UPDATE ECIL-4 2011

Recommendations for CMV and HHV-6 management in patients with hematological diseases

Per Ljungman, Rafael de la Camara, Hermann Einsele, Dan Engelhard, Pierre Reusser, Jan Styczynski, Kate Ward

4th European Conference on Infections in Leukaemia

Diagnosis of CMV infection

DIAGNOSIS OF CMV INFECTION TECHNIQUES

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

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 (BIII).

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 should receive leukocyte depleted (AI) or CMV seronegative blood products (AI) 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 primary CMV infection is not recommended (BI)

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

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 (BIII)
- 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

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, quantitative PCR or a technique for detection of CMV RNA
- Cut-off levels for introduction of pre-emptive therapy should be adapted according to the PCR assay and the transplant modality
- The duration of monitoring should be at least 100 days (BIII).
- Longer monitoring is recommended in patients with acute or chronic GVHD, those having experienced an earlier CMV reactivation, and in patients having undergone mismatched, cord blood, haploidentical 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 might be used in place of intravenous agents (except in patients with severe intestinal GvHD) especially in low-risk patients (BII), solid data concerning toxicity of the drug in the preemptive setting are still lacking, esp. in patients with low bodyweight or renal dysfunction

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)
- Maribavir (BII), leflunomide (BII), and artesunate (CIII) are possible third line options for preemptive therapy in patients resistant or intolerant to other antiviral agents

Patients receiving alemtuzumab

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

CMV prophylaxis – patients treated with alemtuzumab

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

- However, the risk/benefit ratio compared to the strategy of treating when a symptomatic CMV infection develops is still undetermined

CMV prophylaxis patients with other hematological malignancies

- Routine antiviral prophylaxis is not recommended (AIII)

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 (AIII)
- 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 topics

Other topics and future developments

Immunological monitoring after SCT yields important information for patient management although no standard test exists

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

New anti-CMV drugs (CMX 001 and AIC246) and CMV vaccines based on gB and DNA plasmids are in clinical development

Recommendations for HHV-6 management in patients with haematological disease

Encephalitis

- Uncommon 1-2% in some series
- Usually 1-2 months post-Tx
- Apparently more common after cord blood or HLA-mismatched graft
- Clinical picture includes short-term memory loss, seizures, hyponatraemia, CSF pleocytosis, and abnormalities in the medial temporal lobe on MRI

Wang, CID 1999; Zerr J Clin Virol, 2006; Seeley, 2008,

HHV-6 Natural History

- **HHV-6A** — **? disease**
- **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

- **HHV-6A or B (about 75% B)**
- **Prevalence about 1%** *Leong, 2007; Tanaka-Taya, 2004*
- **Vertical transmission**

  Inherited from mother or father

  Daibata, 1998,1999, Tanaka-Taya, 2004

  ≥ 1 copy/leucocyte, hair follicle cells, nail cells & in cells of any other tissue tested *Ward et al., 2006; Hubacek, 2009; Hubacek, 2009; Hubacek, 2009*
- **Characteristic persistent high HHV-6 DNA level**

  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**

UPDATE ECIL-3 2009

CIHHV-6 & HSCT

HHV-6	Horizontally acquired	CIHHV-6 R-/D+ *Clark 2006*	CIHHV-6 R+/D- *Hubacek 2007*
≥ 1 copy/wbc	No	Yes	No
≥ 1 copy/hair follicle or nail cell	No	No	Yes
≥ 1 copy/non haematopoietic tissue cell	No	No	Yes
Persisting DNA blood	No	++++	+/-
Disease	Encephalitis Engraft delayed	No?	No?
Response antiviral drugs	Yes	No	No

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

- ***HHV-6 infection:*** HHV-6 DNA in plasma or serum but need to exclude CIHHV-6

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* (AII)

Note – CI HHV-6 should be excluded (AIII)

* Expressed as genome equivalents/cell

Diagnosis of HHV-6 disease

Diagnosis (2)

- ***HHV-6 encephalitis:*** *typically limbic encephalitis but possibly various other symptoms with MRI abnormalities or diffuse EEG changes* and HHV-6 DNA in CSF (BII)

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

Note – in both cases exclude (be aware of ??) CI HHV-6

Diagnosis (3)

- If 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 specificity is too low (AIII)

  * However if HHV-6 DNA expressed as genome equivalents/cell CI HHV-6 can be diagnosed

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