Radiation-induced mucositis: protective activity of a dextrane derivative.

M Mangoni

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Oral mucositis

The most common and clinically significant toxicity of HNC treatment → \( \frac{2}{3} \) of patients

ERYTHEMA AND ULCERATIONS

✓ impaired nutrition, risk of infection, rapid deterioration of the quality of life

✓ delayed treatment and dose reduction
No approved treatment for OM

### CURRENT THERAPIES

- Bland rinses: saline or sodium bicarbonate
- Topical anesthetics: lidocaine, benzocaine
- Mucosal coating agents
- Analgesics
- Steroids
No approved treatment for OM

### Agents in Clinical Trials

<table>
<thead>
<tr>
<th>Agent</th>
<th>Characteristics</th>
</tr>
</thead>
</table>
| Amifostine                   | - Free-radical scavenger  
                              | - Prevents the upregulation of inflammatory pathways                           |
| Glucagon-like peptide-2 (GLP-2) | - Epithelium-specific growth factor  
                              | - May reduce intestinal mucositis                                              |
| Glutamine supplementation (AES-14)* | - Amino acid  
                              | - Mitigates treatment-induced glutamine deficiency  
                              | - Replenishes glutamine  
                              | - Exerts mucoprotective effects                                               |
| Palifermin†                  | - Keratinocyte growth factor  
                              | - Increases cellular proliferation  
                              | - Mediates epithelial cell repair                                              |
| Tocopherol                   | - Antioxidant  
                              | - Potent form of vitamin E                                                     |
| Velafermin                   | - Growth factor  
                              | - Reduces mucosal barrier injury by increasing mucosal thickness  
                              | - Stimulates epithelial cell division  
                              | - Decreases inflammation by reducing the production of pro-inflammatory cytokines |
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Approved by the FDA in 2004 to decrease incidence and duration of severe OM in pt undergoing high-dose CT w/wo RT followed by bone marrow transplant for hematologic cancers.

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Posner and Haddad, Novel Agents for the Treatment of Mucositis  
An Engineered Biopolymer Prevents Mucositis Induced by 5-Fluorouracil in Hamsters

Frédéric O. Morvan, Brigitte Baroukh, Dominique Ledoux, Jean-Pierre Caruelle, Denis Barritault, Gaston Godeau, and Jean-Louis Saffar

RGTA improved 5FU induced mucositis in hamsters
RGTA® (ReGeneraTingAgents)

Family of dextran derivative biopolymers

✓ provided with heparan-mimetic properties

✓ devoid of heparin associated anticoagulant properties
RGTA® (ReGeneraTingAgents)

✓ protectors of the endogenous HBGF

✓ effective in stimulating tissue repair in several *in vivo* models:

Skin:  Meddahi A et al. Diabetes Metab 1996
Muscle:  Desgranges P et al. FASEB J 1999
          Escartin Q et al. EMBO J  2003
5-FU induced mucositis:  Morvan OF et al. Am J Pathol 2004
Purposes

✓ to evaluate RGTA-OTR4131 on radiation-induced mucositis in mice
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✓ to compare the effects of RGTA to 1. amifostine and 2. amifostine+RGTA
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✓ to evaluate RGTA-OTR4131 on radiation-induced mucositis in mice

✓ to compare the effects of RGTA to 1.amifostine and 2.amifostine+RGTA

✓ to test potential interference of RGTA on tumor response to IR
Mucosal lip reaction to ionizing radiation

C57 black mice

Single dose of 16.5 Gy selectively on oral region

Diet: liquid food (Renutryl®500)

Reagents: RGTA®-OTR4131
Amifostine (Ethyol®)

**Parkins’ scoring system** Parkins CS et al. Radiother Oncol 1983

<table>
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<tr>
<th>Oedema score</th>
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<tbody>
<tr>
<td>0,5</td>
<td>50-50 doubtful if any swelling</td>
</tr>
<tr>
<td>1</td>
<td>Slight but definite swelling</td>
</tr>
<tr>
<td>2</td>
<td>Severe swelling</td>
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<table>
<thead>
<tr>
<th>Erythema score</th>
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<tbody>
<tr>
<td>0,5</td>
<td>50-50 doubtful if abnormally pink</td>
</tr>
<tr>
<td>1</td>
<td>Slight but definite reddening</td>
</tr>
<tr>
<td>2</td>
<td>Severe reddening</td>
</tr>
<tr>
<td>3</td>
<td>Focal desquamation</td>
</tr>
<tr>
<td>4</td>
<td>Exudate or crusting involving about ½ lip area</td>
</tr>
<tr>
<td>5</td>
<td>Exudate or crusting involving more than ½ lip area</td>
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Mucosal lip reaction to ionizing radiation

**RGTA 24 hours post IR**
- IR
- IR+RGTA® (24h)
- IR+AMIF

**p=0.0009**

**RGTA 3 hours post IR**
- IR
- IR+RGTA® (3h)

**p=0.01**

**RGTA every 3 days**
- IR
- IR+RGTA® every 3 days

**p<0.03**
Amifostine-RGTA combination

Mucositis

Parkins score

IR
IR+AMIF
IR+AMIF+RGTA®(24h)

p=0.0003
Histopathological analysis

9 days after IR

Normal tissue

Masson staining

16.5Gy Irradiation

Irradiation+RGTA

Irradiation+Amifostine

Irradiation+Amifostine+RGTA
Leukocyte infiltration

9 days after irradiation

number of leucocytes/field

19 days after irradiation

number of leucocytes/field
Does RGTA-OTR4131 protect tumor?
Effect of RGTA on tumor growth \textit{in vivo}

Balb/c nude mice

Tumor cell lines: HEP2; HT29

Single dose of \textbf{15 Gy} selectively on tumor

Reagents: RGTA®-OTR4131

Tumor response:

\[ \text{Tumor volume} = \frac{\text{length (mm)} \times \text{width}^2 \text{ (mm)}^2}{2} \]
Effect of RGTA on tumor growth *in vivo*

HEP-2 xenograft
Effect of RGTA on tumor growth *in vivo*

**HT-29 xenograft**

**Graphs:**
- *Effect of RGTA on tumor growth in vivo*:
  - **Y-axis:** Increase in tumor volume / initial volume
  - **X-axis:** Days
  - **Legend:**
    - IR+RGTA1mg/kg
    - IR
    - IR+amif+RGTA

- **Comparison:**
  - Control
  - RGTA40mg/kg
In vitro radio-sensitivity assay

**HEP-2 cell line**
- \( \gamma \)-IR: 0-2-4-6 Gy
- Reagents: RGTA 10\( \mu \)g/ml

**HT-29 cell line**
- \( \gamma \)-IR: 0-2 Gy
- Reagents: RGTA 100-300-500\( \mu \)g/ml
Conclusions

In mice, RGTA protects normal tissue from radiation-induced damages.
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- The association of RGTA with amifostine improves the mucosal protection.
Conclusions

✓ In mice, RGTA protects normal tissue from radiation-induced damages.

✓ The association of RGTA with amifostine improves the mucosal protection.

✓ Absence of tumor protection.
Ongoing

- Radioprotective effects on GI & lung tissue
- Optimal sequencing and dosing with fractioned IR
# Acknowledgments

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<tr>
<th>Institut Gustave Roussy Villejuif, France</th>
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**Association pour la recherche sur le cancer (ARC)**

**Istituto Toscano Tumori (ITT)**