An Update on EGFR Inhibitors

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Disclosure

- Leigh M. Boehmer, Pharm.D., has no real or apparent conflicts of interest to report

Objectives

- Summarize the pharmacology of epidermal growth factor receptor (EGFR) inhibitors
- Explain the current role of EGFR's in the treatment of cancers
- Describe a management strategy for patients taking EGFR's

Epidermal Growth Factor Receptor

- Member of ErbB family of receptor tyrosine kinases
- Overexpressed in a variety of epithelial cancers
- Downstream signaling pathway helps regulate:
  - Differentiation
  - Proliferation
  - Tumor migration
  - Angiogenesis
  - Apoptosis

Choong N and Cohen E. *Critical Reviews in Oncology/Hematology*. 2006;57:25-43.

EGFR Activation

Ligand binding

↓

Receptor homo-/heterodimer formation

↓

Stimulation of intrinsic receptor tyrosine kinase

↓

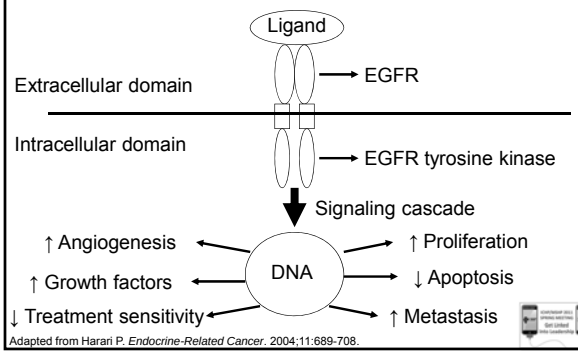
Autophosphorylation

↓

Downstream signaling pathway activation

Reuter C, et al. *British Journal of Cancer*. 2007;96:408-16.

EGFR Structure and Function



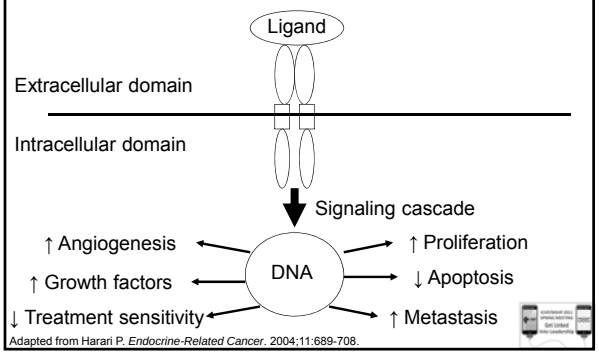
Adapted from Harari P. *Endocrine-Related Cancer*. 2004;11:689-708.

EGFR Overexpression and Prognosis

- Advanced stage at diagnosis
- ↑ tumor size
- ↑ rate of recurrence
- ↓ survival
- ↓ sensitivity to radiation therapy

Choong N and Cohen E. *Critical Reviews in Oncology/Hematology*. 2006;57:25-43.

EGFR Inhibitors



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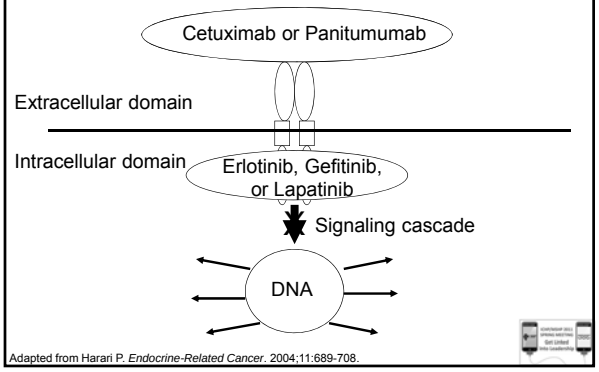
EGFR Inhibitors



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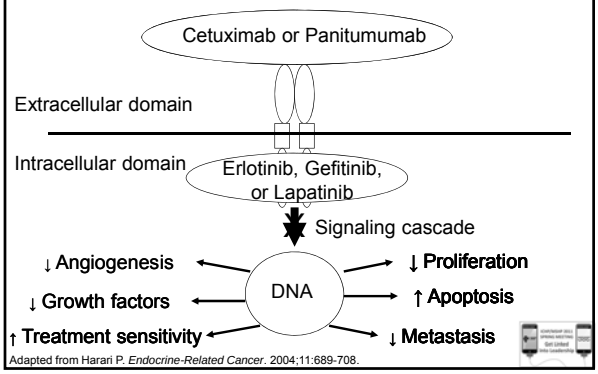

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Cetuximab (Erbitux®)

- Indications:
  - Metastatic colorectal cancer, EGFR-expressing
  - Locally advanced or metastatic head and neck cancer
- Dosing:
  - Loading dose – 400 mg/m^2 IV over 2 hours
  - Maintenance – 250 mg/m^2 IV over 1 hour weekly
- Premeds:
  - H_1 antagonist IV 30-60 mins prior to loading dose
  - Consider: H_2 antagonist IV, corticosteroid IV, and/or albuterol neb 2.5 mg

Panitumumab (Vectibix®)

- Indications:
  - Metastatic colorectal cancer, EGFR-expressing
- Dosing:
  - 6 mg/kg IV every 2 weeks over 1 hour
  - Doses >1000 mg infuse over 1.5 hours
- Premeds:
  - None recommended – fully humanized antibody

Kirsten Rat Sarcoma (KRAS) Mutations

- Signal-transducing protein in the EGFR pathway
- Mutations lead to constitutive downstream signaling without prior EGFR activation
- Mutation frequency ~40% in metastatic colorectal cancer
- Mutation frequency ~25% in NSCLC
- Mutated KRAS may lead to lack of response to EGFR inhibitors and cancer progression

NSCLC = non-small cell lung cancer

Mancl E, et al. *Am J Health-Syst Pharm*. 2009;66:2105-12.

EGFR Inhibitor Response and KRAS Mutation Status

EGFR Inhibitor	Concurrent Therapies	No. (%) with KRAS Mutated	KRAS Mutated Response	KRAS Wild-type Response	P Value
Cetuximab (N=540)[a]	FOLFIRI	192 (36)	PFS 7.6 mo	PFS 9.9 mo	0.007
Cetuximab (N=337)[b]	FOLFOX	99 (42)	PFS 5.5 mo	PFS 7.7 mo	0.0009
Panitumumab (N=463)[c]	Best supportive care	199 (43)	Response rate 0%	Response rate 17% (N=21)	<0.0001
Cetuximab (N=394)[d]	Best supportive care	164 (42)	Overall survival 4.5 mo	Overall survival 9.5 mo	0.01

[a]Van Cutsem E, et al. *J Clin Oncol*. 2008;26(suppl):abstract 2; [b]Bokemeyer C, et al. *J Clin Oncol*. 2008;26(suppl):abstract 4000; [c]Amado R, et al. *J Clin Oncol*. 2008;26:1626-34; [d]Karapetis C, et al. *N Engl J Med*. 2008;359:1757-65.

Erlotinib (Tarceva®)

- Indications:
  - Locally advanced or metastatic non-small cell lung cancer
  - Locally advanced, unresectable, or metastatic pancreatic cancer with gemcitabine
- Dosing:
  - Lung cancer – 150 mg PO daily
  - Pancreatic cancer – 100 mg PO daily
- Dose adjustments:
  - Current smokers – max dose of 300 mg PO daily
  - CYP3A4 inhibitors/inducers

Gefitinib (Iressa®)

- Indication:
  - Locally advanced or metastatic non-small cell lung cancer, continued therapy
- Dosing:
  - 250 mg PO daily
  - Must enroll in Iressa® Access Program
- Notable adverse effect:
  - Pulmonary toxicity – rare, potentially fatal interstitial lung disease

Lapatinib (Tykerb®)

- Indication:
  - Advanced or metastatic breast cancer, HER2/neu overexpressing
- Dosing:
  - With capecitabine – 1250 mg PO daily
  - With letrozole – 1500 mg PO daily
- Dose adjustments:
  - Strong CYP3A4 inhibitor – ↓ to 500 mg PO daily
  - Strong CYP3A4 inducer – ↑ to 4500-5500 mg PO daily

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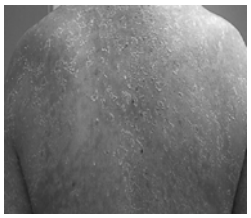
Cetuximab Infusion Reactions

- Premedications required
- Anaphylaxis treatment should be available
  - Epinephrine, hydrocortisone, diphenhydramine
- Monitor during and at least 1 hour after infusion
- 90% severe reactions occur with first dose

Dermatologic Toxicities

- Dose dependent, acneiform skin rash
- ~80% grade 1-2 reaction
- Median onset 1-2 weeks
- Found in seborrheic areas
- Studies show relationship between skin rash and improved response



Segaert S and Van Cutsem E. *Annals of Oncology*. 2005;16:1425-33.

Dermatologic Toxicities

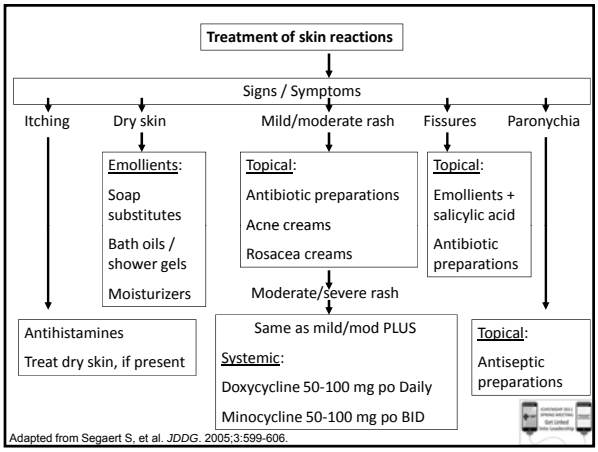
Toxicity	Frequency/Time Course	Characteristics
Xerosis / dry skin	~35%; several weeks	Dry, scaly, itchy skin that can develop into fissures
Paronychia (nail changes)	~15%; weeks to months	Painful inflammation of the nail fold
Hair changes	Progressive appearance with prolonged use	Long, curly eyelashes
Hyperpigmentation	May be seen following acneiform eruption	Post-inflammatory skin discoloration; worsened with sun exposure

Segaert S, et al. *JDDG*. 2005;3:599-606.

General Dermatologic Measures

- Maximize skin hydration
  - Bath oils / shower gels
  - Tepid water
- Emollient creams / lotions
- Minimize direct sun exposure
  - Brimmed hats
  - Sunblock (at least SPF 15)
- Consider dermatology consult

Segaert S and Van Cutsem E. *Annals of Oncology*. 2005;16:1425-33.



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Future Directions

- Irreversible pan-ErbB tyrosine kinase inhibitors
  - Canertinib
  - Neratinib
- Suppression of EGFR T790M mutation
  - BIBW2992
- Dual-target ErbB family inhibitors
  - EGFR, HER2, VEGF
  - EGFR, HER2, HER4

VEGF = vascular endothelial growth factor

McNeil C. *Journal of the National Cancer Institute*. 98;(16):1102-3.

Audience Response

Erlotinib is an inhibitor of the EGFR tyrosine kinase. Inhibition of this kinase activity results in which of the following?

a. Decreased treatment sensitivity

b. Increased angiogenesis

c. Decreased cell proliferation

d. Increased metastasis

An Update on EGFR Inhibitors: Suggested Readings

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Segaert S and Van Cutsem E. Clinical signs, pathophysiology and management of skin toxicity during therapy with epidermal growth factor receptor inhibitors. *Annals of Oncology*. 2005;16:1425-33.

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ICHP/MSHP 2011 Spring Meeting
Clinical Pearls - An Update on EGFR Inhibitors
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121-000-11-015-L01-P

Post Test Questions:

1. EN is a 64 year old male with newly diagnosed metastatic colorectal cancer. His tumor is known to be EGFR-expressing and to harbor a mutated KRAS gene. What recommendation would you give his physician about epidermal growth factor receptor-targeted therapy as part of his initial chemotherapy regimen?

    a. Panitumumab is appropriate for use given his mutated KRAS status.
    b. Lapatinib is not appropriate for use given it only targets HER2/neu.
    c. Erlotinib is appropriate for use given his tumor is EGFR-expressing.
    d. Cetuximab is not appropriate for use given his mutated KRAS status.

2. Two weeks after starting single-agent erlotinib for metastatic non-small cell lung cancer, YM comes to the clinic complaining of an acne-like rash. Upon inspection, you note a Grade 3 moderate/severe maculopapular skin rash on her face and neck. In addition to topical acne cream, which of the following regimens would you recommend?

    a. Doxycycline 100 mg po Daily
    b. Sulfamethoxazole/trimethoprim 1 DS tab po BID
    c. Minocycline 50 mg po Daily
    d. Amoxicillin 500 mg po BID