Engineering Nanomedical Systems

Lecture 14

Challenges of proper drug dosing with nanodelivery systems

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I. Overview of drug dosing problem

A. Problems of scaling up doses from animal systems
B. Basing dosing on size, area, weight of recipient
C. Vast differences between adults in terms of genetics, metabolism
D. Dosing in children – children are NOT smaller adults!
E. Pharmacokinetics – drug distribution, metabolism, excretion, breakdown
F. Conventional dosing assumes drug goes everywhere in the body
G. Targeted therapies – a model for future nanomedical systems?
II. From the animal dosing to human clinical trials

A. Importance of picking an appropriate animal model system
B. Does drug dosing really scale?
C. The “human guinea pig” in clinical trials and beyond!
III. Traditional drug dosing methods

A. Attempts to scale up on basis of area
B. Attempts to scale up on weight/volume
C. Attempts to use control engineering principles
Control Theory for Drug Dosing

Figure 1. The n-compartment mammillary model. The central compartment, which is the site for drug administration, is generally thought to be comprised of the intravascular blood volume as well as highly perfused organs such as the heart, brain, kidney, and liver. The central compartment exchanges the drug with the peripheral compartments comprised of muscle, fat, and other organs and tissues of the body, which are metabolically inert as far as the drug is concerned.

Source: Bailey & Haddad, 2005
IV. Genetic responses to drug dosing

A. All humans are not genomically equivalent!
B. Predicting on basis of family tree responses
C. SNPs, chips, and beyond…predicting individual drug response
D. After the $ 1000 individual genome scan…more closely tailored individual therapies
V. Dosing in the era of directed therapies

A. How directed therapies change the dosing equation
B. Current generation directed antibody therapies dosing
C. Next generation directed nanomedical systems dosing

VI. Most directed therapies are nonlinear processes

A. Current and pending FDA approved directed therapies
B. Some examples of how a few directed therapies work
   1. Complement directed cytotoxicity
   2. ADCC-mediated adaptive immunity switch
   3. Antibody-directed enzyme producing therapy
Some “Directed Therapies”

FDA-approved monoclonal antibodies for cancer treatment

<table>
<thead>
<tr>
<th>Name of drug</th>
<th>Type of cancer used to treat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alemtuzumab (Campath)</td>
<td>Chronic lymphocytic leukemia</td>
</tr>
<tr>
<td>Bevacizumab (Avastin)</td>
<td>Colon cancer</td>
</tr>
<tr>
<td></td>
<td>Lung cancer</td>
</tr>
<tr>
<td>Cetuximab (Erbitux)</td>
<td>Colon cancer</td>
</tr>
<tr>
<td></td>
<td>Head and neck cancer</td>
</tr>
<tr>
<td>Gemtuzumab (Mylotarg)</td>
<td>Acute myelogenous leukemia</td>
</tr>
<tr>
<td>Ibritumomab (Zevalin)</td>
<td>Non-Hodgkin's lymphoma</td>
</tr>
<tr>
<td>Panitumumab (Vectibix)</td>
<td>Colon cancer</td>
</tr>
<tr>
<td>Rituximab (Rituxan)</td>
<td>Non-Hodgkin's lymphoma</td>
</tr>
<tr>
<td>Tositumomab (Bexxar)</td>
<td>Non-Hodgkin's lymphoma</td>
</tr>
<tr>
<td>Trastuzumab (Herceptin)</td>
<td>Breast cancer</td>
</tr>
</tbody>
</table>

Source: http://www.mayoclinic.com/health/monoclonal-antibody/CA00082
“Side Effects” of Directed Therapies

In general, the more common side effects caused by monoclonal antibody drugs include:

• Allergic reactions, such as hives or itching
• Flu-like symptoms, including chills, fatigue, fever and muscle aches and pains
• Low blood cell counts, which may lead to bleeding, fatigue and infection
• Nausea
• Diarrhea
• Skin rashes

Source: http://www.mayoclinic.com/health/monoclonal-antibody/CA00082
FDA Approved Monoclonal Antibodies for Directed Therapies Against Cancer

### Table 1  Therapeutic mAbs approved for use in oncology

<table>
<thead>
<tr>
<th>Generic name (trade name)</th>
<th>Origin</th>
<th>Isotype and format</th>
<th>Target</th>
<th>Indication</th>
<th>Year approved by FDA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unconjugated mAbs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trastuzumab (Herceptin)</td>
<td>Humanized</td>
<td>Human IgG1</td>
<td>HER2/neu</td>
<td>Breast cancer</td>
<td>1998</td>
</tr>
<tr>
<td>Rituximab (Rituxan)</td>
<td>Murine-human chimeric</td>
<td>Human IgG1</td>
<td>CD20</td>
<td>Lymphoma</td>
<td>1997</td>
</tr>
<tr>
<td>Cetuximab (Erbitux)</td>
<td>Murine-human chimeric</td>
<td>Human IgG1</td>
<td>EGF receptor</td>
<td>Colorectal cancer</td>
<td>2004</td>
</tr>
<tr>
<td>Bevacizumab (Avastin)</td>
<td>Murine-human chimeric</td>
<td>Human IgG1</td>
<td>VEGF</td>
<td>Colorectal, lung cancers</td>
<td>2004</td>
</tr>
<tr>
<td>Alemtuzumab (Campath-1H)</td>
<td>Humanized</td>
<td>Human IgG1</td>
<td>CD52</td>
<td>Chronic lymphocytic leukemia</td>
<td>2001</td>
</tr>
<tr>
<td><strong>Imunoconjugates</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ibritumomab tiuxetan (Zevalin) together with rituximab</td>
<td>Murine</td>
<td>$^{90}Y$-radiolabeled murine IgG1</td>
<td>CD20</td>
<td>Lymphoma</td>
<td>2002</td>
</tr>
<tr>
<td>Tositumomab and $^{131}I$ tositumomab (Bexxar)</td>
<td>Murine</td>
<td>$^{131}I$-radioabeled murine IgG2a</td>
<td>CD20</td>
<td>Lymphoma</td>
<td>2003</td>
</tr>
<tr>
<td>Gemtuzumab (Myelotarg)</td>
<td>Human (drug derived from streptomycin)</td>
<td>Human IgG4 conjugated to calicheamicin</td>
<td>CD33</td>
<td>Acute myelogenous leukemia</td>
<td>2000</td>
</tr>
</tbody>
</table>

**Source:** Adams & Weiner, 2005
Not Yet Approved Monoclonal Antibodies for Possible Future Use against Cancer

Table 2  Selected novel (unapproved) mAbs in late-stage trials for cancer

<table>
<thead>
<tr>
<th>Description</th>
<th>Target</th>
<th>Indication</th>
<th>Sponsor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ch14.18. chimeric mAb</td>
<td>GD2</td>
<td>Neuroblastoma. Used in combination with chemotherapy radiotherapy and colony-stimulating factors</td>
<td>NCI</td>
</tr>
<tr>
<td>Rencarex (WX-9250; cG250) chimeric mAb</td>
<td>G250 antigen</td>
<td>Nonmetastatic kidney cancer. Used after surgery</td>
<td>Wiley</td>
</tr>
<tr>
<td>MDX-010 humanized mAb</td>
<td>CTLA-4</td>
<td>Melanoma. Used alone and in combination with gp100 peptide vaccine</td>
<td>Medarex</td>
</tr>
<tr>
<td>Panitumumab (ABX-EGF) human mAb</td>
<td>EGFR</td>
<td>Non-small cell lung cancer</td>
<td>Abgenix/Immunex</td>
</tr>
<tr>
<td>Remitogen (Hu1D10) humanized mAb</td>
<td>MHC class II</td>
<td>Non-Hodgkin lymphoma</td>
<td>Protein Design Labs</td>
</tr>
</tbody>
</table>
Complement-directed Cytotoxicity

Binding of antibodies on cell surface (a) exposes binding sites for proteins to initiate the complement cascade, (b) ultimately triggering release of chemotactic factors, (c) and the formation of the membrane attack complex, (d) which promotes cell lysis.

Source: Adams & Weiner, 2005
Antibodies bind to antigens on the tumor cell surface providing targets for FC-receptors on natural killer cells. Cross-linking of receptors triggers release of perforin and granzymes that lyse the tumor cells.

Source: Adams & Weiner, 2005
Antibody –Directed Enzyme Producing Therapy

(a) The monoclonal antibody-enzyme conjugate binds to a tumor cell surface antigen, (b) prodrug is administered after clearance of unbound antibody, (c) where the prodrug is cleaved removing the inactivating sequence, and (d) releasing active forms of the drug locally.

Source: Adams & Weiner, 2005
VII. Other ways of controlling dose locally

A. Magnetic field release of drugs
B. Light-triggered release of drugs
Light Triggered Dosing at the Molecule Scale

Scheme 1. Generalized Photochemical Reaction of 3,5-Dimethoxybenzoin Esters

$\text{R} \xrightarrow{\text{light}} \text{product} + \text{R-COOH}$

Light Triggered Dosing at the Molecule Scale

Figure 2. Progress of formation of ibuprofen and 1 from 2 in acetonitrile in light and dark conditions. “On” indicates the beginning of a period of light irradiation; “off” indicates the beginning of a period in dark conditions.

References


Miller, A.A Body Surface Area in Dosing Anticancer Agents: Scratch the Surface! Journal of the National Cancer Institute, Vol. 94, No. 24, December 18, 2002