Clinical Case

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History

• A 68 year-old man
• Former smoker: 75 pack-years, quit 2 years ago
• Abdominal aortic aneurysm, for which he received annual computed tomography (CT) scans
• Coronary artery disease
• Hyperlipidemia
• ECOG PS=0 (stays active walking his dog)
• No weight loss, no relevant signs/symptoms

Diagnostic

• Aneurysm on his most recent scan is only 2 cm
• Left lower lobe (LLL) lung mass, prevalently located in the lung periphery was identified plus enlarged mediastinal lymphnode
• In addition a modest bilateral enlargement of the adrenal glands was documented
Based on these results what further procedure would you recommend?

- Biopsy of the primary lesion through fiberbroncoscopy or transthoracic fine needle aspiration biopsy
- Positron Emission Tomography (PET) scan
- Mediastinoscopy, if negative proceed to lobectomy
- Biopsy followed by definitive radiation (with or without chemotherapy)

PLEASE ANSWER

1: Biopsy of the primary lesion through fiberbroncoscopy or transthoracic fine needle aspiration biopsy

- Any patient, unless contraindicated, should be diagnosed
- Any diagnostic attempt should be made to characterize the tumor histologically: cytological diagnosis through sputum cytology, bronchial aspirate or washing or FNA are frequently diagnostic possibilities.
- It is recommended to perform fiberbronchoscopy in a patient with a suspected lung cancer because it contribute to stage properly the tumor and discover synchronous lesions.
2. Positron Emission Tomography (PET) scan

- CT scanning provides anatomic detail that better identifies the location of the tumor, its proximity to local structures, and whether or not lymph nodes in the mediastinum are enlarged.
- FDG-PET reveals higher sensitivity and specificity than chest CT scanning, for staging lung cancer in the mediastinum and even if it contribute to detect unsuspected metastatic lesions.
- FDG-PET is not an exam to make diagnosis of lung cancer: remember false positive (granulomatous diseases, chronic infections) and false negative results (BAC, carcinoids).

3. Mediastinoscopy, if negative proceed to lobectomy

- If performed at this stage mediastinoscopy may be absolutely useless and it will expose the patient to potential unnecessary morbidity (and mortality) if additional examinations will confirm/reveal extrathoracic metastases.
- In addition to mediastinoscopy a variety of less invasive staging tests are available to investigate the mediastinal involvement by the tumor, including thoracoscopy (video-assisted thoracoscopic surgery), transbronchial needle aspiration (TBNA), transthoracic needle aspiration (TTNA), and endoscopic ultrasound with fine needle aspiration (EUS-NA).

4. Biopsy followed by definitive radiation (with or without chemotherapy)

- Again, a lack of information at this point about the extension of the neoplastic disease is making this choice totally wrong.
Diagnostic

- Pt was submitted to FBS which did not revealed any endobronchial lesion and the bronchial aspirate was negative for neoplastic cells.
- In the subsequent days he was submitted to a FNA biopsy of the primary tumor with a diagnosis of adenocarcinoma.

Diagnostic

- As a part of a staging work up the patient received a FDG-PET scan that was positive in the LLL mass and the mediastinal LN seen on CT scan.
- It was also revealed an hot spot (SUVMax 4.5) on the right adrenal gland documented previously modestly enlarged to the CT scan.
- He was clinically classified as stage IV.
There is a proposal for a new classification also for stage IV?

• Are you confident with the diagnosis of adrenal metastasis by PET?

1) Yes
2) No

PLEASE ANSWER
Yes

- Possibility of false positive adrenal enlargements

- Patient was submitted to biopsy of the adrenal gland through a posterior extraperitoneal access and pathological examination revealed adenocarcinoma.

- EGFR-FISH was positive.

- The diagnosis of metastatic adenocarcinoma was confirmed.

- What kind of therapeutic approach would you recommend...
• 1. Anti EGFRi mono-therapy
• 2. Carboplatin/paclitaxel + bevacizumab
• 3. Cisplatin-based chemotherapy
• 4. Cisplatin-vinorelbine plus cetuximab
• 5. Cisplatin-pemetrexed
• 6. A non platinum doublet

PLEASE ANSWER

1: Anti EGFRi mono-therapy
This could be a correct answer…..BUT

Endpoints
- Progression-free survival (non-inferiority)
- Objective response rate
- Overall survival
- Quality of life
- Disease-related symptoms
- Safety and tolerability

Exploratory
- Biomarkers
  - EGFR mutation
  - EGFR-gene-copy number
  - EGFR protein expression

Carboplatin / paclitaxel was offered to gefitinib patients upon progression

PS, performance status; EGFR, epidermal growth factor receptor

Progression-free Survival in EGFR Mutation Positive and Negative Patients

ITT population
Cox analysis with covariates
EGFR Mutation Positive Status and Clinical Characteristics

Overall EGFR mutation positive rate = 59.7% (261 / 437)

<table>
<thead>
<tr>
<th>% of samples</th>
<th>Overall EGFR mutation positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>49.0</td>
</tr>
<tr>
<td>Female</td>
<td>66.6</td>
</tr>
<tr>
<td>PS 0/1</td>
<td>61.1</td>
</tr>
<tr>
<td>PS 2/3</td>
<td>64.7</td>
</tr>
<tr>
<td>Never smoker</td>
<td>57.6</td>
</tr>
<tr>
<td>Light smoker</td>
<td>66.3</td>
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<tr>
<td>Locally advanced</td>
<td>56.7</td>
</tr>
<tr>
<td>Age &lt;45 yrs</td>
<td>48.8</td>
</tr>
<tr>
<td>Age &gt;45 yrs</td>
<td>68.5</td>
</tr>
</tbody>
</table>

2: carboplatin/paclitaxel + bevacizumab
This is a potential treatment option

12 mo. 24 mo.
--- bevacizumab + CP: 52% 22%
--- CP: 44% 17%
HR: 0.77 (0.65, 0.93)
p < 0.007
Medians: 10.2, 12.5

3: cisplatin-based chemotherapy
This is not the best treatment option
• 4. cisplatin-vinorelbine plus cetuximab
  This is a potential treatment option. Cetuximab not yet registered

• 5: cisplatin-pemetrexed
  This is a preferred treatment options among cisplatin-based doublets

• 6: a non platinum doublet
  This is not a treatment option
Consider your answer to the previous question. Is there a biomarker that select by itself the treatment choice? i.e.: K Ras mutation, EGFR mutations, TS, ERCC1, RRM1, other....

Currently the answer is NO

How long would you continue initial treatment in this patient?

1) 4-6 courses
   • This is the right answer
2) 8 courses [PLEASE ANSWER]
   • This is not a correct answer
3) Until progression
   • This is not the correct answer

ASCO Guidelines 2003 (&2008)

“Duration of Therapy: in stage IV NSCLC: first-line platinum-based chemotherapy should be stopped at four cycles in patients who are not responding to treatment. First-line chemotherapy should be administered for no more than six cycles in pts with stage IV NSCLC.”

these statements were predominantly based on the randomized trials by Socinski et al and Smith et al
Would you offer maintenance therapy to this patient?

- Yes, bevacizumab
- Yes, pemetrexed
- No

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Pemetrexed vs Placebo Maintenance

Double-blind, Placebo-controlled, Multicenter, Phase III Trial

- Stage III/IV NSCLC
- PS 0-1
- 4 prior cycles of gem, doc, or tax + cis or carb, with CR, PR, or SD

Randomization factors:
- gender
- PS
- stage
- best tumor response to induction
- non-platinum induction drug
- brain mets

Pemetrexed 500 mg/m² (d1,q21d) + BSC (N=441)*

2:1 Randomization

Placebo (d1, q21d) + BSC (N=222)*

Primary Endpoint = PFS

*B12, folate, and dexamethasone given in both arms

Ciuleanu et al, J Clin Oncol 2008; 26: 8011

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Pemetrexed vs Placebo Maintenance Study Progression-free Survival (N=581)

HR=0.599
(95% CI: 0.49–0.73)

p <0.00001

Placebo: 1.97 mos
(95% CI: 1.54–2.76)

24% censored

Pemetrexed: 4.04 mos
(95% CI: 3.06–4.44)

Ciuleanu et al, J Clin Oncol 2008; 26: 8011