New paradigms of the treatment of Acute Radiation Syndrome

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MC M. Drouet
Acute radiation syndrome, following Total Body Irradiation (TBI) or large partial Body (PBI) must be considered as a global/systemic illness [almost whatever the dose].

ARS can be scored using damages evaluation at the level of 4 key tissues targets.

Metrepol Response Category 1-4
HS can be scored based on Blood cell counts using the Metrepol RC graduation
Hematopoietic Syndrome (HS), mainly the consequence of radiation-induced cell death (apoptosis/ necrosis) of cycling/radiosensitive fraction of hematopoietic stem progenitor cells (inflammation/coagulation disorders / immunosuppression) represents the first therapeutic challenge above 2 Gy TBI.
Hematopoietic Syndrome: niche disease

Vascular niches
MK-Sinusoïde and arteriolar

niche components are highly radiosensitive

Chemokines (CXCL12), cytokines, Ca gradient metabolites

Adipocytes
MK
Mf
Ly
Osteoblast (subtype)
Osteoclast
Osteocyte

Mf
Adipocytes
MK
CAR
HS(P)C
Ly
MK-Sinusoïde
arteriolar
Current HS treatment

Two main therapeutic strategies

- Hematopoietic growth factor administration (H3 Metrepol)
- Allogeneic stem and progenitor cells graft (H4 Metrepol)
CYTOKINES AND RADIO-MITIGATORS
• Based on the non-uniform nature of most of the accidental irradiations due to exposure geometry and body thickness attenuation

• The residual hematopoiesis including the putative intrinsic radioresistant stem cells represent targets

• **G-CSF** (GM) is currently indicated after exposure to less than LD50% in order to shorten neutropenia  *(WHO consensus 2009 early injection; 2015 FDA approved for accidental exposure)*
• The SCF + EPO + Peg-G-CSF (SEG) combination was given to 2 patients in 2006 (de Revel, HIA Percy; Neulasta 12 mg/Darbopoietin Aranesp 500µg on day1 and Stemgen 20 µg/kg/daily)

Late and short-term administration schedule; 3.5-4.2 Gy TBI

• 3 patients in HIA Percy in 2011 for accidental heterogeneous TBI (2.5-4 Gy; H3/4 Metrepol) were given a late administration of G-CSF, TPO, Epo +/- SCF
Stem Cell Factor, FLT-3 ligand, Thrombopoietin, IL-3 (50 µg/kg each; SFT3) in combination given 2 hours and 1 day after irradiation prevented mice from radiation induced lethality and accelerated hematopoietic recovery in monkeys (5-7 Gy TBI) which is the rationale of the Emergency Antiapoptotic Cytokine (EACK) concept (Drouet et al 1999; Hérodin et al 2003; Drouet et al 2004)
New TPO substitutes

- TPO may be immunogenic; **Nplate** and **Eltrombopag** substitutes are FDA approved for ITP

**TPO receptor agonists** lacking sequence homology to TPO designed by grafting a known peptide sequence into the hinge and/or kappa regions of human anti-anthrax antibody (AFRRI) **ALXN4100TPO**

**Armed Forces Radiobiology Research Institute**

**ALXN4100TPO**
OTHER CYTOKINES OR FACTORS

- IL12 (HemaMax), IL11, FGF-2, EGF...

- Natural compounds: Ghrelin (growth hormone secretagogue), delta-tocotrienol (vitE isomere)

- Synthetic non cytokinic drugs early injected (within 24 h post irradiation):
  - P53 inhibitor pifithrine-\(\alpha\)
  - TLR-5 CBLB502 agonist
  - 5-androstenediol stéroïd
  - LPA2 Receptor-specific non lipid agonist
G-CSF as a gold standard
Early vs Delayed treatment neutropenia follow up

2015 : FDA approval for the treatment of accidental/war neutropenia

rhésus Monkeys  7.5 Gy TBI  (6 MV LINAC)  no supportive care
G-CSF D1                       versus                 G-CSF D2  (Neupogen 10µg/kg/D)

Mac Vittie et al 2013-2015
AMedP-7.1 will recommend the injection within **24 hours** for H3 (H4) Metrepol victims.

**Survival study Monkeys 7.5 Gy TBI**

G-CSF **D1** versus G-CSF **D2** (Neupogen 10µg/kg/J)

*Mac Vittie et al 2013-2015*
The aim of this agreement is to lay down the necessary framework for NATO policy to create Medical Radiological Incident Investigation Teams (MED RIIT) for evaluation and initial response following radiological incidents (including nuclear) in order to provide medical advice and initiate all relevant medical remedial measures such as dose assessment/effect prediction and decorporation therapy as soon as possible as well as ongoing casualty care.

To meet the present state of the art in science and technology following Human Factors and Medicine 222 and AMedP-7.1, the custodian suggests some amendments to be implemented in the next edition of the document regarding dose assessments effect prediction, early decorporation, and cytokine therapy and access to reach-back and reference laboratories.

**EARLY TRIAGE**
• Cytogenetic analysis is currently the gold standard…but only available at D3

• Lymphocyte culture phase is required (early cell sampling)
• **Dicentriques Scoring (DIC)** is RI specific (instable thus only for early evaluation)
• semi-automatic (Metasysteme platform analysis)
## PREMATURE CHROMOSOME CONDENSATION (PCC)

<table>
<thead>
<tr>
<th>CRITERION</th>
<th>Dicentric assay</th>
<th>Premature chromosome condensation (PCC)</th>
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</thead>
<tbody>
<tr>
<td>Dose range (Gy)</td>
<td>0.1 - 5</td>
<td>1 - 20</td>
</tr>
<tr>
<td>Sensitivity (Gy)</td>
<td>0.1</td>
<td>1</td>
</tr>
<tr>
<td>Triage approaches (mass casualty situation with more than ca. 20 samples during the first week in one lab)</td>
<td>Yes, but sensitivity is 1 Gy</td>
<td>Yes</td>
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<tr>
<td>How long the technique can be used after exposure? (Optimum time)</td>
<td>Days-weeks</td>
<td>Hours- days</td>
</tr>
<tr>
<td>Standardisation of the assay</td>
<td>ISO standard</td>
<td>-</td>
</tr>
<tr>
<td>Usefulness for partial body exposure</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

- **Low per-sample cost**
- **Less difficult to produce results quickly (shortest culture time)**
- **Well-characterized dose-response**
- **Differentiates partial- from total-body exposures**
- **Less sensitivity than Dicentrics Assay**
- **Difficult to treat a great number of samples at the same time**
- **NOT stable over long periods of time**
- **Chinese Hamster Ovary Cells**

D1 semi automatic PCC?
PREMATURE CHROMOSOME CONDENSATION (PCC)

- Using telomere and centromere Peptide Nucleic Acid (PNA) probes

- Less well-characterized dose-response
- Low per-sample cost
- Better sensitivity than “Giemsa PCC”
- Less difficult to produce results quickly
- NOT stable over long periods of time
- Difficult to treat a great number of samples at the same time
- Chinese Hamster Ovary Cells
Patterns of biochemical markers
Hérodin Valente et al

Total body irradiation vs Partial exposure in baboon model.
200 days follow-up of over 50 Clinical and Biological end-points.

5Gy TBI

5Gy PBI

VS

First days
TBI vs PBI discrimination:
dicentric assay (day 1)

Dose: ANC, ALC ratio, CRP,
citrullin, dicentric assay

Between day 10 and day 21
TBI vs PBI discrimination: ANC, PLT, Hb, Flt-3 ligand

(Clinical re-evaluation of heterogeneously exposed individuals)
Early biochemicals?

- 8 plasmatic biochemical markers and most of hematological parameters to discriminate TBI and PBI animals during the prodromal phase (day 0.5 – day 7) and the manifest illness phase (day 10 – day 28).

  - Early biomarkers: AST, CK, LDH, urea, Flt3-ligand, iron, coagulation factor V, CRP, EPO, monocyte count, and neutrophil to lymphocyte counts ratio
  - Biomarkers for ARS phase: iron, Flt3-ligand, CRP, platelet count, Hb, and ANC
  - Heterogeneity could be distinguished within a range of 2.5 to 5 Gy TBI.

- VE Cadherin as a vascular damage biomarker?

Biomarkers to be validated in clinic (2015-2019)

Time to take into account individual radiosensitivity?
• Metrepol scoring is feasible on large scale for early and secondary triage

• **NATO HFM222-RTG Exercice** (Dörr/Port/Abend)
• Metrepol scoring based on clinic and CBC/biochemicals i.e. lymphopenia D3–D5++

• Scenario: orphan source dissimulated in a train
• 191 cases based on Metrepol (RC1, n=45; intermediate RC2, n=19; severe RC3, n=20; letal: RC4 n=18) and SEARCH (n=24)
• 8 teams from 5 nations
• ARS diagnosis and hospitalization were correctly evaluated (89.6% +/- 3.3 ; 88.8% +/- 4.6)
• RC2 and RC3 were over-scored but RC4 were correctly identified
• Next step: Biodosimetry in the field using innovative biotechnologies?

(see Acubens technology poster)
• Radiobiology Unit

• Dr François-Xavier Boittin
• MP Cyrus Chargari
• Dr Sabine François
• MC Patrick Martigne
• MP Diane Riccobono
• Dr Clélia Le Gallic

• Dr Marco Valente (LDBI)
• Ing Francois Désangles (LDBI)
• TPC Jérome Pateux
• TPC Nathalie Guitard
• TPC Guillaume Cosler