Prophylaxis and treatment of viral infections in HSCT

Diana Hardie
viral infection in HSCT recipients can come from various sources:

- **Community acquired:** Hospital staff, household contacts
- **Donor (antiviral T cells):**
- **Recipient:**
  - CMV, HSV, EBV, VZV, HHV6, BK, JC, adenovirus
  - CMV, parvovirus (hepatitis)
- **Respiratory viruses:** Influenza, adenovirus, RSV
- **Enteric viruses:** other
- **Blood products:**
Factors associated with increased risk of viral infection:

Antiviral immunity relies on functional T cells

Increased risk relates to Poor and late reconstitution:
- T cell depletion of graft
- Allogeneic grafts
- -unrelated
- -HLA mismatch
- Cord blood grafts
- Repeat transplant
- GVHD (immune attack on TEC)
- Older age

Nature Reviews immunology January 2005
Time course for viral infections

Different viruses cause trouble at predictable times post transplant.

Pre-engraftment
- Neutropenia, mucosal damage

post engraftment
- NK recovery, but minimal T and B cells

late phase
- slow recovery of T and B cells; ongoing impairment

Acute GVHD
- HSV

chronic GVHD
- HCMV
- BK, HHV6, Adenovirus

VZV
- EBV PTLD
- Respiratory viruses
  - Influenza, adenovirus, RSV, other

Based on Kedia et al., J Stem Cell Res Ther 2013, S3
Infectious disease burden

Day 0-30
Child, adolescents
48% T cell depleted

n=739
Human cytomegalovirus

Number 1
R+/D-

Disease burden reduced with
- Improved early detection of viraemia
- Pre-emptive therapy

Pre-emptive therapy preferred to prophylaxis

Traditionally, pp65 antigen in WBCs
RealTime qPCR

Thresholds to trigger pre-emptive therapy:
- any positive >200 genome copies/ml
- positive on 2 consecutive occasions
- viral load above log 3
Ganciclovir/valganciclovir:

Drug of choice for treatment and prophylaxis

Acyclic analogues of guanosine

Mono-phosphorylated by viral TK (pUL97)
myelotoxicity

Drug resistance: pUL97 or pUL54

2\textsuperscript{nd} and 3\textsuperscript{rd} line agents:

\textbf{Foscarnet} and \textbf{cidofovir}:

Modest anti CMV activity and significant toxicity

New drugs...
New anti CMV drugs in the pipeline:

**Brincidofovir** (CMX-001)

- Lipid conjugate of CDV
- Acyclic nucleotide inhibitor of UL54
- Lower toxicity, long t1/2
- Broad spectrum activity against DNA viruses: CMV, adenovirus, polyomaviruses, pox viruses
- Phase 2 CMV prophylaxis trial (260 HSCT):
  - Significantly better than placebo
  - Dose limiting diarrhoea

**maribavir**

- Targets pUL97
- Low toxicity, effective in phase 2 trials
- No benefit in phase 3 prophylaxis trial
  - Dose too low
  - Low rate of CMV events
- Resistance pUL97 and pUL27

**leflunamide**

- Immunosuppressive agent
- Activity against CMV, HSV, BK
- Blocks virion assembly
**Letermovir**

Targets the viral terminase:

Cleaves viral genomes

Resistance conferred by a single point mutation in UL56 (terminase)

Phase 2 prophylaxis trial:
131 CMV sero-positive allo-HSCT recipients

Incidence and time to failure of prophylaxis
3 dosages, 12 weeks
60, 120, 240 mg or placebo

Dose dependent reduction in CMV viraemia episodes
Safety profile similar to placebo

Phase 3 trial is planned...
Adenoviral disease

Un-enveloped dsDNA virus
57 Human Adv types, 7 species
Range of clinical disorders
RTI, gastro-enteritis, kerato-conjunctivitis
Highly resistant to inactivation
Nosocomial outbreaks

HSCT:

Horizontal acquisition or reactivation

Children>> adults
First 100 days
Disseminated infection:
-preceded by viraemia
Pneumonia, enteritis, myocarditis, encephalitis
European Conference for Infections in Leukaemia: Recommendations in Allogeneic HSCT:

Diagnostics:
Blood monitoring advised in at risk patients
qPCR based methodologies preferred
>4log10 copies/ml or rapidly rising VL

Prophylaxis and therapy of adenoviral infections:
Prophylaxis is not recommended
Pre-emptive therapy when viraemia is detected (high risk only)

In suspected disease:
Reduce immuno-suppression if possible,
IV cidofovir
Ribivirin not recommended
donor derived HAdV-specific T cells –only in experienced centre

Brincidofovir?? Only case reports so far
BK polyomavirus

BK virus and its role in Haematopoietic stem cell transplantation: evolution of a pathogen
Curr Infect Dis Rep (2014) 16; 417

UBiquitous infection
Primary infection → persistent
Renal tract
Shed in urine in 50-80% HSCT

Clinical associations:
Haemorrhagic cystitis (late)
Encephalitis, pneumonitis, vasculopathy, retinitis
Poorer outcome

Diagnosis:
High viral load in blood and urine with compatible clinical disease

Therapy:
Reduced immunosuppression
Cidofovir, Leflunomide no RCTs, toxicity
Host virus eliminated by conditioning

UBIQUITOUS INFECTION
B lymphocytes

LYTIC INFECTION

HOST CTLs

EBV AND POST TRANSPLANT LYMPHO-PROLIFERATIVE DISORDER

1. One of $10^6$ B cells is EBV infected, proliferation is suppressed by T cells
2. Lack of T cells led to an EBV-driven B cell proliferation - polyclonal
3. EBV lymphoma - monoclonal
4. Loss of CD20 in some clones led to rituximab resistance

EBV VIRAL LOAD IN BLOOD

Bone Marrow Transplantation (2013), 1–5
Risk Factors for EBV associated PTLD after allogeneic HSCT
Haematologica (2014) 99 (2), p346-352

Retrospective analysis of PTLD cases in 1021 HSCT patients between 1996-2011
Karolinska Institute

Risk factors:
- T cell depletion
- Recipient age >50
- Second allogeneic graft
- GVHD
- Cord blood graft

Poor and late T cell reconstitution
Principles of therapy:

Reduction in immunosuppression
No benefit to using anti-virals
Rituximab
  pre-emptive or therapeutic

Adoptive immunotherapy - an alternative approach...
Adoptive transfer of donor derived virus specific T cells

Highly effective at controlling infection in multiple phase 1 trials

**Difficulties:**
- Time delay before cells are ready for use
- Complex manipulations *ex vivo*
- Technologies for expanding virus specific CTLs
- Potential allo-reactivity (GVHD)
- Sero-negative donors, cord blood grafts

**Rapid expansion**
**Durable antiviral protection:** CMV, adenovirus, BK
**Prevention and treatment of EBV-PTLD**

**in vitro expansion** of virus specific T cells

**Limits widespread use**
### Table 1: Clinical trials using *in vitro* expanded VSTs

<table>
<thead>
<tr>
<th>Stimulation</th>
<th>Target</th>
<th>Patients</th>
<th>Prophylaxis or treatment (number of patients)</th>
<th>Viral outcomes</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMV-infected fibroblasts</td>
<td>CMV</td>
<td>14</td>
<td>Prophylaxis</td>
<td>No CMV infections</td>
<td>Walter et al.⁶²</td>
</tr>
<tr>
<td>CMV lysate-stimulated PBMCs</td>
<td>CMV</td>
<td>8</td>
<td>Treatment</td>
<td>6 CR 1 PR 1 NR</td>
<td>Einsele et al.⁵³</td>
</tr>
<tr>
<td>CMV antigen-pulsed DCs</td>
<td>CMV</td>
<td>28</td>
<td>Prophylaxis</td>
<td>23 Responded to VSTs with antivirals</td>
<td>Peggs et al.⁶⁶</td>
</tr>
<tr>
<td>pp65-pulsed or Ad5f35pp65 vector-transduced DCs</td>
<td>CMV</td>
<td>50</td>
<td>Prophylaxis</td>
<td>26 Patients developed CMV infections 9 Required antivirals 1 CMV-related death</td>
<td>Blyth et al.⁵⁹</td>
</tr>
<tr>
<td>EBV-LCLs</td>
<td>EBV</td>
<td>118</td>
<td>Prophylaxis (105) Treatment (13)</td>
<td>No new EBV infections 11 CR 2 Deaths</td>
<td>Rooney et al.⁷⁰  Heslop et al.⁷¹  Rooney et al.⁷²</td>
</tr>
<tr>
<td>EBV-LCLs</td>
<td>EBV</td>
<td>6</td>
<td>Treatment</td>
<td>5 Displayed a decrease in viral load 1 EBV-related death</td>
<td>Gustafsson et al.⁷⁴</td>
</tr>
<tr>
<td>EBV-LCLs</td>
<td>EBV</td>
<td>3</td>
<td>Treatment</td>
<td>3 CR 3 CR</td>
<td>Comoli et al.⁷³</td>
</tr>
<tr>
<td>EBV-LCLs</td>
<td>EBV</td>
<td>19</td>
<td>Treatment</td>
<td>13 CR 1 EBV-related death</td>
<td>Dubrovin et al.⁷⁵</td>
</tr>
<tr>
<td>Ad5f35pp65 vector-transduced EBV-LCLs and PBMCs</td>
<td>AdV</td>
<td>11</td>
<td>Prophylaxis (10)</td>
<td>3/3 CR of EBV infection/PTLD</td>
<td>Leen et al.⁷⁷</td>
</tr>
<tr>
<td>Plasmid-nucleofected DCs</td>
<td>EBV</td>
<td>10</td>
<td>EBV treatment (4)</td>
<td>3 CR 4 CR 1 patient with persistent colitis proceeded with colectomy</td>
<td>Gerdemann et al.⁸¹</td>
</tr>
</tbody>
</table>

**Abbreviations:** AdV, adenovirus; CMV, cytomegalovirus; CR, complete response; DC, dendritic cell; EBV, Epstein–Barr virus; EBV-LCL, EBV-transformed B lymphoblastoid cell line; NR, non-responder; PBMC, peripheral blood mononuclear cell; PR, partial response; PTLD, post-transplant lymphoproliferative disease; VST, virus-specific T cell.
3rd party T cells?

Banked HLA matched antiviral T cells from miscellaneous donors
Only phase 1 trials so far
Safe, immediate
Efficacy depends on HLA match

*Cytotherapy*, 2014; 16: 149–159

With the use of third-party CTL for viral infections after stem cell transplant.

<table>
<thead>
<tr>
<th>n</th>
<th>Target</th>
<th>Type of HSCT</th>
<th>Serious Adverse Events</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>EBV</td>
<td>Cord blood</td>
<td>None</td>
<td>&gt; 4 patients achieved CR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&gt; 1 patient had disease progression</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&gt; CR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&gt; Subsequent relapse treated with 2nd CTL infusion</td>
</tr>
<tr>
<td>1</td>
<td>EBV</td>
<td>Cord blood</td>
<td>None</td>
<td>&gt; 82% CR and partial remission</td>
</tr>
<tr>
<td>44</td>
<td>EBV, CMV, AdV</td>
<td>MRD, MUD, cord blood</td>
<td>&gt; 8 cases of GvHD after CTL (2 cases of de novo GvHD and 6 cases of GvHD recurrence)</td>
<td>&gt; AdV clearance</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&gt; Patient died of CMV</td>
</tr>
</tbody>
</table>
Post transplant vaccination:

Re-vaccination is recommended 2 years post HSCT
Responses depend on degree of T cell recovery

Best in children

<table>
<thead>
<tr>
<th>virus</th>
<th>timing</th>
<th>frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza</td>
<td>4-6 months</td>
<td>annually (patient and contacts)</td>
</tr>
<tr>
<td>Inactivated polio</td>
<td>6-12 months</td>
<td>3 doses</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>6-12 months</td>
<td>3 doses</td>
</tr>
<tr>
<td>Measles*</td>
<td>&gt;24 months</td>
<td>1-2 doses</td>
</tr>
<tr>
<td>Mumps *</td>
<td></td>
<td></td>
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<tr>
<td>Rubella*</td>
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</tbody>
</table>

* Only if off immuno-suppression, no GVHD

Zoster vaccine?


Safety in 110 HSCT patients
Single dose, 2 years post transplant
2 patients developed zoster rash within 42 days of vaccine
None in 1178 months follow up