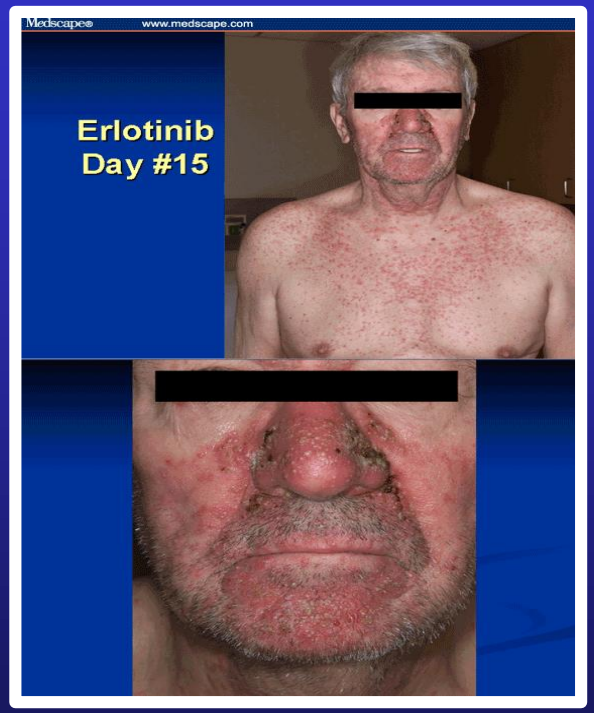
EGFR – Targeted Therapeutic Agents

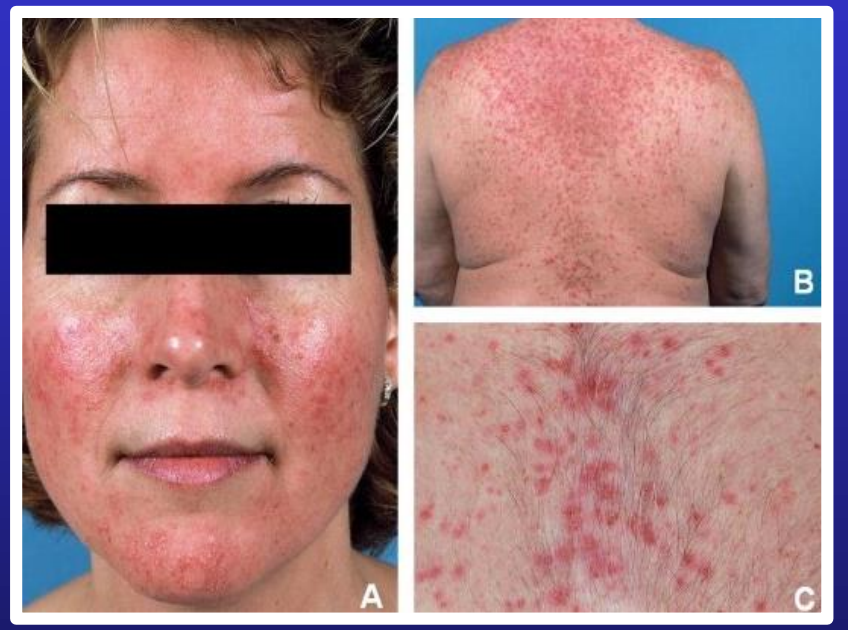
Multiple clinical trials have shown enhanced survival of cancer patients treated with antibodies to the EGFR (cetuximab and panitumumab) as well as inhibitors of the tyrosine kinase (TKI) intracellular portion of the EGFR and two TKIs, gefitinib and erlotinib, are in common clinical use; they compete with ATP binding to the TK region of the receptor complex.

Can. J. Phys. Pharm., 2012.

Examples of rash caused by EGFR inhibitors

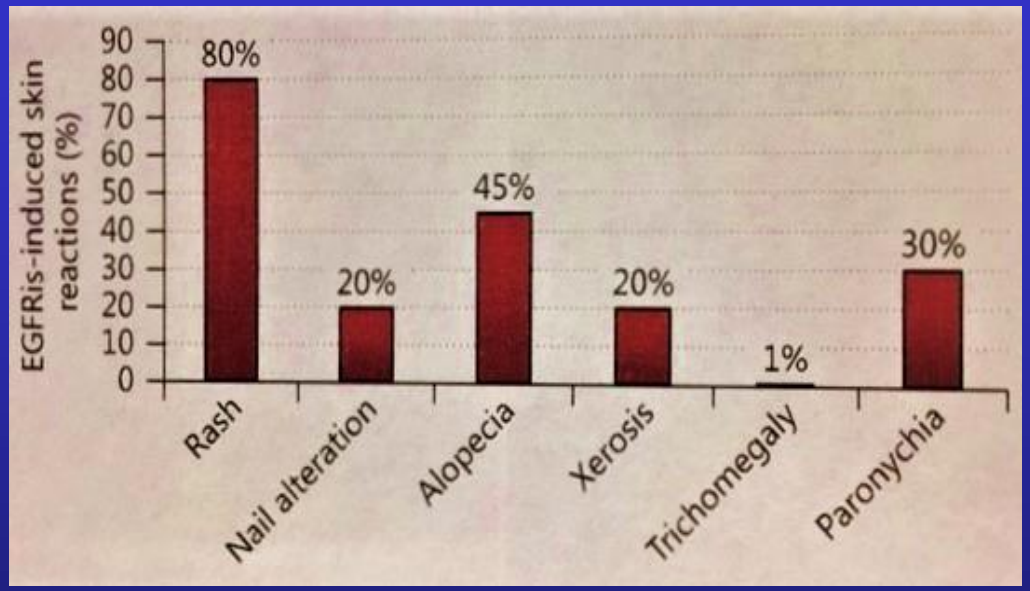


Megan Dunne, RN, MA, APRN-BC, AOCN; Dyana K. Sumner, MSN, ANP-C, OCNEGFR, Inhibitors: Toxicities and Strategies for Effective Management
https://www.medscape.org/viewarticle/579711_8



https://www.lindiskin.com/egfr-face-rash

Incidence of Cutaneous Lesions due to EGFR-TKI Therapy



EGFR Inhibitor – induced Skin Reactions and Hair Loss in 120 cancer patients; 80% had papulopustular rash and 45 % exhibited hair loss (*Skin Appendage Disord 2015; 1:31-37*).

CLINICAL EGFR INHIBITORS LINKED TO PATIENT SKIN RASHES/HAIR LOSS	
DRUG NAME	**INDICATION FOR CANCER THERAPY**
Small Molecule (Oral Rx)	
Tarceva (erlotinib)	metastatic lung and pancreas
Iressa (gefitinib)	metastatic lung
Gilotrif (afatinib)	metastatic lung
Tagrisso (osimirtinib)	metastatic lung
Tykerb (lapatinib)	breast
Caprelsa (vandetinib)	thyroid
Monoclonal antibody (IV Rx)	
Erbitux (cetuximab)	metastatic colorectal, head and neck
Perjeta (pertuzumab)	colorectal
Portrazza (necitumumab)	lung
Vectibix (panitumumab)	metastatic colorectal
Mild to modest incidences of adverse cardiovascular events (LV Systolic dysfunction; QTc interval prolongation) were report for some agents (Kloth et al. Br. J. Cancer (2015) 112, 1011–1016; Pun et al. Eur. Heart J. (2015) 37:2742-2745; and corresponding FDA Drug Label Highlights).	

Clinical Mechanism of Action of Emend (aprepitant)

The active substance of Emend is aprepitant, which is effective in helping to prevent CINV because it antagonizes the NK1 receptor. This receptor is located at the brain stem nuclei of the dorsal vagal complex and is a crucial part of the regulation of vomiting. This is due to the receptor binding with substance P, a peptide neurotransmitter.

http://en.wikipedia.org/wiki/Aprepitant

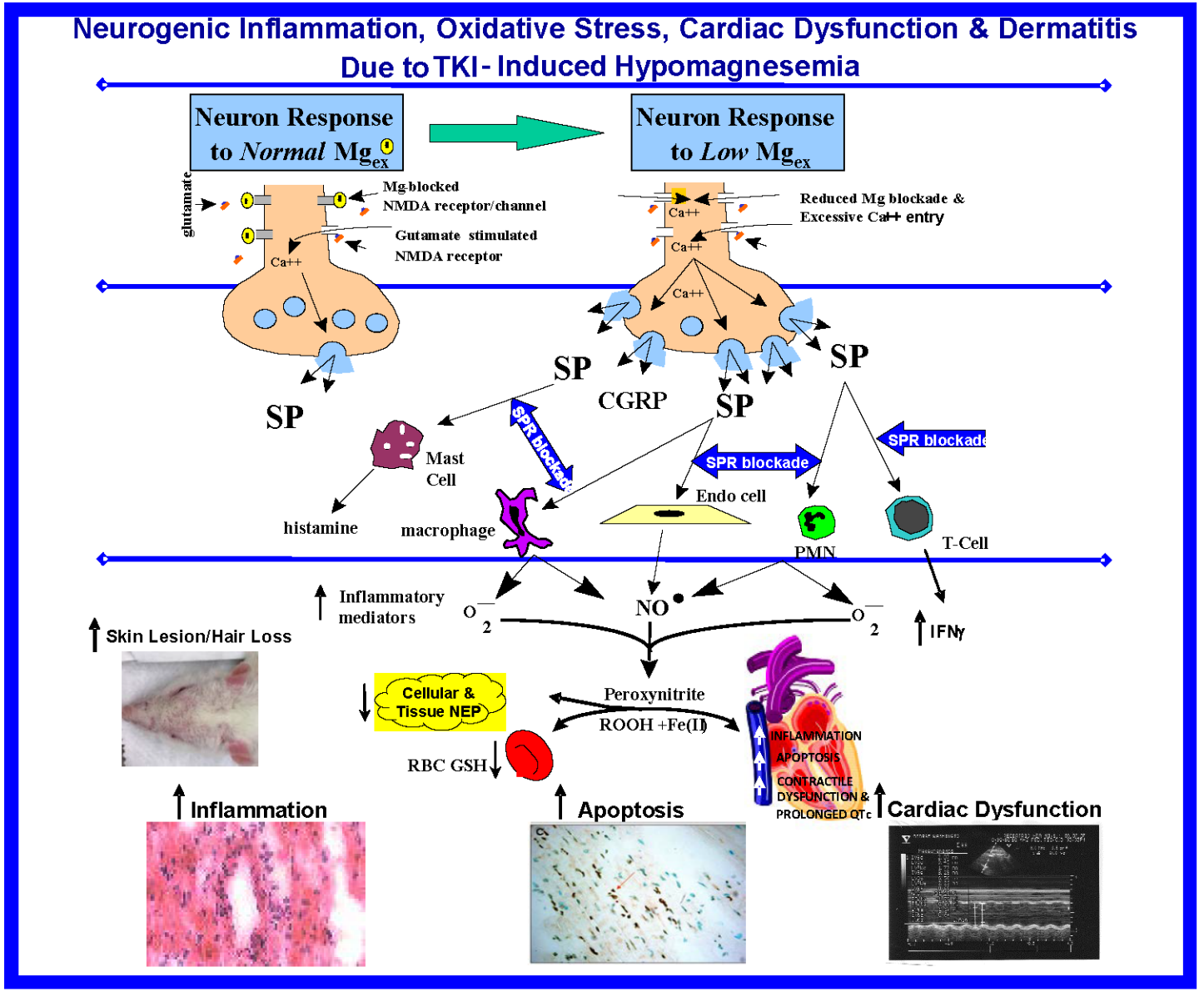


Illustration 1: The substance P receptor (SPR or neurokinin-1 R) blocker, aprepitant, attenuated the cardiovascular, cutaneous, and other systemic oxidative/nitrosative stress side effects of chronic EGFR-TKI therapy with erlotinib (Tarceva). Our study indicates that aprepitant, which is an FDA – approved drug, might be used as a novel clinical intervention against EGFR-TKI cutaneous and cardiovascular side effects during anti-cancer therapy (Weglicki, W.B., Kramer, J.H., Chmielinska, J.J., Spurney, C.F., Mak, I.T. 2019 GWU Technology Commercialization Office (TCO) Innovation Competition.

Solution:

- **The Abstract of US Patent No: 9,474,761 states: “The present disclosure provides methods for alleviating or preventing hypomagnesemia, cardiac dysfunction, and skin lesions, which are induced by EGFR blocking drugs, by administering an NK1-receptor antagonist.”**
- **“ There is a great need in the medical community for the development of novel compounds, compositions, and methods of treatment, which help to alleviate the aforementioned deleterious side effects associated with the administration of EGFR blocking agents in patients.”**

Validation:

- We demonstrated the cutaneous and cardiac side effects of neurogenic inflammation due to EGFR-TKI anticancer drugs.
- The resulting hypomagnesemia triggered neuronal release of pro-inflammatory neuropeptides.
- The systemic side effects due to neurogenic inflammation were blocked by aprepitant (Emend) and significantly inhibited the contractile dysfunction of the heart.
- We recently confirmed the upregulation the substance P receptors in the skin biopsies (immunohistochemically) due to erlotinib, and aprepitant substantially reduced these receptors in the epidermis
- In addition aprepitant prevented both the skin rash and hair loss caused by erlotinib.

DEVELOPMENT PLAN:

Additional pre-clinical animal studies:

- Administration of aprepitant orally or by topical administration may be sufficient to prevent mild cutaneous side effects due to TKIs.

- Oral administration combined with topical application of aprepitant may be needed to effectively treat more severe cutaneous toxicity and cardiovascular abnormalities caused by higher dose or prolonged use of the TKI therapy. Such studies may evaluate drug dose effectiveness.