Viral Kinetic Correlates of Cytomegalovirus Disease and Death after Hematopoietic Cell Transplant

Michael Boeckh, MD
Head, Infectious Disease Sciences Program
Vaccine and Infectious Disease & Clinical Research Divisions
Fred Hutchinson Cancer Research Center
Professor, Department of Medicine
University of Washington
Seattle, Washington
Impact of CMV Seropositivity

Kaplan-Meier Plot of Overall Survival by 3 Years
Transplant Year 2007-2013 (N=1383)
CMV Viral Load as Surrogate

- The surrogate endpoint has to be in the direct pathway of the disease pathogenesis (Fleming et al. 1996).
  - Does CMV viremia predict CMV disease?
  - Does the absence of CMV viremia predict absence of disease?
  - Does viral load, or viral kinetics, predict disease?
  - Does CMV viremia predict mortality or other important clinical endpoints?

- Evidence
  - Observational studies
  - Metaanalyses
  - Randomized placebo controlled trials
Association of Maximum CMV Viral Load before Day 100 with Overall and Non-relapse mortality after Day 100

Green ML et al., Lancet Haematology, 2016
EARLY TREATMENT WITH GANCICLOVIR TO PREVENT CYTOMEGALOVIRUS DISEASE AFTER ALLOGENEIC BONE MARROW TRANSPLANTATION

JAMES M. Goodrich, Ph.D., M.D., Motomi Mori, Ph.D., Curt A. Gleaves, M.S., Charles Du Mond, Ph.D., Monica Cays, R.N., Darlene F. Ebeling, M.S., William C. Buhles, Ph.D., Bernadette DeArmond, M.D., M.P.H., and Joel D. Meyers, M.D.*

N = 281 screened
Weekly blood, urine, throat cxs

GCV
N = 37

0 7 14 21 + cx

BMT

N = 35

Placebo

Vol. 325  No. 23  Dec. 5, 1991
281 Patients provided informed consent and were assessed for eligibility

209 were excluded
87 had no positive CMV cultures
67 died, relapsed, or were discharged early
18 had a positive culture coincident with CMV disease
17 had CMV disease without a positive culture
20 declined participation

72 underwent randomization

37 were assigned to receive ganciclovir
35 were assigned to receive placebo

<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>GANCICLOVIR</th>
<th>PLACEBO</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>37</td>
<td>35</td>
</tr>
<tr>
<td>Age – mean yr (range)</td>
<td>33 (2-56)</td>
<td>31 (3-51)</td>
</tr>
<tr>
<td>Sex – F/M*</td>
<td>20/17</td>
<td>15/20</td>
</tr>
<tr>
<td>Underlying disease – no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute lymphocytic leukemia</td>
<td>4 (11)†</td>
<td>7 (20)</td>
</tr>
<tr>
<td>Acute nonlymphocytic leukemia</td>
<td>16 (43)</td>
<td>11 (31)</td>
</tr>
<tr>
<td>Chronic myelogenous leukemia</td>
<td>11 (30)</td>
<td>11 (31)</td>
</tr>
<tr>
<td>Hodgkin’s disease</td>
<td>1 (3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Non-Hodgkins lymphoma</td>
<td>2 (5)</td>
<td>4 (11)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (8)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>HLA matching – no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient matched with related donor</td>
<td>21 (57)</td>
<td>28 (80)**</td>
</tr>
<tr>
<td>Patient matched with unrelated donor</td>
<td>5 (14)</td>
<td>4 (11)</td>
</tr>
<tr>
<td>Patient mismatched with donor</td>
<td>11 (30)</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Acute GVHD – no. (%)‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>24 (65)§</td>
<td>24 (69)</td>
</tr>
<tr>
<td>Not present</td>
<td>13 (35)</td>
<td>11 (31)</td>
</tr>
<tr>
<td>CMV status before transplantation – no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient negative, donor positive</td>
<td>3 (8)¶</td>
<td>3 (9)¥</td>
</tr>
<tr>
<td>Patient positive, donor negative</td>
<td>15 (41)</td>
<td>13 (37)</td>
</tr>
<tr>
<td>Patient and donor positive</td>
<td>19 (51)</td>
<td>19 (54)</td>
</tr>
<tr>
<td>Days from transplantation to study entry – mean (range)</td>
<td>54 (18-79)</td>
<td>48 (16-77)</td>
</tr>
</tbody>
</table>
CMV Disease

![Graph showing cumulative incidence of CMV disease over days after transplant for Placebo (n=35) and Ganciclovir (n=37). The graph indicates a statistically significant difference at 100 days (p < 0.001) and 180 days (p = 0.004).]
CMV Disease
CMV Disease

Cumulative Incidence of CMV Disease

- Placebo, n = 35
- Ganciclovir, n = 37

- 10 years, p = 0.02
- 20 years, p = 0.01
- 3 years, p = 0.02
- 1 year, p = 0.02
- 180 days, p = 0.004
- 100 days, p < 0.001
Mortality
Mortality

![Graphs showing mortality rates over time post-transplant.]

- **Days after Transplant**:
  - Placebo, n = 35
  - Ganciclovir, n = 37
  - Key points:
    - 100 days, p = 0.04
    - 180 days, p = 0.03

- **Years after Transplant**:
  - Placebo, n = 35
  - Ganciclovir, n = 37
  - Key points:
    - 100 days, p = 0.04
    - 180 days, p = 0.03
    - 1 year, p = 0.01
    - 3 years, p = 0.04
Mortality

- Placebo, n = 35
- Ganciclovir, n = 37

Overall Mortality

- 1 yr, p=0.01
- 3 yr, p=0.04
- 5 yr, p=0.09
- 10 yr, p=0.06
- 180 days, p=0.03
- 100 days, p=0.04

Years after Transplant

- 20 yr, p=0.11
CMV Disease or Death

- Placebo, n = 35
- Ganciclovir, n = 37

180 days, p = 0.004
100 days, p < 0.001
CMV Disease or Death

**Days after Transplant**

- Placebo, n = 35
- Ganciclovir, n = 37

- 180 days, p = 0.004
- 100 days, p < 0.001

**Years after Transplant**

- Placebo, n = 35
- Ganciclovir, n = 37

- 20 years, p = 0.02
- 10 years, p = 0.01
- 3 years, p = 0.01
- 1 year, p = 0.006
- 180 days, p = 0.004
- 100 days, p < 0.001
Viral Load
Viral Load Kinetics

Ganciclovir

Placebo
Kinetics Parameters

- **Peak**
- **Duration**
- **Area Under the Curve**
- **Slope**
- **Δ VL**
- **Δ Days**
- **“Highest” VL**
- **“Most Recent” VL**
- **Duration**
CMV Kinetics Post Randomization

![Boxplot showing CMV kinetics post randomization. The graph compares mean, peak, duration, and area-under-the-curve for different groups.](image)
CMV Kinetics Pre Randomization

Mean VL: p = 0.33
Peak VL: p = 0.22
Duration: p = 0.23
Area-under-curve: p = 0.15

Log CMV (cp/mL), Weeks, or Log CMV (cp/mL)*days

Treatment Group
- Placebo
- Ganciclovir

No Disease Disease
No Disease Disease
No Disease Disease
No Disease Disease
## Viral Load and CMV Disease

Associations between post-randomization CMV kinetics and CMV disease 180 days post-transplant (adjusted for aGVHD, donor CMV serostatus, treatment group).

<table>
<thead>
<tr>
<th>Viral Kinetic Marker</th>
<th>HR (CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most recent VL (for each log increase)</td>
<td>1.5 (1.1,2)</td>
<td>0.004</td>
</tr>
<tr>
<td>Highest VL (for each log increase)</td>
<td>1.7 (1.2,2.3)</td>
<td>0.002</td>
</tr>
<tr>
<td>Duration of viremia (for each week increase)</td>
<td>1.2 (0.9,1.5)</td>
<td>0.23</td>
</tr>
<tr>
<td>Duration of viremia (for each 25% increase)</td>
<td>1.7 (1.1,2.4)</td>
<td>0.008</td>
</tr>
<tr>
<td>Slope (for each log/d increase)</td>
<td>5.9 (1.3,26)</td>
<td>0.02</td>
</tr>
<tr>
<td>AUC (for each log AUC increase)</td>
<td>1.7 (1.2,2.3)</td>
<td>0.002</td>
</tr>
</tbody>
</table>
Prentice criterion 1: Associations between ganciclovir and clinical outcome

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMV disease day 100</td>
<td>0.1</td>
<td>0-0.5</td>
<td>0.003</td>
</tr>
<tr>
<td>CMV disease day 180</td>
<td>0.3</td>
<td>0.1-0.7</td>
<td>0.008</td>
</tr>
<tr>
<td>CMV disease or death day 100</td>
<td>0.2</td>
<td>0-0.5</td>
<td>0.004</td>
</tr>
<tr>
<td>CMV disease or death day 180</td>
<td>0.3</td>
<td>0.1-0.7</td>
<td>0.005</td>
</tr>
</tbody>
</table>
Prentice criterion 2: Associations between viral load post-randomization and outcome

Most recent viral load first event of CMV disease or death 100 days post-transplant

<table>
<thead>
<tr>
<th>Model</th>
<th>Predictor variable</th>
<th>HR (CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo group with VL predictor only</td>
<td>VL</td>
<td>1.7(1.2,2.5)</td>
<td>0.004</td>
</tr>
<tr>
<td>Both treatment groups with GCV predictor only</td>
<td>GCV</td>
<td>0.2(0.1,0.5)</td>
<td>0.004</td>
</tr>
<tr>
<td>Both treatment groups with VL and GCV predictors</td>
<td>VL</td>
<td>1.5(1.1,2)</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td>GCV</td>
<td>0.2(0.1,0.9)</td>
<td>0.03</td>
</tr>
<tr>
<td>Both treatment groups with VL/GCV interaction</td>
<td>Interaction</td>
<td>0.7(0.4,1.3)</td>
<td>0.22</td>
</tr>
</tbody>
</table>
Prentice criterion 3: Association between the Surrogate Endpoint and the Clinical Outcome be the same in the Treatment and Placebo Group

1. Model: association between each viral kinetic and the clinical outcome adjusted for treatment group.

2. Model: interaction between ganciclovir and the proposed viral load surrogates.
Association between each viral kinetic and the clinical outcome adjusted for treatment group

- All except duration in weeks were associated with both clinical outcomes at day 100 and day 180.
- However, treatment group was also significantly associated with clinical outcomes except most recent viral load and
  - CMV disease at day 180 (HR 0.4, 95% CI 0.1-1.0, p = 0.06) and
  - CMV disease or death at day 180 (HR 0.4, 95% CI 0.2-1.0, p = 0.05).
- This finding supports Prentice criterion 2 (proposed surrogates are correlated with clinical outcomes in both treatment groups)
- However, the fact that ganciclovir’s association remained significant despite adjustment for viral load kinetics suggests that ganciclovir’s effect on clinical outcomes may not be entirely mediated by viral load kinetics.
Interaction between Ganciclovir and the Proposed Viral Load Surrogates

• Would imply that the degree of association between viral load and clinical outcomes may be different depending on treatment group.

• We found evidence for significant interactions
  – between most recent viral load and CMV disease at 180 days
  – between slope and CMV disease at 180 days
  – between slope and first event of CMV disease or death at days 100 and 180

• However, we found no evidence for interactions
  – in highest viral load
  – percentage of days with viremia
  – area-under-the-curve
Summary

• Viral load suppression in this randomized placebo controlled trial correlates with improved clinical outcomes.

• Our data provides strong support for viral load kinetics (aside from duration of viremia) as surrogate endpoints in terms of Prentice criteria 1 and 2.

• However, our findings provided only partial support for fulfillment of Prentice criterion 3.
Discussion

• Different cell source, treatment later than in modern cohorts (also a strength for the study)

• Small number of disease events in the treatment group
  – Data support but are not robust enough to support a formal surrogate endpoint analysis

• CMV viral load does not appear to be a full surrogate due to localized tissue disease kinetics not correlating completely with plasma viral load dynamics
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