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Management of Cytomegalovirus Infection after Solid-Organ or Stem-Cell Transplantation

Current Guidelines and Future Prospects

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Summary

Recent developments in diagnosis and therapy of cytomegalovirus (CMV) infection have helped to reduce CMV-associated mortality following organ transplantation. However, CMV is still associated with significant morbidity in recipients of an allogeneic stem cell or solid-organ transplant. The clinical symptoms of active CMV infection *per se* and, most importantly, the prevalence of life-threatening CMV disease show broad variation between different patient populations depending on the type of transplant and the intensity of immunosuppression. Therefore, management of CMV infection must be stratified according to risk profiles of a given patient population.

In the past decade, novel diagnostic assays (such as rapid shell-vial culture, polymerase chain reaction, pp65 antigen assay and sensitive hybridisation techniques) have been developed. Broad variations in the ability of a given test to predict a positive or negative risk of developing CMV disease have been observed between different transplant modalities.

Highly effective therapeutic agents against CMV, such as ganciclovir and foscarnet, have become available, improving the outcome of patients with CMV disease. Moreover, antiviral prophylaxis with ganciclovir or aciclovir has been shown to reduce CMV infection and CMV disease following organ transplanta-

tion. However, these drugs are often associated with considerable toxicity. Moreover, antiviral resistance to ganciclovir and foscarnet has been observed in recipients of organ transplants and, even more frequently, in patients with AIDS.

Short courses of pre-emptive antiviral therapy, administered after CMV infection has been documented by sensitive diagnostic techniques prior to the development of clinical symptoms, help to reduce duration and incidence of adverse effects associated with antiviral drugs and are thus an attractive alternative strategy compared with antiviral prophylaxis. Newer options, such as oral ganciclovir, cidofovir, benzimidavir (1263W94) and lobucavir, are currently under investigation and might further improve the management of CMV infection in recipients of solid-organ or stem-cell transplants.

Despite recent developments in diagnosis and treatment, cytomegalovirus (CMV) infection remains one of the most important opportunistic infections in recipients of solid organ and allogeneic bone marrow transplants (BMT).[1-7] The incidence of CMV infection increases with intensity and duration of immunosuppression, and approaches 70% in allogeneic BMT recipients who are CMV-seropositive and/or receiving a transplant from a CMV-seropositive donor,[1,4] as well as in CMV-seronegative organ allograft recipients with a CMV-seropositive donor.[8-10] CMV disease is still associated with significant morbidity in these high-risk patients and also (despite combined treatment with ganciclovir and high-dose immunoglobulins) with mortality in recipients of an allogeneic stem-cell transplant.[4,11-13] Thus, there have been major efforts to develop sensitive screening assays that allow early initiation and monitoring of antiviral therapy.[2,14-19]

Pre-emptive antiviral therapy for documented asymptomatic CMV infection (based on sensitive screening tests),[1,20,21] as well as antiviral chemoprophylaxis,[3,6,7,10] have been shown to significantly reduce the incidence of CMV disease in high-risk patients. Since these new antiviral strategies were introduced, a change in the clinical manifestations of CMV disease has been observed; for example, CMV retinitis may occur more than 100 days after allogeneic stem cell transplantation.[22] At several centres, new therapeutic strategies to enhance CMV-specific immune reconstitution, such as the adoptive transfer of protective CMV-specific T cells, are currently under investigation.[23-26]

In this article, we discuss diagnostic assays and current and future strategies for the management of CMV infection and disease after solid-organ and stem-cell transplantation.

1. Diagnosis of Cytomegalovirus (CMV) Infection

Cell-culture viral-isolation techniques remain the standard for diagnosis of CMV infection. More sensitive detection systems for CMV-specific proteins and nucleic acid sequences have been developed, and new antiviral strategies based on these assays have helped to improve patient management (table I).

1.1 Culture Assay

Conventional detection of CMV in clinical specimens has been achieved by direct viral culture in human fibroblasts, with follow-up visual examination for cytopathic effects over a period of 14 to 28 days. As rapid results are required for patient management, the standard diagnostic procedure now includes rapid centrifugation cultures [detection of CMV-specific immediate-early antigen fluorescent foci (DEAFF) test, dram vial culture] followed by immediate-early antigen staining with labelled monoclonal antibodies after 12 to 48 hours.[27] Despite these modifications, culture methods lack the sensitivity to diagnose CMV infection in patients early enough to prevent CMV disease after allogeneic BMT.[20,28,29] Moreover,

concomitant antiviral prophylaxis (e.g. aciclovir) can inhibit viral growth. Nevertheless, virus isolation should be attempted in all patients, as the viral stock might be necessary to test for antiviral resistance.[30,31]

1.2 CMV-Antigenaemia Assay

The pp65 antigenaemia assay is widely used in Europe and the US. Cytospin preparations of peripheral leucocytes are stained with monoclonal antibodies directed against the lower matrix protein pp65.[14,16,19] The number of positively stained cells per given cell number can be quantitatively evaluated, given thresholds can be used to decide on initiation of antiviral therapy, and the decrease in the number of positively stained cells can be used to monitor the success of antiviral therapy.[1] The major drawback of the antigenaemia assay is the need for immediate processing of blood samples to achieve optimal sensitivity and the consideration of certain technical aspects in order to avoid pitfalls.[14,15]

1.3 CMV Polymerase Chain Reaction Assay

DNA amplification by the polymerase chain reaction (PCR) has proven to be a reliable method of detecting CMV infection in clinical samples.[2,18,32-34] Depending on technical aspects of the amplification procedure (such as choice of target sequences, characteristics of primers, amplification rounds, nested PCR assays or hybridisation steps targeting internal sequences of the amplicon), the sensitivity can be dramatically increased, which might be crucial for the detection of CMV in certain samples, such as cerebrospinal fluid.

Transport of samples, and a delay of up to 2 days, does not appear to adversely affect PCR analysis.[35,36] PCR assays provide a very high sensitivity and thus a high negative predictive value, whereas their positive predictive values (number of patients with a positive PCR result who develop symptomatic CMV infection) were found to be rather low.[2,9,16,32,33,37,38] The positive predictive values also vary according to the clinical material (e.g. plasma versus leucocytes or whole blood) and the population under study.[17,33,39-43] Most recently, quantitative assessment of PCR reactions

Table I. Diagnosis of cytomegalovirus (CMV) infection: comparison of methods of early diagnosis and monitoring of antiviral therapy, showing their suitability in different patient populations

Detection method	Solid-organ transplant			BMT/PBPCT	
	kidney	liver	heart-lung	autologous	allogeneic
Serology:					
CMV detection	+	–	–	–	–
therapy monitoring	–	–	–	–	–
Virus culture:					
CMV detection	+++	++	++	++	++
therapy monitoring	+	+	+	+	–
pp65 Antigenaemia:					
CMV detection	+++	+++	+++	+++	+++
therapy monitoring	+++	+++	+++	+++	++
DNA–PCR:					
CMV detection	+++	+++	+++	++	+++
therapy monitoring					
qualitative	+	+	+	+	++
quantitative	+++	+++	+++	++	+++

Abbreviations and symbols: BMT = bone marrow transplant; DNA-PCR = DNA amplification by the polymerase chain reaction; PBPCT = peripheral blood progenitor-cell transplant; – = not suitable; + = major disadvantage; ++ = suitable, but minor disadvantages; +++ = suitable.

has become available through the use of internal standards and PCR enzyme-linked immunosorbent assay (ELISA) techniques.[34,44-47] A higher viral DNA load in symptomatic, compared with asymptomatic patients, has been documented in organ allograft recipients and patients with AIDS.[13,46]

To further improve the positive predictive value of PCR assays, reverse transcription (RT)-PCR assays have been developed.[48-51] As these assays are very time- and labour-intensive, routine application for screening clinical samples is not feasible. Comparison of RT-PCR and DNA-PCR assays has shown a higher specificity of the former for predicting the diagnosis of symptomatic CMV infection following solid-organ transplantation;[48,52] however, because of the lower sensitivity of the assay, early diagnosis of CMV infection might be missed.[50]

1.4 Hybridisation Assay

CMV-specific DNA probes are used to diagnose local CMV infection in the gut or in the liver,[53,54] but lack the sensitivity to allow early diagnosis of CMV infection in blood samples.[55] New, commercially available, solution hybridisation antibody capture assays have been developed for the quantitative detection of CMV DNA in leucocytes, and have proven useful for early diagnosis and monitoring of antiviral therapy in patients with AIDS and in solid-organ transplant recipients.[56-59] As PCR, antigenaemia and even culture assays are poorly standardised in different laboratories, commercialised hybridisation assays might help to standardise the diagnosis of CMV infection in multicentre drug trials.

2. Management of Clinical Manifestations of CMV Infection

At the 4th International Cytomegalovirus Workshop in Paris in 1993, criteria were defined for clinical diagnosis of CMV infection and disease.[60] Diagnosis of active CMV infection requires detection of CMV in clinical specimens by conventional or rapid cell culture, or by detection of CMV antigens in peripheral blood leucocytes. PCR is acceptable if the assay applied shows a reasonable correlation with the above-mentioned diagnostic methods. Diagnosis of CMV disease is based on symptoms and/or signs from the affected organ together with CMV detected in tissue specimens from that organ. In transplant recipients, CMV-induced interstitial pneumonia is diagnosed in the presence of clinical symptoms with CMV detected in the bronchoalveolar lavage fluid.

Table II. Results of studies assessing prophylaxis of cytomegalovirus (CMV) infection in transplant recipients

Procedure	Antiviral strategy	CMV (% of patients)			Survival (%)	Reference
		infection	disease	death		
Allogeneic BMT	IV + PO aciclovir	52	9	0	75	6
	IV aciclovir/placebo	49	16	6	63	
	Aciclovir/placebo	61	12	6	59	
	Ganciclovir	20	10	8	70	7
	Placebo	43	24	9	64	
	IV aciclovir + ganciclovir	3	0 (9)	3	70	3
	IV aciclovir + placebo	45	29 (32)	6	74	
Allogeneic + autologous BMT	IV foscarnet	33[a]	17[a]	17[a]	NA	63
Liver transplant	Ganciclovir	5	0.8	0	91	10
	Aciclovir	38	10	0.8	88	
	PO aciclovir	61	28	2.8	NA	64
	IV ganciclovir/PO aciclovir	24	9	0	NA	
Solid-organ transplant	Aciclovir	NA	21	0	NA	8
	Ganciclovir + CMVIG	NA	31.6	0	NA	

a Allogeneic BMT.

Abbreviations: BMT = bone marrow transplantation; CMVIG = CMV hyperimmune globulin; IV = intravenous; NA = not analysed; PO = oral.

Table III. Results of clinical trials assessing pre-emptive antiviral therapy against cytomegalovirus (CMV) infection following transplantation

Procedure	Screening method	Antiviral strategy	CMV (% of patients)			Survival	Reference
			infection	disease	death		
Allogeneic BMT	Virus culture (blood, urine, throat wash)	IV aciclovir + ganciclovir	0	3	0	3	28
		IV aciclovir + placebo	11	43	17	17	
	Virus culture (BAL post-transplant day 35)	Ganciclovir	NA	10	NA	NA	29
		Placebo	NA	70	NA	NA	
	Whole blood PCR	Ganciclovir + CMVIG	59	5.4	0	84	20
	Culture (blood, urine, throat wash)	Ganciclovir + CMVIG	44	23.5	5.8	50	
	pp65 Antigenaemia	Ganciclovir prophylaxis	41	16.1	12	71	1
		Ganciclovir antigen-guided	79	20.2	12	73	
Liver transplant	Virus culture (blood, urine)	Aciclovir prophylaxis	42	29	0	87.5	65
		Ganciclovir (7-21 days)	26	4	0	91	

Abbreviations: BAL = bronchoalveolar lavage; BMT = bone marrow transplant; CMVIG = cytomegalovirus hyperimmune globulin; IV = intravenous; NA = not analysed; PCR = polymerase chain reaction.

The clinical signs and symptoms of CMV disease vary widely between different transplant settings. Following allogeneic BMT and heart-lung transplantation, interstitial pneumonia (IP) is the leading manifestation of CMV disease. Mortality from CMV-IP after allogeneic BMT exceeds 70%,[4] and the pathogenesis seems to have an immunopathological component.[61] However, the mortality from CMV-IP in recipients of solid-organ transplants is substantially lower. CMV hepatitis is most often observed after liver transplantation, and CMV syndrome (comprising fever, malaise, atypical lymphocytosis, leukopenia, myalgia and arthralgia) is most common after renal transplantation.[8,41,62] CMV gastrointestinal disease and retinitis are rarely observed in the transplant population.

As the management of CMV infection depends on the underlying disease, the remainder of section 2 is concerned with diagnostic, prophylactic and antiviral intervention strategies in different patient cohorts (see also tables II and III).

2.1 Allogeneic Bone Marrow Transplantation (BMT)

CMV infection remains the most frequent infectious complication following allogeneic BMT, occurring in approximately 60 to 70% of patients who were CMV-seropositive before transplant or received a transplant from a CMV-seropositive donor.[4] Without antiviral intervention, about 50% of patients with documented CMV infection will develop CMV disease.[4] Combined therapy with ganciclovir and CMV-hyperimmune globulins has led to a pronounced reduction in early mortality from CMV-IP; however, long term survival is low (30 to 40%).[11,13]

Thus, the prevention of acquisition of exogenous virus in CMV-seronegative patients receiving a transplant from a CMV-seronegative donor is of major importance. Primary infection can be efficiently prevented by transfusion of blood products from CMV-seronegative donors or leucocyte-depleted blood products, if a leucocyte depletion of at least 3 log can be provided.[66-68]

Antiviral prophylaxis to suppress reactivation of CMV if the patient and/or donor is seropositive is a highly efficient approach to preventing CMV infection and disease.[3,6,7] High-dosage intravenous aciclovir in a dosage of 500 mg/m^2 3 times daily until post-transplant day 30 significantly reduced the probability and delayed the onset of CMV infection. Most importantly, survival could be significantly improved by high-dosage intravenous aciclovir compared with low-dosage oral administration.[6] Although prolonging aciclovir prophylaxis beyond post-transplant day 30 did not further reduce the risk of developing CMV infection, survival seemed to be improved.[6]

In high-risk allogeneic BMT recipients, prophylaxis with intravenous ganciclovir administered from the time of engraftment until post-transplant day 100, has been assessed in 2 studies.[3,7] In both, a significant reduction in the incidence of CMV infection was demonstrated, and in one study[3] a reduction in CMV disease was observed. Moreover, in both studies, the survival of patients receiving ganciclovir was similar to that of patients in the high-dosage aciclovir trial.[6] However, ganciclovir prophylaxis was associated with significant toxicity, inducing therapy-related neutropenia and secondary bacterial infections.

Preliminary experience in recipients of an allogeneic stem-cell transplant indicates that oral ganciclovir can be safely used in patients with acute graft-versus-host disease (GVHD) of the gut,[69] and further investigation is warranted.

Pre-emptive or early antiviral therapy has been introduced as a novel therapeutic strategy; antiviral drugs are used only in patients with active CMV infection, with the aim of restricting treatment to patients at high risk of CMV disease. Early treatment with ganciclovir, based on a positive virus-culture assay, has been evaluated in 2 large studies.[28,29] Ganciclovir was administered either at the time of first detection of CMV excretion from blood, urine or throat-washing samples,[28] or from a bronchoalveolar lavage sample taken at post-transplant day 35.[29] In both studies, pre-emptive antiviral therapy reduced CMV disease and transplant-related mortality. However, 12 to 13% of patients presented with CMV disease before or coincident with CMV excretion, leading to a 10% CMV-related mortality in patients receiving pre-emptive antiviral therapy.[28,29,70]

Thus, more sensitive techniques, such as pp65 antigenaemia assay and PCR from leucocytes or plasma, have been applied to detect CMV infection before the onset of CMV disease.[2,14,18,19,71,72] CMV was detected up to 20 days earlier by PCR than by the culture technique.[2,17,20,21,44] In a study comparing PCR-based and culture-based pre-emptive antiviral therapy, PCR screening permitted the introduction of antiviral therapy significantly earlier compared with the culture assay.[20] Additionally, stopping and withholding antiviral therapy was found to be safe (i.e. none of these patients developed CMV disease) in PCR-negative patients.[20,32] Moreover, the incidence of CMV disease and CMV-related mortality were decreased, and the duration of antiviral therapy was significantly shorter, in the PCR-monitored group, leading to a reduced incidence of ganciclovir-related adverse effects such as neutropenia and nonviral infections. Overall survival at post-transplant days 100 and 180 was significantly improved in the PCR-monitored group.[20] Highly sensitive assays are mandatory in patients with severe acute GVHD and recipients of a graft from an unrelated donor, who have been shown to develop breakthrough infections while receiving ganciclovir prophylaxis.[1,20,73,74]

The CMV antigenaemia assay has been shown to detect CMV infection in BMT recipients a median of 10 days before the onset of CMV-IP.[14] Moreover, higher antigen levels were detectable in patients with subsequently proven CMV disease, indicating that quantification might help to reduce overtreatment, as it permits the identification of patients at highest risk for CMV disease.[14,75]

Boeckh et al.[1] compared antigenaemia-guided antiviral therapy with ganciclovir prophylaxis starting at engraftment until post-transplant day 100 in 226 CMV-seropositive allogeneic BMT recipients. 16 patients (14%) in the antigenaemia-ganciclovir group developed CMV disease before day 100, compared with 3 (2.7%) in the ganciclovir group. Ten of the 16 patients developed CMV disease before or during the first episode of antigenaemia and 6 after cessation of antiviral therapy. Low-grade antigenaemia progressed to CMV disease only in patients with acute grade III or IV GVHD. The rates of CMV disease, CMV-related death, transplant survival and neutropenia were not significantly different between the 2 groups at post-transplant day 180. Ganciclovir therapy at engraftment was associated with a higher rate of early invasive fungal infection and late (i.e. after post-

transplant day 100) CMV disease, resulting in a similar survival rate in both groups.

The efficacy of immune globulin in preventing CMV infection and disease following allogeneic BMT has been the cause of some controversy. A large meta-analysis has shown that passive immunisation permits a reduction in the rate of CMV infection and CMV-IP,[76,77] but controlled trials have not demonstrated a significant reduction of CMV disease and CMV pneumonia.[78,79] As immunoglobulin infusions are very costly and the results still conflicting, administration of immunoglobulin infusions cannot be recommended without further study.

As a result of the extended use of antiviral drugs in the early post-transplant period, as either prophylaxis or pre-emptive therapy,[30,31] an increased rate of late-onset (after post-transplant day 100) CMV disease has been observed, possibly caused by a delay in the recovery of CMV-specific T cell responses.[80,81] Reconstitution of the CMV-specific cellular immune response has been proven to be protective against CMV disease following allogeneic BMT.[82,83] Thus, the transfer of CMV-specific immunity in these patients is currently under investigation. Riddell et al.[24,25] showed that the transfer of *ex vivo* expanded CMV-specific donor-derived CD8+ cytotoxic T-lymphocyte (CTL) clones to BMT recipients was feasible and well tolerated. In their extended experience in 14 patients, reconstitution of CMV-specific CTL activity and persistence *in vitro* has been demonstrated for up to 12 weeks following transfer of *in vitro* expanded CTL clones.[26] However, cytotoxic activity declined in patients who were deficient for CMV-specific CD4+ T-helper cells, suggesting that T cell assistance is essential for the persistence of transferred CMV-specific CTLs following allogeneic BMT. Further studies are needed to assess protective long term reconstitution of CMV-specific cellular immunity in patients at high risk of developing CMV disease.

In conclusion, both pre-emptive and prophylactic antiviral treatment strategies have helped to significantly reduce CMV-associated mortality in recipients of an allogeneic BMT. Compared with antiviral prophylaxis, pre-emptive antiviral therapy has the advantage of stratifying patients according to individual risk factors (active CMV infection, viral load) and thus helps to reduce the number of patients treated and also the duration of antiviral therapy, which might have important implications for adverse effects and the emergence of antiviral resistance.[31,84] However, sensitive screening is costly and must be performed on at least a weekly basis. Therefore, antiviral prophylaxis remains an attractive approach.

2.2 Autologous BMT and Peripheral-Blood Progenitor-Cell Transplantation

Following autologous BMT and peripheral-blood progenitor-cell transplant (PBPCT), the incidence of CMV infection and disease was found to be much lower compared with allogeneic BMT,[85-88] whereas the case-fatality rate from CMV pneumonia following autologous was similar to that following allogeneic BMT.[85,86] No effective CMV prophylaxis has been reported for seropositive autograft recipients; high-dosage intravenous aciclovir was not effective in preventing CMV disease in this setting.[89]

As the majority of autograft recipients do not develop a positive virus culture before the onset of CMV disease,[89] antigenaemia and CMV-PCR have recently been evaluated. In a prospective study evaluating the pp65 antigenaemia assay in 67 patients undergoing autologous BMT or PBPCT, antigenaemia occurred in 26 patients (38.8%) at a median of 33 days post-transplant. Low-level antigenaemia (<5 positive cells per slide) in 19 patients was not associated with CMV disease, whereas 2 of the 7 patients with high-level antigenaemia (>5 positive cells per slide) developed fatal pneumonia.[90]

Our group[36] prospectively screened 98 patients following autologous BMT and PBPCT for CMV infection, using a sensitive CMV-PCR assay. CMV-PCR positivity was documented in 21 of 53 CMV-seronegative patients (39.6%) at a median of day 20, and in 19 of 45 CMV-seropositive patients

(42.2%) at a median of day 17, post-transplant. Low blood levels of CMV-DNA (1 to 10 pg/L) for 1 week occurred in 31 patients and were never associated with CMV disease. Of the 9 patients who presented with 2 or more consecutive positive PCR results, 1 developed proven CMV pneumonia and 2 developed suspected CMV hepatitis. Thus, according to the results presented, only patients with repeated positive PCR assays or high-level antigenaemia lacking CMV-specific T-cell immunity[91] are at risk of developing CMV disease.[36]

However, because of the low incidence of CMV disease in autograft recipients, monitoring by sensitive assays should be limited to patients at high risk. These patients include CMV-seropositive patients receiving myeloablative conditioning regimens (such as cyclophosphamide/total body irradiation or busulfan/cyclophosphamide), especially when receiving manipulated grafts (e.g. 4-hydroperoxy-cyclophosphamide–purged marrow transplants).[36,90]

2.3 Solid-Organ Transplantation

Cytomegalovirus infection is a common cause of morbidity in recipients of solid-organ allografts, with favourable outcomes in the vast majority of patients. The incidence of active infections is about 30 to 50%,[37] depending on the CMV serology of the donor and recipient before the transplant, the type of transplant and the intensity of immunosuppressive therapy.[8,37,65] CMV-seronegative patients receiving a graft from a CMV-seropositive donor, patients with corticosteroid-resistant rejection treated with monoclonal or polyclonal anti–T cell antibodies, and recipients of a liver or heart-lung transplant, have a very high risk of developing CMV disease.[8,10,41,92-95] Symptomatic CMV infection occurs predominantly during the first 4 months after transplant, and late CMV disease has rarely been reported. Tissue-invasive infections tend to occur predominantly in the organ allograft, while CMV interstitial pneumonitis and gastrointestinal disease occur less often following a solid-organ transplant than after an allogeneic stem-cell transplant.[10,64] Moreover, even established CMV disease responds promptly to antiviral therapy with ganciclovir in the vast majority of patients.

Following renal allografting, rejection and local CMV infection can be very difficult to differentiate, as the clinical symptoms of both complications overlap. Conflicting evidence has been presented regarding the association of CMV infection with allograft rejection. A higher incidence of acute rejection episodes has been observed among CMV-infected kidney allograft recipients compared with noninfected patients in some studies,[96,97] whereas others[98-100] have reported no influence of CMV infection on acute rejection and, most importantly, on long term graft survival. Following heart transplantation an association of coronary artery disease with CMV infection has been described,[101,102] whereas in kidney allografts, obliterative transplant arteriopathy did not seem to be related to direct CMV infection of the graft.[98]

Because of the negligible case-fatality rate of tissue-invasive CMV disease, the need for antiviral prophylaxis following solid-organ transplantation remains a matter for discussion. However, as CMV infection is associated with significant morbidity and costs, various prophylactic strategies have been evaluated.

High-dosage oral aciclovir given for 12 weeks after renal transplantation has been shown to significantly reduce CMV disease in CMV-seronegative patients with a CMV-seropositive donor; however, no impact on patient or allograft survival at 1 year could be demonstrated.[103] Thus, oral aciclovir may be indicated as a prophylactic agent in high-risk renal allograft recipients.[5]

Prophylaxis of CMV infection with intravenous ganciclovir (starting on the day of transplant and continuing until post-transplant day 100) has been found to significantly reduce CMV infection and disease following liver transplantation, compared with high-dosage intravenous aciclovir,[10] whereas a 6-week prophylactic regimen of ganciclovir following lung transplant had no impact on CMV infection.[104] After a mean follow-up of about 2 years, only 2 patients in the ganciclovir group, who were receiving intensive immunosuppression for

chronic rejection, developed late-onset CMV disease and might have been candidates for prolonged antiviral prophylaxis. Intravenous ganciclovir administered for 4 weeks after heart transplantation was associated with a reduced incidence of CMV disease at post-transplant day 120.[105] These results were confirmed by a subsequent study that clearly showed a benefit for CMV-seronegative patients with CMV-seropositive donors, but not for CMV-seropositive patients.[106]

Short-course intravenous ganciclovir (for 1 week *post* transplant) was found to be inferior to oral aciclovir for 12 weeks as prophylaxis in a large cohort of mixed allograft recipients.[8] In contrast, short-course ganciclovir given for documented CMV infection significantly reduced the incidence of CMV disease following liver transplantation, compared with prophylactic high-dosage oral aciclovir for 24 weeks,[65] thus indicating that short courses of pre-emptive antiviral therapy with ganciclovir might be an attractive alternative approach to prevent CMV disease following solid-organ transplantation.

Oral ganciclovir given immediately after orthotopic liver transplantation for 14 weeks significantly reduced the incidence of CMV disease compared with placebo, especially in CMV-seronegative patients with a CMV-seropositive donor. Again, no effect on graft survival or rate of rejection episodes was observed.[107]

Prophylaxis with CMV-specific immunoglobulins has been shown to reduce the incidence of CMV disease in patients undergoing orthotopic liver transplantation,[108] but not the rate of CMV infection, or graft and patient survival, at 1 year after transplant. No effect could be demonstrated in patients at highest risk, such as CMV-seronegative recipients of a graft from a CMV-seropositive donor and in heart-lung transplant recipients.[8,92]

Sensitive and accurate diagnosis of CMV infection is mandatory for early intervention strategies.[109,110] The positive predictive value of a positive blood culture was found to be significantly higher than that of a positive urine or throat-washing sample in renal allograft recipients; however, because of the low sensitivity of the assay, CMV infection was often diagnosed when CMV disease had already occurred.[71,111] Quantitative shell-vial culture has been shown to detect CMV in a similar proportion of patients to PCR and pp65 antigenaemia, but infection was detected earlier by the sensitive assays.[62,112,113]

Recent studies indicate that renal allograft recipients treated with antithymocyte antibodies for corticosteroid-resistant rejection could benefit from PCR- or antigenaemia-guided early antiviral therapy;[112,114] this approach may also be considered after liver or heart-lung transplantation.[5,92] To avoid a high rate of overtreatment,[114] only patients with a high or increasing viral load should be considered as candidates for pre-emptive antiviral therapy.[115,116] As a positive PCR assay might persist for months following organ transplantation, despite antiviral therapy, the best method of monitoring antiviral therapy has still to be defined.

Thus, short courses of antiviral therapy during intensive immunosuppression and, more ideally, during documented CMV infection might be an attractive alternative to antiviral prophylaxis in recipients of a solid-organ transplant. Oral ganciclovir may help to reduce duration of hospitalisation. Moreover, with the availability of quantitative CMV assays, therapeutic decisions could be based on the viral load in the blood. These strategies could help to reduce the high rate of overtreatment and to prevent emergence of ganciclovir- and foscarnet-resistant viral strains.[31,79,84]

3. Conclusions

The development and application of sensitive diagnostic assays such as PCR and pp65 antigenaemia has helped to increase our understanding of the incidence and course of CMV infection after haematopoietic stem cell and organ allograft transplantation. Therapeutic strategies based on these sensitive assays have been successfully applied to patients at very high risk of developing CMV disease, but further study and patient stratification based on the available quantitative diagnostic assays is needed in patients at lower risk (such as

kidney allograft recipients) to avoid a high rate of overtreatment.

After solid organ transplantation, intravenous ganciclovir alone results in resolution of clinical signs of CMV disease in the vast majority of patients. Prophylactic therapy or short courses of preemptive antiviral therapy with ganciclovir based on sensitive detection methods are beneficial in high-risk patients after solid organ transplantation, especially in seronegative patients with a seropositive donor and patients receiving severe immunosuppressive therapy to prevent or to treat allograft rejection. However, ganciclovir is often found to be associated with considerable bone marrow toxicity. Aciclovir is better tolerated but less effective in preventing CMV disease.

In patients after allogeneic stem cell transplantation, intravenous ganciclovir in combination with immune globulin infusions is the currently recommended therapy for established CMV-IP; however, the outcome remains poor. For CMV enteritis and hepatitis, ganciclovir is administered as monotherapy. Thus, pre-emptive or prophylactic antiviral therapy with ganciclovir is clearly indicated. As the recovery of the CMV specific immunity in patients receiving prophylactic or preemptive antiviral therapy with ganciclovir might be significantly delayed, sensitive screening for CMV infection beyond day 100 seems reasonable. Following autologous stem cell transplantation, neither antiviral prophylaxis nor pre-emptive therapy can be recommended at the moment.

Further definitions of risk factors will help to develop risk-adapted antiviral strategies. Novel antiviral drug compounds like cidofovir, benzimidavir (1263W94) or lobucavir show promising efficacy against CMV and are currently under investigation in phase I/II trials. The availability of these new drugs will further increase our therapeutic armamentarium against CMV. Moreover, adoptive transfer of CMV immune responses might be beneficial in defined patient subgroups at greatest risk of developing fatal CMV disease.

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