CMV Infection in Malignancy

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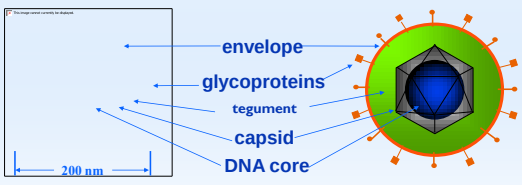
Human Cytomegalovirus Virion Structure



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CMV

CMV comes from the Greek language: *cyto-*, "cell", and *-megalo-*, "large" → is the largest known virus to infect human beings.

Group: double-stranded DNA virus → Family: Herpesviridae → Subfamily: Betaherpesvirinae → Genus: Cytomegalovirus → Species: Human Herpesvirus 5 (HHV-5).

Alphaherpesvirinae (including, HSV 1 and 2 and varicella), Gammaherpesvirinae (including Epstein-Barr virus).

All herpesviruses share a characteristic ability to remain **latent** within the body over long periods.

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Epidemiology of CMV Infection

At least 60% of the US population has been exposed to CMV, with a prevalence of more than 90% in high-risk groups (eg, male homosexuals).

In developing countries, most infections are acquired during childhood, whereas, in developed countries, up to 50% of young adults are CMV seronegative.

Serologic surveys conducted worldwide demonstrate CMV to be a ubiquitous infection of humans, CMV may be found in 40%-100% of people, depending on socioeconomic conditions.

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The Incidence of CMV Reactivation in Hematologic Malignancies

Australian investigators reported that the rate of CMV reactivation over a 5-year period at a single referral center:	Alemtuzumab (50%)
	HyperCVAD (9.7%)
	Denileukin diftitox (6.1%)
	Autologous stem-cell transplantation (4.2%)
	Fludarabine-containing regimens (4.6%)
	Rituximab (2.6%)
	Other standard-dose chemotherapy regimens (<1%)

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CMV Infection versus Disease

- Infection:
  - Definition: detection of virus via culture techniques or changes in serology.
  - Criteria:
    1. Seroconversion with appearance of anti-CMV IgM antibodies
    2. Fourfold increase in preexisting anti-CMV IgG titers.
    3. Detection of CMV DNA-emia by molecular techniques.
    4. Isolation of virus by culture of throat, buffy coat or urine.

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CMV Infection versus Disease

- Disease: requires clinical signs and symptoms, including fever, leukopenia or organ involvement:
  - Hepatitis
  - Pneumonitis
  - Pancreatitis
  - Colitis
  - Meningoencephalitis
  - Myocarditis (rare)

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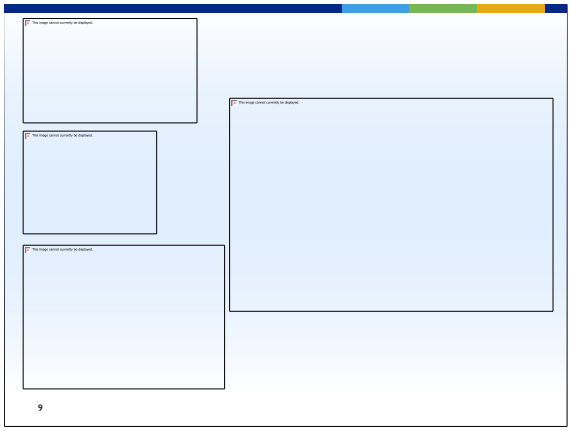

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Pathogenesis of CMV Infection

- CMV is large complex virus that has 20 times the genetic material of HIV, with DNA sequences encoding more than 100 proteins.
- The infection occurs due to impairment of **T-cell immunity**.
- Cytomegalic cells: pathognomonic.

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Pathogenesis of CMV Reactivation in Hematologic Malignancies

Lymphopenia

T-cell depletion

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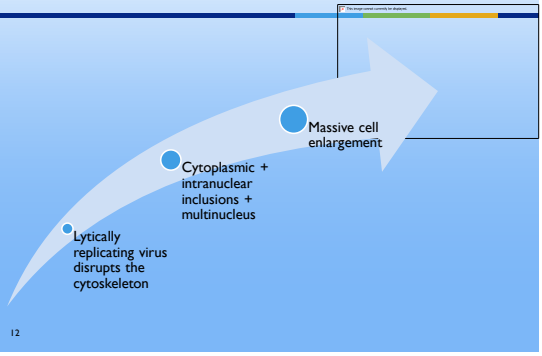
Pathogenesis of CMV Infection



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H & E Stain of CMV Infection

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Pathogenesis of CMV Infection

Important features in pathogenesis

- Ability of the virus to destroy host cells
- Ability to infect wide range of cells and tissues
- Ability to to evade and interfere with host defense mechanisms
- Ability to persist indefinitely in the host

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Pathogenesis of CMV Infection

- Impaired organ function results from combination of lytic infection of cells and vascular compromise
- Dissemination is due to infection of WBC and vascular endothelial cells
- A small proportion of circulating monocytes in seropositive persons harbor latent CMV

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Progression of Infection CMV

Most healthy people who are infected by HCMV after birth have no symptoms

Some develop infectious mononucleosis/glandular fever-like syndrome

After infection, the virus remains latent in the body for the rest of the person's life

Cells that were infected with CMV could create renin that contribute to high blood pressure

CMV infection of blood vessel endothelial cells (EC) in humans is a major cause of atherosclerosis

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CMV Infection in Immunocompetent Patients

The primary infection presents as mononucleosis-like syndrome which soon resolves

Signs & symptoms	Complications
• Fever • Lethargy • Myalgia • Headache • Mild hepatitis	• Rash • Granulomatous hepatitis • Guillain-Barre Syndrome • Meningoencephalitis • Myocarditis • Pneumonia • Hemolytic anemia • Thrombocytopenia

Most of them asymptomatic for life

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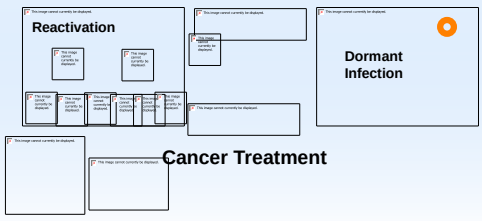
Cancer Therapeutics

Cytomegalovirus (CMV) infection has devastating effects on cancer patient survival.

Immune Evasion



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CMV Infection in Immunocompromised Patients

CMV seropositivity remains associated with a poorer outcome, mainly in highly immunosuppressed patients.

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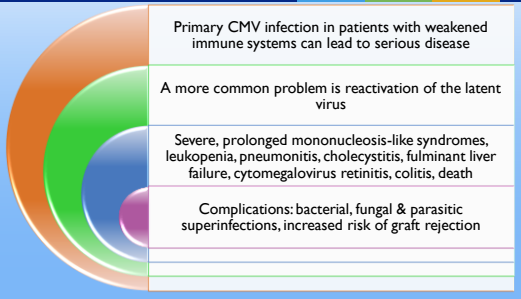
CMV Infection in Immunocompromised Patients



- Primary CMV infection in patients with weakened immune systems can lead to serious disease
- A more common problem is reactivation of the latent virus
- Severe, prolonged mononucleosis-like syndromes, leukopenia, pneumonitis, cholecystitis, fulminant liver failure, cytomegalovirus retinitis, colitis, death
- Complications: bacterial, fungal & parasitic superinfections, increased risk of graft rejection

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Direct & Indirect Effects of CMV

Direct

- Gastrointestinal disease
- CMV pneumonia
- Retinitis
- Encephalitis

Indirect

- CMV also exhibits an immunosuppressive effect, which can lead to an increased susceptibility to invasive bacterial and fungal disease

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CMV Infections in Tumor/Malignancy Patients

- **CMV disease manifestations** include pneumonia, enteritis, encephalitis, retinitis, hepatitis, cholangitis, cystitis, nephritis, sinusitis and marrow suppression.
- **T-cell function is paramount** in the control of CMV, and T-cell depleting agents (e.g., alemtuzumab) and aggressive chemotherapy (e.g., hyper-CVAD, and acute leukemia induction) appear to increase the risk of CMV infection and disease.

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CMV Infections in Acute Leukemia Patients

- An early prospective surveillance study from the University of Maryland Cancer Center reported an **incidence** of CMV infection in patients with acute leukemia that ranged from **32% to 58%**.
- CMV-associated **death** occurred in **8/130 patients** studied.
- CMV disease in these studies was associated with the use of **high-dose cytarabine, fludarabine, or high-dose cyclophosphamide, and increased patient age**.

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CMV Infections in Patients who Receive Alemtuzumab

- Nguyen et al reported CMV viremia in **5/34 (15%)** patients who receive Alemtuzumab. Viremia developed a median of 28 days after starting therapy, and all patients experienced fever, but none of these patients developed CMV disease.
- A similar incidence of CMV infection was reported for patients with lymphoid malignancies who were treated with alemtuzumab and rituximab. CMV antigenemia occurred among **13/48 (27%)** patients. Nine patients received anti-CMV therapy, and no patient died as a consequence of this infection.

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Diagnosis of CMV Infection & Disease

The most frequently used tests for the diagnosis of CMV infection:

- Detection of antigen (the pp65 antigenemia assay)
- DNA (highly sensitive and provide viral load measurements)
- mRNA (not quantitative but appears to work well in preemptive treatment strategies)

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Viral Load

- Definition: number of CMV particles as determined by quantitative DNA-PCR.
- All patients with CMV DNA levels >= 500 copies/ug of total DNA in peripheral blood had clinical evidence of disease, although some with lower viral burdens may be asymptomatic.

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Diagnosis of CMV Infection & Disease

The diagnosis of CMV gastrointestinal disease and pneumonia:

- Rapid cultures
- Direct fluorescent antibody tests
- DNA hybridization
- Cytology

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Diagnose CMV Pneumonia & Gastrointestinal Disease

There are presently no data on what level of CMV DNA in bronchoalveolar lavage (BAL) fluid or tissue correlates best with CMV disease

Due to its high sensitivity, the negative predictive value of PCR is high, so it can be used to rule out disease

But, PCR is not accepted as definitive proof of CMV pneumonia or gastrointestinal disease by current internationally accepted diagnostic criteria

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CMV Infections in Tumor/Malignancy Patients

Prophylaxis of infection or early preemptive intervention remains the foundation of effective CMV infection management for seropositive patients

Both of these approaches have significantly lowered the risk of early mortality from CMV disease, but CMV disease continues to impact patient survival

Two possible reasons for this lack of overall success is the occurrence of late cytomegalovirus infection and disease, and inadequate CMV prophylaxis for patients with latent CMV infection

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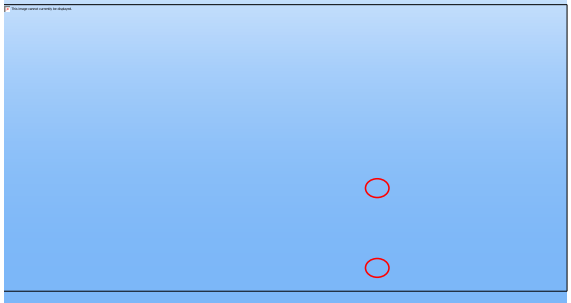
CMV Infections in Tumor/Malignancy Patients



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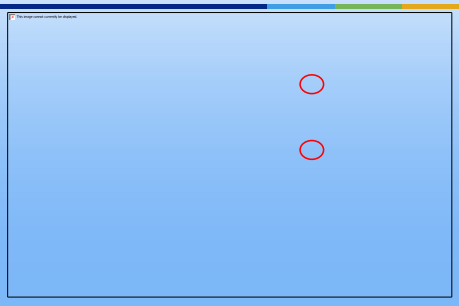
CMV Infections in Tumor/Malignancy Patients



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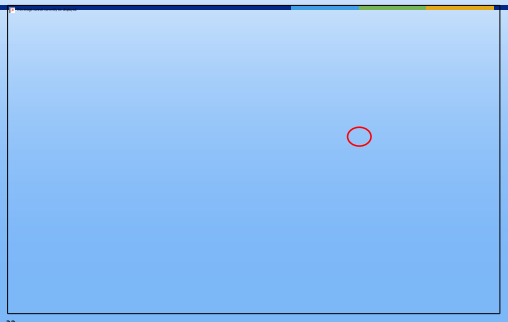
CMV Infections in Tumor/Malignancy Patients



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Management of CMV Infections in Tumor/Malignancy Patients

1) **Antivirals**: **Ganciclovir**, Valganciclovir, Foscarnet, or cidofovir as alternatives.
2) **Supportive treatment**: Antihistamines, antipyretics, drying agents (calamine).
3) **Cytomegalovirus Immune Globulin Intravenous (Human) (CMV-IGIV)**: immunoglobulin G (IgG) containing a standardized amount of antibody to Cytomegalovirus (CMV), used for the prophylaxis of cytomegalovirus disease associated with transplantation of kidney, lung, liver, pancreas, and heart.

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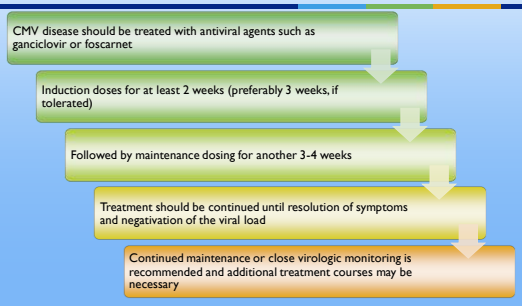
Treatment of CMV Disease



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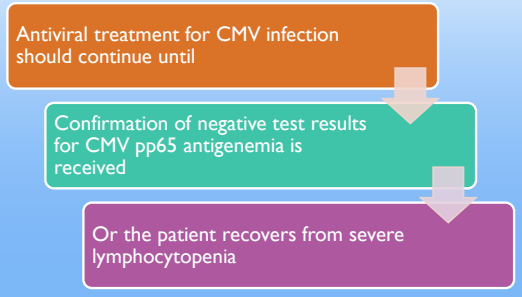
Treatment of CMV Disease



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Anti-Cytomegalovirus Agents

- Ganciclovir
  - An acyclic guanosine analog
  - Requires triphosphorylation for activation
  - Monophosphorylation is catalyzed by a phosphotransferase in CMV and by thymidine kinase in HSV cells
  - ***M.O.A.:*** same as acyclovir
  - ***Uses***: CMV, HSV, VZV, and EBV
  - ***Side Effect***: myelosuppression

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Anti-Cytomegalovirus Agents

- Valganciclovir
  - Monovalyl ester prodrug of gancyclovir
  - Metabolized by intestinal and hepatic esterases when administered orally
  - ***M.O.A.:*** same as gancyclovir
  - ***Uses***: CMV
  - ***Side Effect***: myelosuppression

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Anti-Cytomegalovirus Agents

- Foscarnet
  - An inorganic pyrophosphate
  - Inhibits viral DNA polymerase, RNA polymerase, and HIV reverse transcriptase
  - Does not have to be phosphorylated
  - ***Uses:*** HSV, VZV, CMV, EBV, HHV-6, HBV, and HIV
  - Resistance due to mutations in DNA polymerase gene
  - ***Side Effects:*** hypo- or hypercalcemia and phosphotemia

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Treatment (Induction)

First line:
ganciclovir, powder for injection, 500 mg in vial
Adults: 5 mg/kg i.v twice a day for 14-21 days

Second line:
foscarnet, solution for injection, 24 mg/ml 250 ml, 500 ml
Adults: retinitis; 90 mg/kg i.v daily for 14-21 days for CMV
Adults: CMV oesophagitis; 90 mg/kg i.v twice a day for 14-21 days

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Treatment (Maintenance)

First Line:
ganciclovir, capsules, 250 mg
Adults: 1 g orally three times a day

Second Line:
ganciclovir, powder for injection, 500 mg in vial
Adults: 5 mg/kg i.v daily

Third line:
foscarnet, solution for injection, 24 mg/ml 250 ml, 500 ml
Adults: 90 mg/kg i.v daily

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ALTERNATIVE TREATMENT

Valganciclovir 900mg bid po

Cidofovir 5mg/kg weekly

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A Case Report

Glioma patients are often treated with corticosteroids for prolonged periods to reduce intracranial swelling

Temozolomide (TMZ) is the standard therapeutic agent used to treat patients with malignant glioma

Treatment with TMZ in combination with steroids is believed to cause immunosuppression and subsequent CMV reactivation due to lymphocytopenia

Cause CMV pneumonia, colitis, and transverse myelitis.

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A Case Report

A glioblastoma patient who developed severe lymphocytopenia, continuous fever and hepatitis following surgery and radiotherapy with concomitant TMZ and steroid treatment.

After recovering from CMV reactivation, the patient continued maintenance therapy with TMZ for eight cycles under careful monitoring for CMV reactivation.

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A Case Report

Physicians should be aware of the possibility for CMV reactivation when the ALC or CD4+ T-lymphocyte count of a patient treated with concurrent TMZ and steroids decreases to approximately 500 lymphocytes/μL

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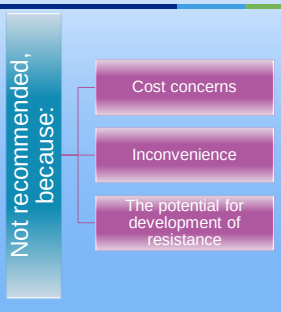
Prophylaxis



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Prophylaxis

Ganciclovir

Prolonged neutropenia is the most important adverse outcome of ganciclovir prophylaxis

Valganciclovir

No randomized clinical trials on valganciclovir prophylaxis

Foscarnet

Foscarnet prophylaxis, which is associated with dose-dependent renal toxicity and electrolyte abnormalities, has not been studied in a randomized fashion

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NCCN Clinical Practice Guidelines in Oncology, v. 2. 2009

Consider all patients receiving alemtuzumab to be at high risk for CMV disease

Intravenous ganciclovir or foscarnet or oral valganciclovir prophylaxis is recommended for 2 months after alemtuzumab administration

Until the CD4 count is 100 cells/mcL or greater

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Prevention of CMV Infections in Tumor/Malignancy Patients

1. Simple hand washing with soap and water is effective in removing the virus from the hands.
2. All preschool-age children should be considered potential sources of infection.
3. Avoid contact with body fluids from young children and careful hand washing
4. Educating women before getting pregnant.
5. Vaccination.
6. Limit transfusion-acquired CMV infection.
7. Prophylactic antiviral treatment and passive immunization to prevent CMV disease after transplantation.

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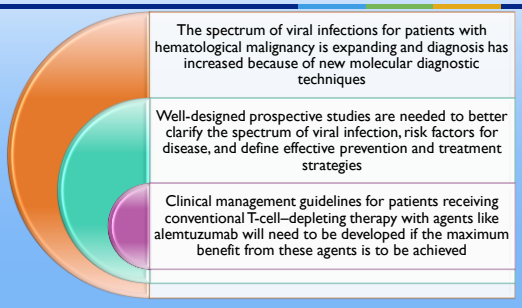
Summary



- The spectrum of viral infections for patients with hematological malignancy is expanding and diagnosis has increased because of new molecular diagnostic techniques
- Well-designed prospective studies are needed to better clarify the spectrum of viral infection, risk factors for disease, and define effective prevention and treatment strategies
- Clinical management guidelines for patients receiving conventional T-cell–depleting therapy with agents like alemtuzumab will need to be developed if the maximum benefit from these agents is to be achieved

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Thank U...