2nd European Conference on Infections in Leukemia

Recommendations for CMV management in patients with hematological diseases

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ELN European LeukemiaNet

EBMT

EORTC European Organisation for Research and Treatment of Cancer

ICHS International Conference on Infections in Immunocompromised Host Society

Definitions

- **Primary CMV infection**
  CMV occurring in a previously CMV seronegative patient
- **Recurrent CMV infection**
  CMV detected in a seropositive patient
- **Symptomatic CMV infection**
  Patients developing symptoms (fever with or without bone marrow suppression) and who have either CMV virions, antigens, or nucleic acid detectable and who have no sign of CMV endorgan disease
- **CMV disease**
  CMV detected from an organ by biopsy or other invasive procedure (BAL, CSF) with a test with appropriate sensitivity and specificity together with symptoms and/or signs from the affected organ. For CMV retinitis, typical findings by ophthalmologic examination are sufficient.
- **Prophylaxis**
  Antiviral agents given to a patient either to prevent a primary CMV infection or a CMV reactivation
- **Preemptive therapy**
  Antiviral agents given to an asymptomatic patient with CMV detected by a screening assay

Randomized studies

- Only published studies with two exceptions

- Allo SCT (n=27)
  - Diagnostic/strategy studies 3
  - Immune globulin studies 7
  - Blood product studies 4
  - Prophylactic antiviral studies 8
  - Preemptive therapy studies 5

- Other patient groups (n=1)
  - Prophylactic studies 1

Other prospective studies
(published with one exception)

- Allo SCT (n=44)
  - Prophylaxis 10
  - Strategy 1
  - Treatment 15
  - Preemptive 13
  - Blood products 3
  - Immune globulin/Mab 2
- Other patients (n=3)
  - Prophylactic 2
  - Treatment 1

Diagnosis of CMV infection

DIAGNOSIS OF CMV INFECTION TECHNIQUES

- The CMV antigenemia assay or techniques detecting CMV DNA or RNA are recommended for diagnosis of CMV infection in peripheral blood (AI).

- Use of a quantitative assay gives additional information valuable for patient management (BII)

Diagnosis of CMV disease

Diagnosis of CMV disease

- The diagnosis of CMV disease must be based on symptoms and signs consistent with CMV disease together with detection of CMV by an appropriate method applied to a specimen from the involved tissue (AII).

- Symptoms of organ involvement together with CMV detection in blood are not enough for diagnosis of CMV disease. There are several possible techniques that can be used for detection of CMV in tissue specimens and each transplant centre should collaborate closely with a good diagnostic virology and histopathological laboratory (AII).

- PCR is usually not appropriate for documentation of CMV disease in tissue specimens since the positive predictive value is too low (BII).

Prevention of primary CMV infection

Allogeneic stem cell transplantation

- Stem cell transplant patients should be tested before SCT for CMV antibodies (AI)
- Stem cell transplant donors should be tested for CMV antibodies (AI)
- If a patient is found to be seronegative, a CMV seronegative donor should be used if possible (AI)
- CMV seronegative allogeneic stem cell transplant patients with CMV seronegative donors (AI) should receive leukocyte depleted or CMV seronegative blood products only.
- If leukocyte depleted blood products are used, the products should contain < 5 x 10^6 residual leukocytes / unit (AII)
- Immune globulin for prevention of CMV infection or disease is not recommended (EII)

Patients with hematological malignancies including autologous SCT recipients

- Patients who might receive alemtuzumab or in whom allogeneic SCT can be envisaged should be tested for CMV antibodies (BII)

- CMV seronegative patients receiving T-cell suppressive therapy should receive leukocyte depleted or CMV seronegative blood products only (BIII)

- CMV seronegative autologous SCT patients should receive leukocyte depleted or CMV seronegative blood products only (BII).

- Immune globulin for prevention of CMV infection or disease is not recommended. (EIII)

Other recommendations – Allo SCT patients

- All patients with CMV disease before HSCT, should be considered as very high risk patients for CMV disease after SCT. If possible, the transplant should be delayed to allow for appropriate treatment duration before SCT (BIII).

- In patients with CMV disease before SCT, use of secondary anti-CMV prophylaxis during SCT could be considered (BIII)

- Such patients should be closely monitored during the SCT procedure and a low threshold for preemptive treatment used (CIII)

- If a patient is CMV seropositive, to select a graft from a CMV seropositive unrelated or mismatched donor should be considered (BII)

Prevention of CMV disease

Prevention of disease

- The prevention of CMV disease is still of major importance in allogeneic SCT patients since the outcome in established disease is still poor

- The prevention of CMV disease in other patients is an important aim for those who might receive an allogeneic HSCT in the future since this has an impact on outcome of the allogeneic SCT

- In other patients, early detection and treatment of symptomatic CMV infection is important

Allogeneic SCT patients

- All allogeneic SCT patients, regardless of whether or not they receive CMV prophylaxis, should be monitored for CMV in peripheral blood at least weekly with either the CMV antigenaemia assay or a technique for detection of either CMV DNA or RNA (AI).

- The duration of monitoring should be at least 100 days (BII).

- Longer monitoring is recommended in patients with acute or chronic GVHD, those having experienced an earlier CMV reactivation, and in patients having undergone mismatched or unrelated donor transplantation (BII).

Preemptive therapy – Allo SCT

- Pre-emptive antiviral therapy based on detection of CMV antigen or nucleic acid is effective for prevention of CMV disease in allogeneic SCT patients (AI).
- Either intravenous ganciclovir or foscarnet can be used for first line pre-emptive therapy (AI).
- The choice depends on the risk of toxicity and which antiviral drugs have been used previously (BIII).
- Valganciclovir has been used only in small studies and might be used in place of intravenous agents especially in low-risk patients (CIII).

Failure regimens

Second and third line preemptive therapy

- The alternate drug of ganciclovir or foscarnet can be considered for second line pre-emptive therapy (AI)
- Cidofovir can be considered for second line pre-emptive therapy (3-5 mg/kg) but careful monitoring of the renal function is required (BII).
- The combination of ganciclovir and foscarnet might be considered for second line pre-emptive therapy (CII)
- Other therapeutic options in patients with multi-resistant CMV are leflunomide and artesunate. The experience with these agents are, however, very limited

Patients receiving alemtuzumab

- A CMV management strategy must be put in place for patients treated with alemtuzumab (BIII)

- Monitoring and antiviral treatment of patients having a positive test for CMV and symptoms compatible with a CMV infection is one management option in patients receiving alemtuzumab (BII).

- In these patients a regular monitoring with antigenemia or PCR is recommended during the period of maximum immunosuppression (during treatment and until 2 months after the end). (BII)

* Treating asymptomatic patients is not obligatory but careful clinical observation of patients with documented CMV reactivation is necessary (BII)
- Withholding alemtuzumab is not considered necessary, unless there are persisting symptoms (BIII).

Other hematology patients

- High-risk autologous SCT patients might potentially benefit from monitoring and the use of preemptive therapy (CII).
- Routine monitoring and preemptive therapy is not considered necessary in other hematology patients (DIII).
- CMV should be considered in patients receiving T-cell suppressive therapy and in CMV seronegative patients who receive stimulated granulocyte transfusions from unscreened donors if they develop symptoms compatible with CMV (unexplained fever, drop in blood counts, lung infiltrates, or gastrointestinal symptoms)(BII).

Anti-CMV prophylaxis

CMV prophylaxis – Allo SCT

- Intravenous ganciclovir prophylaxis is an effective strategy for prevention of CMV disease and could be used in sub-groups of allogeneic SCT patients at high risk for CMV disease (BI).

- Acyclovir or valacyclovir can be used as prophylaxis against CMV in allogeneic stem cell transplant patients (BI). However, their use must be combined with monitoring and use of pre-emptive therapy (AI)

- Immune globulin has today no role as prophylaxis against CMV infection (EII)

CMV prophylaxis – patients treated with alemtuzumab

- Valganciclovir prophylaxis is effective and reduces the risk of symptomatic CMV infection in patients treated with alemtuzumab (BII)

- However, the side effect profile is still unclear as is the risk/benefit compared to the strategy of treating when a symptomatic CMV infection develops (CII)

CMV prophylaxis patients with other hematological malignancies

- Routine antiviral prophylaxis is not recommended (DIII)

Treatment of symptomatic infections

- Allogeneic SCT patients (AI) and patients treated with alemtuzumab (AII) should be given antiviral therapy
- The benefit in other patient groups is lower but antiviral therapy could be considered (CIII)
- Patients with suspected organ involvement of CMV should undergo appropriate diagnostic procedures (BIII)
- The choice of antiviral agent will depend on the individual patient, the risk for progression to CMV disease, and the risk for side effects of the chosen drug.
  - In allogeneic SCT patients i.v. ganciclovir or foscarnet, are first line agents (BII)
  - In other patients such as patients treated with alemtuzumab in addition also valganciclovir may be considered (BIII)

Treatment of CMV disease

Treatment of CMV pneumonia

- Antiviral therapy with ganciclovir is recommended (AII).
- Foscarnet might be used in place of ganciclovir (AIII)
- The addition of immune globulin to antiviral therapy should be considered (CII)
- Cidofovir or the combination of foscarnet and ganciclovir can be used as 2nd line therapy (BII).

Treatment of other types of CMV disease

- For other types of CMV disease and in other patient groups either intravenous ganciclovir or foscarnet given without addition of immune globulin is recommended (BII).

- Cidofovir or the combination of intravenous ganciclovir and foscarnet can be used as second line therapy of CMV disease (BII).

Testing for antiviral resistance

- Rising antigenemia or CMV DNA early after initiation (1-2 weeks) is usually not a sign of virological failure
- Where possible, resistance testing should be performed to allow selection of the correct second line antiviral therapy (BIII).
- If the turn-around time for resistance testing is prolonged, then a change of treatment for a patient with rising viral load or worsening disease in the face of adequate treatment could precede receipt of the test result (BII).

Other recommendations

Other topics

Immunological monitoring after SCT might yield important information for patient management although no standard test exists (CII)

Immunological interventions by infusion of CMV specific lymphocytes or dendritic cell vaccination are interesting options and should undergo controlled prospective clinical trials (CII)

Recommendations for HHV-6 management in patients with haematological disease

HHV-6 Natural History

- **Variant A (HHV-6A)** — **Unknown disease**
- **Variant B (HHV-6B)**
  - **1^0 infection in 1^{st} two years of life** — **Exanthem subitum**
  - **Recurrent infection post-HSCT** — **Encephalitis**, **Delayed engraftment**

Chromosomally integrated HHV-6 (CIHHV-6)

- **HHV-6A or B (about 75% B)**
- **Prevalence about 1%**

  Leong, 2007; Tanaka-Taya, 2004
- **Vertical transmission**

  Inherited from mother or father

  Daibata, 98, 99, Tanaka-Taya, 2004

  ≥ 1 copy/leucocyte & hair follicles

  Ward et al., 2006
- **Characteristic persistent high HHV-6 DNA**

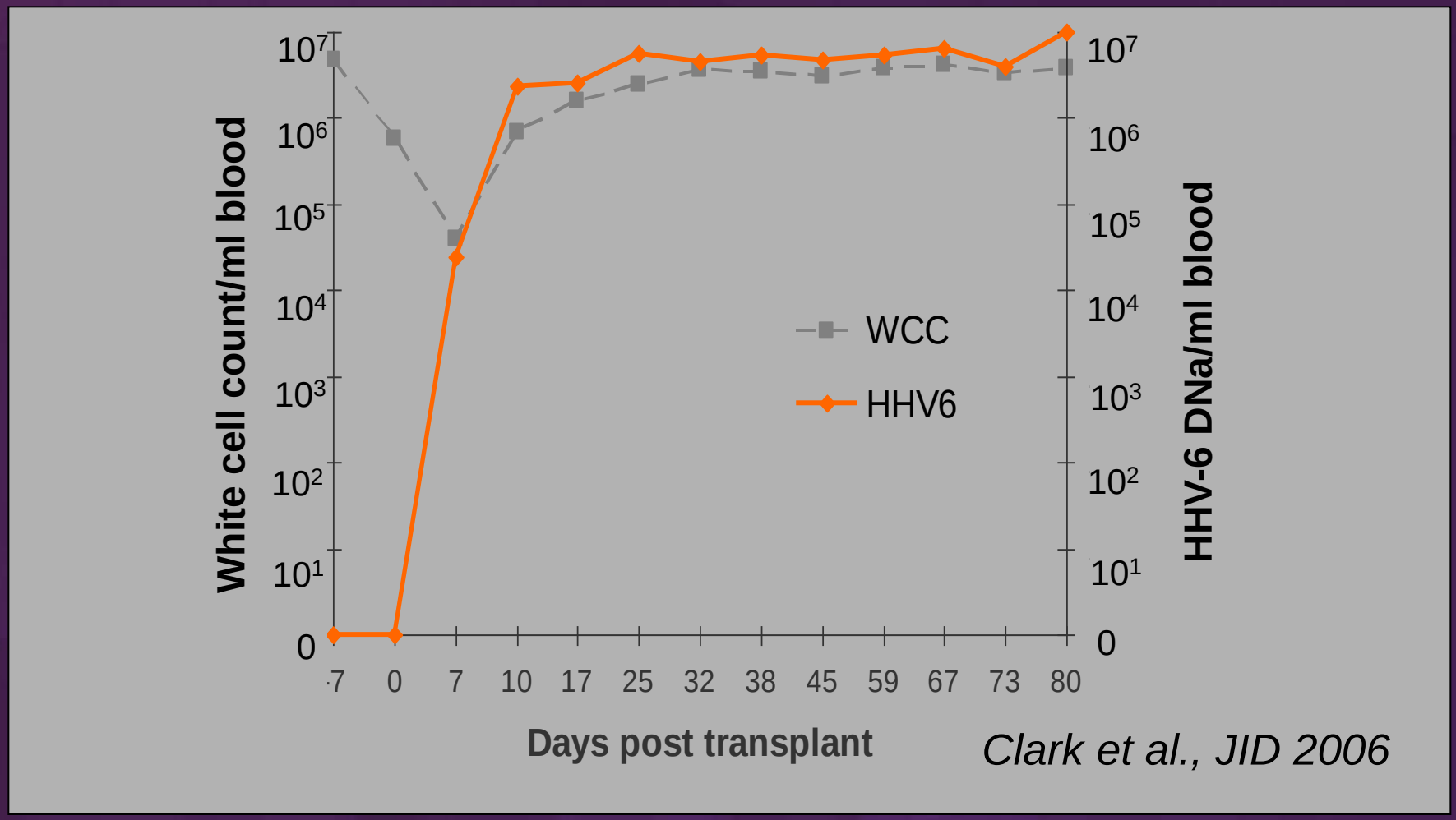
  7.0 (log_{10} copies/ml) whole blood

  5.3 (log_{10} copies/ml) serum

  No evidence of active infection

  No virological response to GCV, foscarnet, cidofovir

Transmission CI HHV-6 DNA after HSCT



Clark et al., JID 2006

Definitions (1)

- ***1^0 infection:*** HHV-6 or HHV-6 antibodies in a previously seronegative individual.

  Note 1 – antibodies to HHV-6A and B indistinguishable

  Note 2 – difficult to interpret in older children & adults

- ***CIHHV-6:*** characteristic & persistent high HHV-6 DNA in whole blood or serum

Diagnosis of HHV-6 infection

Diagnosis of HHV-6 infection Techniques

- **Quantitative PCR for HHV-6A and B DNA in whole blood, plasma or serum (BII)**
  - ***Note* – CI HHV-6 should be excluded (BIII)**

Diagnosis of HHV-6 disease

Diagnosis (2)

- ***HHV-6 encephalitis:*** **varying symptoms often with MRI changes in the hippocampus or diffuse EEG changes and HHV-6 DNA in CSF (II)**

- ***HHV-6 bone marrow suppression:*** **delayed engraftment together with HHV-6 DNA in blood (III)**

Note **– in both cases be aware of CI HHV-6**

Diagnosis (3)

- If other organ disease is suspected it is recommended to test for HHV-6 infection in tissue – there are several possible techniques although these are not generally available (CIII)

- PCR on tissue is not recommended for documentation of HHV-6 disease since its sensitivity is too high (DIII)

Anti-HHV-6 prophylaxis

- Not recommended after HSCT (EIII)
- Not recommended in other patients (EIII)

Treatment of HHV-6 disease

Treatment of HHV-6 encephalitis

Despite the lack of controlled data

- **Foscarnet (60 mg/kg x 3) or ganciclovir are recommended as first line (BII)**
- **Cidofovir is recommended as second line (CIII)**

HHV-7

1^0 infection in 1^{st} five years of life - Exanthem subitum

Recurrent infection post-HSCT - common but not associated with disease

Therefore no recommendations can be made

Recommendations for Kaposi's sarcoma-associated herpesvirus (KSHV or HHV-8) management in patients with haematological disease

Transmission

- **Sexual – prevalence high in homosexual & bisexual men**
- **Non-sexual – in areas of high endemicity, probably via saliva**
- **Iatrogenic – blood transfusion & organ donation**

KSHV & disease

- Little information re HSCT & KS –likely depends on local prevalence
- Fever & marrow aplasia with plasmocytosis after HSCT

Epidemiology - prevalence

Prevalence KSHV Ab (%)/KS	Region	Risk groups
0-5/low	North America Northern Europe East Asia	Homosexual men Tx recipients
5-20/ intermediate	Mediterranean Middle East Caribbean	Homosexual men Tx recipients Older adults
>50/high	Africa	Children Older adults

Diagnosis of KSHV infection

Diagnosis of KSHV infection

- There are currently no generally accepted diagnostic techniques
- Quantitative for KSHV DNA in whole blood, plasma or serum
- Antibody tests (if available) are of variable sensitivity & specificity

KSHV disease

- **Knowledge of risk factors & local seroprevalence should be kept in mind (BIII)**

Diagnosis of Kaposi's sarcoma (1)

- Clinically-defined on the basis of characteristic skin lesions
- Histopathologically-defined on the basis of a malignant tumour in an immunocompromised patient and confirmed by immunostaining for KSHV

Diagnosis of Kaposi's sarcoma (2)

- KSHV detection in blood may assist with diagnosis where KS is suspected and the site of the tumour is inaccessible and biopsy not available (BIII)

Anti-KSHV prophylaxis

- Antibody testing pre-HSCT to predict risk not recommended (DIII)
- Not recommended after HSCT (DIII)
- Not recommended in other patients (DIII)