Soreness and Ulcers 5: Biology, Diagnosis & Management of Cancer Regimen-Related Oral Mucosal Injury

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1. Mammalian target of rapamycin kinase inhibitors
   - Work well in renal cell Ca and others, due to effect on HIF-1 alpha gene expression & reduction of angiogenesis
   - This is a very complex pathway, with lots of potential for error

2. mTOR inhibitor-induced stomatitis
   - Associated with high incidence of dose limiting & treatment limiting stomatitis
   - Different lesions, aphthae like
   - Grayish necrosis, surrounded by epithelium
   - Frequently occur on soft palate ➔ eating very painful
   - ≥ 40% must stop treatment/ dose de-escalate
   - Kinetics/trajectory more acute, 5-7 days post treatment

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mTOR inhibitor-induced stomatitis
Associated with high incidence of dose limiting & treatment limiting stomatitis

Combination therapies
Will continue to grow and potentially impact supportive care druggable targets & increase opportunities

Mucositis interventions

- Despite its frequency and symptomatic, physiologic & economic cost, there is no currently approved SOC that works to prevents OM or reduces its severity
  - Of mechanism-based agents approved for other indications, amifostine and palifermin have been used in this population, but each has issues
  - Frustration due to inability to prevent mucositis development
- The good news: There’s a number of promising medications in the development pipeline (pre-clinical – phase 2/3)
  - Superoxide dismutase mimetic, innate immune modifiers, botanically-derived anti-inflammatory, defensin mimeretic & more
  - Optimistic about an effective treatment

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Mucositis interventions

- Photobiomodulation (low level laser therapy) has been reported to have efficacy
  - A lot of literature; interesting trials in 2 populations:
    1. SC transplant
    2. MNC
  - More work needed regarding biology & mechanism
  - Reported biology is very robust
  - Can stimulate healing, but might negatively impact tumor response to treatment and/or behaviors
  - More work needed to assure that there is no mitigation of tumor response to treatment

Pipeline of mechanistically-based OM interventions

- Clonidine Lauriad
- Doxepin HCI
- SGX942 (innate defense regulator)
- Defensin mimetic
- Superoxide dismutase mimetic
- Direct gene transfer
- Anti-TNF antibody
- Alteration of bacterial genomics TFF
- Naturally-derived products
- LLLT

The pipeline of OM interventions is rich & growing

Prediction of risk

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Risk of toxicity
Not all patients are on an even playing field when it comes to toxicity risk

- There are patients who go through treatment with no/minimal toxicity
- There are patients who develop issues very early on

The precision medicine initiative
Understanding risk of toxicities & disease, patient response and outcomes, to individualize treatment

We’re heading towards personalized medicine

- Who is at risk of disease/toxicity?
- What works best?
We’re heading towards personalized medicine

Some clinical axioms:
- Not all patients are at equal risk of developing a disease
- Many factors associated with risk are genetically driven
- Patients do not respond to drugs in an equivalent way:
  - Some have a brisk response, some moderate & some not at all, and may require different medication
  - Clinical trial efficacy endpoints designed for bell-shaped curve
    - e.g. 100 patients, only 10 respond
    - Drug likely won’t be approved
    - Characterizing those patients may benefit that population

We’re heading towards personalized medicine

Some clinical axioms:
- Not all patients are at equal risk of developing a disease
- Many factors associated with risk are genetically driven
- Patients do not respond to drugs in an equivalent way:
  - Some have a brisk response, some moderate & some not at all, and may require different medication
  - Clinical trial efficacy endpoints designed for bell-shaped curve
  - Response/non-response is often genetically determined
  - Not all patients are at equal risk of toxicity to a drug
    - e.g. some patients respond well to antibiotics, while others suffer GI problems

Not all patients are at equal risk

Patient

- Variables are the greatest determinant of risk
- Many are genomics associated

Toxicity

- Biologically robust
- Interacts & produces byproducts

Tumor

Treatment

- Amount of drug, amount of radiation, etc.
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Genetic determinants of toxicity work at three levels

- Drug metabolism
- Direct cell response to drug
- Bystander biologic targets of drug

Drug metabolism mutations

Studies focus on presence/absence and activity of chemotherapy metabolizing enzymes

Drug metabolism mutations

- 5-FU – commonly used for colorectal cancer, HNC & some breast cancers
- Dihydropyrimidine dehydrogenase (DPD) catabolizes 5-FU
- DPD deficiency in patients receiving 5-FU leads to increased frequency of toxicity
  → Can identify the mutation & determine associated toxicity
- Genetic defect leads to DPD deficiency completely in 0.1% of the population, and partially in 3%-5%
- The observed frequency of toxicities in patients getting IV 5-FU >> than the frequency of the defect

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Drug metabolism mutations

If genes impact risk in a clinically significant way, they have to do it in a way that is associated with toxicity’s broader pathobiology

What are our goals for translational genomics?

- Identify biological targets for treatment & mechanisms of action
- Identify patients at risk for diseases or treatment-related toxicities
- Differentiate responders & non-responders to specific interventions

Ideal:
- Test patient for mucositis risk
- Examine potential treatments & therapies
- Test patient to personalize treatment

Application of genomics to risk prediction & responder/non-responder analysis

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The basics of genomics
Chromosomes, genes & Single nucleotide polymorphisms (SNPs)

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Genes & SNPs

- Important mutations; enable linking to phenotypes
- Can be used to define patient risk & response

How can we identify genes or SNPs associated with a specific phenotype?

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Candidate gene
Generating hypothesis-driven targets

“If I asked experts what I should do, they would have told me to invent a faster horse.”
Henry Ford

“You don’t know what you don’t know”

Candidate gene
Classical model of genetic association

One key

One lock (phenotype)

Candidate gene

The universe of candidates...

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Results of candidate gene studies have been disappointing

Barnett et al. Lancet Oncology 2012:
- 1613 patients with breast or prostate cancer
- Candidate genes (or associated SNPs) evaluated for predictive validity for late RT-induced toxicities
- NONE of the previously reported genes/SNPs validated
- Each of the studies evaluated looked for single genes, ignoring any synergism

Gene & SNP functionality is cooperative

Gene & SNP functionality is cooperative

Radiation pneumonitis
Moving away from one key, one lock

Moving away from one key, one lock

Genome wide association studies

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Genome wide association studies

Re-assess significance

false positives.

So how can cooperative genes or SNPs be detected?

Develop networks to identify cooperative genes/SNPs

Networks define interactions probabilistically →
So we know what’s important & what’s not

Communication Networks

• Nodes are phones
• Edges are phone lines

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A couple of real applications:

- Defining the mechanism(s) by which chemoradiation-induced toxicities occur & targets for therapeutic intervention
- Identifying patients at risk of mucositis, induced by chemotherapy conditioning regimens for SC transplant

Risk prediction: A clinical example

- Palifermin is effective in preventing oral mucositis (OM) in patients conditioned for stem cell transplant
- OM is a significant & debilitating side effect in 40% of patients undergoing SC transplant
- Palifermin is available, but it is expensive (10k$) & must be given pre-conditioning & prophylactically
- Treat 10 patients undergoing transplant → 2 will develop OM, BUT 6 will be treated unnecessarily
- Accurate risk prediction would provide opportunities for directed prophylaxis & reduced side effect burden
- Given the biological basis for OM, genotypically-based risk assessment makes sense

SNP-based bayesian networks define oral mucositis risk, in patients receiving hematotoxic conditioning regimens for autologous hematopoietic stem cell transplantation

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Optimal network

Optimal network

Optimal network

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Optimal network

Analytical method

Results

82 SNP Networks identified mucositis risk with accuracy of 99.3%

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Results
Receiver operating characteristic (ROC) curve

For Mucositis, Area Under ROC Curve = 0.997
For Films Mammography*, Area Under ROC Curve = 0.76

*ROC curve for film mammography for the 42,713 women with fully verified limited cancer status


Exploratory independent validation using post hoc methodology

- A small independent patient cohort was randomly selected for exploratory prospective validation
- Demographics similar to pts. enrolled in discovery set
- 1:1 ratio OM negative to OM positive
- Included similar conditioning regimens & same time interval as pts. in the discovery set
- Accuracy > 80% & no false positives

What do we want in a treatment?

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