Case Studies in Non-Small Cell Lung Cancer

2018 GPO Case Study Day

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Disclosures

- Dr. Steve Kulla
  - None

- Dr. Georgia Geller
  - None
Learning Objectives

• Briefly review:
  o Basic Canadian statistics on non-small cell lung cancer
  o Diagnosis and staging of non-small cell lung cancer

• Discuss treatments for non-small cell lung cancer including surgery and radiotherapy, but in particular systemic treatments including:
  o Chemotherapy
  o Targeted therapies
  o Immunotherapy
Lung Cancer – some basic statistics

Canadian Cancer Society – Canadian Cancer Statistics: A 2018 special report (cancer.ca/statistics)

• Lung cancer was the most commonly diagnosed cancer among Canadians in 2017 (14% of all cancers)

• Smoking remains the most important risk factor
  o 85% of cases are related to smoking

• The incidence rate for lung cancer is higher for males than females (although sex-specific rates among younger adults appear to be converging)
  o Differences in incidence rates between males and females reflect past differences in tobacco use (in females, the drop in smoking occurred ~20yrs later than it did in males)
Lung Cancer – some basic statistics

Canadian Cancer Society – Canadian Cancer Statistics: A 2018 special report (cancer.ca/statistics)

• From 2011-2015, every year in Canada (excluding Quebec), an average of 6823 lung and bronchus, 2494 colorectal, 815 female breast, and 1187 prostate cancers were diagnosed after they had metastasized (stage IV)

• About half (50%) of all lung cancers were diagnosed at stage IV, which is reflected in its low five-year net survival of 17%
  o 5 year net survival for breast cancer = 87%
  o 5 year net survival for colorectal cancer = 64%
  o 5 year net survival for prostate cancer = 95%
Lung Cancer – Some basic statistics


- Overall, lung cancer causes about 25.5% of all cancer deaths in British Columbia (greater than colorectal, breast, and prostate cancer combined)

- Mean age of diagnosis is 70 years old

- The median overall survival is about 8.5 months
Lung Cancer – Some basic statistics


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Lung Cancer Basics

• 2 main types of lung cancer:
  o Non-small cell lung cancer (NSCLC)
  o Small cell lung cancer (SCLC)

• NSCLC accounts for >80% of all lung cancers
  o ~40% of NSCLC cases are adenocarcinoma subtypes
  o ~40% of NSCLC cases are squamous tumors
  o Remaining NSCLC cases are large cell carcinoma and adenosquamous carcinoma

• SCLC is rare among non-smokers. It tends to grow faster and spread more easily than NSCLC
Lung cancer screening

- Currently there is no population based screening for lung cancer

- The Canadian Task Force on Preventative Health Care has released screening recommendations for high-risk individuals using low-dose CT

- Pilot studies are underway

- CXR and sputum cytology are not effective screening tests
Case #1 – Mrs. O

• 61F widow (husband died of lung cancer), former teacher and social worker, no children

• hx of colon cancer 2017
  o Initially presented with anemia and positive FIT
  o Colonoscopy July 2017
  o Resection Sept 2017
  o Found to be stage II, low risk, and thus no chemotherapy at that time

• Otherwise healthy, no regular medications

• Never smoked. Hx of second-hand smoke exposure from her mother

• As part of workup for colon cancer, LUL mass incidentally discovered on staging CT
What would you recommend for workup of the LUL mass?
What would you recommend for workup of the LUL mass?

History:
- Recovered quite well from her colon cancer surgery
- No significant weight loss, no fevers/sweats, no hemoptysis
- Some post-intubation hoarseness and cough
  - Dry cough, exacerbated by activity
- Minor shortness of breath on exertion
- No headaches, vision changes, or neurological deficits

Physical exam:
- Unremarkable – no lymphadenopathy, chest clear, no adventitia

Bloodwork:
- WBC 8.8 (ANC 5.8), Hgb 119, plt 342, creat 67, albumin 45, liver enzymes normal, LDH 167, CEA 1.0
What would you recommend for workup of the LUL mass?

- **Imaging:**
  - Private PET (Aug. 2017)
    - “The left hypermetabolic left upper lobe lung lesion atypical for metastasis and may be a second primary malignancy”
  - PFT's (Nov. 2017)
    - Normal FEV1 and FVC
  - Bronchoscopies & biopsies (Oct & Nov. 2017)
    - Biopsies negative
  - Left upper lobe lobectomy (Nov. 2017)
    - Non small cell lung cancer (pulmonary adenocarcinoma), pT2 N2 (2/4 LN positive), focal lymphovascular invasion, margins clear, tumor was intermediate grade

- **Further Imaging:**
  - CTHead (Dec 2017) - no intracranial mass or enhancing lesion
TNM staging for NSCLC

T, N, M descriptors for the 8th edition of TMN classification for lung cancer - UpToDate

- **T1** – Tumor ≤ 3cm, surrounded by lung or visceral pleura, without invasion more proximal than lobar bronchus

- **T2** – Tumor >3cm but ≤5cm, or tumor with any of the following features:
  - Involved main bronchus, without involvement of the carina
  - Invades visceral pleura
  - Associated with atelectasis or obstructive pneumonitis

- **T3** – Tumor >5cm but ≤7cm or any of the following
  - Directly invades any of the following: chest wall, phrenic nerve, parietal pericardium
  - Separate tumor nodules in the same lobe

- **T4** – Tumor >7cm or
  - Invades the diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina
  - With separate tumor nodules in a different ipsilateral lobe
TNM staging for NSCLC

T, N, and M descriptors for the 8th edition of TNM classification for lung cancer – UpToDate

- **NX** – regional LNs cannot be assessed
- **N0** – no regional LN metastases
- **N1** – Metastasis in ipsilateral peribronchial and/or ipsilateral hilar LNs and intrapulmonary nodes, including involvement by direct extension
- **N2** – Metastasis in ipsilateral mediastinal and/or subcarinal LN(s)
- **N3** – Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or suprACLavicular LN(s)
TNM staging for NSCLC

http://www.bccancer.bc.ca/health-professionals/clinical-resources/cancer-management-guidelines/lung/lung

• MX – presence of distant metastasis cannot be assessed

• M0 – no known distant metastasis

• M1 – Distant metastasis present
## TNM staging for NSCLC

![TNM staging for NSCLC](http://www.bccancer.bc.ca/health-professionals/clinical-resources/cancer-management-guidelines/lung/lung)

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*This is a simplified overview*
Investigations for staging

- CXRs alone are inadequate for staging

- Contrast CT of mediastinum recommended to stage locoregional disease (it should extend inferiorly to include the liver and adrenal glands)
  - Major role of CT is to aid in decisions regarding resectability and to detect synchronous/metastatic cancers not visible on CXR
  - MRI is not superior to CT for staging mediastinal nodes but may be of value in selected cases for assessment of operability of the primary tumor

- CT should be supplemented by mediastinoscopy
  - For patients with clinically operable NSCLC, biopsy is recommended of mediastinal LNs found on CT to be >1cm in shortest transverse axis

- PET is more sensitive and specific than CT in radiologic detection of malignant LNs, yet there is a high false positive rate. As a result, definitive biopsy would be recommended.
  - The role of PET in routine staging of lung cancer has not been established, but it may be useful in select cases:
    - Staging patients with clinical stage I lesions being treated with curative intent
    - Staging of potentially resectable stage II and III disease
    - To aid in planning radical radiotherapy
    - Staging prior to resection of solitary lung metastases
Assessment of Pleural Effusions

http://www.bccancer.bc.ca/health-professionals/clinical-resources/cancer-management-guidelines/lung/lung

• If a pleural effusion is present, all efforts must be made to determine if it is malignant or benign. Useful investigations include:
  o Pleural fluid cytology
  o Pleural biopsy
  o Thoracoscopy

• A benign effusion has no independent significance in staging, whereas a malignant effusion indicates T4 status and inoperability.
Screening for Extrathoracic Metastatic Disease

http://www.bccancer.bc.ca/health-professionals/clinical-resources/cancer-management-guidelines/lung/lung

- The most common extrathoracic metastatic sites for lung cancer are:
  - Supraclavicular nodes
  - Brain
  - Bone
  - Adrenals
  - Liver

- History, physical exam, and investigations should focus on these sites
Screening for Extrathoracic Metastatic Disease

http://www.bccancer.bc.ca/health-professionals/clinical-resources/cancer-management-guidelines/lung/lung

- **Serum chemistry:**
  - Include calcium, albumin, and LFTs
    - Anorexia, nausea and vomiting, and other GI symptoms suggest hypercalcemia
    - Alkaline phosphatase, LDH, AST help assess liver function and possible presence of liver metastases and bone metastases

- **It is not common for the liver to harbour detectable metastases in the absence of liver enzyme abnormalities**

- **Bone scans are not recommended unless the patient has bone pain, chest pain, or elevation of serum calcium and/or alkaline phosphatase**

- **The finding of an isolated adrenal mass on US or CT requires biopsy to rule out metastatic disease if the patient is otherwise considered to be potentially resectable (PET can be useful in select circumstances)**
Screening for Extrathoracic Metastatic Disease

http://www.bccancer.bc.ca/health-professionals/clinical-resources/cancer-management-guidelines/lung/lung

• **Brain Metastases:**
  - There is a high incidence of detectable metastases in patients with specific neurologic findings (focal seizures, focal weakness), and CT is advised in these patients.
  - There is a 25-35% incidence of detectable metastases in patients with non-specific neurologic complaints (headache, personality change, dementia).
  - CT brain screening is not recommended for asymptomatic patients receiving treatment with palliative intent but such assessment should be considered in locally advanced cases where curative intent therapy is planned.
  - MRI is more sensitive than CT, and should be considered in cases where suspicion persists after normal or equivocal CT, or to delineate if there is a solitary lesion or multiple lesions which may affect surgical and radiation planning.
Resectability?

http://www.bccancer.bc.ca/health-professionals/clinical-resources/cancer-management-guidelines/lung/lung#Management

- ~1/3 of NSCLC patients have clinically operable disease
- For patients with clinically operable NSCLC, surgical resection is the treatment with the best potential for cure
- Patients with stage I or II NSCLC are routinely resected
  - Lobectomy is the standard
  - Occasionally pneumonectomy required if extension of tumor across the fissure
  - Segmental or wedge resection may be performed for small peripheral T1N0 lesions in patients with limited lung function
- Only selected stage III patients are resectable
- Stage IV disease is generally unresectable
  - Rarely, a carefully selected patient with a solitary brain metastasis and a stage I to II primary lung tumor will be considered for resection
- Radical radiation treatment may be considered when the patient refuses surgery in otherwise operable situations, or when the patient is medically unfit for thoracotomy
Adjuvant Radical Radiotherapy after Surgery

- Post-operative adjuvant radiotherapy should not be used after complete resection of Stage I or II NSCLC due to an increased risk of non-cancer deaths.
- There is some evidence that it can benefit patients with Stage III NSCLC after complete resection.
- It will decrease the chance of local recurrence in patients with positive bronchial resection margins.
Case 1 Overview

- Mrs. O is a 61 year old widow with resected stage III non-small cell lung cancer (T2 N2 MX with 2/4 LN positive)
Would you recommend systemic treatment for Mrs. O?
• Platinum-based chemotherapy (ie, platinum doublet) regimens are recommended as post-operative adjuvant therapy in patients with completely resected stage II and III NSCLC

  o Cisplatin-based treatment is preferred, but carboplatin-based regimen can be used if there is a contraindication to cisplatin
Would you recommend systemic treatment for Mrs. O?

- Mrs. O’s esteemed Medical Oncologist recommended that for stage III patients, adjuvant cisplatin based chemotherapy had a 10-13% absolute benefit in 5 year survival.

- Mrs. O had a good ECOG status

- Platinum doublet with cisplatin and vinorelbine was recommended (4 cycles)

- Ideally it would be started within 8 weeks of her surgery
What toxicities would you counsel Mrs. O to be aware of?
What toxicities would you counsel Mrs. O to be aware of?

- Hypersensitivity reaction
- Fatigue
- Cytopenias
- Infection (potentially fatal febrile neutropenia)
- Nausea/vomiting
- Neuropathy
- Nephropathy
- Ototoxicity
- VTE
How did Mrs. O tolerate treatment?

• Cycle 1:
  o Tinnitus, no hearing loss
    • Day 15 of cycle was held, and she was sent for hearing test
    • Hearing test showed moderate to severe sensorineural hearing loss at high frequencies
    • Switched to Carboplatin and Paclitaxel
  o Nausea – effectively managed with metoclopramide
  o Fatigue – not as active as normal, but doing ADLs and IADLs
  o No neuropathy

• Cycle 2-4 – well tolerated
Mrs. O completed chemo, now what?
Mrs. O completed chemo, now what?

- NSCLC patients treated with radical intent should be followed up for treatment-related complications, detection of treatable relapse, or occurrence of second primary lung cancer.

- At least 75% of relapses occur in the initial 2-3 years after treatment.

- Suggest a follow-up visit every 3-6 months for the first 2-3 years followed by annual visits thereafter. History, physical exam, CXR and annual CT are appropriate (as CT is the best way to detect a second primary tumor).

- Smoking cessation is of major value in NSCLC patients (especially if treated with curative intent) - decreased risk of mortality, development of second primary or recurrence.
Mrs. O completed chemo, now what?

- Post-chemotherapy CT C/A/P (April 2018):
  - No evidence of metastatic disease within the abdomen and no new pulmonary findings
  - In the right anterior aspect of the S2 segment of the sacrum there is a lytic lesion with peripherally sclerotic margins, new from previous imaging

- NM Bone scan – lesion in S2 highly suspicious for metastatic focus
New bone lesion – What does this mean for Mrs. O?

• This is now Stage IV disease – her cancer is no longer considered curable
What further tests might you consider at this point?
What further tests might you consider at this point?

• Oncopanel:
  o Looks for driver mutations for which there may be targeted therapies, for instance:
    • EGFR
      o ~10-35% of people with NSCLC will have drug sensitizing mutations of EGFR
      o People with these mutations tend to have adenocarcinoma histology and be light smokers or nonsmokers
      o If EGFR mutation (variant) positive, can consider using Tyrosine kinase inhibitor such as erlotinib, gefitinib, afatinib, or osimertinib
    • ALK
      o ALK is positive in 3-5% of NSCLC. The vast majority of cases are adenocarcinomas.
      o ALK lung cancers are found in all ages, but on average these patients tend to be younger. They are more common in light smokers or nonsmokers
      o If ALK positive, can consider using ALK inhibitor such as crizotinib, alectinib, or ceritinib
  o PD-L1 biomarker
    • Utilized to assess for utility of immune checkpoint inhibitors such as nivolumab or pembrolizumab
What further tests might you consider at this point?

• Oncopanel:
  - EGFR – positive - variant of known functional significance detected in exon 18, and second variant of possible functional significance in exon 20
  - ALK protein – negative
  - PDL1 biomarker - <1%

• Repeat PET (May 2018):
  - Solitary 2.5 cm osseous sacral metastasis
What treatments would you recommend at this point?

• She was reviewed at tumor board, and she was felt to be a good candidate for the SABR5 clinical trial.
  o She was advised that SABR could offer a high rate of local control (80-90%), delay the development of other metastatic disease, and delay systemic therapy

• As part of her workup for SABR5, she received a brain MRI (June 2018):
  o Multiple (at least 7) sub-centimeter lesions

• Due to the brain lesions, she was no longer eligible for the SABR5 trial.
Now what?

• To review:
  o 62F with oligometastatic, EGFR mutated, ALK negative, adenocarcinoma of the lung with a single sacral metastasis, and new sub-centimeter brain mets. PDL1 < 1%
  
  o She’s completely asymptomatic from the metastatic disease
Now what?

- Her radiation oncologist explained that the brain lesions were too small for radiotherapy, and did not recommend whole-brain radiotherapy (**Mrs. O did not want WBRT due to risk of cognitive deficits**). He referred her back to Medical Oncology to discuss systemic therapy.

- Regarding the sacral lesion, as it was asymptomatic, Rad Onc recommended no RT at that time, and re-referral for palliative RT should she become symptomatic from it.
What systemic therapy options are available to Mrs. O?
What systemic therapy options are available for Mrs. O

- **EGFR targeted therapy:**
  - Afatinib – a second generation tyrosine kinase inhibitor
    - TKIs, especially 3rd generation drugs have been shown to have good blood brain barrier penetration
    - “Afatinib is a second-generation tyrosine kinase inhibitor. It binds to the kinase domains of EGFR, HER2 and HER4, irreversibly inhibiting tyrosine kinase autophosphorylation, and results in reduction of tumour growth and tumour regression” - BCCA Afatinib monograph

- **Goal of this therapy:**
  - This is a palliative medication given to control her disease and hopefully maintain/improve quality of life

- **Median response quoted to Mrs. O was 11 months, with high rate of response (70%)**

- She started Afatinib July 2018
Potential toxicities of Afatinib?

- EGFR TKI’s are generally better tolerated than chemotherapy

- Typical side effects are:
  - Dry skin
  - Acneiform rash (up to 90% of pts – use topical clinda/HC PRN +/- oral minocycline)
  - Stomatitis
  - Diarrhea (96% of pts – use loperamide PRN)
  - Paronychia (58% of pts)

- Rare but clinically important pulmonary and hepatic toxicity may also occur

- *Cytopenias are not common
How did Mrs. O do on Afatinib?

• First week of full dose:
  o 6 BM/d, responded to loperamide
  o Minor facial rash
  o ECOG 0, good energy, active

• Second week of full dose:
  o Severe diarrhea (16BM/24hr), dehydration necessitating visit to ER for fluids
  o Afatinib held until resolution of symptoms (this took ~5d)
  o Resumption of Afatinib at a dose reduction – well tolerated

• She tolerated dose reduced Afatinib well, and maintained a good QOL. She had a CTH/C/A/P on Oct. 3/18.....
CT H/C/A/P result:

- Unfortunately the CTHead showed increase in size and number of intra-axial lesions, but no other adverse changes.

- What do we do now?
What do we do now?

- She was referred to Radiation Oncology for consideration of stereotactic brain radiotherapy, and a brain MRI was ordered.

- She continues Afatinib.

- MRI showed ~20 intracranial lesions, thus stereotactic radiotherapy no longer an option (it generally cannot be given to >10 intracranial lesions).

- Mrs. O has an appointment with Rad Onc and Med Onc pending.

- We had a very long difficult discussion regarding goals of care:
  - Rad Onc has advised that she recommends all pts with intracerebral lesions stop driving. Driving ++ important to Mrs. O.
  - Mrs. O does not want WBRT. She has ++ fear of cognitive deficits.
  - Mrs. O does not want to wind up in hospital or require full care. She would consider MAID, but at present has full and happy life.
Case #2 – Mrs. S

- 56F, married, previously worked as a care aid, but stopped due to shoulder issues.

- Chronic bilateral shoulder issues, multiple previous surgeries on R shoulder, new L frozen shoulder in summer of 2016 which did not improve with a cortisone injection.

- CT scan to investigate shoulder showed a mass in the L lung.

- Otherwise healthy, on no regular medications, uses Advil PRN for shoulder pain.

- 40 year smoking history.
What would you recommend for workup of the lung mass?
What would you recommend for workup of the lung mass?

- **History:**
  - Systemically well, with no SOB, cough, or hemoptysis
  - No headaches, visual disturbances, seizures, or focal neurological deficits
  - Appetite is good, weight stable

- **Physical Exam:**
  - AVSS, chest clear on auscultation, no supraclavicular LAN, normal neuro exam

- **Bloodwork:**
  - WBC 4.8, ANC 2.7, Hgb 136, Plt 206, Creat 59, Liver enzymes normal, Albumin 41, LDH 158
What would you recommend for workup of the lung mass?

- **Bronchoscopy & biopsy:**
  - Pathology shows non-small cell lung carcinoma, favors squamous cell carcinoma

- **Imaging:**
  - Bone scan (Sept 2016) - no osseous mets

- **PFTs:**
  - Normal

- **Referred by Respirology to Thoracic Surgery**
  - PET scan showed L lung cancer with small ipsilateral nodes. Plan for surgery.
  - CTH head ordered for further staging

- **CT Head (Oct 2016):**
  - At least 8 hyperdense lesions in the cerebral hemispheres

- **What would you do now?**
Case #2 - Mrs. S

Review:
- 56F with LUL mass found incidentally on imaging. Cytology shows NSCLC. PET shows no distant disease. CT Head shows 8 mets. ECOG 0.

Seen by Radiation Oncology (Nov 2016):
- Given known NSCLC, no biopsy of brain lesions recommended
- Stage IV disease - incurable, treatments will be palliative in nature
- Advised algorithm suggests median survival of 6-9 months
- Recommended WBRT rather than stereotactic approach (30Gy in 10 fractions)
- Did not recommend RT to chest as Mrs. S was asymptomatic, as palliative chest RT not shown to improve survival
- Advised by Rad Onc that she should not drive given risk of seizures
- Referred to Medical Oncology for consideration of systemic therapy
What are the potential toxicities of WBRT?
What are the potential toxicities of WBRT?

- Fatigue
- Skin reaction
- Alopecia
- Symptoms of increased intracranial pressure
  - Headache, nausea/vomiting, confusion
  - Mrs. S. did not have symptoms at that time, so prophylactic dex was not started, but Rad Onc advised that if symptoms developed during or following WBRT, dex would be considered
- Long term risk of reduction in memory
Medical Oncology Assessment

- What treatments might Med Onc recommend in the 1st line setting for Mrs. S?
Medical Oncology Assessment

- What treatments might Med Onc recommend in the 1st line setting for Mrs. S?
  - Palliative Platinum doublet chemotherapy x 4 cycles
    - Mrs. S. was prescribed carboplatin and gemcitabine

- What other tests might be ordered at that visit?
Medical Oncology Assessment

- What treatments might Med Onc recommend in the 1st line setting for Mrs. S?
  - Palliative Platinum doublet chemotherapy x 4 cycles
    - Mrs. S. was prescribed carboplatin and gemcitabine

- What other tests might be ordered at that visit?
  - Oncopanel - Molecular testing for EGFR mutations and ALK fusions
    - No EGFR variant detected
    - ALK negative
    - PDL1 > 50%
Advanced NSCLC Treated with Palliative Intent

- Treatment goals are palliation of symptoms and improvement in quality-of-life
- Prognosis is poor for patients with stage IV NSCLC with 6-10 month median survival times typical with even the best available therapies. Most patients die within 1-2 years
- Palliative radiotherapy may be given for metastatic osseous, cerebral, subcutaneous, nodal, or pulmonary metastases
Advanced NSCLC Treated with Palliative Intent

Examples where radiation may be useful for treatment of symptoms due to direct extension of local disease or involvement of LNs:
- Atelectasis
- Obstruction of a main stem bronchus
- Superior vena cava syndrome
- Hemoptysis
- Severe dysphagia
- Pain

Examples where radiation may be useful for the treatment of symptoms due to metastases:
- Bone metastases
- Spinal cord compression
- Brain metastases
- Fungating cutaneous mass

Radiation may be considered in asymptomatic patients if:
- Pending superior vena cava obstruction
- Potential risk of spinal cord compression
- Large lytic lesion in a weight-bearing bone
- Asymptomatic multiple brain metastases
How did Chemo go for Mrs. S?

- Tolerated it reasonably well

- CT to monitor response after 2 cycles showed slight decrease in size of chest lesion and L hilar LAN, no new pulmonary lesions, but found to have a PE (asymptomatic) – started on dalteparin. CT head showed mixed change with decrease in a few lesions, but increase in size of others. Continue treatment.

- Treatment related anemia after cycle 3 – hgb 65, given 2U PRBC

- Platelets fell to 11 after cycle 4 – dalteparin held until platelets >50

- Post treatment CT (May 2017) showed mixed results
What would you recommend for Mrs. S now?

**Review:**

- 56F with metastatic NSCLC to brain.
- Status post WBRT and 4 cycles of carboplatin and gemcitabine, which was complicated by a incidental PE, anemia, and thrombocytopenia.
- Post treatment CT showed mixed response with no change on CT Head, slight increase in size of primary lung lesion.
- ECOG = 0.
What would you recommend for Mrs. S now?

• Review:
  • 56F with metastatic NSCLC to brain.
  • Status post WBRT and 4 cycles of carboplatin and gemcitabine, which was complicated by a incidental PE, anemia, and thrombocytopenia.
  • Post treatment CT showed mixed response with no change on CT Head, slight increase in size of primary lung lesion.
  • ECOG = 0.

  o Immunotherapy!!
    • Immune checkpoint inhibitors were funded at BC Cancer for NSCLC starting March 2017
    • She was started on Nivolumab
Very brief intro to Immune Checkpoint inhibitors

- PD1 (programmed death 1) – a protein on T cells

- PDL1 (programmed death ligand 1) – a protein on the surface of healthy cells that suppresses T cells (to help avoid autoimmunity)

- If a cell doesn’t have PDL1, the T-cell considers it an abnormal cell, and is activated

- Cancer cells can learn to express PDL1 to evade the immune system (“disguising” themselves as healthy cells)
Very brief intro to Immune Checkpoint inhibitors

- Tumors can essentially “hide in plain sight” from the immune system using PD1/PDL1

- Immune checkpoint inhibitors have been approved to treat advanced cancers by taking away this ability

- They are monoclonal antibodies, but rather than targeting a specific protein on cancer cells (like trastuzumab does with HER 2), they take the brakes off the immune system
Why is it important that front line providers understand the difference between immune checkpoint inhibitors and chemotherapy?
Why is it important that front line providers understand the difference between immune checkpoint inhibitors and chemotherapy?

• They have unique toxicities related to their mechanism of action – i.e., immune-mediated toxicities

• Chemotherapy interferes with cell cycle function, thereby affecting rapidly dividing cells (both cancer and non-cancer cells which have a high turnover rate -> cytopenias, nausea, vomiting, diarrhea, neuropathies
Checkpoint inhibitor toxicity – just add “itis”
They are generally well tolerated


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<td>1.0</td>
<td>15.3</td>
<td>6.1</td>
</tr>
<tr>
<td>Hypothyroidism</td>
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<td>0</td>
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<td>0.3</td>
</tr>
<tr>
<td>Hypophysitis</td>
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<td>0</td>
<td>0.3</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>1.3</td>
<td>0.3</td>
<td>6.4</td>
<td>1.0</td>
</tr>
</tbody>
</table>
Immune-related adverse events

- **The common:**
  - Fatigue, rash, pruritis, vitiligo, diarrhea, hyper/hypo-thyroidism

- **The life-threatening:**
  - Pneumonitis, colitis, hepatitis, nephritis, Type I DM and DKA, pancreatitis, hypophysis

- **The unusual:**
  - Guillan-Barre syndrome, inflammatory myopathies, asceptic meningitis
Time to onset of immune mediated adverse events with Nivolumab (any grade, n=474)

Most immune-mediated adverse events are low grade and easily managed, but early recognition is important to prevent progression of toxicity.

The cornerstone of treatment for Grade 3-4 adverse events are systemic glucocorticoids and withholding (or permanent discontinuation) of the immunotherapy.
Back to Mrs. S – How’s she tolerating Nivolumab?

- After 4 cycles, she’s tolerating it well, with no toxicities. ECOG remains 0

- CT to monitor response shows slight increase in the size of the primary lesion

- What would you recommend?
Back to Mrs. S – How’s she tolerating Nivolumab?

- After 4 cycles, she’s tolerating it well, with no toxicities. ECOG remains 0

- CT to monitor response shows slight increase in the size of the primary lesion

- What would you recommend?
  - Continue treatment
Pseudoprogression

- Be aware of pseudoprogression with immune checkpoint inhibitors
  - Initial imaging can suggest tumors have grown, but this is the immune response
  - Discovered in early trials when imaging showed enlargement/progression of lesions. Pts had no other options, and were tolerating tx reasonably well, so stayed on tx and improvement was noted thereafter
Can immune checkpoint inhibitors cross the blood brain barrier?
Can immune checkpoint inhibitors cross the blood brain barrier?

- There is growing evidence the immune checkpoint inhibitors can have positive effect on some brain metastases NSCLC, but early trials tended to exclude patients with brain mets, so more data is needed.
What if Mrs. S’s liver enzymes asymptotically quadrupled?
What if Mrs. S’s liver enzymes asymptomatically quadrupled?

- There is a lot of bloodwork that is monitored during immunotherapy, with the goal of detecting toxicities early, to prevent severe immune-mediated toxicity
  - CBC, creat, electrolytes, liver enzymes, TSH, morning serum cortisol, lipase

- If her liver enzymes quadrupled the concern would be an immune mediated hepatitis:
  - Treatment should be held
  - Medical Oncology should be contacted immediately
  - Pt should be started on 1mg/kg prednisone
Mrs. S is doing well after 30 cycles of Nivolumab. What about the dalteparin for PE?
Mrs. S is doing well after 30 cycles of Nivolumab. What about the dalteparin for PE?

- The PE was asymptomatic, found incidentally while on cytotoxic chemotherapy, but was significant (partially occlusive RLL PE)
- She really wanted to stop LMWH injections
- She saw a Hematologist
  - He advised that the PE was provoked by her cancer and chemotherapy
  - He felt she required ongoing anticoagulation indefinitely
  - He switched her to a DOAC (Rivaroxaban)
    - LMWH has been standard of care
    - Data indicates DOAC can be used in certain situations, but I recommend seeing a Hematologist to aid in this decision as there’s several important factors to consider (eg, GI tumors have increased bleeding on DOAC compared to dalteparin, and there are also potential drug interactions)
How’s Mrs. S doing now?

- Happy to report she’s had 35 cycles of Nivolumab, and continues to do well.

- She has a CT and follow up with her esteemed Med Onc pending this month.
Wrap up

• Non small cell lung cancer is too commonly discovered in Stage IV

• Stage I, II, and some III’s can be resected with goal of cure

• Stage IV is incurable, and treatment is focused on maintaining quality of life for as long as possible, while minimizing the side effects of treatment

• Systemic therapies used in the adjuvant treatment after resection in Stage II & III, and palliatively in Stage IV include:
  o Platinum-doublet chemotherapy
    • Traditionally the first-line systemic therapy, but algorithm is evolving
  o Immunotherapy – Immune-checkpoint inhibitors such as nivolumab or pembrolizumab
    • Immune-checkpoint inhibitors are moving up the treatment algorithm, and are becoming common
  o EGFR mutation positive:
    • EGFR targeted tyrosine kinase inhibitors such as afatinib, gefitinib, erlotinib, and osimertinib
  o ALK fusion oncogene positive:
    • ALK targeted tyrosine kinase inhibitor such as crizotinib, alectinib or ceritinib

• The different systemic therapies have unique potential toxicities that the GPO and front-line primary care physicians should be aware of.
Questions?