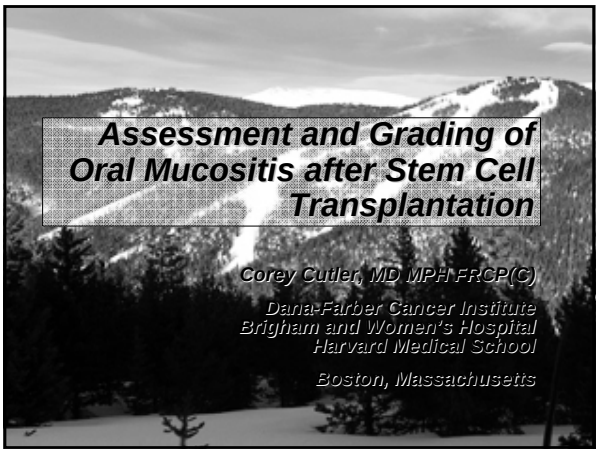

Assessment and Grading of Oral Mucositis after Stem Cell Transplantation

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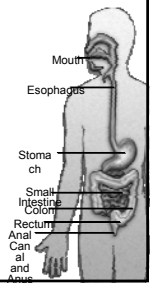
Stomatitis

A fish hook lodges in my throat.
Spittle, kindergarten paste, thickens everything – even vision.
Mouth, pocked with sores & blisters, swollen ulcerated tongue.
Topside, sandpapered with number 7 coarsest grade.
Taste buds, saliva glands, seared.
Cool water, corrosive acid now.
The tongue rests; teeth become enemies.
Coiled steel razored wire atop dentate prison walls.
Only moans escape my lips. I cannot eat or speak.
Inside a howl festers.
Pain lengthens time. *– Anita Hart Balter*

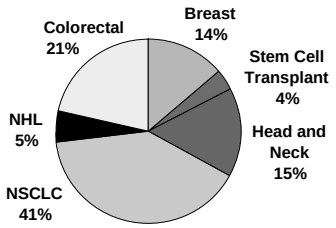
NEJM. 1990;322:704.

Oral Mucositis

- Side Effect of Standard Cytotoxic Chemotherapy
  - Effect on tissues with rapid cell turnover
    - Bone Marrow - Myelosuppression
    - Hair Follicles - Alopecia
    - GI system - Diarrhea
      - Esophagitis
      - Oral mucositis

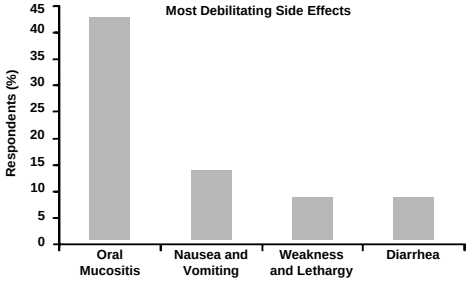


Close to 400,000 Patients Per Year Suffer From Mucositis During Cancer Therapy



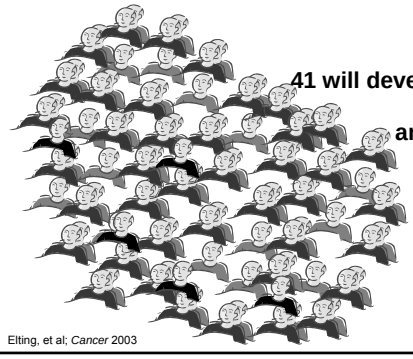
Source: Mattson Jack Database 2003; NCI; Note: 400,000 patients in the US

Oral Mucositis: The Worst Complication of Myeloablative Transplantation



Adapted from Bellm LA et al, *Support Care Cancer*. 2000;8:33-39.

For Every 55 Patients with Severe Mucositis and Myelosuppression…



41 will develop infection

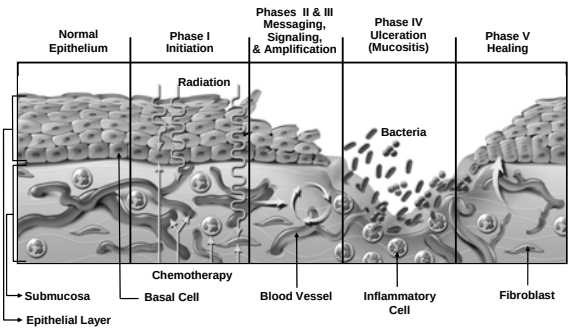
and 5 will die.

Elting, et al; *Cancer* 2003

Relationship of Mucositis to Outcomes in BMT

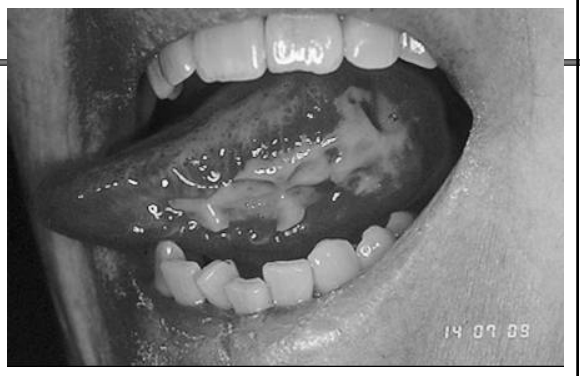
Health Outcome	Increase in Days: Mucositis vs. No Mucositis	
Injectable narcotics	4.80	(<0.01)
TPN days	5.34	(<0.01)
Febrile days	1.59	(<0.02)
Significant infection	2.55	(<0.05)
Hospital days (autos)	11.02	(<0.01)
Hospital days (allos)	6.92	(<0.02)

Pathobiology of Mucositis



Clinical Features of Mucositis

- Erythema
- Ulceration
- Pseudomembrane formation
- Consequences
  - Pain
  - Difficulty in swallowing/chewing food
    - Decreased nutrition
    - Requirement for IV nutrition
  - Infectious risk
    - Breakdown of mucosal barrier
    - Risk of bacteremia secondary to TPN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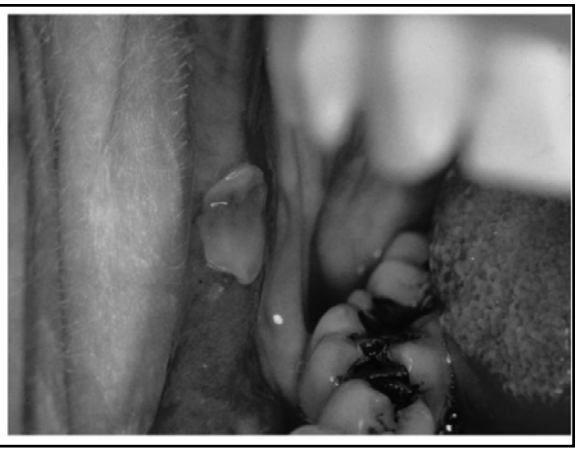
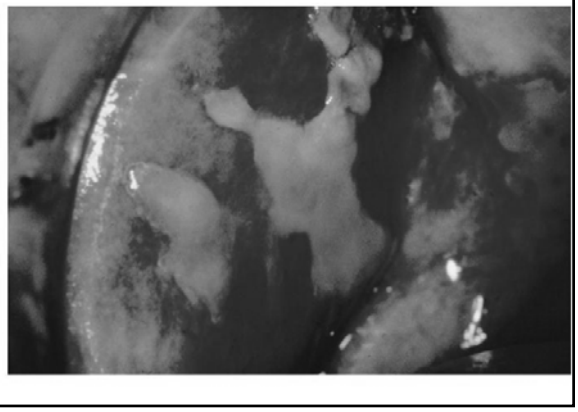




Reasons to 'Measure' Mucositis

- Toxicity description and assessment
- Medical management
- Research
  - Descriptive studies
  - Intervention studies

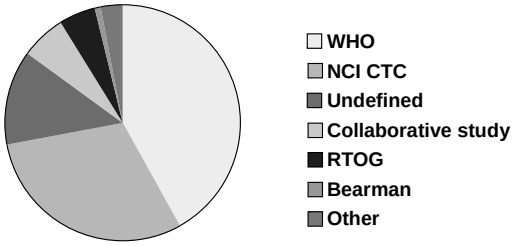
Ideal Mucositis Scale

- Accurately reflects severity and course of objective and subjective clinical changes.
- Easy to teach and use, with minimal inter-observer variability.
- Does not require lesion measurement.
- Sensitive enough to discriminate treatment efficacy.
- Clinically meaningful and easily interpretable end points for clinicians, patients, and FDA.

Mucositis Research Instruments

- No uniformity in end points.
- Wide range of complexity.
- Provide tight, comparable data, but **meaningfulness** of end points may be **difficult** to convey in general clinical settings, ie. How important is a difference between 1.62 vs. 0.77?
- Major value in phase 2 trials and outcome analyses, but of limited value in phase 3 trials.

Mucositis Scale Frequency



Mucositis Scales to be Reviewed

- WHO Oral Toxicity Scale (WHO Score)
- NCI-CTC v3 Mucositis Scale
  - Clinical Score
  - Functional/Symptomatic Score
- OMAS

WHO Score

- Based on a combination of subjective, objective and functional outcomes:
- Subjective– Soreness as described by the patient
- Objective – Presence of erythema and ulcerations
- Functional– Ability to eat solids, liquids or nothing by mouth

WHO Score

- Grade 0 – No objective findings, function irrelevant
- Grade 1 – Erythema plus pain, function irrelevant
  - – May include mucosal scalloping with or without erythema or soreness
- Grade 2 – Ulceration, ability to eat solids
- Grade 3 – Ulceration, ability to eat liquids
- Grade 4 – Ulceration, nothing by mouth

WHO Oral Mucositis Scale

Severe oral mucositis

Grade				
0	**1**	**2**	**3**	**4**
None	Soreness +/– erythema No ulceration	Erythema, ulcers Patients can swallow solid diet	Ulcers, extensive erythema Patients cannot swallow solid diet	Mucositis to the extent that alimentation is not possible

Diet Assessment – Food Definitions

- Solids
  - – Foods that have to be chewed
  - – Chunky soups, meats, grains, pasta or whole vegetables
- Liquids
  - – Foods that take the shape of their container
  - – Pureed soups, Jell-O®, pudding, mashed potatoes, baby food, Ensure® or other liquid supplement
- Nothing Per Os
  - – No eating or drinking, except enough liquid to allow for taking of medications

WHO Scale Grading Nuances

- Pain in the absence of objective findings = 0
- Erythema without pain = 0
- Ulcers, automatically ≥ 2
- Extent or size of ulcers is not a driver

WHO Grading Tips

- Grade 1 : If there is an ulcer, it's not Grade 1
  : May include mucosal scalloping with or without erythema or soreness.
- Grade 2 : Can't be a Grade 2 unless there is an ulcer. Solid diet.
- Grade 3 : Ulcers. Liquid diet. No solids.
- Grade 4 : Mucositis of such severity that eating/drinking is impossible.
  : PO meds don't count

WHO Grading Examples

Subject has a fetanyl patch, large ulceration, no erythema, can eat Jello® and pudding	**4**
Subject is taking an NSAID (within the last 24 hrs) for mouth pain, is now not sore and has erythema	**0**
Subject has no erythema, no soreness, can eat solids and has an ulcer	**2**
Subject has severe erythema, mouth pain and can only tolerate liquids	**1**

NCI-CTC v3 Scoring

- Two Components
  1. Clinical Score – Objective findings
  2. Functional/Symptomatic Score – Functional findings

CTC Clinical Score

- 0 = No oral mucositis
- 1 = Erythema
- 2 = Patchy ulceration or pseudomembrane formation
- 3 = Confluent ulceration or pseudomembrane, confluent ulceration occupies >50% of the mucosal surface of the designated anatomic site
- 4 = Tissue necrosis

CTC Functional/Symptomatic Score

- 1 = Ability to eat solids
- 2 = Requires liquid diet
- 3 = Not able to tolerate a solid or liquid diet
- 4 = Symptoms associated with life-threatening consequences

- NOTE: If diet is limited for reasons other than mucositis, the CTC Functional/Symptomatic Score is based on what the subject feels he/she could eat.

Anatomic Site-Directed Scoring

- Inner aspect of upper lip
- Inner aspect of lower lip
- Right cheek mucosa
- Left cheek mucosa
- Right bottom and side of tongue
- Left bottom and side of tongue
- Floor of mouth and frenulum
- Soft palate

Oral Mucositis Assessment Scale (OMAS)

Location	Ulceration/pseudomembrane* (circle)				Erythema** (circle)		
Upper lip	0	1	2	3	0	1	2
Lower lip	0	1	2	3	0	1	2
Right cheek	0	1	2	3	0	1	2
Left cheek	0	1	2	3	0	1	2
Right ventral and lateral tongue	0	1	2	3	0	1	2
Left ventral and lateral tongue	0	1	2	3	0	1	2
Floor of mouth	0	1	2	3	0	1	2
Soft palate/fauces	0	1	2	3	0	1	2
Hard palate	0	1	2	3	0	1	2

*Ulceration/Pseudomembrane:
0 = no lesion
1 = < 1 cm^2
2 = 1 cm^2-3 cm^2
3 = > 3 cm^2

**Erythema:
0 = none
1 = not severe
2 = severe

Sonis *et al*, Cancer 1999

Correlations Between Peak OMAS Score and Selected Clinical and Economic Outcomes

Febrile days	0.13
Sig infection	0.26*
TPN days	0.39*
Injectable-narcotic days	0.36*
Total hospital days	0.28*
Total hospital charges	0.48*

How Frequently Should Evaluations Be Done?

- Depends on the reason for the assessment.
- Mucosal condition in chemotherapy responds relatively acutely.
- Consequently, accuracy of assessment tracks well with frequency of evaluation.
- Since duration of significant mucositis is the most important driver of untoward outcomes of mucositis, less than daily assessment is risky, especially in clinical trials.

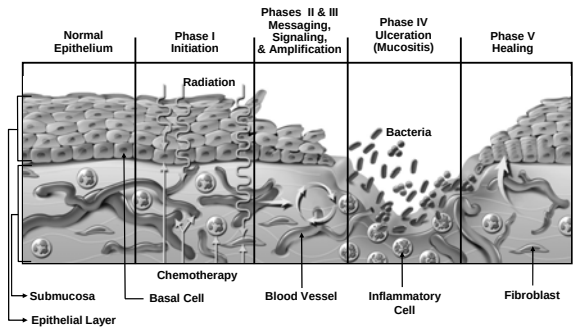
Why Does Mucositis Matter

- BMT CTN 0401 – Will intervention make mucositis worse???
- BMT CTN 0402 – Will intervention make mucositis better???
- New interventions exist - Palifermin

0401: Bexxar-BEAM vs BEAM

- Autologous transplantation – standard for relapsed non-Hodgkin's Lymphoma
  - Usual regimen: High-dose chemotherapy – BEAM or equivalent.
  - 0401 – Tests hypothesis that the addition of ^{131}I-Tositumomab to high-dose chemotherapy will increase response rate → survival
  - BUT: Addition of radio-immunotherapy may increase mucositis

Pathobiology of Mucositis



0402: Effect of Methotrexate Elimination

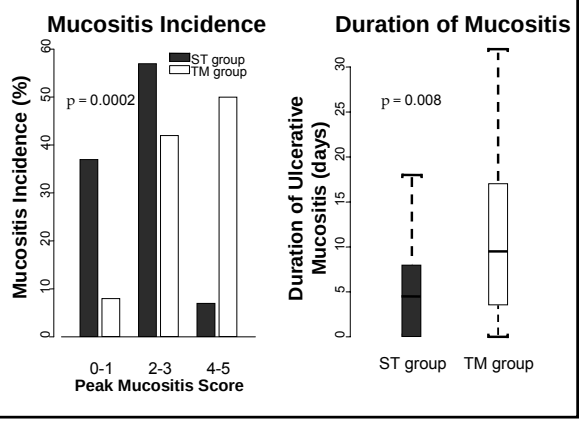
- Retrospective cohort analysis (2001-2003)
  - Cohorts designated by GVHD prophylaxis:
    - Sirolimus/Tacrolimus vs. Tacrolimus/Methotrexate
    - Cy-TBI MRD PBSCT
- Oral Mucositis
  - Mucositis assessed 2-3x/week by members of the Oral Medicine service
  - OMAS scale

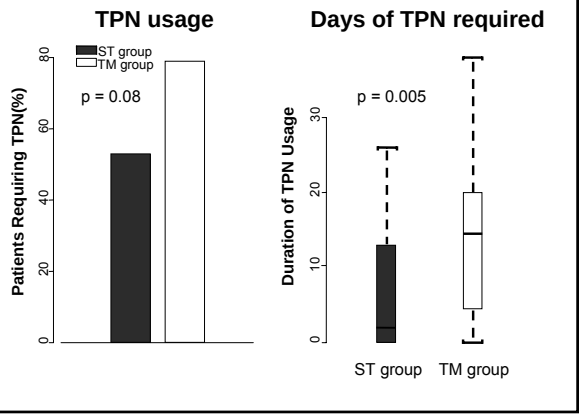
Other Outcomes

- Total Parenteral Nutrition
  - Total number of days of use recorded
- Narcotic use
  - Conversion of all narcotics to intravenous mg morphine equivalents (MME) using accepted conversion factors
- Duration of Hospitalization
  - From day of transplantation to 1st discharge

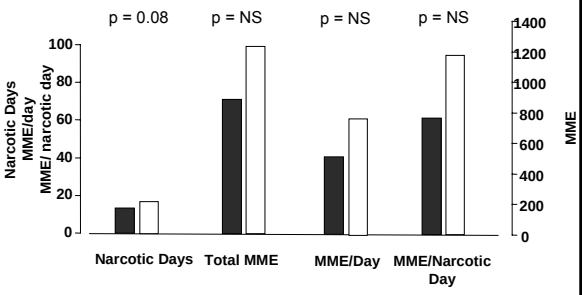
Data

	Siro / Tacro	Tacro / Mtx	p
Sample Size	30	24	
Median Age	42 (19-54)	43 (24-58)	0.46
Male Gender	16 (53%)	11 (46%)	0.78
Malignancy			
AML/MDS	15 (50%)	16 (67%)	
CML	7 (23%)	3 (13%)	
NHL/ALL	8 (27%)	5 (21%)	0.52
Time To ANC > 500	14 (11-17)	15 (11-25)	0.04
Gr II-IV GVHD	3 (10%)	6 (25%)	0.16
Mucositis Assessments	5	6.5	0.36



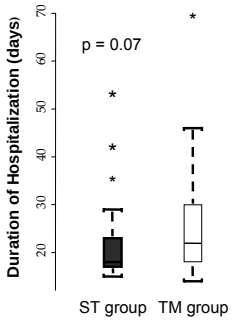


Narcotic Utilization



MME = mg Morphine Equivalents

Duration of Hospitalization



Methotrexate Conclusions

- GVHD prophylaxis with Sirolimus-Tacrolimus is associated with less oral mucositis than with a Methotrexate-containing regimen
- Patients who do not receive Methotrexate require less TPN and less narcotics
- Hospitalization duration is shortened in patients not treated with Methotrexate
- The improved mucositis outcomes with non-Methotrexate containing regimens may be associated with substantial cost savings.

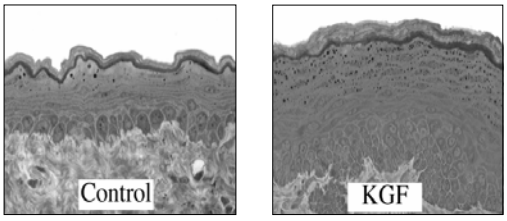
Prevention of Oral Mucositis

- "Many are called, but few are chosen"
  - Multiple agents failed in randomized trials;
  - Until recently, no standard
- Palifermin
- Velafermin

Palifermin

- The mouth is covered in specialized epithelium called keratinocytes
- Palifermin is a recombinant N-terminal truncated version of Keratinocyte Growth Factor (KGF) with same biological activity but increased stability
- KGF is a 28kD, heparin-binding member of the fibroblast growth factor family
- Ameliorates mucositis in murine model

Palifermin-Induced Thickening of Normal Tongue Mucosa



Ventral surface of rodent tongue mucosa in absence or presence of palifermin (rHuKGF) 5 mg/kg/day for 3 days

Palifermin

- Phase I (Meropol *et al,* JCO 1993):
  - Doses of 80 ug /kg x 3 d appeared safe
- Phase II (Sonis *et al,* Cancer 1995)
  - Etoposide, Cytarabine, Melphalan preparative regimen
  - Reduced mucositis and weight loss
- Phase III (Spielberger *et al*, NEJM 2004)
  - Palifermin vs. placebo in XRT-containing preparative regimen for autologous transplant

Palifermin vs. Placebo - Design

- Inclusion
  - > 18 yo
  - KPS $\geq$ 70%
  - Autotransplant planned for heme malignancy
- Treatment
  - Etoposide/Cytoxan/TBI preparative regimen
  - Palifermin @ 60 ug/kg x 3d iv prior to XRT
  - Palifermin @ 60 ug/kg x 3d iv d0, 1, 2
  - Double blind
  - G-CSF given from d0 to recovery

Palifermin vs. Placebo - Endpoints

- Mucositis assessment daily, multiple scales
  - WHO
  - RTOG
  - WCCNR
- Patient-reported outcomes
  - Sore throat
  - ADL participation
- Narcotic use
- TPN use
- Primary endpoint: duration of WHO gr3/4 mucositis

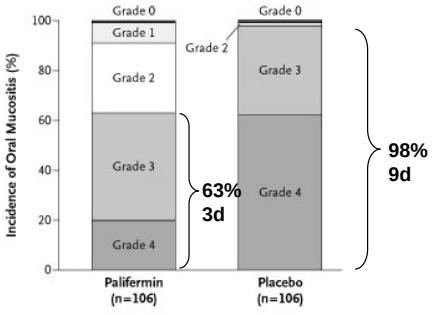
Palifermin vs. Placebo - Patients

Table 1. Baseline Characteristics of the Patients.

Characteristic	Palifermin Group (N=106)	Placebo Group (N=106)
Male sex — no. (%)	59 (56)	72 (68)
Age — yr		
Median	48	49
Range	18–69	19–68
Diagnosis — no. (%)		
Non-Hodgkin's lymphoma	72 (68)	69 (65)
Hodgkin's disease	21 (20)	23 (22)
Multiple myeloma	11 (10)	9 (8)
Leukemia*	2 (2)	5 (5)
Karnofsky performance-status score — no. (%)		
70	3 (3)	1 (1)
80	15 (14)	19 (18)
90	59 (56)	58 (55)
100	29 (27)	28 (26)
Total no. of CD34+ cells reinfused — $\times 10^6$/kg		
Median	5.2	5.0
Range	1.8–87.0	1.5–41.0

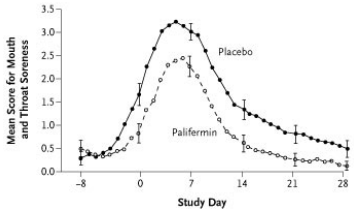
Spielberger, R. et al. N Engl J Med 2004;351:2590-2598

Palifermin vs. Placebo - Results



Spielberger, R. et al. N Engl J Med 2004;351:2590-2598

Palifermin vs. Placebo – Patient-Reported Outcomes



Spielberger, R. et al. N Engl J Med 2004;351:2590-2598

Palifermin vs. Placebo - Results

- Lower dose of opioids administered (morphine equivalents): 212 vs. 535 mg
- Lower duration of opioid administration: 7 vs. 11d
- Lower incidence of febrile neutropenia: 75 vs. 92%
- Lower incidence of blood-borne infections: 15 vs. 25%
- Lower incidence of TPN use : 31 vs. 55%

Palifermin vs. Placebo - Safety

- Rarely discontinued
- Most events with > 5% frequency in palifermin group (and not in placebo group) were due to effect of drug on skin and oral epithelium
- SAE: Rash; Hypotension
- Deaths: 1 in each group
- 12 month PFS is similar in both groups
- No excess of cancer deaths in either group (ie KGF does not protect tumors)

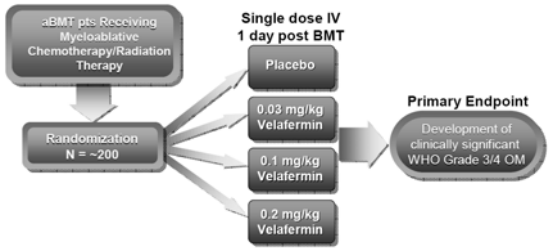
Palifermin vs. Placebo - Conclusions

- Palifermin was effective in reducing the incidence and duration of severe and life-threatening mucositis
- Reduction in opioid and TPN use probably beneficial for pts
- Other Questions:
  - Role in Allo transplant – not effective as GVHD prophylaxis

Velafermin

- Recombinant Human Fibroblast-Growth Factor-20
- Promotes Epithelial and Mesenchymal cell proliferation – prevents mucositis in animal models
- Being tested in Ph II trials in people undergoing autologous transplantation

Velafermin Trial



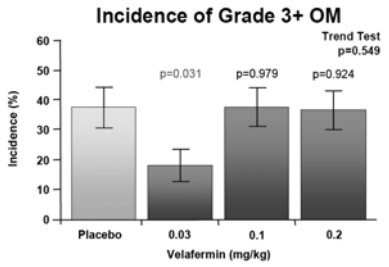
Schuster et al, ASCO 2006

Velafermin – Patient Population

	Placebo	Velafermin (mg/Kg)			Total[1]
		0.03	0.1	0.2	
	(N=51)	(N= 50)	(N= 56)	(N= 55)	(N= 212)
Gender - no.(%)					
Male	28 (55%)	31 (62%)	37 (66%)	28 (51%)	124 (58%)
Female	23 (45%)	19 (38%)	19 (34%)	27 (49%)	88 (42%)
Age - yr					
Median	53	53.5	56	55	54
Range	18-71	18-69	21-71	22-69	18-71
Diagnosis[2] - no.(%)					
HL	6 (12%)	6 (12%)	5 (9%)	6 (11%)	23 (11%)
NHL	10 (20%)	13 (26%)	15 (27%)	15 (27%)	53 (25%)
MM	32 (63%)	24 (48%)	34 (61%)	31 (56%)	121 (57%)
AML	1 (2%)	3 (6%)	1 (2%)	1 (2%)	6 (3%)
Other	2 (4%)	4 (8%)	1 (2%)	2 (4%)	9 (4%)
Therapy[3]					
CT	49 (96%)	47 (94%)	52 (93%)	51 (93%)	199 (94%)
CT+ TBI	2 (4%)	3 (6%)	4 (7%)	4 (7%)	13 (6%)

Schuster et al, ASCO 2006

Velafermin - Outcomes



*** Non-Dose Dependent Pharmacology suggested in animal studies**

Schuster et al, ASCO 2006

Velafermin

- Primary Endpoint not met in this trial –
- Safety established
- Further studies planned at optimal dose

Summary

- Mucositis - An important complication of myeloablative transplantation
- Scoring – Important for research and patient care
- New agents may change incidence and severity
- New agents may prevent mucositis – need to be tested further

♦ Acknowledgements
- Nathaniel Treister, DMD
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