736

Molecular concepts

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Much has been learned about the molecular changes and importance of signal transduction pathways in lung cancer over the last decades. There is great hope that therapeutic interventions aiming at specific molecular pathways might overcome the impasse of therapeutic advances seen with systemic chemotherapy and that molecular properties of tumors with prognostic and predictive significance might lead to new therapeutic approaches. The first clinical studies on targeted therapy involved the substitution of inactivated tumor suppressor genes by viral transfection through intratumoral application. Now a multitude of agents are being investigated for their antitumor activity by systemic application. Three major classes of agents are being explored: Antibodies to extracellular proteins such as antibodies to VEGF and EFG receptor, small molecules such as tyrosine kinase inhibitors and proteosome inhibitors, and antisense oligonucleotides such as antisense molecules against the antiapoptotic protein bcl-2. For some of the new targeted agents there are already phase III data available. Virtually all of these studies focused on the question, whether the addition of target agents to chemotherapy would be superior to chemotherapy alone. Unfortunately in lung cancer, these trials have been negative so far, including the studies on matrix metalloprotein inhibitors, the studies with the antisense oligoncleotide against protein kinase Cα, the studies with the EFGR thyrosine receptor antagonist gefitinib. Phase III results on the VEGF antibody bevacizumab in lung adenocarcinoma and the bcl-2 antisense oblimersene are pending. Major knowledge has been gained from the clinical development from gefitinib, a drug that has been approved for third line treatment of non-small cell lung cancer in several countries, an new questions have arisen: Which of the new target therapies should be given concomitant and which sequential with chemotherapy, on what bases could patients responding to targeted treatment be preselected, and how could one predict which tumor depends on which molecular pathway? To answer these questions it has become necessary to integrate molecular analysis of tumors on all patients giving consent to participate in clinical trials.

737

Integration of functional imaging (PET) into radiotherapy planning of non-small cell lung cancer

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Positron Emission Tomography (PET) using 18-fluoro-2-deoxyglucose (FDG) is a functional imaging technique that relies on the fact that most neoplasms have an increased glucose metabolism as compared to normal tissue. The PET tracer, ^{18} FDG, is a positron emitter and can be measured using (preferentially) a dedicated (full ring) PET scanner. FDG-PET provides metabolic activity of tumor cells but lacks precise anatomic information. It is now well-established that PET is significantly more accurate than CT to detect locoregional lymph node spread and distant metastasis in NSCLC. The addition of PET to conventional staging procedures contributes to a better staging and selection of NSCLC patients that can benefit from radical/curative RT.

The conventional imaging modality for RT planning is CT. CT provides electron density information, which is required for dosimetry calculations. As PET provides a better staging of the mediastinum, the integration of PET data could assist the radiation oncologist to define the nodal target volume more accurately, especially in RT dose escalation protocols and concurrent chemoradiation schedules in which the elective nodal irradiation is often omitted. In addition, for patients with atelectasis, the information provided by PET can lead to significant reductions in irradiated lung volume. The development of techniques for image correlation has facilitated the integration of metabolic information provided by PET and morphologic information provided by CT. Moreover, very recently scanners became available that can combine acquisition of both PET and CT.

At present, the resolution of clinical PET scanners is limited. In practice, it is in the order of 7 mm. The gantry aperture is limited to 60 cm. This implies that the RT treatment position of the patient cannot always be reproduced on the PET scanner. Registration errors in the order of 4 mm can occur. Given the different FDG uptake intensity in each patient, an individual threshold value needs to be determined. Furthermore, no studies are available that have investigated the correlation between the true tumor extension on surgical specimens and both activity detected on PET and morphological changes visualized on CT. For such a study, correction for respiration artifacts during acquisition of PET and CT images would be mandatory. Several groups are studying the feasibility of a respiration gating technique to reduce motion artifacts in PET imaging of lung cancer.

PET is a promising complementary imaging technique to CT in the RT planning of NSCLC. It improves our ability to more accurately define the nodal target volume. It still needs to be evaluated whether the improvement of target definition by integration of PET will lead to a better intrathoracic tumor control.

738

Has the page turned for adjuvant treatments?

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If surgery remains the keystone in the treatment of lung cancer, only one third of the patients will be alive 5 years later. Failures are related to local relapse, distant metastasis or second primary. Two meta-analysis have drawn the scene for adjuvant treatments. They demonstrated a clear detrimental effect of postoperative radiotherapy and alkylating agents while cisplatine based regimens yield a low non-significant benefit (less than 5%). Current trials are conducted aiming to demonstrate such low but important benefit. A problem with adjuvant chemotherapy is the low compliance of patients as observed in the recent ALPI trial. The negative impact seen in the PORT meta-analysis may be due to a poor radiation technique but then to disappear for stage III or N2 disease. This suggests perhaps a therapeutic effect due to a better local control as observed in some trials. Nevertheless, there is no place for radiation after a complete resection of a stage I or II tumour. So, an induction program with or without radiotherapy was believed to let to a better tolerance and efficacy. Five phase III trials have addressed the issue of induction chemotherapy with controversial results: the Rosell and Roth trials were positive for stage IIIa disease but included only 60 patients while Tsuchiya and Depierre trials were negative. The later trial was the only one to include a large number of patients (350 patients) and showed a positive effect in a subgroup analysis, stage I and II. Preoperative radiotherapy was tested in the 70's without success. Combined chemoradiotherapy was used in a large series of phase II trials including stage IIIa and b disease allowing the following conclusions: acute toxicity and surgical morbidity were increased while there was a higher number of complete pathological response (10-20%). So, before considering an induction program as a classical approach for non-small cell lung cancer, there is a clear need for more large scale and well designed phase III trials. Furthermore, better tools are necessary to identify the patients eventually candidate for an induction program: the current staging system is not always helpful as a T4 may be operated or not and there is not always a clear correlation between stage and tumour volume. Nevertheless, we should remember that any small benefit in such a common disease will have a great impact.

739

The role of chemotherapy

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Until recently the management of lung cancer has often been characterised by a negative therapeutic attitude among many physicians and wide variations occur from region to region influenced by variations and traditions, knowledge, health care systems, and available resources.

In the past decade we have, however, seen major changes in lung cancer treatment. First and foremost there is a more optimistic therapeutic approach using a combination of the major treatment modalities: surgery, chemotherapy and radiotherapy applied concurrently and/or sequentially in early stage disease.

Small cell lung cancer (SCLC) is characterised by a higher metastatic potential with early spread to organs outside the lung. SCLC is also more a sensitive tumour than non-small cell lung cancer (NSCLC). Chemotherapy is therefore the cornerstone of treatment, and it is combined with radiotherapy to the chest in patients staged as having localised disease. Frequently used combinations are etoposide and platinum analogues given for 4-6 months. Major issues when applying chemotherapy in SCLC are: dose intensity, maintenance therapy, treatment at relapse, choice of drugs in the elderly patients, or patients with poor performance status.

For NSCLC chemotherapy is applied either alone or combined with radiotherapy and/or surgery in stage III and IV, while the role as adjuvant therapy in stage I and II is uncertain at present. As second line treatment single agent chemotherapy results in both prolongation of life and quality