MINIREVIEWS

Cytomegalovirus infection in the bone marrow transplant patient

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Abstract

Cytomegalovirus (CMV) infection is an important contributor to the morbidity and mortality associated with bone marrow transplantation (BMT). Infection may lead to CMV disease involving multiple organs such as pneumonia, gastroenteritis, retinitis, central nervus system involvement and others. CMV seropositivity is an important risk factor and approximately half of BMT recipients will develop clinically significant infection most commonly in the first 100 d post-transplant. The commonly used tests to diagnose CMV infection in these patients include the pp65 antigenemia test and the CMV DNA polymerase chain reaction (PCR) assay. Because of its greater sensitivity and lesser turnaround time, the CMV PCR is nowadays the preferred test and serves as a main guide for pre-emptive therapy. Methods of CMV prevention include use of blood products from seronegative donors or leukodepleted products. Prophylaxis or pre-emptive therapy strategies for CMV prevention may be used post-transplant with the latter becoming more common. The commonly used antivirals for pre-emptive therapy and CMV disease management include intravenous gancyclovir and foscarnet. The role of intravenous immunoglobulin, although used commonly in CMV pneumonia is not clear.

Key words: Cytomegalovirus; Infection; Bone marrow transplant

Core tip: Cytomegalovirus (CMV) infection and CMV disease may be associated with serious complications in the bone marrow transplant patient. The most commonly used test to monitor CMV replication is the CMV DNA polymerase chain reaction assay and serves a guide for preemptive therapy. Gancyclovir followed by foscarnet are most commonly used in CMV management.

Bhat V, Joshi A, Sarode R, Chavan P. Cytomegalovirus infection in the bone marrow transplant patient. *World J Transplant* 2015; 5(4): 287-291 Available from: URL: http://www.

INTRODUCTION

Cytomegalovirus (CMV) is a member of the beta-herpesvirinae subfamily. CMV is the largest among all herpes viruses, with a size of 150-200 nm, containing a linear double stranded DNA molecule in its nucleo-capsid[1]. CMV has a tendency to cause prolonged latent infection with characteristic enlargement of infected cells with prominent intranuclear inclusion bodies. CMV can infect several types of body cells such as epithelial cells, haematopoietic cells, and connective tissue[2]. Cytomegalovirus has a wide spectrum of clinical presentation. It can present generally as asymptomatic and persistent infections in healthy individuals however, it can also lead to serious disorders among transplant recipients, immunodeficient patients and patients on immunosuppressive treatment[3]. CMV infection can appear as primary infection, reinfection or reactivation. Incidence of CMV infection is increasing, as the number of immunocompromised patients is increasing, especially in transplant cases. CMV infection is a major problem in allogeneic bone morrow transplant (BMT) cases, 30%-50% cases show clinically significant infection[4]. Human leucocyte matched(HLA) transplantation is preferred for prevention of adverse outcome, but haploidentical stem cell transplantation (Haplo-SCT) can be used as an alternative for transplantation candidate lacking HLA matched donors[5]. One major drawback of Haplo-SCT is impaired recovery of adoptive immunity,which adversely affects treatment outcomes by increasing the chances of CMV, fungal and bacterial infections[6]. Regardless of the prior seropositive status of donor or recipient, 32%-70% cases can acquire CMV infection after allogeneic BMT[1]. There is more risk of acquiring CMV infection in first 3-4 mo of transplantation[7]. CMV infection is generally seen in immediate to late post engraftment period.

Pathogenesis

CMV can ubiquitously infect any cell in human body. CMV infection to endothelial cells and haematopoietic cells will lead to systemic spread of infection[8]. Arterial vasculature remains the most common site for harbouring latent CMV[9]. Its pathogenesis is a highly complex involving human leukocyte antigens, various endothelial adhesion molecules and cytokines[10]. In immunocompetent individuals CMV infections generally remains asymptomatic and virus persist in body in latent stage[11]. Majority of CMV infections in transplant cases are due to reactivation of virus from its latent stage[12]. In adults immune reconstitution following transplantation depends mainly upon peripheral expansion of mature T lymphocytes in the allograft because of poor thymic functioning. The process of immunr reconstitution is influenced by age, HLA disparity, source of stem cells and graft composition, various conditioning regimens and steroid administration[5].The serological status of the transplant recipient is a significant risk factor for CMV reactivation in bone morrow transplant cases[13]. Other studies also showed that serology status of the recipient remains a predominant risk factor for BMT rejection[14,15] and associated mortality. Host immune system recognises virion after infection, and lead to activation of host immune system. Several studies have reported that after bone marrow transplantation CD-4 T cells regenerate relatively at slow rate, which subsequently provide limited help to cytotoxic T cells for control of CMV replication[16,17]. Patients undergoing Haplo-SCT have higher incidence of CMV antigenemia than HLA matched transplantation[18].Other risk factors for CMV infections in hematopoietic stem cell transplantation (HSCT) cases are advancing age, immunosuppresion because of whole body irradiation, antithymocyte globulins, chemotherapeutic regimens and transplantation of umbilical cord blood[19,20]. Recipient of non-myeloablative (HSCT) are more prone to have late CMV infection, mostly due to chemotherapy containing alemtuzumab or antilymphocyte globulins[20].

Clinical manifestations

Infection with CMV is a major cause for morbidity and mortality in immunocompromised patients, particularly in transplant recipients[21,22]. The following clinical types are commonly recognized.

CMV pneumonia: CMV pneumonia is a potentially fatal disease with non specific symptoms in most of the cases[23]. Incidence of CMV pneumonia is showing a decreasing trend because of the effective use of anti-viral prophylaxis or pre-emptive therapy after HSCT[24]. Among autologous recipients, the incidence is about 1%-6% and among allogeneic recipients it is high, around 10%-30%[25]. Diagnosis of CMV pneumonia is based on clinical and radiological evidences. In addition microbiologically CMV can be detected in blood, broncho alveolar lavage or in lung tissue. Immunohistochemical staining for viral identification or demonstration of its inclusion body in lung biopsy is a gold standard investigation, but biopsy is not always a feasible option in such cases[26]. As compared to pre-antiviral era, mortality rate of CMV pneumonia has reduced to less than 50% because of use of specific antivirals or high dosage of immnuoglobulins (0.2-0.5 mg/kg per day)[23].

Gastrointestinal infections

Incidence rate of CMV gastrointestinal (GI) infections is around 2%, usually observed within one to two years of transplantation[27]. It is an ulcerative condition which can occur anywhere along whole GI tract; however upper GI tract involvement is more common in patients with haematological malignancies or in patients after BMT[28].

CMV esophagitis commonly presents with odyno-phagia and dysphagia. Endoscopic examination

reveals characteristic ulceration which is confirmed by presence of CMV inclusion bodies[29]. CMV gastritis presents with severe and continuous epigastric pain. Colorectal involvement is more commonly seen in BMT patients[28]. CMV colitis generally presents with diarrhea, abdominal pain, anorexia and fever. Colonic perforation, haemorrhage and peritonitis can occur as a complication of CMV colitis[30].

Central nervous system infections

Central nervous system (CNS) involvement is seen in patients with profound immunodeficiency disorder as in BMT or acquired immunodeficiency syndrome (AIDS) patients[31]. CMV CNS involvement is generally seen in the later stage of disease[32]. It presents with rapid progression of cognitive disorder along with cranial nerve palsies[33]. Diagnosis is generally made by radiological investigation and polymerase chain reaction (PCR) for detection of CMV in CSF is a useful tool for its diagnosis[32].

CMV retinitis

CMV retinitis can present as a late complication after BMT. It account for 5% of all late CMV manifestations[34]. It is a slow progressive disorder which generally starts from a peripheral site of retina, causing minimal damage to visual abilities of patients in the early stage of infection[35]. Lymphopenia is an important risk factor for development of CMV retinitis. PCR on aqueous humour can be used as diagnostic tool in ophthalmic manifestations[36].

Miscellaneous disorders

Cystitis, nephritis, myocarditis, pancreatitis can also be rarely seen in patients with CMV infection in BMT cases[37].

Diagnosis

Several diagnostic methods are available for diagnostic surveillance of patients at risk of acquiring CMV infection. Methods that have been described for detection of CMV infection include serological tests for detection of antigens or antibodies, viral culture and quantitative or qualitative CMV genomic detection from various body fluids like blood, urine or broncoalveolar lavage[38]. The common tests used in HSCT patients include pp65 antigenemia and the CMV DNA PCR. Monitoring of viral levels is important to guide preemptive therapy. The pp65 antigen test detects the CMV antigens on mononuclear cells in peripheral blood but its limitations include subjectivity and a relative lack of standardization, labour intensive nature of the test and lesser sensitivity as compared to PCR[39,40]. Various techniques used for detection of CMV viral load have been proven to be useful as a prognostic indicator and allowing monitoring of antiviral treatment[41,42]. Highly conserved regions of CMV such as US 17, UL 50, US 54, LC 342, LC 383 and the immediate early (IE) gene have been used as primer targets for the CMV PCR assay[38,43]. The advantages of

real time RCR for detection of CMV in whole blood and plasma is that it is automated, more sensitive[39], has a reasonably limited turnaround time and has replaced the pp65 antigenemia assay in most centres.

Prevention of CMV

Prevention of CMV infection and disease is an important component of post transplant monitoring and management. Serum CMV IgG levels must be determined to know the baseline status of the recipient before the transplant. CMV negative allogeneic recipients must receive blood products from CMV negative donors or leucodepleted blood products[44], the same is also recommended for autologous patients. Strategies such as prophylactic or preemptive therapy have been advocated in allogeneic patients[45]. In prophylactic therapy, Gancyclovir, acyclovir, valacyclovir and forcarnet have been shown to be effective. When laboratory support in the form of availability of sensitive rapid molecular tests such as CMV DNA PCR is available, the pre-emptive strategy is preferable and most centres now prefer this approach[46,47]. Patients must be screened for viremia or antigenemia once a week from days 10-100[45]. Many centres use a cut-off of 1000/mL copies of CMV DNA or a fivefold rise of baseline levels (whichever is lower) as the threshold for initiating preemptive therapy. Gancyclovir is most commonly used followed by foscarnet and cidofovir[48,49]. Ganciclovir (GCV) is a nucleotide analogue which by catalysing CMV DNA polymerase action, competitively inhibits CMV DNA synthesis. The therapy may be given for 2 wk or till the virus falls to below detection levels or up to d-100[34]. In early phase of HSCT, Ganciclovir therapy can lead to neutropenia and thrombocytopenia. Antiviral resistance must be suspected if antigenemia or CMV DNA levels continue to increase after 2 wk of therapy. The genotype of the infecting CMV strain can be tested and Second line drugs must be considered[24]. Foscarnet is preferred in cases with myelosuppression or known GCV resistance but nephrotoxicity which may lead to acute renal failure or electrolyte abnormality is a major limiting factor[50]. Cidofovir is a third line agent for CMV, but again, myelotoxicity and nephrotoxicity are major side effects.

Treatment of CMV disease

Gastrointestinal CMV is generally treated with intravenous gancyclovir for several weeks; alternatively foscarnet may also be used[24]. Current standard of care for CMV pneumonia involves the use of the above mentioned drugs along with intravenous immunoglobulin (IVIG). However the supposed beneficial role of CMV specific immunoglobulin or pooled IVIG is still not clear from available studies[51,52]. CMV retinitis and other manifestations of CMV in the BMT patient are also usually treated with Ⅳ gancyclovir and foscarnet[47].

Future perspectives

There is a need to further standardize and evolve a consensus on the frequency and cut off values of viral

load estimations used in pre-emptive therapy. Newer drugs such as maribavir, are under trail and would be indicated in case of toxicity and/or resistance to the conventional antivirals[47]. Maribavir in high dosage can be used for treatment of resistant cases[53]. Maribavir does not cause myelosuppression. Immune augmentation by using transfer of donor derived CMV specific T-cells have shown promising response in refractory cases without significant toxicity[54]. The anti CMV effect of drugs like artisunate and sirolimus also need to be further explored[24]. Tests to detect antiviral resistance should be available more easily. Larger studies are indicated to clearly define the role of IVIG in CMV disease treatment. Further research and development in the above mentioned areas would improve the management of CMV in the HSCT patient.

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