Medical Countermeasures Against Radiological Terrorism

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Radiological Terrorism Countermeasures

Before Event  | Event  | After Event
---|---|---
**Prevention**  | Protection of responders  | Cleanup
Guarding radio-isotopes  | Radioprotectors  | Facilities

**Detection**  | Dosimetry  | Environment
Radiation monitors  | Biological dosimeters  | Forensics

**Decontamination**  | Mitigation/treatment of GI injuries  | Who did it?
Decorporation agents  | Mitigation/treatment of hematological injuries

**Mitigation/treatment of late injuries**
Why Worry about Things other than Bone Marrow?

- The 30-day 50% lethal dose at Chernobyl was about 6 Gy

Hematologic lethality at Chernobyl (Mould, 1988)

• The 30-day 50% lethal dose at Chernobyl was about 6 Gy
Why Worry about Things other than Bone Marrow?

- With approaches developed since Chernobyl we can probably boost hematological tolerance by 50-100%.
  - Largely due to work done by the bone marrow transplant community.

Hematologic lethality at Chernobyl (Mould, 1988)

Incidence of Injury

- Dose (equivalent single dose in Gy)

- Hematologic lethality at Chernobyl (Mould, 1988)
We Will Still have to Worry about GI Injury

- The techniques used to boost marrow tolerance may not affect GI tolerance

Incidence of Injury

Acute GI Distress (Anno et al.,’95)

Bone Marrow

Dose (equivalent single dose in Gy)

0%
10%
20%
30%
40%
50%
Renal Failure Will Also Become an Issue

- Renal failure is already being seen in patients who received total body irradiation (TBI) in preparation for bone marrow transplantation (BMT)
Lung, Cardiac and CNS Injury Could Also Occur

- **Radiation pneumonitis** is common in patients who received TBI in preparation for BMT
  - Chronic lung injury is common in the A-bomb survivors
- **CNS and cardiac injury** are being reported in children who received TBI
Why the Focus on Mitigation?

- **Pharmacologic prevention** of radiation injuries (*i.e.*, agents that must be given prior to irradiation) will be of little utility against terrorism.

- **Treatment** will be easier to justify than mitigation:
  - Treatment involves individual patients with manifest radiation injuries.

- **Mitigation** is the medical countermeasure we need:
  - Victims will want something done immediately:
    - Knowing that injuries can be mitigated may be crucial to avoiding wide-spread panic.
  - Known post-irradiation interventions work best when started before the injury is clinically evident.
Improvements Needed in All Areas

• Better mitigation is useless without biodosimetry to tell us who needs it

• Better biodosimetry is not much use if there are no effective ways to mitigate radiation injuries

• Improved treatment of bone marrow injury will require the ability to deal with later non-hematopoietic injuries

• Conversely, if we cannot deal with bone marrow injury, victims will not live long enough to be at risk for late tissue injuries
Contamination vs. Exposure vs. Dose

Martz et al, Operat Rad Safety, ‘11)
Contamination vs. Exposure vs. Dose

• The distinction between assessing contamination and measuring dose is not well-understood outside the radiation community.

• We have sophisticated instrumentation for measuring contamination
  • And they are reasonably well distributed

• BUT for medical intervention we need isotope and chemical form
  • Here the needed equipment is not widely distributed

• And we need DOSE, preferably organ-specific dose
  • Our methods for this are primitive
  • The lack of methods for assessing dose will severely impede triage and medical intervention
If a Mass Casualty Event Occurred Now

- The ONLY rapid dose assessment method now available is time to emesis

2x2 rule:
If no vomiting in 2 hrs
dose MAY BE ≤2 Gy

Problems:
- There are other things that cause vomiting
- Some irradiated people (even at high doses) did not vomit

Adapted from Nicholas Dainiak, Course: Response to and Management of a Radiological Crisis
If You Had More Time

• **Lymphocyte depletion kinetics:**
  - Requires at least 24 hrs (preferably 72 hrs)
    One sample 24-72 hrs after exposure, and known time of exposure
    **OR**
    Two samples 24-72 hrs apart

• **Dicentric chromosomes in peripheral blood lymphocytes:**
  - Must be shipped to a central lab:
    - Bethesda (MD) and Toronto are closest
  - Takes 5-7 days
  - Current capacity is less than 1000/wk in all of US + Canada
What’s on the Horizon?

EPR of nails and teeth
Genomics, proteomics, metabolomics
Automation of lymphocyte genotoxicity endpoints

Harold Swartz, Dartmouth (Univ Rochester)
EPR of Nails and Teeth

• Looks quite promising in the laboratory:
  • Signal is sensitive to doses ≤1 Gy
  • Signal is stable for days

• Barriers to deployment:
  • Someone to manufacture a portable device
    ~$100,000 per unit
    Is there a market??
  • FDA approval
    - FDA approves actual devices, not just concepts
    - Both the assay and the machine need approval
  • Making sure the units would be useable when needed
    - Units need regular maintenance and trained personnel
Genomics, Proteomics, Metabolomics

• **Most promising right now:**
  • Gene expression in peripheral lymphocytes
  • Serum proteomics
  • Urine proteomics

• **Barriers to deployment:**
  • Making sure signal is radiation-specific
  • Finding a signal that is stable for at least 24 hrs (preferably 72 hrs)
  • Developing a portable machine
    - And finding a market for it
  • Getting FDA approval
    - Again, both the assay and the machine need approval
Automation of Lymphocyte Genotoxicity Assays

David Brenner (Columbia University)
Automation of Lymphocyte Genotoxicity Assays

• Prototypes exist that can:
  • Analyze >5,000 samples per day for the micronucleus assay
  • Analyze >10,000 samples per week for dicentrics

• Barriers to deployment:
  • Someone to manufacture a portable device
  • FDA approval
  • Making sure the units would be useable when needed
    Units need regular maintenance, up-to-date reagents, and trained personnel

• Advantages:
  • Assays are proven, so only the device needs FDA approval
  • The possibility of a machine that would have other medical uses:
    - Amniocentesis?
    - Forensics?
Personal Dosimeters

• Why not build dosimeters into a common personal product?
  • Watches, buttons and mobile phones have been suggested

• Barriers to deployment:
  • The current personal dosimeters (e.g., film badges) are not FDA-approved
    - They are not licensed for determining need for medical treatment
    - They are licensed for assuring conformation to regulations
  • Needs a system for reading large number of dosimeters quickly
    - Or if they were self-reading, a system for calibration and maintenance

• Advantages:
  • They would always be there
Treatment of Acute Radiation Sickness

- **Available right now:**
  - Supportive care
  - Some cytokines

- **Under development:**
  - Other cytokines
  - *Ex vivo* amplification of cord blood
Supportive Care
(Georges et al, Fred Hutchinson, Seattle)

- In the 1990’s the LD$_{99}$ for dogs given TBI was $\sim 4$ Gy
  - The use of cytokines and cell therapy raised it to $\sim 5$ Gy

- With human standard supportive care the canine LD$_{50}$ is now $\sim 7.5$ Gy
  - Adding cytokine therapy (GCSF, Flt3 and KGF) boosts the LD$_{50}$ to $\sim 8.2$ Gy
Supportive Care for Humans

• At Hiroshima/Nagasaki the 30-day LD$_{50}$ was 2-4 Gy
  • At Chernobyl it was 5-7 Gy
  • In recent accidents, victims have survived for more than 2 months after TBI doses ≥8 Gy

• In a radiological terrorism event with doses above ~4 Gy:
  • Providing supportive care to large numbers of victims will be the immediate challenge
    - Many victims may have combined injuries
      radiation + trauma
      radiation + burns
      radiation + pre-existing disease
  • But survivors of these doses will be at risk for late effects:
    - GI, Lung, CNS, Renal, Cardiovascular, and Cancer
Non-Hematological Injuries in Radiation Accident Survivors
(Fliedner et al, 2005)

Patients with severe (grade H3) hematological injuries who survived ≥90 days

Fraction of survivors with “severe” injuries

- Skin
- GI
- CNS
- Kidney
- Liver
- Lung
- Heart
Can Late Effects Be Mitigated?

- **Mitigation proven in at least two experimental systems:**
  - Kidney (ACE inhibitors, All blockers)
  - Lung (ACE inhibitors, All blockers, SOD/catalase mimetics)
  - CNS (ACE inhibitors)
  - Skin (ACE inhibitors)

- **Promising mitigation data in one experimental system:**
  - Kidney (SOD/catalase mimetics, selenium)
  - Lung (statins, genistein, curcumin)
  - CNS (statins)
  - Skin (SOD/catalase mimetics, HDAC inhibitors)
  - Cardiac (All blockers, curcumin)
  - Combined injury (ACE inhibitors, SOD/catalase mimetics)
Mitigation of Radiation Nephropathy
(Moulder et al, Radiat Res, ‘11)

**Mitigators:**
- Captopril (an FDA-approved ACE inhibitor) started 10 days after TBI
- Cozaar® (losartan, an FDA-approved AII blocker) started 10 days after TBI

**Azotemia**
(as BUN in mg/dl) after 26 wks

<table>
<thead>
<tr>
<th>TBI Dose (Gy)</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>20</td>
</tr>
<tr>
<td>10</td>
<td>40</td>
</tr>
<tr>
<td>12</td>
<td>60</td>
</tr>
</tbody>
</table>

Graph showing the comparison of TBI Alone, TBI + Captopril, and TBI + Cozaar® with respect to Azotemia (as BUN in mg/dl) after 26 weeks.
Mitigation of Pulmonary Vascular Injury
(Ghosh et al, Int J Rad Oncol Biol Phys, ’08)

Planar angiograms 2 months after irradiation
- Irradiation causes vascular drop-out in the lung within 2 months after irradiation

Mitigator: Captopril (an FDA-approved ACE inhibitor) started 1 week after irradiation
Mitigation of Pulmonary Fibrosis
(Kma et al, J Radiat Res. ‘12)

Mitigators: Three different FDA-approved ACE inhibitors started 1 wk after irradiation
Mitigation of Pneumonitis

Mitigator:
EUK-207 (an experimental SOD/catalase mimetic) started immediately after irradiation
Mitigation of Optic Neuropathy
(Kim, Brown et al, Radiat Res, ‘04)

Myelin staining (Luxol Fast Blue) of the optic nerves 6 months after irradiation. Luxol Blue staining is normal for a functioning neuron.

Mitigator: Ramipril (an FDA-approved ACE inhibitor) started 2 wks after irradiation
Mitigation of Radiation Injuries in Humans

• Clinically, there are no proven mitigators of radiation injury:
  • ACE inhibition is as close as we have come

• Two clinical trials to date:
  • A Phase II RTOG trial of captopril after lung irradiation
    Terminated because of poor accrual
  • A single-institution Phase III trial of captopril after TBI/BMT
ACE Inhibition after TBI/BMT (Cohen et al, 2008)

Adults and children receiving TBI as preparation for BMT
- Captopril (ACE inhibitor) started at engraftment and continued for one year

Not proof of mitigation of radiation injuries:
- Radiation is not the only cause of chronic renal failure in these patients
ACE Inhibition after TBI/BMT
(Cohen, Irving *et al*, MCW)

Survival is diverging after the last incidence of BMT nephropathy
- Something in addition to radiation nephropathy is being mitigated

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Can Mitigation be Done with FDA-Approved Agents?

• FDA-approved for other indications:
  • The ACE inhibitors (captopril, enalapril, ramipril)
  • The statins (atorvastatin, lovastatin)
  • Some of the AII blockers (*e.g.*, losartan)

• In Phase I/II trials for other indications:
  • Genistein
  • Some SOD/catalase mimetics

• As mitigators, the FDA-approved agents could be used “off-label”
  • This is legal under the “practice of medicine” rule as long as it is done on an individual patient basis
Labeling of Agents as Mitigators?

• Currently there are no agents with an FDA label for “mitigation of radiation injury”

• Why does that matter?
  • Agents will not be put in the National Strategic Stockpile unless they are explicitly labeled for “mitigation of radiation injury”
  • Neither agencies of government, nor anyone else, can advocate the use of agents “off-label”
  • Without a “label” relatively few will know how to use these agents

• Labeling will require:
  • Safety testing in normal humans
    - Both sexes and a range of ages
  • Efficacy testing in “appropriate” animal models
The FDA “Animal Efficacy Rule”

• This is the route for proving efficacy of an agent when:
  “efficacy studies in humans cannot be ethically conducted”

• The burden-of-proof required by the “animal efficacy rule” is huge
  • It may be insurmountable for mitigators of non-hematologic radiation injuries

• The track record is minimal:
  • Few agents (and no mitigators) approved by this route to date

• According to FDA, this is the “least approved route of approval”
  • Proving efficacy in cancer patients will not be sufficient to establish efficacy against injuries from radiological terrorism
  • But there appears to be no other option for mitigators
“Animal Efficacy Rule” Issues

“The effect is demonstrated in more than one animal species...”
Currently the data are from rodents only.

The work is done according to “Good Laboratory Practices”
Currently there appears to be a few GLP-compliant radiobiology laboratories

“The effect is demonstrated in [a] species expected to react with a response predictive for humans...”
With no “gold standard” agents, it is unclear how you establish that an animal model is predictive
“Animal Efficacy Rule” Issues

“A reasonably well-understood pathophysiological mechanism of the toxicity of [radiation] and its prevention or substantial reduction by [mitigators]”

We don’t actually understand the pathophysiology of late radiation injuries

We don’t understand how most of the proven agents are working as mitigators of radiation injury

Unlike drugs approved via human studies, approval under the animal rule requires understanding of mechanism of action
What About Nutraceuticals?

• Agents already in use as nutraceuticals (e.g., food supplements, health foods, vitamins) will still require FDA labeling for use in the terrorism countermeasures arena
  • This applies even to natural products
  • It also applies to products “generally regarded as safe”
  • It applies to products you can buy over-the-counter in your local pharmacy or health food store
Would Mitigators Be Used after a Radiological Terrorism Incident?

• FDA-approved agents may (will?) get “Emergency Use Authorization” for treatment of radiation injuries

• EUA’s are less likely to be issued for mitigators:
  • Mitigation involves treatment of large numbers of asymptomatic victims to benefit an unidentifiable (and small?) subgroup
  • FDA-approved, organ-specific, biodosimetry might change this

• But:
  • Physicians who know about the research will use FDA-approved agents off-label for their patients
  • Victims who find out about the research will use any agents they can find (nutraceuticals, OTC drugs, prescription drugs)
If Something “Small” Happens Now

We will still have no tools for rapid and accurate dose estimation. But we will get lymphocyte-based biodosimetry within 7-10 days.

The acute lethal dose will be higher than at Chernobyl. There may be survivors at risk for late normal tissue injury. Mitigators will probably be used under “practice of medicine”. Treatment agents will probably be available under EUA's.
If Something “LARGE” Happens Now

We will still have no tools for rapid and accurate dose estimation.
  We will NOT get lymphocyte-based biodosimetry.
  We will use incident reconstruction and symptoms.

The acute lethal dose MAY BE higher than at Chernobyl.
There MAY BE survivors at risk for late normal tissue injury.
  Mitigators will probably NOT be used.
Treatment agents will probably be available under EUA's.
Current Advice

- Do what you can to make sure nothing like this really happens.

Martz et al, Operat Rad Safety, ‘11)
Current Advice

- Load the REMM database on workstations and laptops.

http://www.remm.nlm.gov