CMV UPDATE

FINAL SLIDE SET

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Grading system

(According to ESCMID)

Strength of a recommendation		
Grade A	ECIL	strongly supports a recommendation for use
Grade B		moderately supports a recommendation for use
Grade C		marginally supports a recommendation for use
Grade D		supports a recommendation against use
Quality of Evidence		
Level I		Evidence from at least one properly designed randomized, controlled trial
Level II*		Evidence from at least one well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 centre); from multiple time series; or from dramatic results of uncontrolled experiments
Level III		Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies, or reports of expert committees

*Added index:

$_r$: Meta-analysis or systematic review of randomized controlled trials.

$_t$: Transferred evidence, that is, results from different patients' cohorts, or similar immune-status situation.

$_h$: Comparator group is a historical control.

$_u$: Uncontrolled trial.

$_a$: Published abstract (presented at an international symposium or meeting).

CMV Epidemiology

- **Infection and serology**
  - Incidence of viremia, as expected, remains unchanged since the introduction of the preemptive therapy
  - CMV-seropositive patients still have a poorer outcome than CMV-seronegative
  - Negative effect of CMV seronegative donors for CMV seropositive patients
    In the largest and latest study of the Infectious Diseases Working Party of the EBMT, a negative effect of CMV seronegative donors on OS for seropositive patients was demonstrated only in unrelated HSCT with myeloablative conditioning

CMV Epidemiology

Trends in allogeneic transplantation: an increase in patients at risk of CMV complications

- Increase in the percentage of CMV seropositive patients
  - Increase in the patients' age (now, 30% of allogeneic SCT are ≥ 60 years at transplant)
  - Increasing HSCT activity in parts of the world that previously have a low rate of activity. This is the case of Latin America for example, where the CMV seroprevalence of the population is higher than in Europe and North America

- Increase in the proportion of CMV seronegative donors due to the increasing use of unrelated donors, that usually are young and frequently CMV seronegative

- As consequence: an increase of SCT of CMV positive patients with a negative donor

CMV and relapse

A highly controversial issue

- CMV (positive serology or infection) has been associated with a decrease in leukemic relapses after HSCT, particularly in AML and CML, but to a lesser extent in MDS, ALL and NHL patients.
- It is not a new finding; it was first reported by Lönnqvist et al in 1986
- In 2011 a study by Elmaagacli et al reactivated the interest on the role of CMV in decreasing relapses after SCT, defining this association as “virus-versus-leukemia” effect
- There are more than 30 studies that have evaluated the role of CMV in relapse. They can be summarized as follows:
    - Usually multicentric studies do not find a protective effect of CMV on relapse, being unicentric studies those who find it
    - In the 5 largest studies, with more than 96,000 patients, no effect of CMV (serology or infection) on relapse was found
    - There even are several studies that shown the opposite effect: a higher risk of leukemic relapse with CMV infection /seropositivity

CMV and relapse

Strategies with the aim of obtaining more infection (higher rate or higher viral load) in order to reduce leukemic relapse is NOT recommended (DIIu)

Epidemiology of CMV in haploidentical HSCT

- Haploidentical HSCT is rapidly increasing using different techniques.

- Literature review : non T-cell depleted haplo-HSCT with post-transplant cyclophosphamide (PT-Cy):
  - 25 papers
  - 22 abstracts
  - 3 reviews

Haplo HSCT - Infection, disease and resistance

The outcome of CMV seronegative patients after non-T-cell depleted haplo-HSCT with PTCy appears to be better than CMV seropositive ones (evidence level III) *

The incidence of CMV infection and CMV disease is variable (infection: 31-76%, disease: 0-17%) among the reported series of non-T-cell depleted haplo-HSCT with PTCy (II) and comparative studies do not support the existence of significant differences with respect to matched-related and unrelated donors (II)**, or T-cell depleted haplo-HSCT (II)***

Data on resistant cases are scarce, and the frequency reported in one study is 7% (one patient with a M460V mutation of the UL97 gene) ****

***** **Crocchiolo BMT 2016; McCurdy Blood 2015**
****** **Di Stasi BBMT 2014; Baker BBMT 2016**
******* **Tischer Ann Hematol 2015; Dufort BMT 2016; Ciurea BBMT 2012**
******** **Slade TID 2017**

Pre-transplant testing - serology

All patients undergoing HSCT as well as potential donors should be tested for the presence of CMV IgG antibodies close to the time of transplant (AIIu).

The analytical performance of commercially-available serological assays is not equivalent.

The use of highly specific assays should be priorized over those optimized for sensitivity at the expense of specificity (BIII)

Choice of donor – CMV serological status

A CMV seronegative donor should be chosen for a CMV seronegative recipient (AI; haplo AIII).

A CMV seropositive donor should be chosen for a CMV seropositive recipient when possible in the setting of unrelated Allo-HSCT with myeloablative conditioning (BIIu).

Either a CMV seropositive or seronegative donor is suitable for a CMV seropositive recipient undergoing non-T-cell depleted haplo-HSCT with PTCy (BIIu, provisional)

Monitoring

Allogeneic SCT patients should be monitored for CMV in peripheral blood (AIIu)

Quantitative real-time PCR assays are more sensitive than the pp65 antigenemia assay and thus are the primary choice for CMV monitoring (BIIu)

Whole blood and plasma are the preferred specimens for CMV surveillance. Both are equally suitable specimens for CMV DNA load monitoring **.**
CMV DNA loads in whole blood are higher than in plasma specimens.

For a given patient CMV DNA load monitoring should be performed using the same DNA extraction method, Q-RT-PCR assay, and specimen (AIII).

Monitoring

CMV real-time PCR assays should be calibrated to the first WHO standard and CMV DNA load values be reported as International Units (IU)/ml . Recalibration of the different Q-RT-PCR assays (coupled to different DNA extraction methods) to the 1st WHO standard improves interassay agreement, yet, interlaboratory discrepancies in CMV DNA loads produced persist. The use of commercial systems that carry out all assay steps minimizes such discrepancies

Commercially-available real-time PCR methods are preferred over in-house developed method owing to their higher reproducibility. Higher intra- and interassay variabilities have been reported for the latter.

Monitoring

The duration of CMV monitoring should be at least 100 days (BIIu)

CMV monitoring should be performed at least once a week within the first 100 days after transplant (AIIu).

Longer monitoring is recommended in patients with acute or chronic GVHD, those having experienced an earlier CMV reactivation, in patients having undergone mismatched, cord blood, haploidentical (non-post tx cy), or displaying persistent immunodeficiency (AIII)

Monitoring

CMV DNA load cut-off levels for initiation of pre-emptive therapy should be adapted at each center according to the DNA extraction method and real-time PCR used and the transplant modality (AIII)

Pre-emptive antiviral therapy is normally given for at least two weeks and could be discontinued after one or two negative (undetectable) real-time PCR result (BIIu).

The CMV DNA doubling time may be a valuable parameter for interassay and inter-institutional results comparison owing to the linearity of Q-RT-PCR assays above their limit of quantification, with slope coefficients that vary minimally when testing standard calibration panels and its use may be advantageous for therapeutic management of CMV infection.

Immune monitoring

The number or frequency of IFN-γ-producing CMV-specific $CD8^+$ T and CD4+ T cells quantitated in blood determine the risk of a subsequent episode of CMV DNAemia (initial or recurrent). Cut-off cell levels of CMV-specific IFN-γ-producing T cells affording protection from CMV pp65-antigenemia, CMV DNAemia or CMV end-organ disease have been proposed, but lack extensive clinical validation.

There are two commercially available IFN-γ- release assays, one based upon enzyme-linked immunosorbent spot (ELISPOT) technology (Lophius kit T-Track® CMV, Lophius Biosciences, Germany) and the the QuantiFERON CMV assay (QFA; Qiagen).

Only two intervention studies : Avetisyan et al., BMT 2007 and Navarro et al. OFID, 2016.

Sequential monitoring of IFN-γ-producing CMV-specific T cells provides potentially useful information for the management of CMV infection and may be ancillary to CMV DNA load monitoring for individualizing pre-emptive therapy, and for identifying patients at highest risk of developing recurrent CMV infections and end-organ disease (BIIt)

CMV resistance; mutations in the viral genome

- Ganciclovir/valganciclovir: UL 97 (kinase) mutations, UL54 (polymerase) mutations
- Foscarnet: UL54 (polymerase) mutations
- Cidofovir: UL54 mutations
- New drugs (maribavir, letermovir, brincidofovir)

How common is antiviral resistance?

Varies between patient populations

Ganciclovir resistance

0% in a prospective randomized study (Boeckh et al Ann Intern Med 2015)

0% in auto and allo HSCT non-haplo recipients in a large prospective cohort study

9.6% in haploidentical in vitro T-cell depleted allo HSCT recipients (Shmueli et al JID 2013)

Testing for CMV Resistance

- Clinical diagnosis of drug resistance unreliable and need laboratory confirmation

- Phenotypic Assays
  - Drug vs. viral in cell culture (EC50 value)
  - Difficult to standardize, slow to perform
  - Impractical for clinical diagnosis

- Genotypic Assays
  - Detect resistance mutations in relevant genes
  - Rapid (<1 wk), can be done without viral isolate
  - Requires informed interpretation of genotypes, inferred phenotypes, and potential pitfalls

Genotypic Resistance Testing

- Sequencing of relevant genes for resistance mutations
  - UL97, UL54, or other loci for new antivirals
- Nested PCR usually required, 1 – 3 kb templates
  - specimens with viral loads <1000 IU/mL less reliable, may miss lower abundance mutants and introduce artifacts
  - design primers to avoid interstrain sequence variation
- Typical codon ranges, may need future expansion
  - UL97 codons 400-650 (335-708 is better). Most common mutations are M460V, H520Q, C592G, A594V, L595S, C603W
  - UL54 codons 300-1000 (94-1100 is better)
  - UL56 codons 229-370 (for letermovir only)
- Sanger dideoxy sequencing is current standard
  - align output sequences to reference strain (usually AD169)

CMV antiviral resistance

- Definitions
  - Genotypic resistance
  - Phenotypic resistance
  - Clinical resistance (most common)

- It should be recognized that the viral load might be substantially higher if there is a delay of at least 3 days in starting antiviral therapy from the day of the indicator sample. If that is the case, a new sample should be obtained

- There is no consensus on when CMV antiviral resistance should be suspected and testing performed. A working guideline could be:
  - Patients in whom the viral load increase > 1 $\log_{10}$ after at least two weeks appropriate antiviral therapy.
  - Patients in whom the viral load does not decrease > 1 $\log_{10}$ after at least three weeks appropriate antiviral therapy
  - Patients who has CMV disease and whose symptoms worsen after at least 2 weeks appropriate antiviral therapy.

Prophylaxis

Prophylaxis in allogeneic HSCT

- Antiviral drugs
  - Aciclovir/valaciclovir
  - Ganciclovir/valganciclovir
  - Letermovir
  - Maribavir
  - Brincidofovir
- Immuneglobulins (Ig)
- CMV vaccines
  - Phase II studies
  - Phase III ongoing

Prophylaxis in allogeneic HCT; Antiviral drugs

Drug	Grading	References	Comment
Aciclovir	CI	Prentice, *Lancet* 1994 Milano, *Blood 2011*	Less efficient than valaciclovir
Valaciclovir	BI	Ljungman, *Blood* 2002 Winston *CID* 2003 Milano, Blood 2011	Association with preemptive strategy
Ganciclovir/ valganciclovir	CI CIIh	Winston, *Ann Intern Med* 1993 Goodrich , *Ann Intern Med* 1993 Montesinos, *BBMT 2009*	 Cord blood SCT
Foscarnet	DIIu	Ordemann, *Ann Hematol* 2000 Bregante et al, *BMT* 2000	
Letermovir	AI (provisional)	Ljungman, *EBMT 2017*	

Prophylaxis in allogeneic HSCT
Immune globulins (Ig)

Drug	Grading	References
Ig	DI	Cordonnier, *Ann Intern Med* 2003 Winston *BMT* 2003 Raanani, *JCO* 2009
Specific antiCMV Ig	DI	Zikos, *Haematologica* 1998 Raanani, *JCO* 2009

Prophylaxis of CMV infection and disease in allogeneic HCT; ongoing anti-CMV vaccine studies

- A **Phase III** Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Protective Efficacy and Safety of a Therapeutic Vaccine, ASP0113, in CMV-Seropositive Recipients Undergoing Allogeneic HSCT
- A **Phase II** Immunogenicity Trial of CMVGlycoprotein B Vaccine in Allograft Candidate Recipients
- Multi-antigen CMV-MVA Triplex Vaccine in Reducing CMV Complications in Patients Previously Infected With CMV and Undergoing Donor HSCT (**Phase II**)
- Vaccine Therapy in Reducing the Frequency of CMV Events in Patients With Hematologic Malignancies Undergoing Donor HSCT (**Phase II**) (CMVPepVax)
- Vaccine Therapy in Preventing CMV Infection in Patients With Hematological Malignancies Undergoing Donor HSCT (**Phase I**)

CMV prophylaxis – Allo SCT

CMV vaccines are in development but no recommendation can currently be made

Preemptive therapy

First line preemptive therapy

- The only data available for preemptive therapy of asymptomatic patients exists in allogeneic HSCT recipients.
- Preemptive antiviral therapy based on detection of CMV nucleic acid (or antigen) is effective for prevention of CMV disease (AI)
- Either iv ganciclovir or foscarnet can be used for first line preemptive therapy (AI)
- Valganciclovir can be used in place of iv ganciclovir or foscarnet (except in patients with severe gut GVHD); AIIu)
- The combination foscarnet+ ganciclovir is not recommended (DIII)
- The choice of drug depends on time after HSCT, risk of toxicity, and previous antiviral drug exposure

Dosages of antiviral drugs for preemptive therapy

- Ganciclovir 5 mg/kg BID for at least two weeks. Maintenance with 5-6 mg/kg/day can be given but continuing with full dose is also an option.

- Valganciclovir 900 mg BID for at least two weeks. Maintenance have not been studied. Dosage for children according to the prescribing information.
- Foscarnet 60 mg/kg BID for at least two weeks. Maintenance with 90 mg/kg/day can be given but continuing with full dose is also an option

- All dosages have to be adapted to the patient's renal function. Therapeutic drug monitoring of ganciclovir could be helpful to reduce toxicity.

Second and third line preemptive therapy

(see slide 21 for indications for resistance testing)

- The alternate drug of ganciclovir/valganciclovir or foscarnet can be considered for second line pre-emptive therapy (AIIu)
- Cidofovir can be considered for second/third line pre-emptive therapy (3-5 mg/kg/week) but careful monitoring of the renal function is required (BIIu).
- The combination of ganciclovir and foscarnet might be considered for second/third line pre-emptive therapy (CIIu)
- Reduce immunosuppression if possible (BIII)
- No recommendation can be given for the antiviral drugs in development
- Leflunomide or artesunate can be considered in patients resistant/refractory to available antiviral drugs (CIII)
- Addition of iv immune globulin for preemptive therapy is not recommended (DIII)

CMV disease

CMV definitions for use in clinical trials

Disease	Proven	Probable	Possible
Pneumonia	Yes	Yes	Yes
Gastrointestinal disease	Yes	Yes	Yes
Hepatitis	Yes	No	No
Retinitis	Yes	No	No
Encephalitis/ventriculitis	Yes	Yes	No
Nephritis	Yes	No	No
Cystitis	Yes	No	No
Myocarditis	Yes	No	No
Pancreatitis	Yes	No	No
Other end-organ diseases	Yes	No	No
Syndrome	No	Yes	No

All 3 categories require appropriate clinical symptoms and/or signs.

Ljungman et al; CID 2017; 64: 87-91

How do use the definitions in clinical practice

- The definitions are thought to be used in clinical trials. In clinical practice, it is not always possible to establish the formal criteria.
- The definitions were developed for HSCT patients and solid organ transplant patients so they have to be used with caution for other patient categories.
- 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.
- 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.

CMV pneumonia

- **Proven** disease requires clinical symptoms and/or signs of pneumonia such as new infiltrates on imaging, hypoxia, tachypnea, and/or dyspnea combined with CMV documented in lung tissue by virus isolation, rapid culture, histopathology, immunohistochemistry, or DNA hybridization techniques.

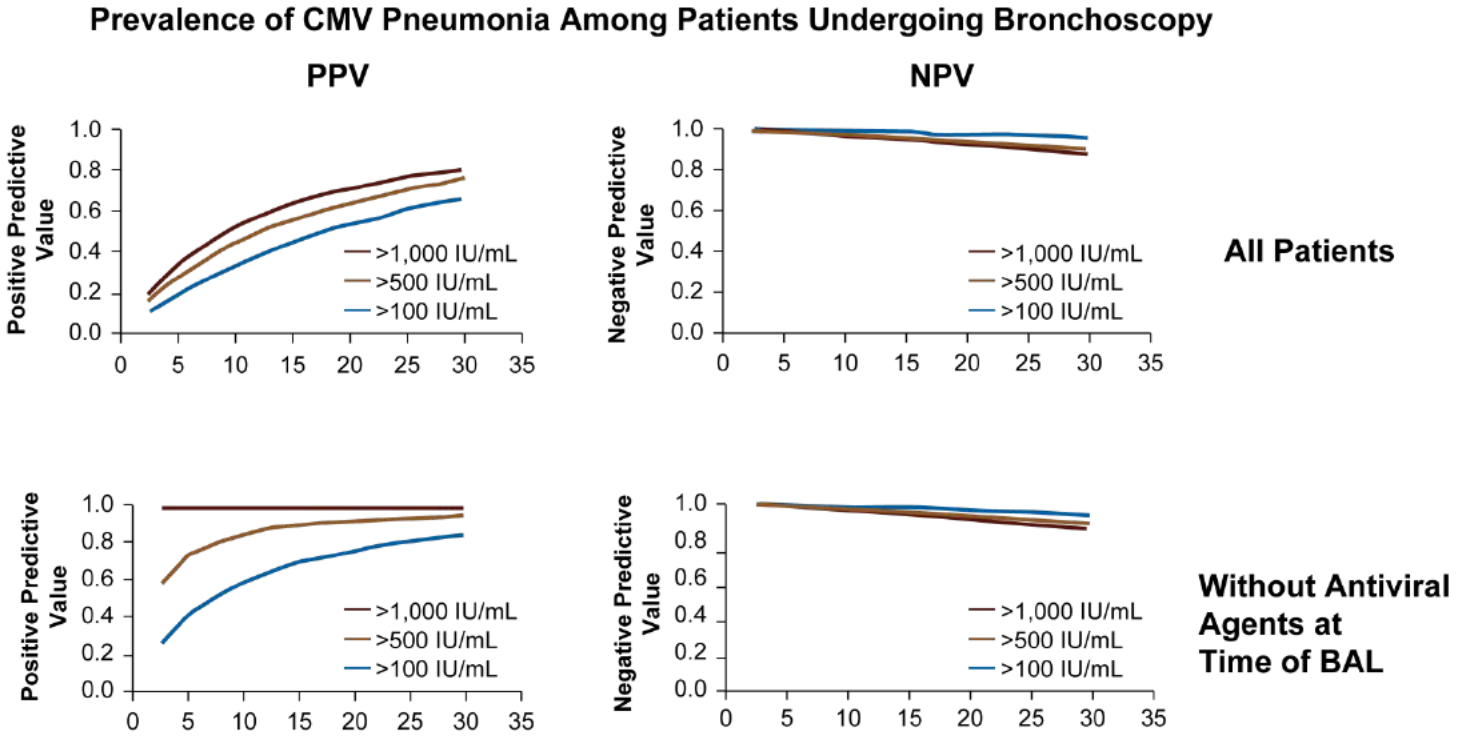
- **Probable** CMV pneumonia is defined as the detection of CMV by viral isolation, rapid culture of BAL fluid, or the quantitation of CMV DNA in BAL fluid combined with clinical symptoms and/or signs of pneumonia.

- **Possible** CMV pneumonia is defined as detection of DNA by quantitative PCR in a lung biopsy

CMV pneumonia

- A negative CMV DNA test in the BAL fluid has a negative predictive value close to 100% and therefore excludes the possibility of CMV pneumonia
- The likelihood for CMV pneumonia increases with increasing DNA viral load.
- A definite cut-off for CMV DNA load cannot be established at the present time
  - The cut-off is likely to vary between different patients and according to how the BAL procedure and processing are performed and the assay used for CMV DNA quantitation. Furthermore, CMV DNA levels may vary considerably between patients with varying degrees of severity of CMV pneumonia, which may impact the predictive values of any cut-off.
  - There is no data allowing to set a cut-off value in other patients than allogeneic HSCT patients with lower positive predictive values.
  - A CMV viral load >200-500 IU/ml in BAL fluid has a positive predictive value of ~50% for pneumonia in allogeneic HSCT recipients based on disease prevalence figures of approximately 10% among patients at risk for CMV pneumonia undergoing BAL testing (Boeckh et al JID 2017)
  - Lower levels in BAL likely indicate pulmonary shedding.

Which threshold is most predictive for CMV pneumonia?



1. Boeckh M et al. *J Infect Dis*. 2017.

CMV GI disease

- **Proven** disease requires upper and/or lower gastrointestinal (GI)-symptoms **plus** macroscopic mucosal lesions **plus** CMV documented in tissue by histopathology, virus isolation, rapid culture, immunohistochemistry or DNA hybridization techniques. Information regarding the presence or absence of gut GVHD (in HSCT recipients) and the number of CMV positive cells in biopsies is needed to assess likelihood of CMV GI disease.
- **Probable** GI disease requires upper and/or lower GI-symptoms and CMV documented in tissue but without the requirement for macroscopic mucosal lesions. Information regarding the presence or absence of gut GVHD (in HSCT recipients) and the number of CMV positive cells in biopsies is needed to assess likelihood of CMV GI disease.
- **Possible** GI disease: The use of quantitative PCR on gut biopsies is an evolving field. Presently, these findings could be defined as possible GI-disease
- CMV documented in blood by NAT (e.g., PCR) or antigenemia is not sufficient for the diagnosis of CMV GI-disease.

Special forms of CMV disease

- Pre-engraftment CMV disease: a rare event associated with a very high mortality, now even more rare due to the use PCR techniques for CMV surveillance
- CMV central nervous system (CNS) disease: a rare, late form of disease (median 7 months) associated with severe and protracted T-cell immunodeficiency, a history of recurrent CMV viremia treated with multiple courses of preemptive therapy, ganciclovir-resistant CMV infection in a high proportion of cases (90%), and very high mortality (90%)

Special forms of CMV disease

CMV Retinitis:

- A infrequent type of disease in adults after allogeneic SCT, with a frequency of 0.2%-2% , that might being recognised with increasing frequency. It is a late form of disease with a median time of presentation of 150 days after transplant, and usually is not associated with other forms of CMV disease.

- In children seem to be more frequent (4%) with data supporting CMV retinitis may as an immune reconstitution inflammatory syndrome (IRIS)-like response after recovery of CMV-specific immunity

- Viremia is detected frequently before the diagnosis of retinitis but negative at the time of diagnosis in a high proportion of cases, what might indicate an IRIS-like response, or that retina is a privileged/sanctuary site with poor access to systemic drugs

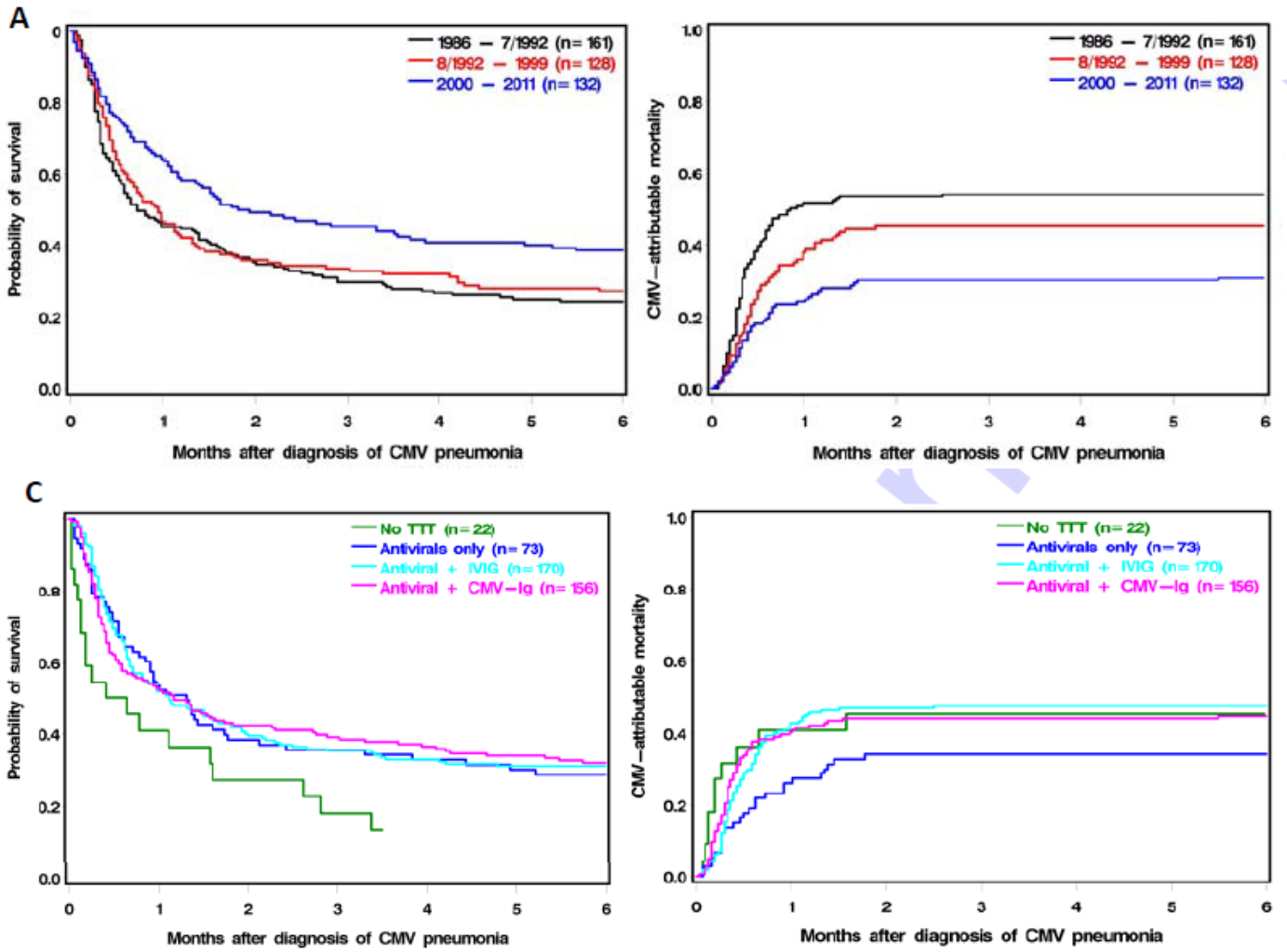
Other disease entities

CMV syndrome should not be used in trials of stem cell transplant or patients with hematological diseases although it is recognized that symptomatic CMV infection frequently causes fever and other symptoms compatible with the CMV syndrome definition in hematology patients.

Treatment of CMV pneumonia

- Antiviral therapy with iv ganciclovir is recommended (AIIu).
- Foscarnet might be used in place of ganciclovir (AIII)
- The addition of immune globulin/hyperimmuneglobulin to antiviral therapy can be considered (CIII)
- Cidofovir or the combination of foscarnet and ganciclovir can be used as $2^{nd}/3^{rd}$ line therapy (BIIu).
- No recommendation can be given for the antiviral drugs in development

Treatment of CMV pneumonia



Erard et al; CID 2015

Treatment of other types of symptompatic CMV infection or disease

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

- Intravitreal injections of ganciclovir can be used for treatment of CMV retinitis (BIIt).

- Valganciclovir can be used in place of iv ganciclovir or foscarnet (except in patients with severe GI GVHD); BIII)

- Cidofovir or the combination of intravenous ganciclovir and foscarnet can be used as 2nd or 3rd line therapies of CMV disease (BIIu).

Dosages of antiviral drugs for CMV disease

- Ganciclovir 5 mg/kg BID for at least three weeks.
- Valganciclovir 900 mg BID for at least three weeks. Can also follow induction with iv. ganciclovir if prolonged therapy is needed.
- Foscarnet 60 mg/kg TID or 90 mg/kg BID for at least three weeks.
- Cidofovir 3-5 mg/kg together with probenicide once weekly for three doses followed by dosing every two weeks.
- All dosages have to be adapted to the patient's renal function

Immune therapy

Adoptive CMV-directed T Cell Therapy

1. Reconstitution of an antiviral T cell response prevents CMV reactivation/disease

2. Prophylactic Adoptive Transfer:
   cloned donor-derived T cells sensitized in vitro with autologous CMV-infected fiboblasts reduced CMV reactivation and disease post-transplant

3. Phase I/II trials Therapeutic Applications
   CMV-specific T cell lines transferred to small patient cohorts of recipients of an allo-graft (including CBT/Haplo-transplant recipients) were safe and at least partially effective in chemotherapy-refractory CMV infection/disease.
   Different selection strategies for CMV-specific T cells applied (stimulation with APC pulsed with viral peptides/MHC multimers/cytokine catch assay)

Riddel SR et al, Science 1992
Walter EA et al, New Engl J Med 1995
Einsele H et al, Blood 2002
Peggs KS et al, Lancet 2003
Rauser G et al, Blood 2004
Feuchtinger T et al, Blood 2010
Cobbold M et al, J Exp Med 2005
Schmitt A et al, Transfusion 2011
Stemberger C et al, Blood 2014
Bramanti S et al, BMT 2017

Immune therapy

4. Multipathogen specific T cells can be generated/transfused safely/effictively

Hanley et al, Blood 2009
Khanna N et al, Blood 2011
Gerdemann U et al, Mol Ther 2013

5. No randomized trials evaluating CMV-directed T cell therapy published

6. Conflicting results of transfer of CMV specific T cells from third party donors

Prockop SE et al, Blood 2014
Leen AM et al, Blood 2013
Neuenhahn M et al, Leukemia 2017

Immune therapy

In patients with chemotherapy-refractory CMV infection post-transplant adoptive T cell therapy is a valid therapeutic option (BIIu)

The efficacy in patients receiving high-dose (≥2mg/kg) corticosteroids is likely to be low

A commercial product is now available

CMV Epidemiology – autologous SCT

- Similar rate of CMV infections (30-50%) compared with patients receiving an allogeneic HSCT, but a significantly lower CMV disease rate in the majority of centers (<1%)

  - Nonetheless, a large variation of CMV disease incidence between centers have been described (0-8%) for reasons that are not clear. One of the reasons may be the different meaning of CMV in BAL in auto-SCT compared with allogeneic HSCT

  - Nonetheless, the case fatality rates of CMV pneumonitis in autologous HSCT is similar to allogeneic HSCT

Autologous HCT

- The risk of CMV infection after autologous HSCT is 2 to 5 times lower than after allogeneic HSCT

Han *J of Clin Microbiol* 2007
Marchesi *World J Transpl* 2015
Piukovics *Ann Hematol* 2017
Al-Rawi *Med J Hematol Inf Dis* 2015
Fassas *BJH* 2001

- Pretransplant bortezomib based regimens may have an increased risk of symptomatic CMV infection after autologous HSCT

Marchesi *Transpl Inf Dis* 2014;16:1032-1038
Marchesi *Transpl Inf Dis* 2014;16:158-164

- Tandem auto for multiple myeloma : controversial data
  - Increased risk after tandem auto (after the 2nd auto) for MM vs single autologous HSCT OR=5.112; 95%CI [1.27-20.60]; P=5.022

Kim *BBMT* 2012

  - No increased risk of symptomatic infection after 2nd transplantation

Marchesi *Transpl Inf Dis* 2014

Autologous HSCT patients

- For standard autologous HSCT patients routine monitoring and preemptive therapy is not recommended (DIIu).

- High-risk autologous HSCT patients such as patients with autoimmune disease with CD34 selection or receiving ATG might potentially benefit from monitoring and the use of preemptive therapy (CIIu).

Other situations than HSCT

- The risk of CMV infection and disease for non HSCT patients is 4 times lower than for allogeneic HSCT recipients and 2 times lower than autologous HSCT recipients

- Among non-HSCT recipients CMV has been reported during treatment with :
  - Alemtuzumab
  - Idelalisib
  - Followed by HyperCVAD therapy, Fludarabine, Cyclophosphamide
  - Lymphoid disease : higher risk than myeloid disease
  - Dasatinib
  - Bendamustin in combinations
    - Brentuximab (no specific risk)

Ng *Haematologica* 2005
Nguyen *CID* 2001
Tay *Leuk Lymph* 2014

- CMV disease before HSCT is a risk factor of CMV disease after HSCT

Fries *BBMT* 2005

Patients receiving alemtuzumab :

- A CMV management strategy must be put in place for patients treated with alemtuzumab for hematological malignancy (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 (BIIu).
- 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). (BIIu)

* Treating asymptomatic patients is not obligatory but careful clinical observation of patients with documented CMV reactivation is necessary (BIIu)

- Withholding alemtuzumab is not considered necessary, unless there are persisting symptoms (BIII).

Idelalisib

- Specific inhibitor of adenosine-5’-triphosphate in the PI3K-Akt pathway
- Approved by EMA in 2014
  - in association with Rituximab
    - for relapsed chronic lymphocytic leukaemia (CLL)
    - for first line CLL with del17p or TP53 mutation
  - In monotherapy for refractory follicular lymphoma

- 5 trials in CLL and indolent non-Hodgkin lymphoma (iNHL) prematurely stopped because of an increased risk of severe infectious complications (pneumocystosis and CMV infections and diseases)

- 52 cases of CMV infections/2204 patients (2,4%)

Idelalisib

- In relapsed/refractory CLL studies, severe CMV infections occurred when Idelalisib was given in association with Bendamustine
- In relapsed/refractory iNHL, severe CMV infections occurred both when Idelalisib was given alone or in association with Rituximab or Rituximab + bendamustine
- 75% (39/52) of the CMV infections/diseases occurred in the 6 first months of therapy?
- Sites of CMV disease/infection
  - 10 gastro-intestinal
  - 5 pneumonia
  - 4 multi-organ
  - 3 retinitis
  - 23 unspecified
  - 7 peripheral blood

Idelalisib

- A CMV management strategy is recommended for patients treated with Idelalisib (BIIu)
- For CMV seronegative patients, leukocyte depleted or CMV seronegative blood products should be given (BIII)
- For patients with symptoms compatible with CMV, testing for CMV should be considered (BIIt)
- Antiviral therapy with ganciclovir or valganciclovir should be given to symptomatic patients (BIIt)
- For CMV seropositive patients monitoring with CMV PCR could be considered (CIII)
- Preemptive CMV therapy could be considered (CIII)
- In case of clinical signs consistent with CMV disease it should be considered to stop Idelalisib until resolution of symptoms (BIII)

Other hematology patients/drugs

- 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)

- Routine antiviral prophylaxis is not recommended (DIII)

- Routine monitoring and preemptive therapy is not considered necessary in other hematology patients (DIII).

These slides are open for public consultation until November 1st, 2017

Any comment, question, suggestion, should be sent by @mail to

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by Nov 2, 2017