



Guidelines for the management of cytomegalovirus infection in patients with haematological malignancies and after stem cell transplantation from the 2017 European Conference on Infections in Leukaemia (ECIL 7)

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Cytomegalovirus is one of the most important infections to occur after allogeneic haematopoietic stem cell transplantation (HSCT), and an increasing number of reports indicate that cytomegalovirus is also a potentially important pathogen in patients treated with recently introduced drugs for hematological malignancies. Expert recommendations have been produced by the 2017 European Conference on Infections in Leukaemia (ECIL 7) after a review of the literature on the diagnosis and management of cytomegalovirus in patients after HSCT and in patients receiving other types of therapy for haematological malignancies. These recommendations cover diagnosis, preventive strategies such as prophylaxis and pre-emptive therapy, and management of cytomegalovirus disease. Antiviral drugs including maribavir and letermovir are in development and prospective clinical trials have recently been completed. However, management of patients with resistant or refractory cytomegalovirus infection or cytomegalovirus disease is a challenge. In this Review we summarise the reviewed literature and the recommendations of the ECIL 7 for management of cytomegalovirus in patients with haematological malignancies.

Introduction

Cytomegalovirus causes multiorgan disease both early and late after haematopoietic stem cell transplantation (HSCT).¹⁻³ Seropositivity for cytomegalovirus remains a risk factor for non-relapse mortality despite major advances in early diagnosis and management.^{1,2} The relevance of seropositivity in other patient populations is less well studied. The introduction of new types of cancer therapies has highlighted that cytomegalovirus might be of importance outside of the transplant setting. A working group within the 2017 European Conference on Infections in Leukaemia (ECIL 7) reviewed the literature and developed recommendations (panel 1), which we present in this Review alongside a discussion of the relevant literature on the diagnosis, prophylaxis, and management of cytomegalovirus infection after HSCT and in patients with haematological malignancies.

Definitions and diagnosis of cytomegalovirus disease

For cytomegalovirus infection and disease, definitions were developed specifically for transplant patients and are described in detail by Ljungman and colleagues.⁵ Symptoms of organ involvement together with cytomegalovirus detection only in the blood, regardless of the method, are insufficient for the diagnosis of cytomegalovirus disease given the possibility of other infectious and non-infectious causes (such as graft-versus-host disease [GvHD]). To date, insufficient evidence exists to support the use of quantitative PCR (qPCR) for documentation of cytomegalovirus disease in tissue specimens, for which the positive predictive value is too low³ and no cut-offs have been defined.

The diagnosis of cytomegalovirus pneumonia is problematic as asymptomatic viral shedding in the airways is common. A few points should be considered in the diagnosis of cytomegalovirus pneumonia: (1) a negative result in a DNA test for cytomegalovirus in the bronchoalveolar lavage (BAL) fluid has a negative predictive

Panel 1: 2017 European Conference on Infections in Leukaemia (ECIL 7) procedures for writing the guidelines on cytomegalovirus management

- MEDLINE (including MEDLINE In Process) searches were done with no start date (all studies published) until June 30, 2017, to identify potentially relevant English language studies related to cytomegalovirus infection or disease in patients following haematopoietic stem cell transplantation and in patients with haematological malignancies. References were also screened for other potentially relevant papers.
- The relevant studies were analysed, with particular attention given to the study design, the population, and the endpoints.
- Recommendations were developed, which were graded on the amount of evidence and strength of the recommendation according to the European Society of Clinical Microbiology and Infectious Diseases grading system (panel 2).⁴
- These suggested recommendations were presented in a plenary session of the ECIL 7 (Sept 22, 2017).
- The recommendations were discussed until a consensus was reached and were thereafter made available on the ECIL website from October 2, 2017, until March 1, 2018, for open consultation.

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The European Conference on Infections in Leukaemia (ECIL) group is a joint project of the European Organisation for Research and Treatment of Cancer-Infectious Diseases Group, European Society for Blood and Marrow Transplantation-Infectious Diseases Working Party, European LeukemiaNet-Project 15: Supportive Care, and the International Immunocompromised Host Society

For the ECIL website see www.ecil-leukaemia.com

value close to 100% and is strong evidence against cytomegalovirus pneumonia;⁶ (2) the positive predictive value of cytomegalovirus DNA detection in BAL fluid for cytomegalovirus pneumonia increases with higher viral DNA load in the BAL and with increasing underlying risk for cytomegalovirus disease in the tested patient (pretest probability);⁶ and (3) a cutoff for viral DNA load in the BAL cannot be established because it can vary between patients, by how the BAL procedure and processing are done, by the assay used for DNA quantitation, and by the severity of symptoms.

Cytomegalovirus epidemiology in allogeneic HSCT recipients

Cytomegalovirus disease incidence and mortality

Historically, cytomegalovirus disease developed in 10–40% of patients undergoing HSCT, as pneumonitis in most cases, and was associated with a high mortality (around 70%). At present, the incidence of cytomegalovirus disease is 2–3% in the placebo control groups of several randomised prophylaxis trials^{7–11} and between 5% and 10% in real-world practice.^{3,12} New transplant methods affect the risk of cytomegalovirus infection and disease. **Haploidentical and cord blood transplantations have been reported to have similar frequencies of cytomegalovirus reactivation.**¹³ Comparative studies do not show notable differences in the frequencies of cytomegalovirus infection or disease between different modes of haploidentical HSCT.^{14–16} By contrast, **GvHD prophylactic regimens including therapy with sirolimus have been associated with a lower risk for cytomegalovirus infection.**¹⁷

Cytomegalovirus epidemiology in cord blood HSCT

Cytomegalovirus is common after cord blood HSCT, probably because of delayed immune reconstitution.^{18–20} Cytomegalovirus seropositivity and reactivation following cord blood HSCT have been associated with increased non-relapse mortality when compared with other stem cell sources.^{21–23} More intensive preventive strategies have therefore been suggested for after HSCT, especially unrelated cord blood HSCT.²⁴ The numbers of cord blood transplants are decreasing because of the increased use of haploidentical HSCT.

Cytomegalovirus epidemiology in haploidentical HSCT with ex-vivo graft manipulation

Haploidentical HSCT with ex-vivo graft manipulation is commonly used in paediatric patients.^{25–27} In early reports, cytomegalovirus was found to be the cause of death in 14 out of 27 (52%) infection-related fatal events.²⁸ Patient–donor pairs who were cytomegalovirus seronegative had better leukaemia-free survival than the other combinations (pairs with mixed serostatus or seropositive pairs; 45% vs 16%, $p=0.01$).²⁹ Later studies reported an incidence of cytomegalovirus infection after ex-vivo T-cell-depleted haploidentical HSCT of 42–66%,^{14–16,30} furthermore, 25–50% of non-relapse

mortality was attributed partly or exclusively to cytomegalovirus.^{15,16} However, with selective depletion of cells positive for T-cell receptor alpha/beta and CD19, this risk has been substantially reduced, as observed among children with a non-relapse mortality of 5% and no deaths due to cytomegalovirus.³¹

Cytomegalovirus epidemiology in haploidentical HSCT with post-transplant cyclophosphamide

The use of high-dose cyclophosphamide after unmanipulated haploidentical HSCT has become the most commonly used platform in adults in Europe.³² The incidence of cytomegalovirus infection has been reported to be 35–76%^{13,32–39} and of cytomegalovirus disease to be 0–17%.³⁹ Two retrospective studies showed similar frequencies of cytomegalovirus infection and disease with post-transplant cyclophosphamide when given after haploidentical HSCT, compared with after HLA-matched, related HSCT and unrelated donor HSCT.^{35,40}

Cytomegalovirus disease

The incidence of cytomegalovirus disease occurring within the first 100 days after HSCT has shown a continuous decline over the past few decades.^{12,41} Pre-engraftment cytomegalovirus disease, although rare, is associated with a notably high mortality. In recent years, studies have reported gastrointestinal cytomegalovirus disease as the most frequently diagnosed type (70–80% of all cases).^{7,42} Several studies have shown that the antigenaemia test and, to a lesser extent, PCR, are frequently negative at the time of diagnosis of gastrointestinal cytomegalovirus disease.^{42,43} Thus, cytomegalovirus load in plasma or whole blood does not adequately represent cytomegalovirus replication in the gastrointestinal mucosa, possibly because gastrointestinal disease, at least initially, is a local tissue event, frequently associated with GvHD.

Pre-emptive therapeutic or prophylactic use of high potency anticytomegalovirus drugs has been shown to result in an increased risk of late cytomegalovirus disease (>100 days after HSCT).⁴¹ Cytomegalovirus pneumonitis is generally common in late-occurring disease, although most cases will have received pre-emptive therapy.⁴⁴ In a randomised, double-blind trial, a pre-emptive strategy based on weekly PCR monitoring until 9 months post-transplant was as effective as valganciclovir prophylaxis in preventing cytomegalovirus disease without an increase in late disease events.¹⁰

Donor and recipient cytomegalovirus serological status

The cytomegalovirus serological status of patients and donors strongly influences the outcome of HSCT. Cytomegalovirus-seropositive patients have a poorer outcome than seronegative patients.^{1,45} The use of a cytomegalovirus-seronegative donor for a cytomegalovirus-seronegative patient reduces the risk of non-relapse

mortality.^{46,47} Several studies have shown that use of cytomegalovirus-seronegative donors over seropositive donors for seropositive patients has negative effects, including delayed cytomegalovirus-specific immune reconstitution,^{48,49} repeated reactivations,⁵⁰ higher peak virus load,⁵¹ the need for repeated antiviral therapy courses,⁴⁸ late cytomegalovirus recurrence,⁵² development of cytomegalovirus disease,^{50,53} and a decrease in survival.⁴⁷

During 2000–15, the proportion of HSCT recipients older than 60 years tripled, from less than 10% in 2000–06, to around 30% in 2015,⁵⁴ resulting in increased numbers of patients who were cytomegalovirus seropositive undergoing HSCT over the same period. A study comparing 1995–2005 data with 2006–14 data showed a significant increase in the proportion of transplants that were cytomegalovirus donor-negative and recipient-positive (odds ratio 1.68).⁵⁵

No consistent effect has been observed of patient–donor matching for cytomegalovirus serostatus after haploidentical HSCT with post-transplant cyclophosphamide.^{33,56–60} An analysis published in 2018 of almost 1000 cytomegalovirus-positive patients found no significant effect with respect to non-relapse mortality and overall survival of donor serostatus.⁶¹ In cord blood transplant recipients, cytomegalovirus seropositivity has been associated with increased non-relapse mortality.⁶²

Recommendations for pretransplant testing of serological status

All patients and donors should be tested for cyto-megalovirus IgG antibodies close to the time of HSCT (grade of recommendation according to the European Society of Clinical Microbiology and Infectious Diseases [panel 2]: AIIu). The performance (sensitivity and specificity) of commercially available serological assays is not equivalent; highly sensitivity assays should be prioritised over those optimised for specificity (grade BIII).

Recommendations for choice of donor based on cytomegalovirus serological status

A cytomegalovirus-seronegative donor should be chosen when possible for a cytomegalovirus-seronegative recipient (grade AI [for haploidentical HSCT, grade AIII]). A cytomegalovirus-seropositive donor should be preferentially selected for a cytomegalovirus-seropositive recipient in the setting of unrelated allogeneic HSCT with myeloablative conditioning (grade BIIu). Either a seropositive or seronegative donor is suitable for a seropositive recipient undergoing haploidentical HSCT with post-transplant cyclophosphamide (grade BIIu).

Cytomegalovirus and leukaemia relapse

An association between cytomegalovirus infection and reduced likelihood of leukaemia relapse after HSCT has been discussed for more than 30 years.⁶³ Numerous studies have evaluated the role of cytomegalovirus in relapse. In summary, several of these studies, many small, have found associations between cytomegalovirus reactivation

and decreased relapse risk especially for acute myeloid leukaemia.^{64–67} In the largest multicentre study to date involving 9469 patients, no effect of cytomegalovirus (serology or infection) on relapse was found.² One study showed a higher relapse risk with cytomegalovirus infection or seropositivity.⁶⁸ Several mechanisms have been proposed (eg, involvements of natural killer cells, $\gamma\delta$ T cells, and cytotoxic T cells with activity against both cytomegalovirus and leukaemia antigens), but none have been proven.

Recommendation regarding cytomegalovirus and leukaemia relapse

Strategies permissive for cytomegalovirus reactivation with the aim of reducing leukaemic relapse are not recommended (grade DIIu).

Cytomegalovirus monitoring

Real-time qPCR methods are recommended for guiding the initiation of pre-emptive antiviral therapy and monitoring the response. Commercially available assays are preferred over so-called laboratory-developed assays, owing to the lower intra-assay and interassay variabilities of commercial kits.⁶⁹ Assays differ in the gene target subject to amplification, the number of gene targets, the nature of the probe, and the platform used for PCR performance and analysis. These factors contribute to variability.^{70,71} The efficiency of DNA extraction systems varies widely, affecting cytomegalovirus DNA load.⁷² Whole blood and plasma

Panel 2: Grading system of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID)⁴ used to classify the 2017 European Conference on Infections in Leukaemia recommendations for the management of cytomegalovirus infection

Strength of a recommendation

- Grade A: ESCMID strongly supports the recommendation for use
- Grade B: ESCMID moderately supports the recommendation for use
- Grade C: ESCMID marginally supports the recommendation for use
- Grade D: ESCMID is against the use of the recommendation

Quality of evidence

- Level I: evidence from at least one properly designed randomised, controlled trial
- Level II: evidence from at least one well designed clinical trial, without randomisation; from cohort or case-controlled analytical studies (preferably from more than one 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 for level II quality of evidence

- r: meta-analysis or systematic review of randomised controlled trials
- t: transferred evidence, that is, results from different patient cohorts, or a similar immune status situation
- h: comparator group is a historical control
- u: uncontrolled trial
- a: published abstract (presented at an international symposium or meeting)

specimens are equally suitable for cytomegalovirus DNAemia monitoring. Overall, cytomegalovirus DNA loads are higher in whole blood, although plasma and whole blood levels significantly correlate.⁷³ For a given patient, cytomegalovirus DNA load monitoring should be consistently done with the same DNA extraction method, qPCR assay, and type of specimen.

Cytomegalovirus DNA load yielded by qPCR assays should be normalised to the WHO cytomegalovirus international standard⁷⁴ and reported as international units (IU) per mL. Recalibration of the assays to this standard improves interassay agreement, although interlaboratory discrepancies of up to 1.5 log₁₀ IU/mL in cytomegalovirus DNA loads can persist.^{74,75} The use of commercial systems minimises such discrepancies.⁷⁶

Kinetic analyses of plasma cytomegalovirus DNA load might be useful. Specifically, a viral DNA load doubling time of less than 2 days anticipates the eventual need for pre-emptive therapy in a subset of patients.⁷⁷ In turn, initiation of pre-emptive antiviral therapy on detecting a doubling time of less than 2 days can lead to a reduction in days on antiviral therapy.⁴¹

Monitoring of cytomegalovirus DNA load should be done at least weekly for the first 100 days post-transplant and for longer in patients with persistent T-cell immunodeficiency.^{41,42,78} No consensus is available on a viral DNA load cutoff for initiation of antiviral therapy, as the cutoff for triggering therapy can be adapted according to baseline or post-transplant risk factors.^{41,42}

Recommendations for monitoring of cytomegalovirus in plasma and whole blood

Allogeneic HSCT recipients should be monitored for cytomegalovirus in plasma or whole blood (grade AIIu). qPCR assays are more sensitive than detecting viral antigen pp65 (the pp65 antigenaemia assay) and are the primary choice for monitoring viral load (grade BIIu). Monitoring should be done at least weekly for the first 100 days after the transplant (grade AIIu). For a given patient, cytomegalovirus monitoring should be done with the same DNA extraction method, PCR assay, and specimen type (grade AIII). Longer monitoring is recommended in patients with acute or chronic GvHD, in those having experienced cytomegalovirus reactivation, in patients having undergone mismatched, cord blood, haploidentical HSCT (without post-transplant cyclophosphamide), in those on long-term effective prophylaxis, or in those displaying persistent immunodeficiency (grade AIII). Cytomegalovirus DNA cutoff values for pre-emptive therapy should be adapted according to the monitoring technique used and the transplant method (grade AIII).

Immunological monitoring

Functional cytomegalovirus-specific CD8 T cells are pivotal in the control of cytomegalovirus infection. Host responses to the cytomegalovirus pp65 antigen and immediate early 1 antigen are immune-dominant and elicit protective immune responses in most individuals.^{79–82}

Reconstitution of cytomegalovirus-specific CD4 T cells has been found to be crucial for the expansion and persistence of functional CD8 T cells.⁸³

The number of peripheral cytomegalovirus-specific CD8 T cells that produce interferon- γ appears to be a reliable marker of protection. A few prospective clinical studies have explored this assumption,^{49,84,85} and commercial assays now exist.^{86,87} Cut off values for cytomegalovirus-specific, interferon- γ -producing T cells that afford protection from cytomegalovirus pp65-antigenaemia, DNAemia, or end-organ disease have been proposed, but lack extensive clinical validation.

Recommendation regarding immunological monitoring of allogeneic HSCT recipients

Although data are scarce, sequential monitoring of interferon- γ -producing cytomegalovirus-specific T cells seems to provide potentially useful information for the management of cytomegalovirus infection, and could be ancillary to viral DNA load monitoring to individualise pre-emptive therapy and identify patients at highest risk of developing new episodes of cytomegalovirus infection and end-organ disease (grade BIII).

Cytomegalovirus management strategies

Prevention of primary cytomegalovirus infection

Cytomegalovirus-seronegative patients have a low risk of contracting cytomegalovirus infection with proper transfusion management. Blood products from seronegative donors or leucocyte-depleted blood products should be used.^{88–91} Leucocyte filtration should be done at the blood bank and the established quality standard of less than 1 × 10⁶ residual leucocytes per unit followed.⁹¹ Intravenous immunoglobulin has a minor effect and has been replaced by other more effective strategies as outlined.

Prevention of cytomegalovirus reactivation and disease

Cytomegalovirus replication itself has been associated with increased non-relapse mortality in patients who have undergone allogeneic HSCT.^{2,3} Therefore, prevention of cytomegalovirus replication by systemic prophylaxis would be logical. Two possible caveats should be considered with this strategy: not all patients will reactivate cytomegalovirus,^{7–9} meaning that some patients will receive antiviral drugs unnecessarily, exposing them to side-effects; and late cytomegalovirus disease can occur after discontinuation of the prophylaxis.⁵²

Antiviral chemoprophylaxis aims to prevent cytomegalovirus reactivation in seropositive patients (table). This method to prevent primary infection in a cytomegalovirus donor-positive and recipient-negative setting has not been adequately studied after HSCT.

In randomised studies on allogeneic bone marrow transplantation, high doses of aciclovir or valaciclovir reduced the risk of cytomegalovirus infection but not cytomegalovirus disease.^{103,104} One of these studies comparing aciclovir with placebo reported improved

survival, although the underlying mechanism was unclear.¹⁰³ Intravenous ganciclovir prophylaxis was also tested in randomised trials for allogeneic marrows transplants^{105–108} and reduced the risk of cytomegalovirus disease compared with placebo, but did not improve survival. No difference was observed in cytomegalovirus disease risk or patient survival between ganciclovir and valganciclovir prophylaxis regimens,¹⁰⁸ nor between ganciclovir prophylaxis and pre-emptive therapy.¹⁰⁷ Foscarnet prophylaxis has only been used in uncontrolled trials and prolonged use is limited by toxicity.^{109,110}

Letermovir, a cytomegalovirus terminase inhibitor, was studied in cytomegalovirus-seropositive HSCT recipients under a 12-week drug regimen.¹¹ Letermovir reduced clinically significant cytomegalovirus infection at 24 weeks (in 122/325 [37.5%] patients on letermovir vs 103/170 [60.6%] patients on placebo) with no major toxic effects. Furthermore, all-cause mortality was reduced with letermovir at 24 weeks. Letermovir is only active against cytomegalovirus and therefore aciclovir or valganciclovir prophylaxis is necessary to prevent herpes simplex and varicella zoster virus infections. Patients who have received prophylaxis should be monitored after discontinuation of letermovir.

Maribavir at 100 mg twice a day was unable to prevent cytomegalovirus disease in a phase 3 trial.⁷ **Brincidofovir** was also unable in a phase 3 trial to reduce clinically significant cytomegalovirus infection at week 24 and was associated with statistically and clinically significant gastrointestinal toxic effects.¹¹¹

However, none of these studies were powered to examine differences in survival. In 2018, two systematic reviews^{112,113} and an accompanying meta-analysis¹¹³ examined the effects of antiviral prophylaxis in HSCT recipients.

Other prophylactic strategies include regular and cytomegalovirus-specific immunoglobulin, which have minor effects on the prevention of cytomegalovirus infection or disease¹¹⁴ and are not recommended for prophylaxis (grade DI).

Pre-emptive antiviral therapy

Monitoring by a sensitive technique such as PCR tests of whole blood allows intervention before development of cytomegalovirus disease. Pre-emptive therapy can be used as a stand-alone strategy or combined with antiviral prophylaxis.

First-line pre-emptive therapy

Ganciclovir is the most commonly used drug for pre-emptive antiviral therapy. Valganciclovir is the prodrug of ganciclovir, and two pharmacokinetic studies showed that equal or even higher drug exposure can be achieved with oral valganciclovir compared with intravenous ganciclovir,^{115,116} although efficacy and safety were similar between the two drugs.¹¹⁷ The effects of valganciclovir have also been analysed in uncontrolled studies.^{117–119} With

	European Society of Clinical Microbiology and Infectious Diseases recommendation grading ^a	Study	Comment
Aciclovir	CI	Prentice et al (1994) ⁹² Milano (2011) ⁹³	Less effective than valganciclovir
Valganciclovir	BI	Ljungman (2002) ⁹⁴ Winston (2003) ⁹⁵ Milano (2011) ⁹³	Used together with pre-emptive therapy
Ganciclovir	CI	Winston (1993) ⁹⁶ Goodrich (1993) ⁹⁷	Used at engraftment
Valganciclovir	CIH	Montesinos (2009) ⁹⁸ Boeckh (2015) ⁹⁹	Cord blood HSCT used in Montesinos et al; ⁹⁸ prophylaxis against late cytomegalovirus disease
Foscarnet	DIIU	Ordemann (2000) ¹⁰⁰ Bregante (2000) ¹⁰¹	NA
Letermovir	AI	Marty (2017) ¹⁰²	Only effective against cytomegalovirus

HSCT=haematopoietic stem cell transplantation. NA=not applicable.

Table: Recommended drugs for antiviral prophylaxis after allogeneic HSCT

younger age in children, higher doses of ganciclovir are frequently needed. Foscarnet has been shown in a randomised trial to be as effective as ganciclovir for pre-emptive treatment.¹²⁰

The duration of therapy should be at least 2 weeks, aiming for at least one negative cytomegalovirus test. Increasing cytomegalovirus DNA load (or antigenaemia) within the first 2 weeks of antiviral therapy does not necessitate a change of therapy. If cytomegalovirus is still detected after 2 weeks of therapy, maintenance therapy with antiviral therapy given once daily can be considered.¹²⁰ Repeated courses of pre-emptive therapy or a prolonged duration of initial pre-emptive therapy might be needed in patients showing slow decreases in viral load.

Recommendations regarding first-line pre-emptive therapy

Pre-emptive antiviral therapy based on detection of cytomegalovirus DNA (or antigen) in whole blood or plasma is effective for the prevention of cytomegalovirus disease (grade AI). Either intravenous ganciclovir or foscarnet can be used for first-line pre-emptive therapy (grade AI). Oral valganciclovir can be used in place of ganciclovir or foscarnet, except in patients with severe gastrointestinal GvHD (grade AIIU). The choice of drug depends on time after HSCT, risk of toxic effects, and previous antiviral drug exposure. A combination of foscarnet plus ganciclovir at half doses is not recommended (grade DIII). All doses (appendix) should be adapted to the patient's renal function. Therapeutic drug monitoring of ganciclovir might help to reduce toxic effects and guide therapy.

See Online for appendix

Second-line pre-emptive therapy

A patient developing a second episode of cytomegalovirus infection can usually be retreated with the same drug, albeit with consideration given to common side effects of the drug. The alternative drug of ganciclovir (or valganciclovir) or foscarnet is indicated in patients with refractory cytomegalovirus infection, by increasing viral load or the development of resistance. Cidofovir is usually used as a third-line therapy because of its renal toxicity.^{121–123} The combination of ganciclovir and foscarnet was studied in HSCT recipients, but showed increased side effects and no improvement in efficacy compared with ganciclovir alone.^{124,125} Maribavir is under investigation as a treatment for resistant or refractory cytomegalovirus infection.¹²⁶ A small amount of data exist for letermovir and brincidofovir. As such, no recommendations can be given for maribavir, letermovir, and brincidofovir. Case reports have been published of treatment with leflunomide or artesunate in patients for whom other antiviral therapies were unsuccessful, with varying results.^{127–131}

Recommendations regarding second-line pre-emptive therapy

The alternative drugs of ganciclovir (or valganciclovir) and foscarnet can be considered for second-line pre-emptive therapy (grade AIIu). Cidofovir can be considered for second-line or third-line pre-emptive therapy (5 mg/kg per week)^{121,122} but careful monitoring of renal function is required (grade BIIu). The combination of ganciclovir and foscarnet at half doses might be considered for second-line or third-line pre-emptive therapy (grade CIIu).^{124,125} For all second-line and third-line therapies, immunosuppression should be reduced if possible (grade BIII). Leflunomide or artesunate can be considered in patients resistant or refractory to other second-line and third-line antiviral drugs (grade CIII). The addition of intravenous immunoglobulin to second-line or third-line treatment is not recommended (grade DIII).

Treatment of cytomegalovirus disease

Historically, the standard therapy for cytomegalovirus pneumonia, although never formally studied in controlled trials, has been a combination of intravenous ganciclovir and high-dose intravenous immunoglobulin.^{132–134} Addition of granulocyte colony-stimulating factor can be considered to allow prolonged ganciclovir therapy. A large retro-spective analysis in 2015 did not find a positive effect of regular or cytomegalovirus-specific immunoglobulin on outcome and its use remains controversial;⁴⁴ no data support any advantage with cytomegalovirus-specific immunoglobulin over standard immunoglobulin. The addition of immunoglobulin for the treatment of manifestations of cytomegalovirus disease other than pneumonia is not recommended.¹³⁵

Either foscarnet, cidofovir, or the combination of intravenous ganciclovir and foscarnet, each given at full dose, might be used as a second-line therapy for

cytomegalovirus disease. Promising phase 2 data exist for the use of maribavir for resistant or refractory cytomegalovirus disease¹²⁶ and a phase 3 study is ongoing (NCT02931539). No data exist to support letermovir or brincidofovir as treatments for cytomegalovirus disease, and thus no recommendations can be given for these drugs.

Recommendations for the treatment of cytomegalovirus disease

Antiviral therapy with intravenous ganciclovir is recommended for cytomegalovirus disease (grade AIIu); however, foscarnet might be used instead of ganciclovir if ganciclovir can't be given because of toxic effects or antiviral resistance (grade AIII). The addition of immunoglobulin or hyperimmune globulin to antiviral therapy can be considered for the treatment of cytomegalovirus pneumonia (grade CIII). Cidofovir or the combination of foscarnet and ganciclovir at full doses can be used as a second-line or third-line therapy for cytomegalovirus disease (grade BIIu). For cytomegalovirus disease manifestations other than pneumonia, either intravenous ganciclovir, valganciclovir, or foscarnet given without addition of immunoglobulin or hyperimmune globulin is recommended (grade BIIu). Intravitreal injections of ganciclovir or foscarnet can be used for the treatment of cytomegalovirus retinitis combined with systemic therapy (grade BIIu). Valganciclovir can be used in place of intravenous ganciclovir or foscarnet (except in patients with severe gastrointestinal GvHD; grade BIII). Cidofovir or the combination of intravenous ganciclovir and foscarnet can be used as second-line or third-line therapies for cytomegalovirus disease (grade BIIu). All doses (appendix) need to be adapted to the patient's renal function.

Antiviral resistance

Resistance to antiviral drugs is infrequent in HSCT recipients,^{136,137} and usually does not emerge until after several weeks of therapy. Rising cytomegalovirus antigenaemia or DNA load, or progression of cytomegalovirus disease symptoms might indicate clinical or viral resistance.¹³⁸ Clinical resistance depends on host factors, whereas viral resistance is due to mutations in the viral genome. The frequency of antiviral resistance varies between 0% and 10% between different patient populations (depending on variables such as transplant type, age, used regimens, and risk factors), with the highest frequency found in ex-vivo T-cell depleted allogeneic HSCT recipients.^{10,30}

The presence of antiviral resistance is established by genotypic assays. DNA sequencing can be used to screen for the most common mutations. Ganciclovir resistance mutations are usually found in the human cytomegalovirus gene UL97 but can also be found in gene UL54. Foscarnet and cidofovir resistance is mediated through mutations in UL54. Development of double and triple resistant strains is rare but does occur. Letermovir resistance is most commonly mediated through mutations in UL56.¹³⁸ No consensus

is available on when cytomegalovirus antiviral resistance should be suspected and testing done. The current recommended definitions are:¹³⁸ patients are refractory when the blood or plasma viral load increases by more than $1 \log_{10}$ after at least 2 weeks of appropriate antiviral therapy; patients are probably refractory when the viral load persists but does not increase by more than $1 \log_{10}$ after at least 2 weeks of appropriate antiviral therapy; and patients are resistant when symptoms of cytomegalovirus disease worsen after at least 2 weeks of appropriate antiviral therapy. However, the viral load might be substantially higher if the start of antiviral therapy is delayed by at least 3 days after taking the index sample. In such cases, a new sample should be obtained.

Cytomegalovirus immunotherapy

Several studies have aimed to prevent or treat cytomegalovirus infection and disease by the transfer of cytomegalovirus-specific T cells.^{83,139–143} For these transfers, the cytomegalovirus-specific T-cell lines and clones were mostly derived from the stem cell donor, but in some studies also from a third party donor or from the patient's own cytomegalovirus-specific T cells obtained before HSCT. Although some studies show efficacy of third party T cells, a 2017 trial showed that the cytomegalovirus-specific CD8 T cells selected by streptamer staining persisted only transiently.¹⁴⁴ Cytomegalovirus-specific T-cell clones can be produced from peripheral blood mononuclear cells and repetitively stimulated with cytomegalovirus-infected fibroblasts or other cyto-megalovirus-antigen presenting cells.^{83,140,145} However, during long-term culture, the antigen-specific T cells lose their proliferative capacity and persist only for small amounts of time after in-vivo transfer. Therefore, the success of these strategies has been low.¹⁴⁰ Techniques such as the cytokine capture assay and the tetramer, pentamer, and streptamer assays have been applied to generate cytomegalovirus-specific T cells. The transfer of such cells can reconstitute virus-specific T-cell immunity and successful transfer has been reported with as few as 1×10^3 cytomegalovirus-specific T cells per kg.¹⁴⁶ When given therapeutically to patients with refractory cytomegalovirus infection, viral load decreased after an increase in the number of cytomegalovirus-specific T cells.^{146–148} High-dose steroids (>1 mg prednisolone per kg) might interfere with cytomegalovirus-directed cytotoxic T-cell function and potentially interfere with the efficacy of adoptive T-cell therapy.

The cytokine catch and streptamer assays allow the selection of not only cytomegalovirus-specific T cells but also multipathogen-specific or even multiantigen-specific T cells.¹⁴⁹ Trials are ongoing (NCT02108522 and NCT02510417) to study the transfer of these multiantigen-specific T cells following T-cell depleted HSCT to build on results from initial studies.^{142,149}

Recommendation for immunotherapy of cytomegalovirus infection and disease

Adoptive T-cell therapy can be considered in patients with refractory cytomegalovirus infection post-transplant (grade BIIu).

Cytomegalovirus infections in autologous HSCT recipients and in patients with haematological malignancies

Autologous HSCT recipients show similar frequencies of cytomegalovirus infections (30–50% in seropositive individuals)^{150–152} as patients receiving an allogeneic HSCT, but have lower cytomegalovirus disease incidence and frequency (<1%). In some situations, the risk of cytomegalovirus reactivation seems to be increased, for example in CD34-selected patients and patients receiving high-dose antithymocyte globulin for the treatment of autoimmune disease.¹⁵³

Recommendations for management of cytomegalovirus infection and disease after autologous HSCT

For standard autologous HSCT recipients, routine monitoring and pre-emptive therapy is not recommended (grade DIIu). High-risk patients receiving autologous HSCT, such as patients with autoimmune disease with CD34 selection or receiving antithymocyte globulin, might benefit from monitoring and the use of pre-emptive therapy (grade CIIu).

Other patients

Cytomegalovirus serological status has an important effect on the incidence of cytomegalovirus infection also in non-transplant patients with haematological malignancies. In an epidemiological analysis, cytomegalovirus-seronegative patients had a frequency of pp65 antigenaemia of 2·5% compared with 14·3% in seropositive patients.¹⁵⁴ **The non-HSCT patient groups most at risk of developing cytomegalovirus-associated complications are patients with lymphoid malignancies, patients receiving T-cell suppressive therapy with purine analogues, and patients receiving alemtuzumab.**^{155–158} Cytomegalovirus infection and end-organ disease were also frequent in patients receiving hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (occurring in about 10% of these patients).^{159,160}

Several drugs recently introduced into clinical practice have been associated with symptomatic cytomegalovirus infection and rare cases of cytomegalovirus disease. Idelalisib is a selective competitor inhibitor of adenosine-5'-triphosphate in the phospho-inositide 3-kinase/Akt pathway. Interim results of a phase 3 study comparing idelalisib or placebo in combination with bendamustine and rituximab in relapsed or refractory chronic lymphocytic leukaemia showed cytomegalovirus infection and disease in 13 of 207 patients (6%) in the idelalisib group, compared with three of 209 patients (1%) in the placebo group.¹⁶¹ The UK Medicines and Healthcare products

Regulatory Agency recommends that patients receiving idelalisib are monitored regularly for clinical and laboratory signs of cytomegalovirus infection.¹⁶² Symptomatic cytomegalovirus infection has also been reported occasionally in patients treated with other new drugs including dasatinib, ibrutinib, brentuximab vedotin, and daratumumab. More data are needed to assess these infection risks and no recommendations relating to management strategies with these new drugs can be made. An increasing amount of data also highlights cytomegalovirus as an important pathogen in patients managed in intensive care units, and therefore testing for cytomegalovirus should be considered in patients with **haematological malignancies requiring intensive care** with unexplained fever or with symptoms compatible with cytomegalovirus disease.¹⁶³

Recommendations for patients treated with alemtuzumab

Monitoring of and antiviral treatment for patients testing positive for cytomegalovirus and showing symptoms compatible with a cytomegalovirus infection is one management option in patients receiving alemtuzumab (grade BIIu). Regular monitoring is recommended during the period of maximum immunosuppression (grade BIIu). Treating asymptomatic patients is not mandatory but careful clinical observation of patients with documented cytomegalovirus reactivation is necessary (grade BIIu). Withholding alemtuzumab is not considered necessary, unless symptoms persist (grade BIII).

Recommendations for patients treated with idelalisib

A cytomegalovirus management strategy is recommended for patients receiving idelalisib (grade BIIu). For patients who are cytomegalovirus seronegative, leucocyte-depleted or cytomegalovirus-seronegative blood products should be given (grade BIII). For patients with symptoms compatible with cytomegalovirus infection, testing for cytomegalovirus should be considered (grade BIIu); antiviral therapy with ganciclovir or valganciclovir should be given to symptomatic patients (grade BIIu). For patients who are cytomegalovirus seropositive, PCR monitoring of cytomegalovirus could be considered (grade CIII). Pre-emptive cytomegalovirus therapy could be considered (grade CIII). In cases with clinical signs consistent with cytomegalovirus infection, stopping idelalisib should be considered until symptoms resolve (grade BIII).

Recommendations for other patients with haematological malignancies

Routine anticytomegalovirus prophylaxis is not recommended (grade DIII). Routine monitoring and pre-emptive therapy are not considered necessary (grade DIII).

Conclusion

Cytomegalovirus is a major pathogen in patients with haematological malignancies, especially after allogeneic HSCT. New methods of transplantation pose challenges

in determining optimal management strategies for cytomegalovirus infection and disease. New diagnostic techniques including monitoring of the cytomegalovirus-specific immune response need further study. Recently, letermovir, given as prophylaxis, was shown to reduce the risk of clinically significant cytomegalovirus infection. The treatment of resistant or refractory cytomegalovirus infection and disease remains to be a major therapeutic challenge.

Contributors

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