Clinical knots

Is cytomegalovirus viraemia a useful tool in managing CMV disease?

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HIV related cytomegalovirus (CMV) disease results from reactivation of latent infection when the CD4 count falls below 100 cells $\times 10^6/l$. Before the introduction of highly active antiretroviral therapy (HAART) up to 40% of HIV infected patients developed CMV disease, predominantly retinitis. Early diagnosis of retinitis may result in a better response to therapy and reduced loss of vision. As retinitis is often asymptomatic in the early stages, other methods of identifying individuals at risk are required.

CMV viraemia precedes disease so the detection of CMV viraemia identifies individuals at highest risk. Cell culture based methods of detection have now been superseded by polymerase chain reaction (PCR) and pp65 antigenaemia assays. The application of quantitative techniques has shown that elevated CMV load increases the risk of CMV disease in congenital infection¹ and following renal,² liver,³ and bone marrow⁴ transplantation.

Identification of patients at risk of CMV disease

The detection of CMV reactivation by polymerase chain reaction (PCR) is a strong predictor of disease.⁵⁻⁷ CMV load is significantly higher in patients who develop disease and the risk of disease increases with increasing CMV load; high CMV load also correlates with decreased survival.⁵ Two large randomised controlled trials of CMV prophylaxis showed that CMV PCR positivity at baseline is a significant risk factor for CMV disease and is associated with an increased risk of death independent of CD4 count.^{8,9} In addition, CMV load has a stronger correlation with death than HIV load.¹⁰ Therefore, regular screening of patients with a CD4 count below 100 cells $\times 10^6/l$ by CMV PCR can identify those at highest risk of CMV disease and death. This allows for interventions to prevent development of disease or to optimise early diagnosis and treatment.

Monitoring of response to therapy

In the absence of anti-CMV therapy, CMV load continues to increase with progression of CMV disease up to the time of death.¹¹ Treatment with anti-CMV therapy results in a decline in CMV load, usually to undetectable.¹² Patients with high CMV load at diagnosis of retinitis are less likely to respond to induction therapy and have a decreased time to first progression.¹² Response to anti-CMV treatments can therefore be monitored and induction therapy should ideally be continued until

CMV PCR is negative. Failure to suppress CMV viraemia in a previously treated individual should raise the possibility of drug resistance and prompt consideration of treatment with an alternative agent.

Monitoring of patients on maintenance therapy

In a study of patients receiving ganciclovir maintenance for retinitis, recurrent CMV PCR positivity and increasing CMV load were observed before progression of retinitis.¹³ Recurrent CMV viraemia was also associated with the development of CMV disease at other sites. Regular screening of patients on maintenance therapy by PCR can therefore be recommended. The recurrence or persistence of CMV viraemia is an indication for systemic anti-CMV treatment in addition to local therapy (intraocular injection or implant) to reduce the risk of extraocular disease.

Prophylaxis and pre-emptive therapy

Spector *et al* reported that prophylaxis with oral ganciclovir reduced the incidence of CMV disease to 16% from 30% in the placebo group.¹⁴ Subgroup analysis by baseline CMV PCR status showed that the lowest incidence of disease was seen in patients with negative CMV PCR or low CMV loads. This suggests that early treatment of low level CMV viraemia with oral ganciclovir is effective and reduces risk of disease development. However, this is inadequate for those with high CMV loads and alternative drugs with better oral bioavailability, such as valganciclovir, are required.¹⁵ Another prodrug, valganciclovir, was as efficacious as intravenous ganciclovir in a trial of induction therapy for CMV retinitis and is therefore also an attractive agent for use as prophylaxis.¹⁶

The approach of directing treatment to patients at highest risk is termed pre-emptive therapy and offers a logical way of reducing CMV disease while avoiding drug related adverse events in those at low risk. However, the need for such strategies has decreased following the widespread introduction of HAART.

Effect of HAART on CMV disease

The studies quoted above were conducted before the widespread use of HAART. The death rate from AIDS and the incidence of all opportunistic infections, including CMV, has declined dramatically since the introduction of HAART.¹⁷ The survival of patients following CMV retinitis has increased and the risk of relapse has decreased following HAART.^{18,19}

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Figure 1 Suggested management of patients on HAART using CMV PCR. CMVR = CMV retinitis, + = CMV PCR positive, - = CMV PCR negative.

There are reported cases of CMV retinitis resolution with HAART alone.^{20, 21} However, recent reports describe the development of inflammatory complications of retinitis, such as vitritis, following HAART.^{22, 23} This has been attributed to immune reconstitution and may cause significant loss of vision in the absence of active retinitis.

Monitoring of patients on HAART

A study of patients with asymptomatic CMV viraemia at the time of initial HAART demonstrated clearance of CMV viraemia following HAART in the absence of specific anti-CMV therapy.²⁴ This was sustained for a median of 21 months of follow up and correlated with a greatly reduced risk of CMV disease. In a study of patients with low CD4 counts commencing HAART, CMV PCR positivity at baseline was the only factor associated with the development of CMV disease.²⁵ The risk was greatest in those with the highest CMV loads and most cases occurred in the first 90 days of HAART. Identification of patients who are CMV PCR positive at the time of initiation of HAART is therefore important, as they will require careful monitoring for CMV disease. Pre-emptive treatment for CMV may be considered before HAART, especially if the CMV load is high. At our hospital all patients who have ever had a CD4 count of 100 cells $\times 10^6/l$ or less undergo continued monitoring for CMV by PCR as part of a trial protocol. However, it would be reasonable to discontinue this if the CD4 count is sustained above this for more than 6 months; monitoring should be reintroduced if there is a subsequent decline in the CD4 count.

Maintenance therapy for CMV retinitis in patients on HAART

Several studies have shown that maintenance therapy for CMV retinitis can safely be withdrawn in selected patients following successful HAART.²⁶⁻³⁰ Using the criteria applied in these studies, discontinuation of maintenance may be considered if there is inactive retinitis after more than 6 months of HAART, the CD4 count has increased above 100 cells $\times 10^6/l$, there is an undetectable HIV load (or greater than 1 log₁₀ reduction in HIV load), and an absence of CMV viraemia. It is nevertheless important that individuals discontinuing maintenance therapy are monitored closely. Recurrence of CMV viraemia should prompt review of the patient's therapy, as this may be an early indicator of antiretroviral failure. The risk of CMV disease appears to be re-established if the CD4 count falls again following HAART failure or interruption.^{31, 32} In this situation consideration should be given to the alteration or intensification of HAART and to the re-institution of anti-CMV therapy.

It is unclear how long the impact of HAART may be sustained and there is concern that HAART failure will be accompanied by a re-emergence of opportunistic infections. CMV PCR therefore remains an important tool in monitoring patients in this era of rapidly changing therapy for HIV. Figure 1 shows our current investigational algorithm for monitoring patients on HAART with CMV PCR. However, this may require modification as treatments progress and, to this end, monitoring of these patients is continuing.

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