A Collaborative Practice Approach to Managing Patients With Advanced Non-Small Cell Lung Cancer

Clarifying the Selection of Newer Treatment Options

Corey Langer, MD, FACP
Beth Eaby-Sandy, CRNP, OCN®
Abramson Cancer Center
University of Pennsylvania

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Disclosure

Ms. Eaby-Sandy has served on speakers bureaus for Merck, Genentech, and Eli Lilly, and has acted as a consultant for Amgen.

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Case Study #1

- 78 y/o male fell and fractured his arm requiring surgical rod placement. Pre-operative CXR shows R and L sided masses and a R-sided pleural effusion.
  - Thoracentesis of the R effusion is (+) for adenocarcinoma of the lung.
  - PET/CT: R- and L-sided masses exhibit FDG uptake
  - Brain MRI is negative

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Case Study #1 cont.

- History
  - Smoking: Yes, 1 PPD x 50 yr, quit 8 yr ago
  - HTN, controlled on amlodipine
  - COPD, not on oxygen or inhalers
  - Wife and daughters were at visit and appear supportive

PPD = pack per day; HTN = hypertension; COPD = chronic obstructive pulmonary disease.

Case Study #1 cont.

- What information would be helpful to guide treatment decision in this case?
  - Do we know histology?
  - Do we know molecular marker status?
  - What are comorbidities and performance status?
  - What are the patient's goals?
    - Discussion of prognosis
    - Begin discussion about code status

Case Study #1 cont.

- His molecular markers are negative, has adenocarcinoma, minimal and controlled comorbidities, and PS is 0. Patient and family would like to pursue aggressive treatment to prolong life.

For this patient with adenocarcinoma of the lung, which regimen would you be most likely to start him on?

A. Single-agent pemetrexed **487827**
B. Combination of gemcitabine and carboplatin **487828**
C. Combination of pemetrexed and carboplatin **487829**
D. Combination of pemetrexed, carboplatin, and bevacizumab **487830**

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Collaboration and Patient Care

- Goals are to optimize treatment response, deliver care safely, and to deliver holistic care.
- MD and PA/CRNP: The UPENN experience
  - Collaborative clinic (shared responsibility)
  - Availability to symptom-manage
  - Avoid ER visits and readmissions

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Advanced Practitioner Concerns

- Combination chemotherapy with pemetrexed/carboplatin/bevacizumab
  - Blood counts, renal function (CrCl > 45 for Pem)
  - Pem: Vitamin supplementation, steroid prep
  - Nausea: Follow NCCN guidelines for moderately emetogenic chemotherapy
  - HTN, hemoptysis: What are risks with bevacizumab, proteinuria

CrCl = creatinine clearance; NCCN = National Comprehensive Cancer Network.

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Most Common (grade 3-5) Side Effects in E4599 in Bev Arm vs Control

- HTN 8% vs 0.7%
- Neutropenia 27% vs 17%
  - FN 5% vs 2%
- Fatigue 16% vs 13%
- VTE 5% vs 3%
- Infections 7% vs 3%
- Proteinuria 3% vs 0%

**Fatal pulmonary hemorrhage was 2.3% in the bev arm and 0.5% in the control arm.

Sandler, A. (2006). *N Engl J Med*, ECOG 4599.

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Management of Hypertension

- Obvious lifestyle and diet modifications
- No algorithm reported in literature
- CCBs, ACE inhibitors, ARBs good options
- Diuretics, BBs also considerations
- Should be individualized depending on your patient's PMH and comorbidities

CCB = calcium channel blocker; ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blockers; BB = beta blocker; PMH = past medical history.

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Study of Hypertension Management in VEGF

- *JCO* 2009, study of HTN management (VEGFI was cediranib), 126 patients with solid tumors
- Patients randomized to CCB prophylaxis vs no HTN prophylaxis
- Treating HTN did not interfere with efficacy of VEGFI
- It decreased severe HTN in favor of prophylaxis arm, however, not real difference in HTN in both arms for mild/moderate HTN (both easily controlled)

Langenberg, M. H. G., et al. (2009). *J Clin Oncol, 27*, 6152-6159.

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If Following JNC 7 Guidelines

- Thiazide-type diuretics first choice to treat HTN
- If diabetic HTN or chronic kidney disease, ACE inhibitors or ARBs also reduce nephropathy and albuminuria
- If HF or ischemic heart disease, BB is first choice
- African American patient's HTN responds best to diuretics and CCBs. Increased risk of angioedema with ACE inhibitors.

http://www.nhlbi.nih.gov/guidelines/hypertension/express.pdf

HF = heart failure.

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JNC 7 Report on Blood Pressure

Table 1. Classification and management of blood pressure for adults*

BP Classification	SBP* mmHg	DBP* mmHg	Lifestyle Modification	Initial drug therapy: Without Compelling Indication	Initial drug therapy: With Compelling Indications (See Table 8)
Normal	<120	and <80	Encourage		
Prehypertension	120–139	or 80–89	Yes	No antihypertensive drug indicated.	Drug(s) for compelling indications.‡
Stage 1 Hypertension	140–159	or 90–99	Yes	Thiazide-type diuretics for most. May consider ACEI, ARB, BB, CCB, or combination.	Drug(s) for the compelling indications.‡ Other antihypertensive drugs (diuretics, ACEI, ARB, BB, CCB) as needed.
Stage 2 Hypertension	≥160	or ≥100	Yes	Two-drug combination for most† (usually thiazide-type diuretic and ACEI or ARB or BB or CCB).	

JNC 7 report on Blood Pressure 2003. available online. http://www.nhlbi.nih.gov/guidelines/hypertension/

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Hold Drug for HTN When…

- IF the BP on a single visit rises significantly
- IF it has reached a level after several visits that qualifies as stage I to stage II HTN
- PERMANENTALY DISCONTINUE if the patient develops a hypertensive crisis or RPLS

BP = blood pressure; RPLS = reversible posterior leukoencephalopathy syndrome.

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Proteinuria

- Likely occurs due to damage of the glomerular endothelial cells
- Bevacizumab PI states to assess "serial" urine protein measures
- Gold standard is the 24-hour urine when the dip is in question

Adverse Grade	1	2	3	4
Proteinuria	+1 on dip less than 1 g/24 hr	+2 on dip 1-3.4 g/24 hr	nephrotic syndrome ≥ 3.5 g/24 hr	

NCI CTC grading criteria V 4.03

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Management of Proteinuria

- Can do a dipstick, random urine protein, or 24-hour urine protein.
- If dipstick +2, or random urine protein is at 30 g/dL, ok to treat, but should do a 24-hour urine protein prior to next treatment.
- **Suspend treatment if 24-hr protein is > 2 g/L**
- OK to resume once the level decreases below 2 g/L

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Case Study #2

- 48 y/o woman presents to her primary care MD's office with a persistent dry cough. After treatment for allergies and upper respiratory infection with no relief, a CXR is ordered, revealing multiple bilateral lung nodules.

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Case Study #2 cont.

- A CT-guided needle biopsy of a dominant mass reveals metastatic adenocarcinoma of the lungs.
- The patient is a never-smoker.
- There is not enough tissue from the needle biopsy to perform molecular testing.

What is your next step with this patient?

A. Give chemotherapy with platinum-based doublet **487831**

B. Re-biopsy to get more tissue, but don't wait for the molecular results and start on chemotherapy a while **487832**

C. Re-biopsy to get more tissue and wait for the results before starting on chemotherapy **487833**

Case Study #2 cont.

- Molecular results show that the patient has an EGFR mutation.
- The oncologist discusses starting the patient on a first-line EGFR inhibitor.

Which drug is FDA indicated for the first-line treatment of EGFR mutation + NSCLC?

A. Erlotinib **486879**
B. Afatinib **487119**
C. Crizotinib **487252**
D. A and B **487824**
E. All of the above **487826**

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Collaborative Management for This Patient

- MD prescribes medication and may consent patient and discuss potential side effects
- CRNP/PA reinforce teaching of side effects, see the patient in follow up for side effect management, phone call protocol?, oral meds can present a challenge for follow-up and compliance

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Most Common Side Effects: EGFRIs

- Rash, papulopustular eruption
- Diarrhea
- Fatigue
- Other cutaneous toxicities
- Interstitial lung disease (rare, can be fatal)
- Elevations in LFTs (transaminases)

LFT = liver function tests.

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Incidence and Severity of Rash

Drug	All Rash Incidence	Grade 3/4 Incidence
Cetuximab	89% (70% in FLEX trial)	12% (10% in FLEX trial)
Erlotinib	75%	9%
Gefitinib	Rash: 43% Acne: 25%	0% (only reported ≥ 5%) 0%
Panitumumab	89%	12%
Afatinib	89%	16%

Erbitux® prescribing information, 2013; Tarceva® prescribing information, 2010; Iressa® prescribing information, 2010; Vectibix® prescribing information, 2013; Yang, et al., 2012.

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Strategies to Prevent Dermatologic Toxicities: Pre-Emptive

- STEPP in metastatic colorectal cancer patients who received panitumumab-containing regimens

  95 total patients:
  - Significant improvement in EGFR rash and quality of life with pre-emptive doxycycline and topical hydrocortisone cream.
  - At 6 weeks, grade ≥ 2 skin toxicities were reduced by more than 50% in the pre-emptive arm

STEPP = Skin Toxicity Evaluation Protocol With Panitumumab.
Lacouture et al, 2010.

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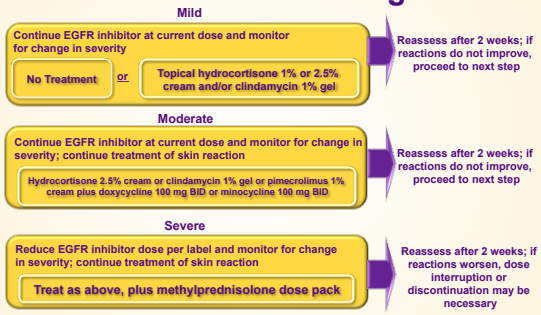
EGFR Rash Treatment Algorithm



BID = twice daily.
Lynch et al., 2007.

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MASCC Rash Prevention and Treatment Guidelines

Preventive (Weeks 1-6,8 of EGFR Inhibitor initiation)	Recommend	Not Recommended	Level of Evidence	Recommendation Grades	Comments
Topical	Hydrocortisone 1% cream with moisturizer and sunscreen BID	• Pimecrolimus 1% cream • Tazarotene 0.05% cream • Sunscreen as single agent	II[a]	C	Doxycycline is preferred in patients with renal impairment. Minocycline is less photosensitizing.
Systemic	• Minocycline 100 mg daily • Doxycyline 100 mg BID	Tetracycline 550 mg BID	II[a]	A	
Topical	• Alclometasone 0.05% cream • Fluocinonide 0.05% cream BID • Clindamycin 1%	Vitamin K1 Cream	IV[a]	C	Fluocinonide 0.05% cream BID should not be used on the face for more than 2 weeks at a time.
Systemic	• Doxycycline 100 mg BID • Minocycline 100 mg daily • Isotretinoin at low doses (20-30 mg/d)	Acitretin	IV[a]	C	Isotretinoin is photosensitizing and can cause xerosis. Monitor lipids and liver enzymes with retinoids.

[a]EGFR inhibitor study. MASCC = Multinational Association for Supportive Care in Cancer. Lacouture et al, 2011.

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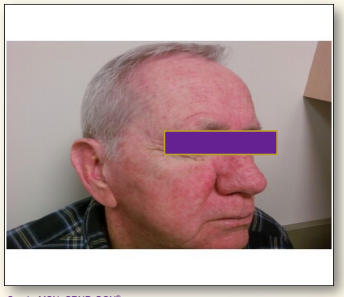
Mild Rash



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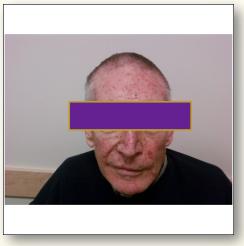
Moderate Rash



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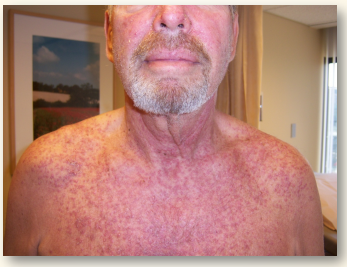
Severe Rash



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Other Cutaneous Toxicities

- Xeroderma
- Alopecia/scalp rash
- Paronychia
- Hypertrichosis
- Fissures
- Pruritus

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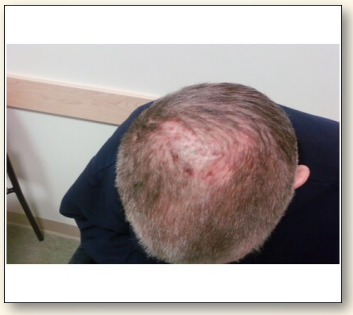
Scalp Rash



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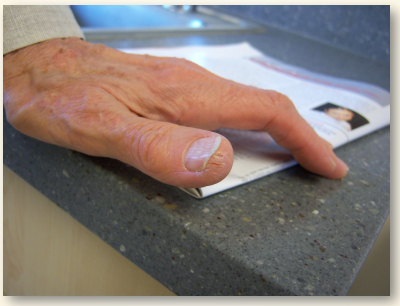
Scalp Rash From EGFRIs

- Can be tough to manage
- Use Selsun Blue shampoo, massage into scalp
- Move to Capex shampoo, clobetasol foam (prescription)
- Treat systemically with doxy or minocycline
- Avoid manipulation of scalp
- Watch sun exposure

Fingertip Splitting on Erlotinib

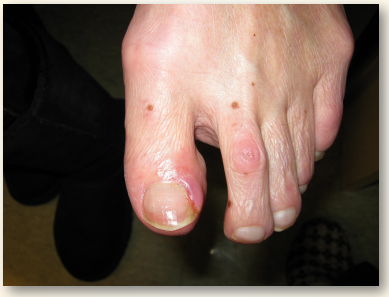


Fissures/Cracking

- Thick moisturizers or zinc oxide creams
- Liquid glues or cyanoacrylate to seal cracks
- Topical steroids or steroid tape, hydrocolloid dressings, topical antibiotics
- Bleach soaks to prevent infection
- Wear protective footwear and gloves if needed

MASCC. (2011). *J Support Care Cancer.*

Paronychia on Cetuximab



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Paronychia

- Warm soaks, with very dilute betadine/vinegar or liberal amounts of epsom salt
- Topical antifungals or antibiotics (1% mupirocin or 0.05% fluocinonide)
- Oral antibiotics (keflex, doxycycline), culture first is recommended
- Avoid restrictive shoes
- Derm or podiatry consult for nail avulsion if needed
- Hold drug

http://journals.lww.com/oncology-times/Fulltext/2011/06250/MARIO_LACOUTURE__How_Do_I_Treat_a_Patient_with.2.aspx

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Ocular Toxicity From Erlotinib

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Hypertrichosis (Eyelashes)

- Trim carefully
- Do not pluck or bleach
- Erythromycin ophthalmic ointment for crusting/erythema
- Ophthalmology consult

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Pruritus

- Thick moisturizers: Sarna Ultra, Eucerin, Aveeno
  - For scaly areas, lactic acid creams (Lac-hydrin, Am-lactin creams)
- Antihistamines

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End-of-Life (EOL) Discussions: Role of the CRNP/PA

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Palliative Care in NSCLC

- Temel paper in *NEJM*
- Early palliative care in metastatic NSCLC patients led to:
  - Improved QOL
  - Improved mood
  - Less aggressive care at end of life
  - **Increase in survival**

Temel, J. (2010). *NEJM.*

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Prognostic Acceptance

- Coming to terms with terminal illness is very complex:
  - Personality
  - Social supports
  - Spiritual/existential views on life
- Non-acceptance associated with:
  - Suffering, depression, hopelessness
  - Difficulties with social-relational concerns

Thompson, G. N. (2009). *J Clin Oncol.*

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End-of-Life Discussions

- Current NCCN guidelines state that EOL discussions should begin earlier in patients with incurable cancer, during periods of medical stability, and with physician who knows the patient well.
- On average, EOL discussions occur 33 days before death.

Mack, J. W., et al. (2012). *J Clin Oncol.*

NCCN guidelines V2.2013.

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EOL Information

- Informing a patient when death is imminent at EOL does not increase pain, anxiety, confusion, nausea, or respiratory problems
- It was also associated with principles of a "good death"
  - Died in preferred place of death
  - Family informed and received bereavement counseling

Lundquist, G. (2011). *J Clin Oncol, 29,* 3927-3931.

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Conclusions

- MD/CRNP/PA collaboration key to optimizing patient care and experience
- The CRNP/PA can be instrumental in managing patients in clinic for routine chemotherapy visits, managing side effects or new symptoms, and facilitating end-of-life discussions and plan

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