MANAGEMENT OF LUNG CANCER CYTOTOXIC AND TARGETED THERAPY TOXICITIES

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PRESENTER DISCLOSURE

- **Faculty:** Rick Prayag Pharm D

- **Relationships with commercial interests in last 12 months:**
  - **Grants/Research Support:** None
  - **Speakers Bureau/Honoraria:** None
  - **Consulting Fees:** None
  - **Other:** None

LEARNING OBJECTIVES

At the end of this workshop, participants will be able to:

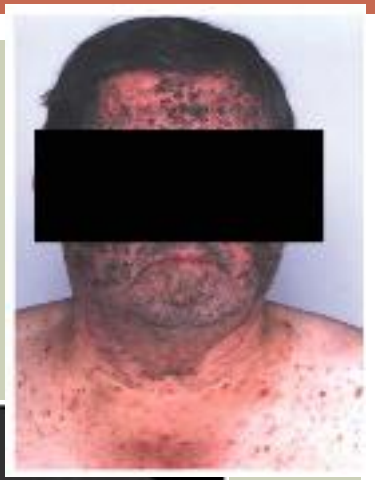
1. Identify common toxicities of lung cancer cytotoxic regimens
2. Identify management strategies for toxicities due to cytotoxic agents
3. Identify common toxicities of targeted agents used in lung cancer
4. Identify some management strategies for targeted agent toxicities

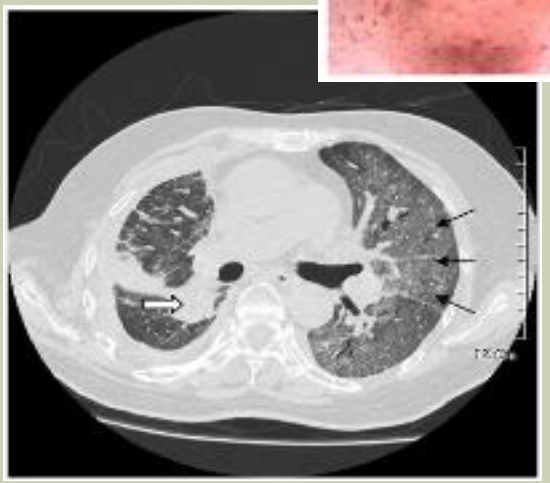
EGFR TKI

- 1st generation
  - Gefitinib
  - Erlotinib
- 2nd generation
  - Afatinib
- 3rd generation
  - Osimertinib

EGFR TKI - TOXICITY

- Fatigue – 52%, severe 18%
- **Rash** – dry, itchy skin, acneiform (face + trunk)
  - 75%, severe 9%
- Nail changes + cracking of hands - <10%
- **Diarrhea** – 54%, severe 7%
- Dyspnea – 41%, severe 28%
- **Interstitial lung disease** – 0.6%
- Anorexia
- Conjunctivitis
- GI hemorrhage – 2%
- Hepatotoxicity – 1 -2% (failure)





Kuo Med Oncol 2011; 28: 79.
Dy. CA Cancer J Clin 2013; 63: 249.
Chu. Physicians' Cancer Chemotherapy Drug Manual 2012.
BC Cancer Drug Manual, Cancer Care Ontario Formulary 2013

EGFR TKI – TOXICITY MONITORING

- BASELINE LABS: CBC, Liver enzymes, creatinine(afatinib)

- During treatment :
  - CBC, liver enzymes q2 weeks for one month then at each subsequent visit (1 month and q3 months thereafter)
  - Creatinine with each follow-up visit (1 month; q3months)

- Rash, diarrhea, GI bleeds, dyspnea, ocular disturbances; with each q3 monthly follow-up visit AND educate patient to contact clinic whenever the same arise

EGFR TOXICITY MANAGEMENT

- Diarrhea
  - Imodium 4 mg of loperamide immediately after symptoms begin and then 2 mg after each loose stool to a maximum of 20 mg daily
  - Hydration
  - Dose reduction if needed
- Rash
  - 1% hydrocortisone cream BID PRN
  - Tetracycline, minocycline, doxycycline
    - doxycycline 100 mg po daily

- Ocular disorders: symptoms such as acute or worsening eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye should be referred promptly to an ophthalmology specialist. For any diagnosis of ulcerative keratitis, treatment should be interrupted or discontinued.

EGFR TOXICITY MANAGEMENT

DOSE MODIFICATIONS:

- 1. Rash/skin toxicity: If prolonged or severe, may require treatment interruption and/or dose reduction.
- 2. Diarrhea: treatment interruption is recommended for grade 3 diarrhea or grade 2 diarrhea lasting ≥ 48 hours despite adequate antidiarrheal treatment. Upon recovery, resume treatment at a reduced dose level.
- 3. Renal impairment: renal impairment increases exposure to AFAtinib. Patients with moderate renal impairment (CrCL between 30-50 mL/min) may be at an increased risk of adverse events and should be closely monitored. Discontinue treatment if CrCL is < 30 mL/min.
- 4. Elevated liver enzymes: no guidelines for dose modification for mild to moderate hepatic impairment. Dose interruption may be necessary in patients who develop worsening of liver function. In patients who develop severe hepatic impairment, treatment should be discontinued.
- Gefitnib – dose modifications not possible

ALK INHIBITORS

- 1st generation
  - Crizotinib
- 2nd generation
  - Ceritinib
  - Alectinib

CRIZOTINIB - TOXICITY

- Fatigue – 27%, severe 1-2%
- Hepatotoxicity – 10-15%, severe 4-7%
- Nausea/Vomiting – 30-50%, mainly grade 1
- Neuropathy – 15%, severe <1%
- Diarrhea – 43-60%, mainly grade 1
- Interstitial lung disease – 1-2%
- Rash – 7-9%
- Vision symptoms – 60%
  - diplopia, photopia, blurry vision,
  - impaired vision, and vitreous floaters
- **Cardiotoxicity** (QTc, bradycardia) – 2-14%

BC Cancer Drug Manual, Cancer Care Ontario Formulary 2017

ALK TOXICITY MONITORING

BASELINE :

- CBC & differential, platelets, liver enzymes (including ALT), bilirubin, electrolytes, creatinine, ECG

During treatment:

- CBC & differential, platelets, liver enzymes (including ALT), bilirubin should be checked two weeks after starting crizotinib and at each subsequent visit. Creatinine should be checked with each visit. (< 30mL/min)

As required:

- ECG, electrolytes, heart rate and blood pressure to monitor for cardiotoxicity; chest X-ray and scans to monitor index lesions; chest radiograph for monitoring of dyspnea to rule out development of pneumonitis.

ALK TOXICITY MANAGEMENT

TABLE III Dose modifications for crizotinib related adverse events[16]

Toxicity	*CTCAE grade*	*Toxicity description*	*Dosing*
Hematologic toxicity			
	Grade 3	ANC: <1.0 to 0.5×10^9/L Platelets: <50.0 to 25.0×10^9/L	Withhold until recovery to grade 2 or lower. Resume at same dose schedule.
	Grade 4	ANC: $<0.5\times10^9$/L Platelets: $<25.0\times10^9$/L	Withhold until recovery to grade 2 or lower. Resume at 200 mg twice daily[a].
Hepatotoxicity			
	Grade 3 or 4 ALT or AST elevation *and* Grade 1 or lower total bilirubin	AST and ALT Grade 2: >3.0 to 5.0×ULN Grade 3: >5.0 to 20.0×ULN Grade 4: >20.0×ULN	Withhold until recovery to grade 1 or lower. Resume at 200 mg twice daily[b].
	Grade 2, 3, or 4 ALT or AST elevation *and* concurrent grade 2, 3, or 4 total bilirubin elevation[c]	Bilirubin Grade 2: >1.5 to 3.0×ULN Grade 3: >3.0 to 10.0×ULN Grade 4: >10.0×ULN	Permanently discontinue.
Pneumonitis			
	Any grade[d]		Permanently discontinue.
QTc prolongation			
	Grade 3[e]	QTc ≥ 500 ms	Withhold until recovery to baseline or to a QTc ≤ 480 ms Resume at 200 mg twice daily[b,f]
	Grade 4	QTc ≥ 500 ms *and* life-threatening signs or symptoms	Permanently discontinue.

Rothenstein JM, Curr Oncol 2014

CYTOTOXIC THERAPY

Platins:

- backbone of lung cancer cytotoxic regimens
  - Cisplatin, Carboplatin
- Platin Doublets: used 1st line in all lung cancer subtypes

ANTINEOPLASTIC REGIMENS

NSCLC Antineoplastic Agents

- Cisplatin + Gemcitabine / Vinorelbine / Pemetrexed / Docetaxel
- Carboplatin / Paclitaxel

SCLC Antineoplastic Agents

- Cisplatin / Etoposide

Mesothelioma Antineoplastic Agents

- Cisplatin / Pemetrexed

CYTOTOXIC TOXICITY

Platin Toxicities:

- Ototoxicity – 31 %
- nausea & vomiting - >90%
- Neuropathy- 4-10 %
- Nephrotoxicity – 28-36%
- BMS, FNE – 25-30%
- fatigue
- Cisplatin > Carboplatin
- except for BMS where Carbo is > Cisplatin(anemia)

CYTOTOXIC TOXICITY MONITORING

Baseline:

- CBC & differential, platelets, creatinine, liver function tests, bilirubin, electrolytes

Before each treatment:

- CBC & differential, platelets, creatinine, Liver enzymes, bilirubin, electrolytes

- Educate patient to contact clinic for: ototoxicity(audiogram as clinically indicated), neurotoxicity, FNE, nephrotoxicity

CYTOTOXIC TOXICITY MANAGEMENT

RENAL DYSFUNCTION

For CISplatin:

Clcr (mL/min) - greater than or equal to 60

Dose: 100%

CLCr : 45 to 59

Dose: 75 % CISplatin or go to CARBO

CLcr < 45

Dose :Hold CISplatin or delay with additional IV fluids or go to CARBOplatin option

COMMON TOXICITIES OF SELECTED AGENTS

Medication	Toxicity
Platins	• Nephrotoxicity – SCr Pre each cycle • Nausea and vomiting • Ototoxicity • Neuropathy • Electrolyte disturbances (Mg, Ca) Pre each cycle
Pemetrexed	• Supplementation with Vitamin B12 & Folate • Increased efficacy, tolerated better
Gemcitabine	• Strong radio sensitizer • 2 week washout period
Doxorubicin	• Cardiotoxicity - MUGA scans
Cyclophosphamide	• Delayed nausea • Hemorrhagic cystitis
Pemetrexed	• Use in squamous histology ?

CASE 1: 60 Y.O. ♂ UNRESECTABLE MALIGNANT PLEURAL MESOTHELIOMA

Labs		
WBC- 6.3	Na- 135	Scr- 93
HGB- 110	K+- 3.7	BUN- 6
Plts -230	Ca- 2.5	Bili (TOT)- 6
ANC-1.9	Mg- 0.9	AST- 20
	Phos- 1.2	ALT- 15
		GGT- 12
		LDH-160
		ALP- 75

P. M. H.
Diabetes
HTN
Dyslipidemia

Meds	
Metformin	500 mg tid
Lipitor	20 mg OD
Ramipril	10 mg OD

CASE 1: TX RECOMMENDATION

- Cisplatin / Pemetrexed q21 days
- After one cycle:
  - Complains of diarrhea, mucositis
  - What agent is the most likely culprit?

- Review his outpatient Rx:
  - Metoclopramide 10-20 mg po q4-6h prn
  - Dexamethasone 4 mg po bid x 6/7 (start the day before)
  - Vitamin B12 1000 ug IM q 9 weeks
  - Folic acid 1 mg po od

CASE 2: 47 Y.O. ♀
STAGE II NSCLC

Tx:

1) Surgery

2) Adjuvant chemotherapy – cisplatin and Vinorelbine x 4 cycles

Pre-Chemo Labs	
WBC- 7.3	BUN- 5
HGB- 110	SCr- 60 (74 ml/min)
Plts -310	Bili (TOT)-7
ANC- 2.2	Lytes normal
	LFT's normal

CASE 2: 47 Y.O. ♀
STAGE II NSCLC 158 CM 70 KG

Post Cycle #1 Day 8 – burning in chemo arm
- PICC line inserted

Pre cycle #2 labs:

Labs	
WBC- 6.1	BUN- 6
HGB-103	SCr- 120
Plts- 200	Bili(TOT)-8
ANC- 2.3	Lytes Mg- 0.6 Ca - 2.01
	LFT's normal

CASE 2: 47 Y.O. ♀
STAGE III NSCLC 158 CM 70 KG

What is the next step?

Repeat Blood work: SCr 130 umol/L

Labs	
WBC- 6.1	BUN- 6
HGB-103	SCr- 120
Plts- 200	Bili(TOT)-8
ANC- 2.3	Lytes Mg - 0.6 Ca - 2.01
	LFT's normal

CASE 3: 65 Y.O. ♂
SCLC – LIMITED STAGE

Labs
WBC- 7.3
HGB- 105
Plts- 270
ANC- 3.2
BUN- 3
SCr- 63

P. M. H.
HTN
MI (Remote)

Labs	
Lytes	normal
LFT's	normal

CASE 3: 65 Y.O. ♂
SCLC – LIMITED STAGE

- Tx: Cisplatin / Etoposide x 4 cycles
  - CT Post Tx: disease progression
- 2nd Line Tx: CAV – Cyclo, Doxo, Vincristine
  - What baseline tests/bloodwork to order?
- Pre Cycle #2 Exam:
  - Patient's urine is pink tinged. No discomfort.
  - Ongoing nausea.
  - Cause? Tx?

CASE 4: 58 Y.O. ♀
NSCLC STAGE IV (SQUAMOUS)

PMH - healthy

Medication
Tylenol prn

Labs	
WBC- 7.3	BUN- 3
HGB-112	SCr- 57
Plts- 210	Bili(TOT)-25
ANC- 1.9	Lytes: Na - 133 Phos- 1.43 K+ -3.6 Ca- 2.43 Mg- 0.97
	LFT's: LDH- 360

CASE 4: 58 Y.O. ♀
NSCLC STAGE IV (SQUAMOUS)

- Completed chest radiation one week ago
- Chemotherapy: Cisplatin/Gemcitabine q21 days x 4

- Any concerns with labs?
- Is it okay to start chemotherapy today?

CASE 4: 58 Y.O. ♀
NSCLC STAGE IV (SQUAMOUS)

Pre-Cycle #2 Exam

- Tolerated Cycle #1 well
-

Labs	
WBC- 6.1	BUN- 4
HGB-110	SCr- 63
Plts- 175	Bili(TOT)-21
ANC- 1.8	Lytes Na - 136 K+ -3.8
	LFT's: LDH- 385

Any other labs to order?

CASE 5: 70 Y.O. ♀
SCLC LIMITED STAGE

PMH	Medication
Type II Diabetes	Glyburide 5 mg bid
HTN	Cilazapril 5 mg bid
Dyslipidemia	Atorvastatin 10 mg od

Labs	
WBC- 8.3	BUN- 5
HGB-110	SCr- 67
Plts- 210	Bili(TOT)-6
ANC- 3.4	Lytes OK
	LFT's: LDH- 440

CASE 5: 70 Y.O. ♀
SCLC LIMITED STAGE

- Tx Plan:
  - Cisplatin / Etoposide x 4-6 cycles
  - Anti-emetics: Dexamethasone 4 mg po bid x 4 days (4-7)
  - Metoclopramide 10-20 mg po q 4-6 h prn
  - Ondansetron 8 mg po OD in the evening of chemotherapy days
- Patient calls on Day 5 of Cycle #1
  - Ongoing nausea
  - No vomiting

CASE 5: 70 Y.O. ♀
SCLC- LIMITED STAGE

- Action?
  - Question patient on how she uses her anti-emetics
  - She indicates she does not always take her prn metoclopramide
  - She waits for nausea to pass
  - Advised her to take metoclopramide as needed
- Exam Pre-Cycle #2
  - Nausea controlled
  - Complains of feeling jittery
- Recommendations?
  - Change prn antinauseant
  - Emend

CASE 6: 64 Y.O. ♂
NSCLC STAGE IIIB

PMH	Medication
HTN	Irbesartan / HCTZ (150 mg / 12.5 mg) od
O.A.	Acetaminophen Arthritis 650 mg q 8h

Labs	
WBC- 6.2	BUN- 8
HGB-115	SCr- 57
Plts- 320	Lytes OK
ANC- 2.1	LFT's OK

CASE 6: 64 Y.O. ♂ NSCLC STAGE IIIB

- Chemotherapy:
  - Cisplatin / Gemcitabine x 4-6 cycles
- Cycle #1 Day 8
  - Patient mentions some transient ringing in his ears
- Recommendation?
- Exam – Pre Cycle #2
  - Transient ringing in ears. Otherwise fine
- Post Day 1 Cycle #2
  - Patient indicates ringing in ears continuous

CASE 6: 64 Y.O. ♂ NSCLC STAGE IIIB

- Recommendation?

- Cycle #2 Day 8 blood-work
  - Patient indicates ringing is worse and difficulty hearing high frequency
- What Actions?
  - Dose reduced
  - Switch to Carbo

TAKE HOME MESSAGE

- Baseline labs, clinical assessments
- Monitoring throughout therapy
- Patient education to contact clinic for any changes- encourage dialogue.