Emerging Drugs to Treat HNSCC: Sensitization of HNSCC to Cisplatin Through the Use of a Novel Curcumin Analog

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Presenter Disclaimer:

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Introduction:
Squamous Cell Carcinoma (SCC)

• HNSCC is the 8th leading cause of deaths worldwide, 11000 US deaths
• Despite advances in surgery and chem/XRT → no improvement in survival in last 4 decades
• Current surgery and chemo/xrt → very morbid
• Stagnant overall survival had driven the search for novel therapeutic agents
SCC: Two Flavors

• Cutaneous SCC:
  – Sun exposure, immunocompromised, fair skin, red hair, blue eyes

• Upper aerodigestive SCC:
  – Mucosal lining from lips to below vocal cords
  – Tobacco, EtOH, HPV, 5th-6th decade of life
HNSCC Treatment: Multidisciplinary Approach

Medical Oncologist  
Head & Neck Surgeon  
XRT Oncologist
HNSCC Treatment: New Multidisciplinary Approach

Biologist

Medical Oncologist

Chemist

Head & Neck Surgeon

XRT Oncologist
HNSCC: Role of Chemotherapy

• Chemotherapy: adjuvant therapy with XRT, i.e. not a cure
  – Advanced disease, high risk features, i.e multiple positive lymph nodes, ECS, perineural invasion

• Advantages: simultaneous therapies may synergistically maximize therapeutic effect
  – Chemo sensitizes cells to xrt and can kill micrometastatic disease→distant disease (lungs)
  – Postulated mechanisms:
    • chemo inhibits repair of cells that may recover from XRT before next cycle of XRT
    • Concomitant therapy damage cells in different ways that may otherwise be resistant

• Disadvantages:
  – Increased side effects from concurrent therapy
  – Partial response→30% of HNSCC only respond
HNSCC Chemotherapy Agents: Alkylating Agents

- **Cisplatin**
  - Mechanism: intracellular binding → bifunctional covalent links that interfere with normal DNA
  - Side effects: nephrotoxicity, ototoxicity (SNHL, oscillopsia)
  - 15-30% respond

- **Carboplatin**
  - Analogue of cisplatin
  - Less overall toxicity

DNA crosslinking = cell death
HNSCC Chemotherapy Agents: Antimetabolites

• Methotrexate (MTX)
  – Mechanism: inhibits dihyrdofolate reductase to form folic acid → de novo synthesis of thymidine
  – Side effects: immunosuppression, hepatic fibrosis

• 5-Fluouracil
  – Mechanism: blocks conversion of uridine into thymidine and synthesis of proteins
  – Side effects: similar to MTX
HNSCC Chemotherapy Agents: Microtubule Stabilizers

• Paclitaxel
  – Awesome history → NCI, Holton, BMS = $$$$  
  – Mechanism: stabilizes tubulin and prevent cell division in mitosis
  – Recently approved for HNSCC
  – Side effects: hair loss, bone pain, immunosuppression, etc
HNSCC Chemotherapy Agents: Epidermal Growth Factor Receptor (EGFR) Inhibitor

- Cetuximab: monoclonal antibody
  - 2006, first FDA molecular targeted therapy for HNSCC
  - Inhibits EGFR: transmembrane glycoprotein, overexpressed in HNSCC
    - Phosphorylation of tyrosine kinase → cell signaling for survival and proliferation
  - Cetuximab + XRT sustained survival of 9% (5-yr OS, 45 vs 36%)
Why Do We Need New Chemotherapy Agents?

- The development of new agents with greater efficacy and tolerability is needed
- Overall survival has been stagnant
- Surgery is morbid (fun for me but not for the patient!)
- Chemotherapy (cisplatin) saved this patient’s life!
Sensitization of HNSCC to Cisplatin Through the use of a Novel Curcumin Analog

• Objective: To determine if curcumin analog, FLLL 32 (inhibitor of STAT3?), would induce cytotoxic effects in STAT3-dependent HNSCC and would sensitize tumors to cisplatin
Signal Transducer and Activator of Transcription Factor 3 (STAT3)

- STAT3: member of a family of transcription factors regulating expression of many critical genes in tumor growth and survival
- Overexpressed in various cancer cells: leukemia, lymphoma, breast, pancreas, RCC, HCC, prostate, lung etc
- Oncogene: phosphorylated via IL-6 and EGFR
- HNSCC models overexpression of pSTAT3 plays a role in cell growth, migration and inhibiting apoptosis
  - May contribute to tumorigenesis and treatment resistance
  - STAT3 expression correlated with cisplatin resistance
Study Design

• Two HNSCC cell lines
  – Cells susceptible to cisplatin (UM-SCC-74B) and cells not (UM-SCC-29)
  – Both cells lines express pSTAT3
• Three arms with 4 concentrations of therapy = 12 groups x 2 cell lines = 24 assays
• One arm: Untreated
Outcomes Measured

• Primary outcomes:
  – The proportion of apoptotic cells after cisplatin, FLLL 32, and combination therapy

• Secondary outcomes:
  – FLLL 32 treatment on the expression of pSTAT3 and other key proteins in cell apoptosis
Results: pSTAT3 expression

- Western blot analysis:
  - densitometry analysis demonstrated significant down regulation of pSTAT3 protein w cells treated with FLLL 32 vs. untreated and cisplatin alone (P< 0.05).
  - Did not affect total STAT3 or JAK2 (activates STAT3)
Results: Therapy Cytotoxic Effects on Cisplatin Sensitive HNSCC

- Cell survival assays
  - In UM-SCC-74B (cisplatin sens), FLLL 32 potentiates the effects of cisplatin
  - FLLL 32 with cisplatin (1.56 μM) induced tumor cytotoxic effects = cisplatin @ 6.25 μm (4x)
Results: Therapy Cytotoxic Effects on Cisplatin Resistant HNSCC

- Cell survival assays
  - In UM-SCC-29 (cisplatin res.), FLLL 32 again potentiates the effects of cisplatin
  - FLLL 32 with cisplatin had a suppressive effect (proliferation) and synergistic cytotoxic effect
Results: FLLL 32 Potentiates Apoptosis in HNSCC

- Apoptosis assays
  - FLLL 32 alone induced an increase in apoptosis in both cells lines
  - Combination therapy induces greater apoptosis than monotherapy alone (do not report stat. sig)
Discussion

- Platinum-based compounds are often used as first-line agents in HNSCC→toxic, not selective
  - Patients relapse with cisplatin-resistant disease
  - Efflux of drug, increased detoxification of drug
- HNSCC has multiple mutations so one therapy does not work for all (caveat: HPV SCC)
- Disruption of STAT3 through FLLL 32 has been shown in vitro to be very effective
Conclusion

• Head and neck cancer drug market is rapidly evolving.

• Coordination between drug and biomarker development efforts may soon yield targeted therapies that can achieve the promise of better personalized cancer medicine.
THANK YOU!

Chemists Rule!