since a complete resection may be the most appropriate curative treatment for such patients.

RADIOTHERAPY

Radiotherapy has an important role in both the curative and palliative treatment of NSCLC. Approximately three-fourth of patients with NSCLC eventually benefit from radiotherapy (Delaney et al., 2003). Recent advances in radiotherapy for lung cancer have been more strongly influenced by developments in technology rather than by an improved understanding of the radiobiology of the disease.

Precise definition of the tumor anatomical extent is critical for accurate placement and shaping of the radiotherapy beams together with gating techniques. With recent advances in stereotactic radiotherapy (Baumann et al., 2009) and with the introduction of radiofrequency ablation (Simon et al., 2007), elderly patients, those with poor lung function and those with local relapse and those patients who are not candidate for a surgical resection can now be offered a wide range of local therapeutic modalities.

CHEMOTHERAPY, TARGETED AGENTS, AND VACCINES

Despite optimal surgical management, 5-year survival rate of resected NSCLC ranges between 30 and 80% according to pathological stage. The update of the individual data-based NSCLCCG meta-analysis has showed a significant benefit for adjuvant cisplatin-containing chemotherapy with a 4% improvement of survival at 5 years (HR = 0.86; Stewart et al., 2007). A similar benefit has been reported with preoperative chemotherapy in another recent meta-analysis (5% improvement at 5 years; HR = 0.88; Burdett et al., 2011). A comparison of preoperative versus postoperative chemotherapy has been done in the NATCH trial. No significant difference was observed among patients in this trial (Felip et al., 2009). Targeted agents and vaccine therapy are also being evaluated as an adjuvant treatment for operable NSCLC. Randomized studies are ongoing (Tyagi and Mirakhur, 2009).

Rather than asking whether neo-adjuvant or adjuvant chemotherapy should be preferred, the key issue may be to determine which patients should be treated with peri-operative medications. Some tumor markers such as ERCC1, RRM1, MSH, beta-tubulin, or BRCA1 may have a predictive value for selecting those patients who will mostly benefit from adjuvant treatments (Olaussen et al., 2006; Rosell et al., 2007; Seve et al., 2007; Zheng et al., 2007; Kamal et al., 2010). Developing molecular-based therapeutic strategies will certainly be one of the major challenges over the next few years. The neo-adjuvant approach offers a unique opportunity to test new drugs and to compare the tumor characteristics prior to and following induction therapy (Altorki et al., 2010). Several randomized adjuvant studies have recently been initiated in Europe and in North America, based on the molecular characteristics of patients tumor.

The benefit obtained with the combination of radiotherapy and chemotherapy in locally advanced inoperable NSCLC is modest but significant and well established. Several randomized trials comparing radiotherapy–chemotherapy given sequentially or concomitantly have suggested a better outcome when both modalities are given early and simultaneously (Auperin et al., 2006). But there is still room for a large improvement with the use of cytotoxic and targeted agents in combination with modern radiotherapy.

Platinum-based chemotherapy still remains the standard treatment for most of fit patients with advanced NSCLC; Drug selection has not been based on histological subtype until recently when it was recognized that the multi-targeted anti-folate agent, pemetrexed was less active in patients with squamous carcinoma (Scagliotti et al., 2009). The addition of targeted agents to platinum-based doublets has been studied extensively in numerous clinical trials over the past decade and no additional benefit has been observed except for the angiogenesis inhibitor bevacizumab, a monoclonal antibody targeting vascular endothelial growth factor (Sandler et al., 2006). Cetuximab, a monoclonal antibody directed against the epidermal growth factor receptor, has also been evaluated extensively with chemotherapy for NSCLC. Although all trials demonstrated higher response rates, most failed to confirm either a statistically significant or clinically meaningful survival benefit (Pirker et al., 2009).

Numerous predictive and prognostic markers have been evaluated in NSCLC, but until recently, no single molecular marker has been found useful for either patient selection or to select specific drugs (Shepherd and Rosell, 2007; Coate et al., 2009).

In the last years, several randomized trials have compared the EGFR Tyrosine kinase inhibitors gefitinib and erlotinib to standard chemotherapy. All these studies have showed that patients with sensitizing mutations in exons 19 or 21 of the EGFR TK domain, derived significantly greater benefit from EGFR TKI Inhibitors, whereas the opposite was true for patients with wild-type EGFR ($p < 0.0001$; Mok et al., 2009; Maemondo et al., 2010; Mitsudomi et al., 2010; Rosell et al., 2011). Gefitinib has been the first agent to be approved based on a molecular test in NSCLC.

It has always been admitted that six cycles of first-line chemotherapy were enough, mainly because the toxicity of continued doublet therapy. Recently, however, there has been renewed interest in evaluating maintenance therapy with single-agent chemotherapeutic agents or molecularly targeted agents. The largest and most convincing trial assessed the value of maintenance pemetrexed in patients with NSCLC not progressing after four cycles of doublet chemotherapy. This study demonstrated both a statistically significant and a highly meaningful survival benefit for patients with non-squamous histology who received maintenance pemetrexed (Ciuleanu et al., 2009). An advantage for maintenance has also been reported with erlotinib (Cappuzzo et al., 2010).

Currently docetaxel, pemetrexed (in non-squamous carcinoma only) and the EGFR TKIs (erlotinib and gefitinib) are approved for the second-line treatment of NSCLC. These agents all have been shown

to prolong survival and improve symptoms. Whether chemotherapy or an EGFR TKI should be selected in this clinical setting has been studied in a large randomized trial comparing second-line single-agent docetaxel to the EGFR TKI gefitinib. This trial demonstrated non-inferiority for gefitinib, but molecular sub-studies suggest that in patients with EGFR activating mutations, the benefit from gefitinib is the greatest (Kim et al., 2008).

In a large randomized trial, erlotinib was compared to placebo in the third-line setting for advanced NSCLC. Treatment with erlotinib was associated with significant prolongation of survival and delay in time-to deterioration of symptoms (Shepherd et al., 2005).

Molecular sub-studies showed that patients with high EGFR copy number and EGFR sensitizing mutations derived numerically greater benefit, but significant interaction could not be demonstrated, and so in this end-stage setting (in contrast to the first-line setting), treatment is not restricted to patients with a particular EGFR gene profile.

With treatment of proven benefit in the first-, second-, and third-line settings, the evaluation of several new drugs for advanced NSCLC is now occurring in patients who have had two lines of chemotherapy and a tyrosine kinase EGFR inhibitor.

STRATEGY

The greatest challenge of the coming years will be to use and combine all these new techniques and therapeutic modalities, mostly focused on the tumor at the moment, in each individual patient. This will require an enormous effort of multidisciplinary approach for each patient, taking into account a lot of clinical and biological parameters in addition to more and more genetic characteristics which are presently ignored in almost all cases.

Which are the best candidates for screening? Can we identify any genetic/proteomic characteristics that make these individuals more likely to develop a lung tumor? How to stage more accurately patients prior to decide the best combined modality option? When can we optimally use our growing number of targeted agents? Prior to local treatment, in a curative intent, or in the palliative setting, when the war is already lost? Most investigators are presently involved in drug registration processes and the academic part of the job, i.e., the optimal use of our armamentarium for each patient at the right time, is still pending. The next generation of clinical trials will have to include all these questions through large academic collaborations.

OTHER THORACIC MALIGNANCIES

Several other thoracic malignancies are also candidate for a new molecular-based therapeutic management. Because they are less frequent, many of them have not benefited from recent research and/or are not in the scope of pharmaceutical companies. There is no doubt that small cell lung cancer tumors, mesothelioma, and mediastinal tumors are also to be considered.

IN CONCLUSION

Thousands of teams are working on these issues worldwide but the processes of publication are not flexible. They are slow when any signal, positive or negative, should be published as soon as it is discovered. That is the reason why an on-line journal with the fastest review process would be highly appreciated and would be extremely time-saving.

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