Galectin-3 Inhibition in Diffuse Large B-Cell Lymphoma

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Overview

• Diffuse large B-cell lymphoma (DLBCL)
• Galectin-3 and apoptosis
• Therapeutic application of a galectin-3 inhibitor (GCS-100)
Diffuse Large B-Cell Lymphoma

- 56,000 new cases of non-Hodgkin’s lymphoma per year in US (4% of all cancers)
- Diffuse Large B-Cell (DLBCL) is the most common subtype
- Clinically aggressive
Non-Hodgkin’s Lymphoma

Diffuse Large B-Cell Lymphoma

Normal lymph node

DLBCL
International Prognostic Index

Risk factors:

- Age >60
- Elevated LDH
- Stage III or IV
- ≥ 2 extranodal sites
- Performance status ≥2

Sehn LH. Blood 2007: 109(5); 1857.
Apoptosis and DLBCL

• Apoptosis (programmed cell death) is a critical mechanism in controlling cell growth in normal cells
• Dysregulation of apoptosis has been implicated in many cancer types
• In DLBCL:
  – BCL-2 (overexpressed in 40-60% of cases)
  – Others: p53, INK4a, TRAIL, FAS, cFLIP…
• Potential target in cancer therapy (eg bortezomib, oblimersen)
Galectin-3

- Galectins = family of proteins that bind to carbohydrates
- Signaling at diverse locations
  - Intracellular: nucleus, mitochondria
  - Extracellular: secreted galectins bind to glycoproteins on cell surface, or extracellular matrix
- Function depends on cell type and localization
  - Proliferation, apoptosis, adhesion, migration…
Galectins and Apoptosis

Galectin-1

Galectin-3

Slide courtesy of Linda Baum, MD
Galectin Lattices

CD45 localization

Galectin-3 and BCL-2

- Gal-3 carbohydrate binding domain has homology with BCL-2, an anti-apoptotic protein
- Possible mechanism of action at the mitochondria
## Galectin-3 and DLBCL

<table>
<thead>
<tr>
<th>Lymphoma type</th>
<th>Galectin-3+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follicular lymphoma</td>
<td>0/17 0%</td>
</tr>
<tr>
<td>Burkitt lymphoma</td>
<td>0/15 0%</td>
</tr>
<tr>
<td><strong>DLBCL</strong></td>
<td><strong>21/32 66%</strong></td>
</tr>
<tr>
<td>Marginal zone lymphoma</td>
<td>0/8 0%</td>
</tr>
<tr>
<td>MALT/BALT lymphoma</td>
<td>0/9 0%</td>
</tr>
<tr>
<td>B-SLL</td>
<td>0/8 0%</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>4/16 25%</td>
</tr>
</tbody>
</table>

Hoyer KK et al.  Am J Path 2004
Galectin-3 and DLBCL

Myeloma

Diffuse large B-cell lymphoma

Hoyer KK et al. Am J Path 2004
Galectin-3 Protects From Fas-mediated Apoptosis

Hoyer KK et al. Am J Path 2004
GCS-100

- Derived from citrus peel
- Displaces galectin-3 from its receptor on cell surface
- Over 100 patients with advanced solid malignancies treated in Phase I trials
- Dose limiting toxicity = vasculitic rash
GCS-100 Sensitizes Galectin-3+ Lymphoma Cells to Apoptosis

Gal-3(+) cell line

Gal-3(-) cell line

Data courtesy of Linda Baum, MD
GCS-100 Induces Apoptosis in Multiple Myeloma Cells

Chauhan D. Cancer Res 2005
Phase II Trial of GCS-100 With Chemotherapy in Relapsed DLBCL

- Combine GCS-100 with RICE chemotherapy (rituximab, ifosfamide, cyclophosphamide, etoposide), a common salvage regimen for DLBCL.
- For patients with relapsed or refractory disease after first-line therapy.
GCS-100 + R-ICE in DLBCL

- Relapsed or Refractory DLBCL
  - R-ICE x2
    - Good response → Autologous stem cell transplant
    - Poor response → GCS-100 + R-ICE

- GCS-100 + R-ICE
GCS-100 + R-ICE in DLBCL

PET-CT → GCS-100 + R-ICE x2 cycles

No response → Off study

Repeat PET-CT

Response → Continue GCS-100 + RICE

Evaluate for autoSCT
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