cascade, such as endothelial cell proliferation, migration, survival and capillary formation (1).

Vandetanib (ZD6474, Zactima) is a novel anilinoquinazoline which has shown activity as a potent and reversible inhibitor of VEGFR-2 tyrosine kinase. It is a small molecule with good oral bioavailability and constant plasma drug levels.

Furthermore, vandetanib also inhibits epidermal growth factor receptor tyrosine kinase activity combining activity against neoangiogenesis and signal transduction pathway (2).

Vandetanib has shown inhibition of tumor cell growth in a broad range of preclinical models including lung cancer xenografts after oral administration with an acceptable preclinical toxicology profile. It was possible to demonstrate inhibition by vandetanib of EGFR-stimulated cell proliferation and inhibition of both VEGFR and EGFR tyrosine kinase in vitro, and preclinical models have shown activity against NSCLC xenografts (3).

Vandetanib (ZACTIMA™; ZD6474) is a once-daily oral anticancer drug at the moment in phase III clinical development in a broad population of patients with advanced NSCLC. Vandetanib targets clinically validated signaling pathways in NSCLC by inhibiting VEGFR-dependent tumor angiogenesis and EGFR-dependent tumor growth and survival. Vandetanib also inhibits RET kinase activity, which is an important growth driver in certain types of thyroid cancer.

Phase I evaluation in patients with advanced solid tumors showed vandetanib was generally well tolerated at daily oral doses of ≤300 mg. Common adverse events included rash, diarrhea and asymptomatic QTc prolongation, all of which were controlled by standard management. A second trial comparing vandetanib 300 mg with gefitinib (IRESSA™, 250 mg) in 244 patients with advanced non-small cell lung cancer (NSCLC) showed that vandetanib was well tolerated with manageable toxicities overall. The combination was associated with a modest clinical benefit.

In 300 patients who were refractory to previously used chemotherapy, vandetanib 100 mg + docetaxel versus placebo + docetaxel in 2nd-line NSCLC (6474IL0032); and vandetanib 100 mg + pemetrexed versus placebo + pemetrexed in 2nd-line NSCLC (6474IL0036).

A randomized phase III trial comparing carboplatin paclitaxel and vandetanib vs the same chemotherapy alone, has been recently completed in 300 patients.

Clinical development is also ongoing in other tumor types, including hereditary medullary thyroid cancer, where encouraging antitumor activity has been observed.

Bibliography


M14-01 How to Stage the Mediastinum, Thur, Sept 6, 10:30 - 12:00

Mediastinal staging of NSCLC and 18FDG PET

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Introduction

To date, the glucose analogue 18FDG still is the best PET tracer for staging of lung cancer. Experiments with thymidine-analogues, choline etc. have not revealed diagnostic superiority in terms of TNM staging. Moreover, the conceptually present biological (i.e. prognostic) value of tracers like 18FLT has not yet been elucidated.

At the crossroads of tomographic imaging and intervention, the introduction of PET-CT and the increased application of non-surgical therapeutic modalities are the main developments in the past decade.

PET-(CT) and staging

The diagnostic accuracy of PET needs to be stratified for nodal size at CT [1]. In meta-analysis the pooled sensitivity of PET to identify ≥N2 stage in patients with non-enlarged nodes, was 0.75 (95% CI: 0.59-0.87); in combination with pre-test probability of N2 in this situation [2], it is predicted that the negative predictive value of PET is about 94%. Hence, even if invasive preoperative staging procedures would have a sensitivity of 100% (which is clearly not the case), at least 16 invasive procedures would be required to identify a single patient with N2 disease. More recent studies confirm that the yield of invasive staging procedures in patients with normal-sized and FDG-PET negative nodes is indeed extremely low [3]. In the meta-analysis of Gould et al, the sensitivity of PET in patients with enlarged nodes was 0.91 (95% CI: 0.79-0.96). It is likely that this 16% lower sensitivity of PET (vs. non-enlarged nodes) is caused by partial volume effects.

The prevalence of malignancy to identify ≥N2 above the centimeter limit, these effects are much less than 5-7 mm. Above the centimeter limit, these effects are much less likely to affect diagnostic performance. The prevalence of malignancy in mediastinal nodes [4] with 10-15mm short axis diameters is 0.29 (95%CI 0.23-0.36), vs. 0.68 (95%CI 0.52-0.81) for nodes of 16-20 mm (i.e. similar to even larger nodes). Reasoning that partial volume effects are irrelevant with deposits > 10 mm, one can predict that the post-test probability of N2 disease in patients with 10-15mm nodes and
a negative PET scan is about 5%. Combined with a realistic sensitivity of mediastinoscopy of about 85%, we predicted that 25 patients need to undergo invasive staging in order to identify a single patient with N2 disease. In a sensitivity analysis (dropping PET sensitivity and specificity for this subset to 0.85 and 0.70, respectively), we found that these data are robust. With nodes >15mm short axis diameter, the post-test probability of N2 disease is 0.21, suggesting that invasive evaluation is indicated in patients with such nodes at CT without positive 18FDG signal. Since 18FDG is not a tumor-specific agent, clinically decisive PET-positive lesions need to be confirmed except in cases of widely disseminated extrathoracic tumor spread.

PET reading

Visual detection of ‘hot spots’ is the mainstay of mediastinal PET readings. PET allows for very accurate signal quantification. In the clinical setting, one uses the standardized uptake value (SUV), which basically is the ratio of measured activity in the tumor and the injected 18FDG dose. Because SUV can be readily obtained from whole body scans, it is the most widely applied method. The aim of adding quantification to PET reading systems would be to improve specificity and perhaps reduce observer variation. Even though there is some evidence to support this notion [5] there is no generally accepted SUV cut-off (and due to the abovementioned partial volume effects it is unlikely that there is one). Since prevailing PET methods are heterogeneous meta-analysis is impossible. Several initiatives are underway to promote interinstitute calibration and standardization [6,7]. Functional imaging with PET involves biology and physics, and as such clearly puts higher demands on its users than we were used to in anatomical imaging: in order to obtain generally applicable data (e.g. SUV numbers) the full trajectory of patient preparation, image acquisition -, - reconstruction procedures and data-analysis need to be covered, and this is not trivial. Alternatively, use of PET-CT rather than visual co reading of PET and CT adds specificity by identifying aspecific non-nodal uptake.

Requirements for rational use of mediastinal PET readings

1. The primary tumor needs to be 18FDG avid, since PET-detection of malignant tissue depends on contrast between uptake in target vs. background. Broncho-alveolar cancer cells can lack GLUT-1 transporters rendering the PET signal negative. On average, squamous cell cancer tends to have somewhat higher 18FDG uptake than adenocarcinoma, but in meta-analyses no clear difference in PET accuracy was reported. Assessment of a lower level 18FDG avidity relies upon the nuclear medicine physician’s judgment rather than upon a specified level of avidity (SUV) - for the same reasons as outlined before. Fortunately, this visual assessment has a low observer variation [8]. Therefore, with high clinicopathological suspicion of NSCLC but low 18FDG uptake in the primary process, a negative mediastinal reading should not guide clinical management.

2. Nodal stations directly adjacent to the primary tumor are likely not to be recognized at PET but remain hidden in the activity of the primary tumor. Note that most PET acquisitions are obtained during shallow breathing, unlike diagnostic CT scans; fusion of low-dose CT scans and PET (as customary with PET-CT) accounts for the potential effect of tumor shift during deep inspiration. The nuclear medicine physician should report which stations are subject to this potential problem.

3. Similarly, spatial resolution limitations reduce anatomical confidence of PET readings when trying to separate N1 and adjacent N2 stations.

PET(CT) and restaging

Several studies have investigated the diagnostic accuracy of PET to restage the mediastinum after induction therapy for locally advanced NSCLC. The results are clearly more heterogeneous than in the upfront staging situation. Among the potential effect modifiers one needs to consider the included patient spectra, the quality of the reference test (gold standard), type of induction therapy (chemo- and/or radiotherapy), timing of PET vs. the intervention, PET vs. PET-CT, and PET classification systems and - interpretation criteria. Obviously, once the diagnostic accuracy of PET to provide mediastinal mapping is clarified, these data need to be fitted into diagnostic and management algorithms. Preferably, research in either domain should be ‘in sync’ to prevent that diagnostic procedures keep pace with therapeutic developments. With the transition from induction chemotherapy to chemoradiation, this was clearly not the case. The standardization momentum in the PET community may be an important vehicle to allow for such joint efforts.

References


M14-03 How to Stage the Mediastinum, Thur, Sept 6, 10:30 - 12:00

How to stage the mediastinum: mediastinoscopy

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Lung cancer more commonly spreads to the mediastinum than to other anatomic sites requiring thorough evaluation of the mediastinum in cases where there is no other evidence of metastases. The decision to treat for multimodality therapy hinges on the. An unanswered question is whether pre- versus post-operative chemotherapy provides better survival. Though, preoperative treatment allows for higher chemotherapeutic drug delivery and more delivery to the loco-regional area of the primary tumor. By identifying those patients less likely to benefit from surgical resection, such as contralateral and/or multinodal station/gross tumor involvement, unnecessary or “futile” thoracotomies should be minimized. Previously estimated to be as high as 30-40% now appear to be in the 5 to 10% range given the availability of high-resolution computed and positron emission tomographies (CT, PET, PET/CT) and even lower with a thoroughly pathologically-staged mediastinum. To highlight the importance of mediastinal lung cancer involvement, the American Joint Committee for Cancer Staging and Results Reporting and the American Thoracic Society adopted the Naruke staging map by provide systematic information on the prognosis of lung cancer patients. Each region is numbered in the mediastinum and hilar, as it relates to the trachea, the main stem bronchi and the great vessels. The goals of mediastinoscopy are to better understand the biology of the patient’s disease. It allows selection of those patients who are at risk for earlier recurrence and poorer lung cancer survival and reduces the likelihood for a futile thoracotomy.

Mediastinoscopy is the “gold standard” method for assessing lung cancer mediastinal involvement and provides a minimally-invasive means of evaluating the mediastinal lymph nodes for the presence and degree of metastatic involvement, including microscopic, gross and trans-capsular involvement and “matted” of nodes; as well as direct extension of the primary tumor into the mediastinal pleura and into...