Advances in clinical management and endpoints

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CMV and allogeneic HSCT in 2014

- CMV remains an important pathogen
- CMV serological status influences outcome after especially high risk HSCT
- Management options, although having improved a lot, still have important limitations
- Data support a relationship between CMV reactivation and reduced risk for leukemic relapse
Association of CMV Serostatus with Patient Survival

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Underlying disease</th>
<th>CMV-seropositive recipients compared with CMV-seronegative recipients with a seronegative donor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Broers, 2000</td>
<td>115 Mixed</td>
<td>24% absolute decline in OS (p=0.01)</td>
</tr>
<tr>
<td>McGlave, 2000</td>
<td>1423 CML</td>
<td>20% relative decline in DFS (p=0.002)</td>
</tr>
<tr>
<td>Cornelissen, 2001</td>
<td>127 ALL</td>
<td>38% relative decline in DFS (p=0.05)</td>
</tr>
<tr>
<td>Craddock, 2001</td>
<td>106 CML</td>
<td>22% absolute decline in OS (p=0.006)</td>
</tr>
<tr>
<td>Kroger, 2001</td>
<td>125 Mixed</td>
<td>41% absolute decline in OS (p=0.001)</td>
</tr>
<tr>
<td>Castro-Malaspina, 2002</td>
<td>510 MDS</td>
<td>46% relative decline in DFS (p=0.001)</td>
</tr>
<tr>
<td>Doney, 2003</td>
<td>182 ALL</td>
<td>99% relative rise in TRM (p=0.01)</td>
</tr>
<tr>
<td>Yakoub-Agha, 2006</td>
<td>236 Mixed</td>
<td>16.4% absolute decline in OS (p=0.01)</td>
</tr>
<tr>
<td>Craddock, 2011</td>
<td>168 Primary refractory AML</td>
<td>13% absolute decline in OS (p=0.09)</td>
</tr>
</tbody>
</table>

1Table modified from Boeckh, M and Nichols, WG Blood, 15 March 2004
Indirect effects of CMV in transplantation

GVHD (?)
Acute allograft rejection (bidirectional relationship)

Chronic allograft rejection and dysfunction
  TCAD – transplant coronary vasculopathy
  BOS – bronchiolitis obliterans syndrome
  TIF/CAN – chronic allograft nephropathy

Opportunistic infections

Leukemia relapse

Mortality

Razonable RR and Limaye AP. Transplant Infectious. 2010; 22(3)
What are the “new” options in 2014?

- WHO standard for testing
- New CMV antivirals
- New CMV vaccines
- Adoptive T-cell therapy
Treat established CMV disease

- A failure of strategy

- Associated with significant mortality in the most severely immunosuppressed HSCT patients
Timing of management options

Viral load

- Treatment of established disease
- Pre-emptive therapy
- Prophylaxis

Time

Viral disease

Diagnosis of viral infection
Where are the advances in management?

- Sensitive diagnostic tests are available
- Possibility to judge responses by viral load measurements
- Reduction in the rates of CMV end-organ disease
- Easy access to safe blood products
Where are the major challenges?

- No real impact has been achieved in managing CMV disease
- The drugs are still too toxic
- High risk patients have problems with immune reconstitution and no drug alone can solve that problem
Potential groups to target in prospective studies

- High risk tx patients for prophylaxis
- Standard risk patients for preemptive therapy
- Patients who are refractory/resistant to standard therapy
What is the rationale for prophylaxis?

- To prevent CMV disease we should prevent CMV replication
- CMV seropositivity in the patient decreases survival
- CMV is associated with indirect effects most likely based on the replication itself
- Placebo controlled studies are ethical
The maribavir story

- Very promising phase II results
- Failure of the phase III studies
CMV infection or disease ≤100 days after transplant (Phase II)

<table>
<thead>
<tr>
<th></th>
<th>ITT population n (evaluable, n)</th>
<th>pp65 antigenemia</th>
<th>Plasma CMV DNA PCR</th>
<th>Initiation of anti-CMV therapy</th>
<th>CMV disease n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>28 (28)</td>
<td>11 (39)</td>
<td>13 (46)</td>
<td>16 (57)</td>
<td>3 (11)</td>
</tr>
<tr>
<td>Maribavir</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100 mg bid</td>
<td>28 (27)</td>
<td>4 (15)</td>
<td>2 (7)</td>
<td>4 (15)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>400 mg qd</td>
<td>28 (27)</td>
<td>5 (19)</td>
<td>3 (11)</td>
<td>8 (30)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>400 mg bid</td>
<td>27 (26)</td>
<td>4 (15)</td>
<td>5 (19)</td>
<td>4 (15)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

*Winston et al. Blood 2008*
Time to onset of CMV infection or disease

Maribavir 100 mg bid p=0.01
Maribavir 400 mg qd p=0.06
Maribavir 100 mg bid p=0.006†
Placebo

†Cox proportional model hazard regression model

Maribavir phase III results

Disease

- Maribavir
- Placebo

pp65 Ag

- Maribavir
- Placebo

PCR

- Maribavir
- Placebo

Marty et al, Lancet ID 2011
Lessons for endpoints

- CMV disease can not be used as the primary endpoint in HSCT studies
- Techniques for diagnosing CMV infection are critical
What are critical CMV assay requirements?

Test sensitivity and specificity

Conserved target not affected by variant and mutant species
Relevant specimen e.g. whole blood or plasma

**Precision** such that changes in values represent biologically and presumably important changes in viral replication

**Accuracy** to trigger start and stop of antiviral therapy

**Linearity** throughout important medical decision points
Interlaboratory comparison of non-standardized QNAT for CMV in plasma

Figure 3: Result linearity over dynamic range for 35 panels from 33 laboratories. Each line represents results from one panel. (A) Commercial assays (n = 17) and (B) Laboratory-developed assays (n = 18). The x-axis shows expected results based on stock quantified reference laboratories.

Pang et al. 2009 Am J Transplant 9:258
What is the impact of an international standard?

Using a commutable international standard can improve comparability across different laboratory assay results.

What the (potential) problems with prophylaxis?

- Patients are treated that don’t need the drug
- Will effective prophylaxis prevent adequate CMV-specific immune reconstitution?
- Can complete prevention increase the risk for relapse?
CMV replication och relapse

Reduced risk of recurrent leukaemia in bone marrow transplant recipients after cytomegalovirus infection

B. Lönnqvist, O. Ringdén, P. Ljungman, B. Wahren and G. Gahrton
1Division of Clinical Haematology and Oncology, Department of Medicine, and 2Departments of Transplantation Surgery and Clinical Immunology, Huddinge Hospital, Huddinge, and 3National Bacteriological Laboratory, Stockholm, Sweden

Blood

Early human cytomegalovirus replication after transplantation is associated with a decreased relapse risk: evidence for a putative virus-versus-leukemia effect in acute myeloid leukemia patients

Ahmet H. Elmaagdci, Nina K. Steckel, Michael Koldehoff, Yael Hegerfeldt, Rudolf Trenschel, Markus Ditschkowski, Sandra Christoph, Tanja Gromke, Lambros Kordelas, Hellmut D. Ottinger, Rudolf S. Ross, Peter A. Horn, Susanne Schnittger and Dietrich W. Beelen

Regular Article

TRANSPLANTATION

CMV reactivation after allogeneic HCT and relapse risk: evidence for early protection in acute myeloid leukemia

Margaret L. Green, Wendy M. Leisenring, Hu Xie, Roland B. Walter, Marco Mielcarek, Brenda M. Sandmaier, Stanley R. Riddell and Michael Boechk

1Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center, Seattle, WA; 2Department of Medicine, University of Washington, Seattle, WA; 3Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA; and 4Department of Biostatistics, University of Washington, Seattle, WA
CMV and relapse

- CMV replication reduces the risk for leukemia relapse at least in myeloid malignancies
- Unclear if this is a direct effect or an effect mediated through an immune phenomenon
- The effect occurs early after HSCT
- The potential positive effect on survival is counterbalanced by an increased non-relapse mortality
What endpoints would I then like to see?

- A clear reduction in the risk for detecting CMV replication

- Introduction of preemptive therapy could be included but should not be necessary

- An innovative way to look at viral replication. AUC? Proportion to reach certain cut-offs

- Safety is paramount

- Supportive evidence on prevention of indirect effects
What is the rationale and requirements for monitoring and preemptive treatment

- Only patients developing CMV replication are subjected to treatment
- A sensitive diagnostic test must be available
- A positive result is predictive for development of disease
- Early intervention can prevent disease
- An effective (and safe) antiviral drug is available
Preemptive therapy today; HSCT

- Proven efficacy
- Allows short treatment courses
- Low risk for CMV disease
- Standardized monitoring techniques are now available
Viral load and CMV disease

Initial viral load correlate with CMV disease

- Liver tx (OR 1.82 [1.11-2.98; p=0.02)
- Renal tx (OR 1.34 [1.07-1.68], p=0.01)
- HSCT tx (OR 1.52 [1.13-2.05], p=0.006)

per 0.25 log10 increase in viral load

The rate of increase in CMV load correlates with CMV disease
(0.33 log10 vs 0.19 log10 genomes/mL daily, p<0.001)

Emery et al; Lancet 2000
Effects on antiviral therapy on viral load

![Graph showing Log₁₀ decrease in viral load over days of antiviral therapy.](image)

Mattes et al JID 2005
## Response to therapy and CMV disease

### Analysis of first course response

<table>
<thead>
<tr>
<th>Patients</th>
<th>Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>w/o CMV disease</td>
<td>0.7 log/decrease/week</td>
</tr>
<tr>
<td>who developed CMV disease</td>
<td>0.4 log/decrease/week</td>
</tr>
</tbody>
</table>

### Multivariate analysis

<table>
<thead>
<tr>
<th>Event</th>
<th>RR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quick decrease in viral load</td>
<td>0.08 (0.01-0.8)</td>
<td>.03</td>
</tr>
<tr>
<td>Acute GVHD II-IV</td>
<td>11.2 (1.2-73)</td>
<td>.009</td>
</tr>
</tbody>
</table>

Ljungman et al. Haematologica 2006
Requirements and questions for preemptive studies

- Can an antiviral effect be used as primary endpoint?
- What about CMV disease in this setting?
- What should a new drug be compared to?
  - Iv GCV? Valganciclovir? Local standard?
What endpoints would I then like to see?

- Quick and reproducible reduction in viral load when antiviral therapy is introduced
- Safety is important should be better than today’s drugs
- No increase in the risk for CMV disease
- Comparator?
Management of repeated CMV replication episodes

- More common in high risk patients
- Concomitant problems such as GVHD are common
- Associated with poor T-cell control of CMV
- Frequently poor activity/tolerability of existing antiviral drugs
- Clinical/viral resistance
- Unmet medical need
Immunological monitoring might add important information for management.

Treatment of refractory patients

6 treated patients
6 CMV disease
Median 4 prev. agents
4 proven resistant

4 cleared virus
5 survived
1 developed resist.

Avery et al; TID 2010
What endpoints would I then like to see?

- Quick and reproducible reduction in viral load when antiviral therapy is introduced
- Low risk for progression to disease
- Low risk for development of resistance
- Compared to what?
- How to deal with innovative approaches? T-cells
Thank you for your attention!