Mucositis and New Drugs: To Prevent or to Treat?

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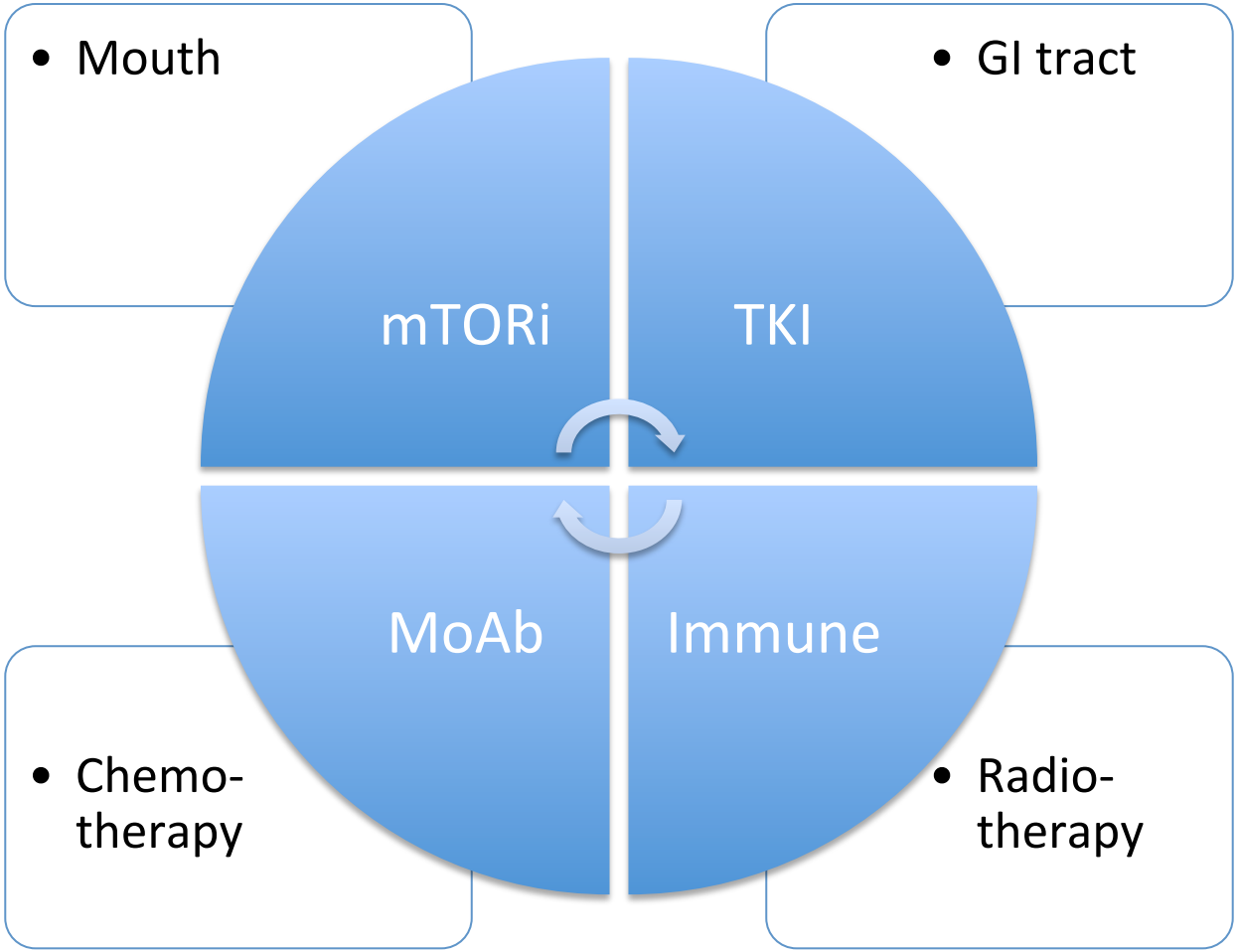
What is Mucositis?

- It used to be mouth ulcers after chemotherapy or radiotherapy
- Now it is any mouth or gut toxicity following cancer treatment of any type
  - And that is a problem!

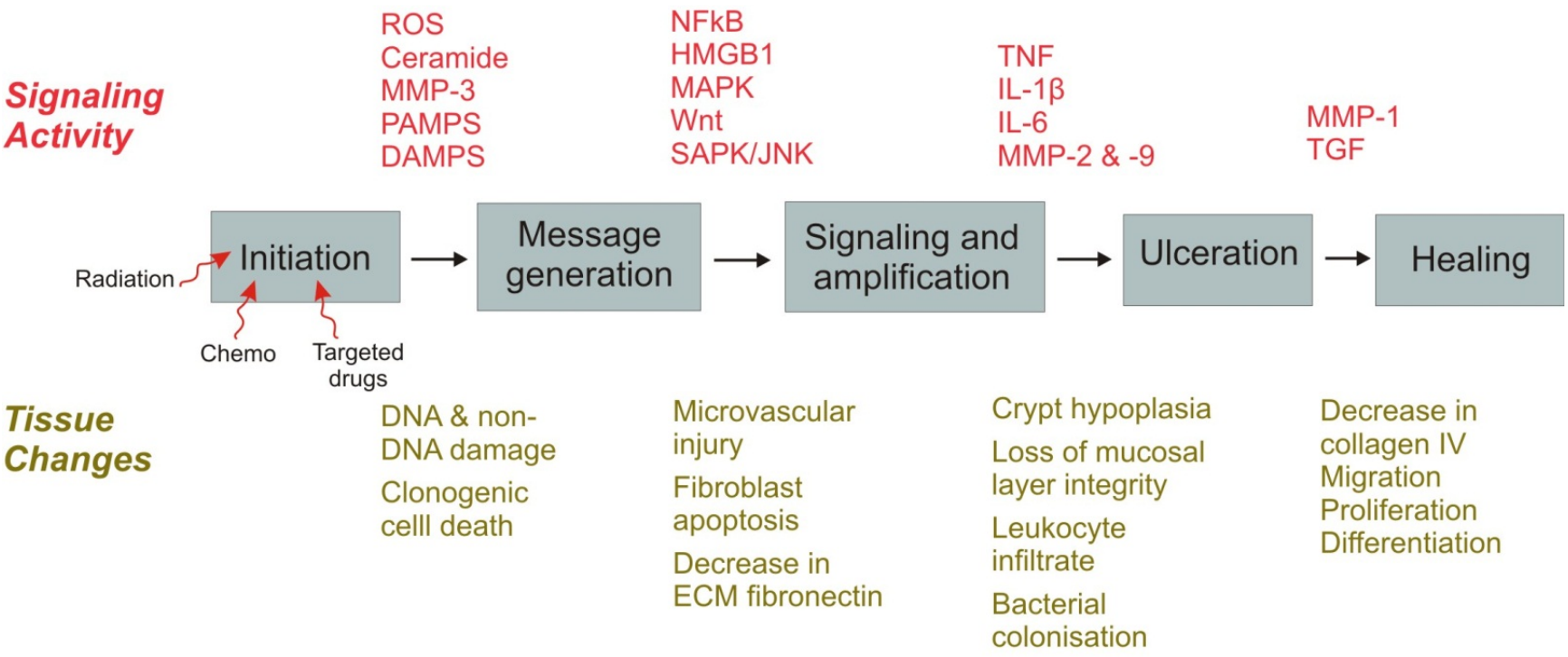
Mucositis today



Risks

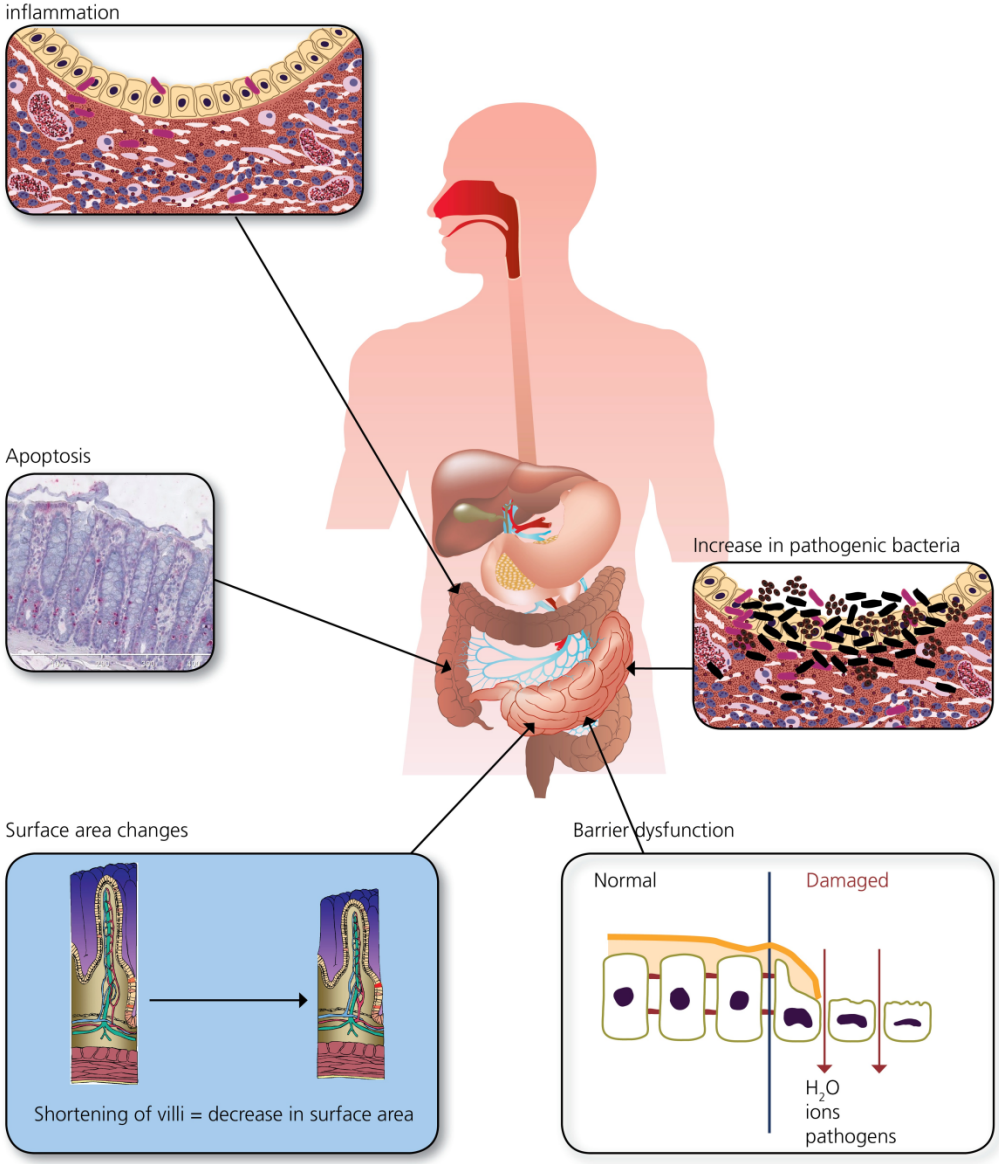
- If we don’t understand the pathology, we can’t use it to drive the intervention
- We can’t just use mucositis guidelines to treat new mucositis

Mechanism of Mucositis



Al-Dasooqi 2012

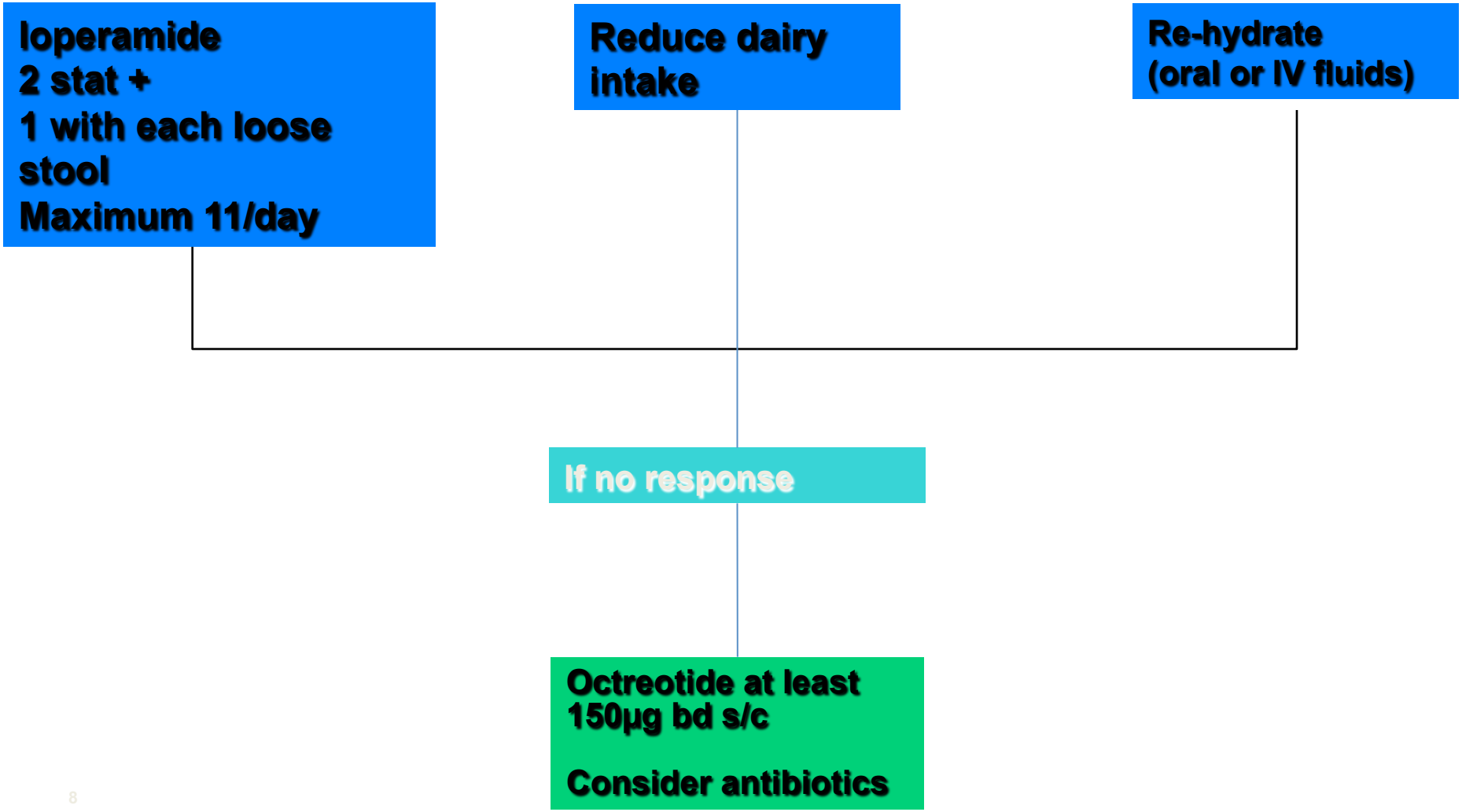
The histo-pathological features of GI toxicity



Do new agents actually cause 'mucositis'

- Not really
- But
  - For want of a better term we should probably keep it
  - It does give us an umbrella
  - It allows us to drive the research agenda

Treatment of Diarrhea



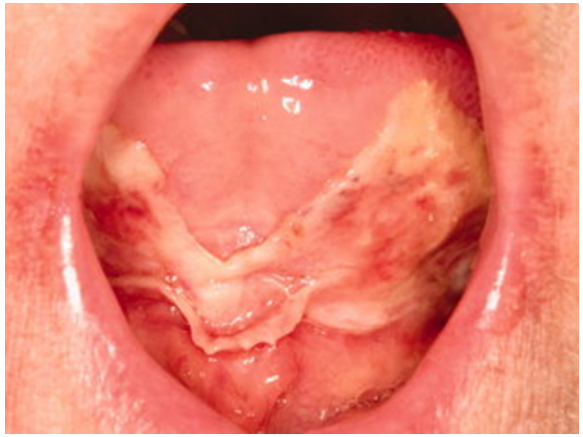
Now we need a new algorithm

What is the cause?	What is the risk of mucositis?	What is the Mechanism of mucositis?	What is the best treatment of the mucositis?	Should it be prevention or treatment?
Chemotherapy	40%	known	MASCC guides	Both
Radiotherapy	80%	known	MASCC guides	Both
mTORi	30%	aphthous	Steroid rinse	Treatment
smTKI	30%	unknown	Loperamide?	Treatment
Immunotherapy	40%	Immune colitis	Steroids	Treatment?

Questions for the new algorithm

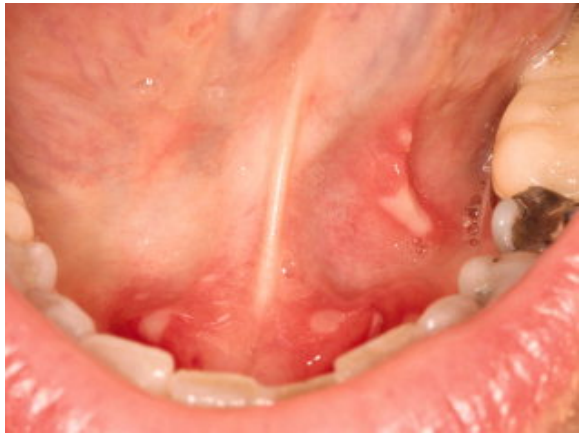
- Is it oral or GI mucositis or both?
- Was it single agent or combination?
- Are there evidence-based guidelines?
- Is there an intervention for the cause?
- Will that mess up something else?
- Is there anything else that could be exacerbating it?

Oral lesions associated with inhibitors of mammalian target of rapamycin in cancer



Chemotherapy: extensive, deep ulceration of ventral tongue. Pseudo-membrane thicker than with mTOR inhibitor assoicated stomatitis (mIAS) ulcers. Typically, architecture not defined as well as ulcers associated with mIAS.

Minor (L) and Major (R) aphthous stomatitis from mTOR inhibitors. Shallow ulceration and peripheral erythema, irregular edge of the major ulcers. These are extremely painful.



Cancer
Volume 116, Issue 1, pages 210-215, 27 OCT 2009 DOI: 10.1002/cncr.24696
http://onlinelibrary.wiley.com/doi/10.1002/cncr.24696/full#fig1

Incidence of Immune-Related Adverse Events associated with Ipilimumab and Pembrolizumab

	Ipilimumab (%)		Pembrolizumab	
Toxicity	All Grades	Grade 3-4	All Grades	Grade 3-4
GI (enterocolitis)	33	9	1	<1
Pneumonitis	<1	<1	2.9	<1
Hepatitis	2	1	<1	<1
Skin	45	3	11-30	0
Thyroiditis	2	<1	10	<1
Nephritis				

www.cancernetwork.com

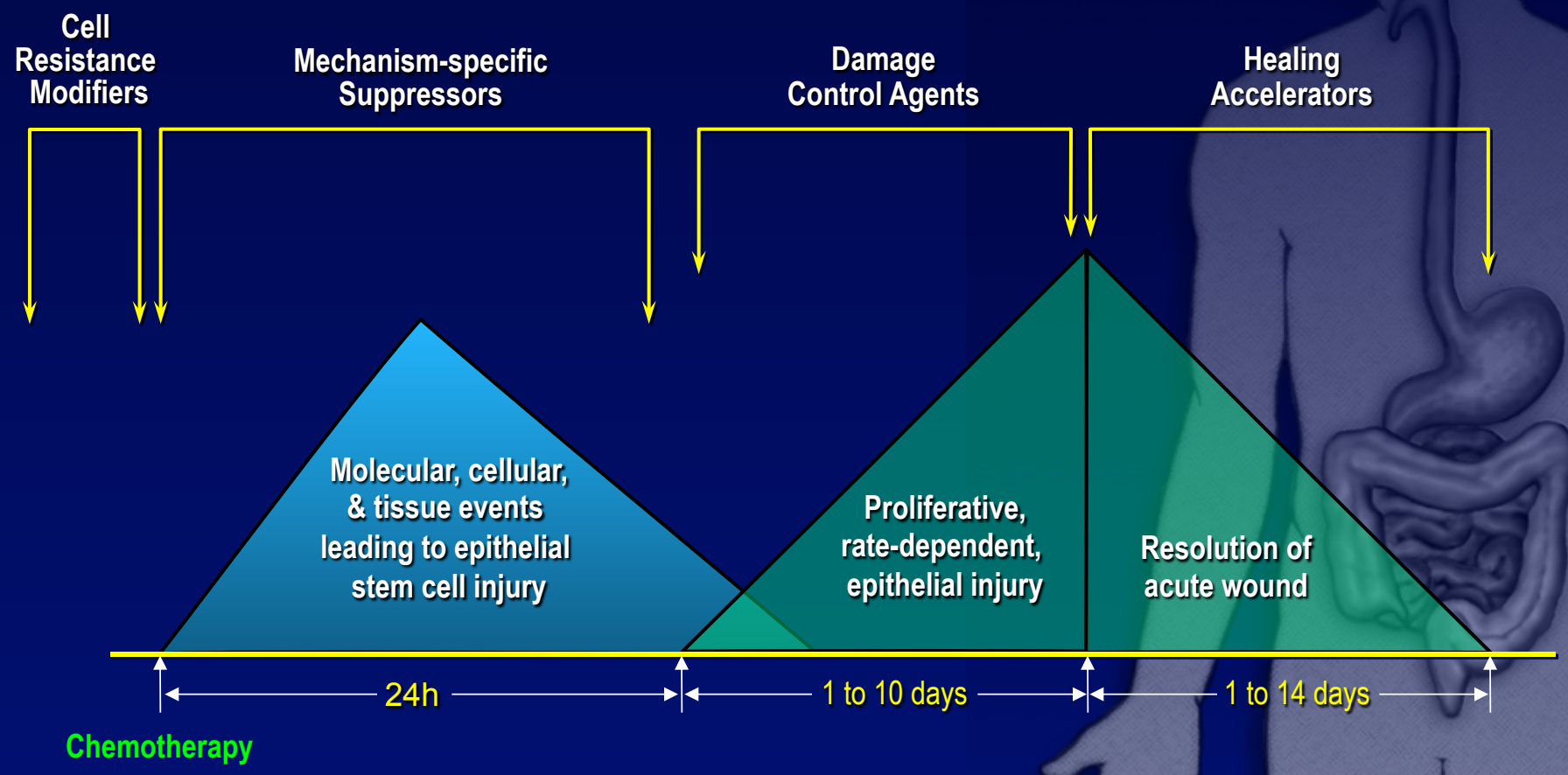
Management of Immune Checkpoint Inhibitor toxicity

- Patients should be seen prior to each cycle of therapy
- The clinical visit should include specific focus on common and serious toxicities
  - Skin changes
  - Diarrhea and abdominal pain
  - Headache
  - Fever
  - Shortness of breath
  - Cough
  - Neurologic changes

Diagnosis of Immune-Related Adverse Events (IrAE)

- Is one of exclusion. Could be
  - Progression of underlying malignancy
  - Infection
- Other possible causes must be ruled out prior to identifying a given toxicity as an irAE.
- Checkpoint-blockade therapy should be withheld until workup is complete

When is the Optimum Time for Mechanistically Based Intervention?



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Prevention versus Treatment

- Have to give prevention to 100% unless have a predictive biomarker
  - Expensive
  - Wasteful
  - Potentially toxic
- Waiting to treat may be too late
  - Forces morbidity
  - May be fatal
  - But is cheaper upfront

CTCAE

- 1 = mild
- 2 = moderate
- 3 = severe
- 4 = life-threatening
- 5 = death

Imagine a Grade 1 toxicity being life-threatening

- So, if you think “Grade 1 pneumonitis is potentially life-threatening”
- Then it isn’t Grade 1
- It is Grade 4

- and your toxicity scale is wrong!

EGFRi

- We (MASCC) changed the skin toxicity grading scale to reflect the new reality of the EGFRi skin toxicity
- We need to do the same with Immune related adverse events (IrAE)

IrAE continued

- Permanent discontinuation for
  - Life-threatening adverse events
    - including grade 3 pneumonitis, nephritis, or hepatitis;
  - Any recurrent grade 3 adverse event
  - Inability to reduce prednisone to 10 mg daily after 12 weeks.
  - Need for infliximab or alternative immunosuppression

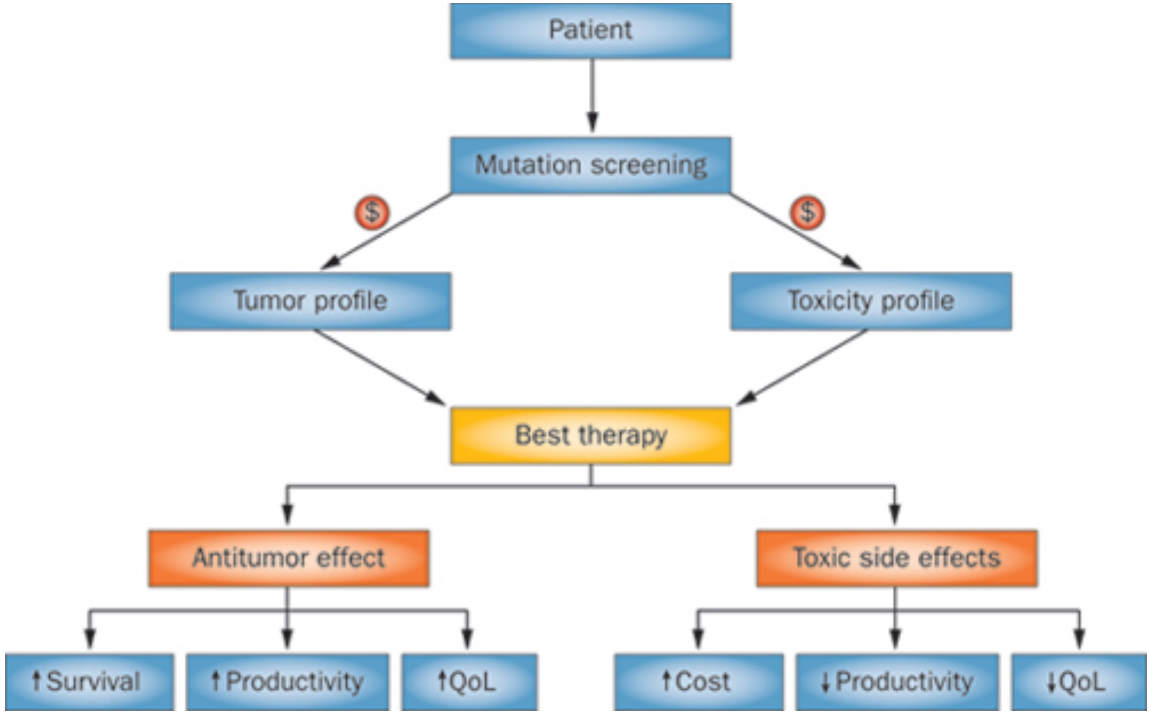
Combinations of Drugs

- Expect synergy of effect but downplay likelihood of synergy of toxicity
- Can lead to life-threatening problems

Current situation: patient pinball

- Target Alpha
- Pull the pin and…
  - Hit a side effect
  - Hit a benefit
  - Go round in circles
  - Get picked up & sorted
  - Get picked up & dropped
  - Meet a nurse
  - Meet a researcher
  - Get a new toxicity
  - Die
  - Get cured but feel awful
- Get cured and feel well!!

Personalised cancer medicine: increased tumor control and decreased toxicity



Keefe, D. M. K. & Bateman, E. H. (2011) Tumor control versus adverse events with targeted anticancer therapies
Nat. Rev. Clin. Oncol. doi:10.1038/nrclinonc.2011.192

nature REVIEWS CLINICAL ONCOLOGY

Key Points

- You shouldn’t use the drugs if you don’t know
  - How they are toxic
  - How often they are toxic
  - The mechanism of the toxicity
  - How to prevent or treat the toxicity

- They are wonderful but scary drugs

Conclusion

- We can't stop using the new drugs
  - They have some fantastic results
  - They also have some horrible toxicity
- We need more research
  - Strong, evidence-based protocols
  - Updates to the toxicity grading scales to avoid false sense of security
- We need to take toxicity seriously