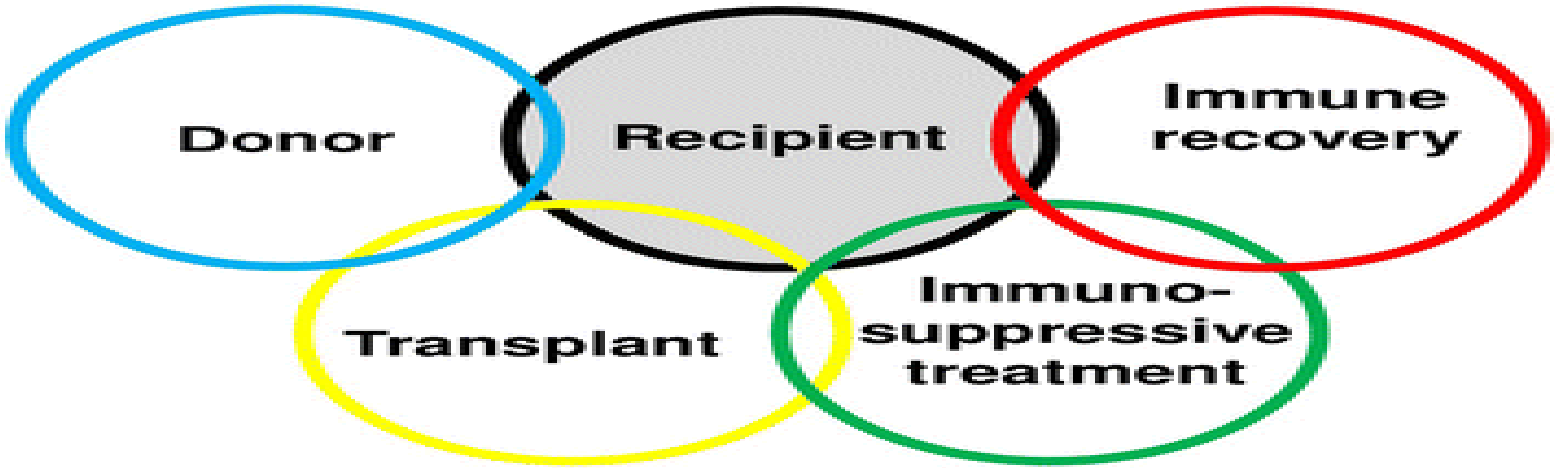
IN THE NAME OF GOD

CMV IN PEDIATRIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

BIBI SHAHIN SHAMSIAN
MOFID CHILDREN HOSPITAL



CMV IN PEDIATRIC HSCT : A CASE-BASED PANEL DISCUSSION OF CURRENT CHALLENGES

- A 10-year-old boy with **chronic granulomatous disease**
- **CMV seropositive** , without history of a documented CMV-related illnes
- **HSCT: Match-unrelated donor** (HSCT).
- **What type of CMV monitoring and prevention strategies will you use for this patient?**
- **Answer : Monitoring and preemptive therapy**

JPIDS 2018:7 (Suppl 2) • Danziger-Isakov et al

Cincinnati Children Hospital .USA & Switzerland

CMV IN PEDIATRIC HSCT : A CASE-BASED PANEL DISCUSSION OF CURRENT CHALLENGES

- 40 days after HSCT , **a CMV viral load of 150 000 IU/mL.**
- Therapy -**Ganciclovir,** / **cleared** his viral load,
- Remained **on valganciclovir** prophylaxis
- **100 day after** HSCT , CMV viral load again is elevated **(60 000 IU/mL)**
- **He has poor Engraftment**.

- **What treatment should be used for this child who is already on valganciclovir prophylaxis?**

JPIDS 2018:7 (Suppl 2) • Danziger-Isakov et al

Cincinnati Children Hospital .USA & Switzerland

CMV IN PEDIATRIC HSCT : A CASE-BASED PANEL DISCUSSION OF CURRENT CHALLENGES

- **Start: Foscarnet**
- After 7 days of therapy, his **CMV viral load has increased to 180 000 IU/mL**
- Do you perform **resistance testing** at this time?

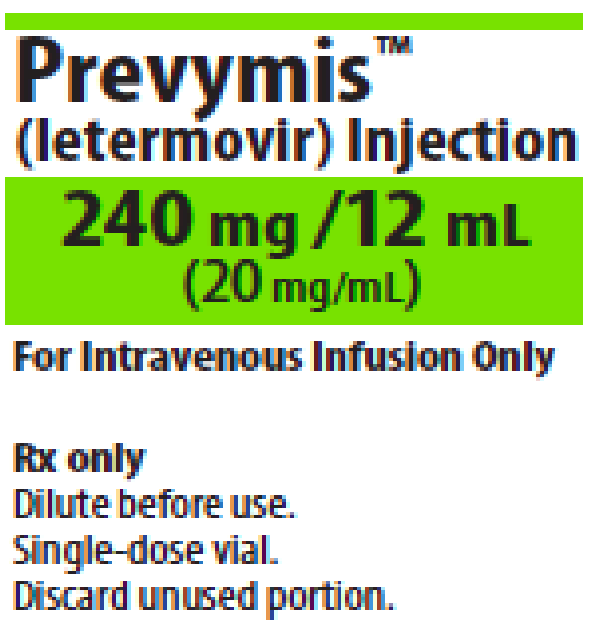
- Resistance testing **revealed mutations** in **both UL97 and UL54**, which confer resistance to both **Ganciclovir and Foscarnet.**
- **Last Question?**

JPIDS 2018:7 (Suppl 2) • Danziger-Isakov et al

Cincinnati Children Hospital .UDS & switzerland ,...

CMV -PHSCT TREATMENT DRUGS

WHAT ADDITIONAL OPTIONS EXIST FOR THIS PATIENT?



RISK FACTORS /CASE HSCT

- **CMV IGG POSITIVE**
- **UNRELATED DONOR HSCT**
- **EARLY REACTIVATION**
- **RECURENCY**
- **RESISTANCE**

CMV -PEDIATRIC HSCT RESULTS OF AN EBMT SURVEY .

- **3 strategies: prophylactic, pre-emptive or therapeutic medicines. Which option is the best strategy?**
- Questionnaire to the EBMT centers in children. **56 / 196 responded (28.5%).**
- **21/56 Centers use of prophylactic measures**

Conclusion: There is no uniform procedure for:

- **Researching Resistance Strain**
- **Antiviral Second-line therapy**
- **Cell therapy.**
- **Suggests: prospective trials**

T Bontant.Bone Marrow Transplantation (2014) 49, 276–279

MANAGEMENT AND PREVENTION OF CMV INFECTION IN PAEDIATRIC (HSCT) RECIPIENTS: A BINATIONAL SURVEY

- From HSCT & ID team : unexpected divergence between ID & HSCT team in local practice and recommendations.

- **Suggest:**
- Improve **communication and collaboration between HSCT & ID groups** are **needed**

- **Ttraining of transplant-specific pediatric ID subspecialists** may be useful to bridge the gap.

Laila S. Al Yazidi.2019 .Australia

CYTOMEGALOVIRUS - CMV

- (CMV)-Human B-Herpesvirus Double strand DNA (type 5)
- Infects 50–90% of the adult population worldwide
- Infects; leukocytes, Epithelial cells, & Neural cells
- Latent for decades
- Most common opportunistic infection in Allogeneic (HCT) recipients
- CMV reactivation is rare after Autologous transplantation
- Donor & Recipient serostatus is the primary risk factor for CMV reactivation.
- **Without prophylaxis, CMV reactivation occurs:**
  - 80% of CMV-seropositive
  - 30% of CMV-seronegative HCT Recipients receiving Grafts from seropositive donors

Jose F. hematol Oncol Stem cell ther.2017 USA
R. Grant Rowe .Biol Blood Marrow Transplant.2017. DFC.Massachusetts

EMERGING CONCEPTS IN CMV INFECTION FOLLOWING HEMATOPOIETIC STEM CELLTRANSPLANTATION.

- **Despite of** Molecular methods for the detection of (CMV) & highly effective
- preemptive strategies, CMV remains a **leading cause of morbidity and mortality**
- **in (HCT) recipients**

- **CMV infection** : Increased risk of secondary Bacterial & Fungal infections, & GVHD

❑ **CMV Disease : Independent risk factor for :**

- Aspergillosis (Hazard ratio 7.0) Candidemia (relative risk 16.4)

- **Each week of Ganciclovir treatment is associated with 1.4-fold increase in Risk of invasive Aspergillosis**

Int J Mol Sci. 2019 Jun; 20(11): 2666.

Jose F. hematol Oncol Stem cell ther.2017 USA

CMV / MORBIDITY- MOTRTALITY IN P HSCT

- Mortality in HCT recipients with **CMV disease** can be **as high as 60%.**

- CIBMTR : 9469 HSCT **2003 -2010**; CMV reactivation remains associated with poor post-transplant outcomes

Lancet Haematol. 2016 Mar; 3(3): e119–e127.

Jose F. hematol Oncol Stem cell ther.2017 USA

RISK OF CMV

- Risk of CMV is highly Dependent on:
  - **Donor (D& Recipient (R) Serostatus**

- (**D-/R +** > D+/ R+ >D+ / R- >D-/R-)
- Risk is highest among, seropositive Allo HSCT recipients (R+) who receive grafts from seronegative donors

(D- ; lacking CMV immunity)

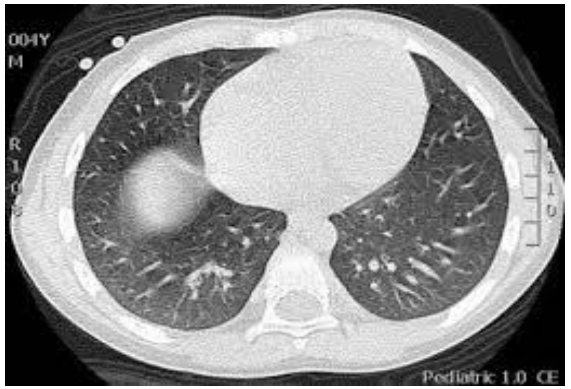
R. Grant Rowe .Biol Blood Marrow Transplant.2017. DFC.Massachusetts

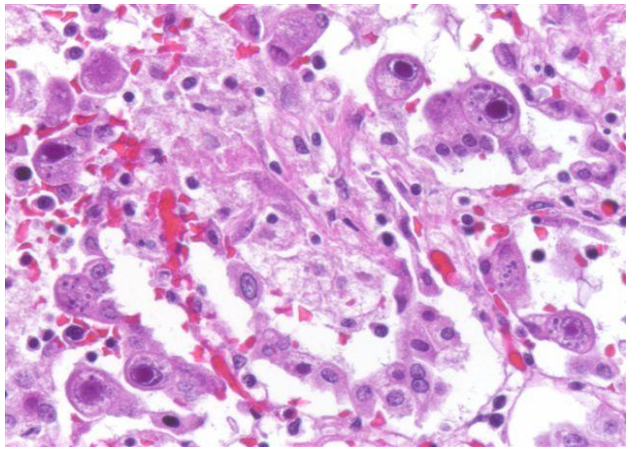
CMV PRESENTATION

Reactivation Early or Late or primary infection, (45% - 65%)

- **Late: / Infection after 100 days post HSCT**

- **CMV Disease :**
  - **Pneumonia***,10-30% Allo , 1-6% Auto . Fatal**
  - Gastroenteritis-Colitis
  - Retinitis
  - Central Nervus System(CNS)
  - Hepatitis
  - …..
- CMV disease : **Biopsy-proven target-organ involvement**





Lauren Stern.Front. Microbiol., 28 May 2019

R. Grant Rowe .Biol Blood Marrow Transplant.2017. DFC.Massachusetts

RECURRENT CMV/PHSCT

- **Incidence Report of Recurrence CMV: 10% - 38%**
- BOSTON Children's Hospital(DFCI): Recurency Rate of 27%

Risk factors:

- **Unrelated Donor SCT**
- **Antiviral treatment duration beyond 4 weeks for first infection**
- **Prolonged Lymphopenia ;potent Lympholytic in conditioning, systemic Corticosteroids**

Infect Dis Ther. 2018 Mar; 7(1): 1–16.

Jose F. hematol Oncol Stem cell ther.2017 USA

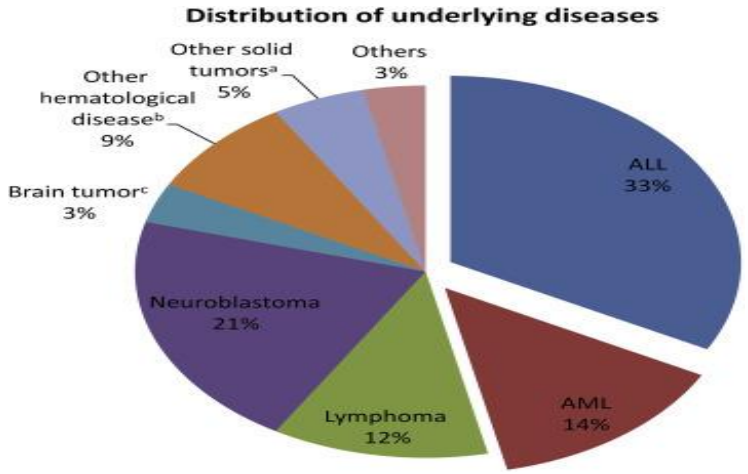
R. Grant Rowe .Biol Blood Marrow Transplant.2017. DFC.Massachusetts

PLAN FOR CMV IN PEDIATRIC HSCT

- **prophylactic antivirals**
  - **Toxicity**
  - **Delay acquisition of CMVs Specific Graft-Derived Immunity*****
  - Detect individualized **risk for CMV infection** would be of great benefit
    - **Pre-emptive antiviral treatment**

Jose F. hematol Oncol Stem cell ther.2017 USA

RISK FACOTORS /CMV-PHSCT



- Lymphoid Malignancy
- Serology Status R&D
- **Immune Dysregulation** ; GVHD & Therapies
- **Mismatched or Unrelated donors**

❑ Conditiong regimen & T-cell depletion (Alemtuzumab or ATG , Whole Body Irradiation)

❑ Umbilical Cord Blood (UCB) :**50% to 55% -CMV antigenemia**

- Lower Donor T- cell doses and lack cells with CMV-specific immunologic memory
- Absence of anti-CMV acquired immune function in UCB-derived lymphoid cells
- Slower Hematopoietic recovery
- **Haploidentical –HSCT (T Cell Depletion)**

➢ **Antecedent early(45% /16%) result to recurrence**

Grant Rowe .Biol Blood Marrow Transplant.2017. DFC.Massachusetts

Jose F. hematol Oncol Stem cell ther.2017 USA

Jaing et al. Medicine (2019) 98:4

CMV INFECTION IN PEDIATRIC HSCT. RISK FACTORS FOR PRIMARY INFECTION & CASES OF RECURRENT & LATE INFECTION AT A SINGLE CENTE

- Cohort of 91 pediatric SCT patients at risk in 4-year period
- Risk factores :
  - **Umbilical cord blood**
  - **Acute GVHD ;odds ratio, 4.018**
  - **CMV seropositivity ;odds ratio, 16.525**

- **Recurrence of post-SCT CMV viremia : 50% all-cause mortality rate**

R. Grant Rowe .Biol Blood Marrow Transplant.2017. DFC.Massachusetts

Dziedzic M.Anticancer Res. 2017 Dec;37(12):6551-6556.

CMV INFECTION IN PEDIATRIC HAPLOIDENTICAL HSCT AT A SINGLE CENTER

- 92 pediatric 2004 -2016 ,Haploidentical HSCT
- Ex vivo T cell-depleted grafts at Asan
- 1th Group: $CD3^+$ T cell depletion without CMV prophylaxis
- 2th Group : $CD3^+$ T cell depletion with CMV prophylaxis +Ganciclovir
- 3th Group :Alpha-beta T cell receptor ($TCR_{\alpha\beta}$) was depleted+Gancyclovir

- 49/92 (53.3%) ; CMV reactivation after Haploidentical HSCT
- CMV disease : High **CMV pp65 antigenemia greater than 40/200,000 cells** (hazard ratio, 3.568)

Conclusions : Haploidentical HSCT

- *Ganciclovir prophylaxis :reduce CMV reactivation*
- Close monitoring

Sung Han Kang. Blood 2016 128:2209

CMV –PHSCT RISK FACTORS

- **Not all Seropositive individuals with these risk factors develop CMV**
- **Regulating CMV-specific T-cell responses, play a major role**
- **Data : Inability to control CMV reactivation following Allo-HCT is due to the impaired function of antigen-specific CTLs cells**

Jose F. hematol Oncol Stem cell ther.2017 USA

MONITORING & DIAGNOSIS CMV INFECTION IN PEDIATRIC -HSCT

Monitoring of viral levels is important to guide preemptive therapy

- **Serological Tests; PP65 Antigenemia test (** positive cells per 2×10^5 leukocytes)in PB
- **Lesser sensitivity and lack of standardization**
- Leukopenia ;pitfalls of antigen detection test

- **Real-time PCR :CMV DNA polymerase chain reaction (PCR) assay. (Blood and plasma , urine ,BAL), Cost : High**
- **CMV PCR : preferred test**

Giovanni Breda.pathog Glob Health. 2013 Sep; 107(6): 312–319

Vive Bhat.W.J.T. 2015

MONITORING HUMAN CMV INFECTION IN PEDIATRIC -HSCT

- **2011-2012, 1179 samples / 82 recipients <15 years old Allo- HSCT**

- **Q PCR : Earlier and with Higher sensitivity than Antigen pp65 .**
- **Optimal cutoff value for starting pre-emptive therapy : 1284 IU/ml plasma**
- **Risk factors: GVHD severity & Relationship of donor & Recipient**

- **Cutoff value of 1067.5 :100% sensitivity and 71% specificity.(Brazil)**

Behzad Khansarinejad . Transplant international .2015

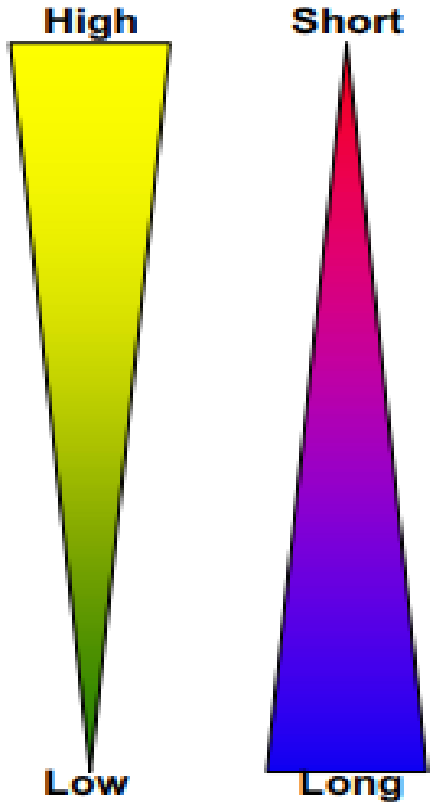
Giovanni Breda.Pathog Glob health.2013 Sep; 107(6): 312–319

CUT OFF CMV PHSCT

- **Cut Off CMV Load /PCR assay**
- Several CMV DNA emia cutoff values, ranging (200 -20 000 copies/ml
- 10-fold vari tion as to the threshold to start pre-emptive therapy (1000-10 000 copies/mL)
- No consensus DNAemia cutoff ,duo to various variables that may influence the Q-PCR
- **Pre Emptive therapy Cutoff ; 1000 /mL copies of CMV DNA or a 5-fold rise of baseline level**

Behzad Khansarinejad . Transplant international .2015

CMV VIRAL LOAD TO START PREEMPTIVE THERAPY (PET) USED AT THE FHCRC IN SEATTLE, WA, & KAROLINSKA INSTITUTE, STOCKHOLM, SWEDEN. BLOOD, 8 DECEMBER 2016 X VOLUME 128, NUMBER



Risk Groups	CMV Plasma DNA Level to Start PET at FHCRC*	CMV Whole Blood DNA Level to Start PET at Karolinska Institute**
Cord blood	Any level	1000 copies
Allograft - High-dose steroids+ - T cell depletion - Anti-T cell antibodies - CD34 selection	> 100 copies/mL	1000 copies
Allograft - Low dose steroids - No T cell depletion or anti T cell antibodies	> 500 copies/mL > or 5-fold ⬆ †	1000 copies
Allograft - after day 100	> 1000 copies/mL > or 5-fold ⬆ †	1000 copies if GVHD Other individual assessment based on ⬆

PREVENTION CMV HSCT

- **Strategies : prophylactic or preemptive therapy**
- **CMV negative** Blood products -CMV negative D and R
- **Leucodepleted Blood products**
- Monitotring :CMV DNA PCR once a week from (days 10100)
- **preemptive strategy is preferable**
- **Pre emptive therapy Cutoff ; 1000 /mL copies of CMV DNA or a 5 -fold rise of baseline level**

  - **Vivek Bhat.W.J.T. 2015**

PREVENTION CMV PHSCT

- Boston Children's Hospital: Routinely uses prophylactic Acyclovir for 30 days after SCT in at-risk patients,

- Sero negative patients & Seropositive grafts : worse overall survival
- **CMV-seropositive grafts for seronegative recipients is a reasonable approach**
- **Is not a large risk : CMV morbidity.(Boston-CH: 4% duo to prophylaxis)**

R. Grant Rowe .Biol Blood Marrow Transplant.2017. DFC.Massachusetts

DRUGS FOR PROPHYLAXIS AND TREATMENT /CMV PHSCT

- **Acylovir/ prophylaxis** (500 mg/m2 IV / 3 times daily) & **Val Acyclovir**
- **Ganciclovir** (1989) ; Nucleotide analogue , inhibits CMV DNA synthesis ,IV
- **Valgancyclovir** (2001); **Valin ester prodrug,po**
- **Foscarnet (1991)** Foscarnet as prophylaxis of CMV disease remains undefine?
- **Cidofovir (1996)**

- **Brincidofovir,** a lipid-conjugated prodrug high oral bioavailability and long half-life ,lower renal toxicity
- **Leflunamide**
- **Maribavir**
- **Letermovir (New)**

Sung-Yeon Cho ·Open Access*Int. J. Mol. Sci.* **2019**, *20*(11), 2666

Jose F. hematol Oncol Stem cell ther.2017 USA

TREATMENT /CMV PHSCT

- **CMV-specific Cytotoxic T-lymphocyte**

- **Role of CMV specific IG or pooled IVIG is still not clear????**

Sung-Yeon Cho ·Open Access*Int. J. Mol. Sci.* **2019**, *20*(11), 2666

Jose F. hematol Oncol Stem cell ther.2017 USA

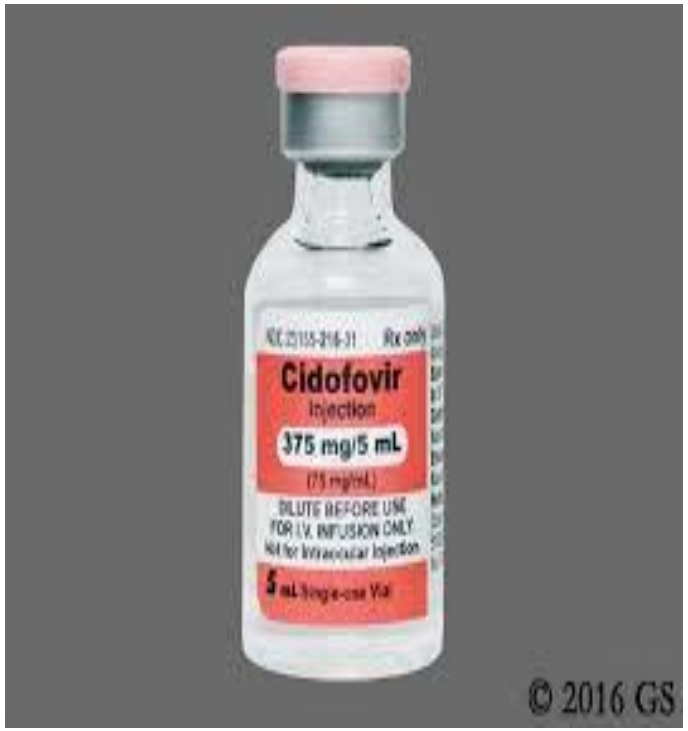
CMV -PHSCT TREATMENT DRUGS

NDC 0006-5003-02

Prevymis™
(letermovir) Injection
240 mg /12 mL
(20 mg/mL)

For Intravenous Infusion Only

Rx only
Dilute before use.
Single-dose vial.
Discard unused portion.



LETERMOVIR FOR PROPHYLAXIS OF CMV IN ALLOGENEIC HSC RECIPIENTS TEXAS, USA. *CHO, J.C*

- Approved ; prophylaxis of CMV infection and disease in CMV-seropositive recipients of aAllo (HSCT) over the age of 18 Y
- Interfering with the viral pUL56 gene product, **disrupting the viral terminase complex**
- Orally & IV : 480-mg and 240-mg dosage forms
- 480 mg p.o./i.v. once daily ;day 0 -day 28 post-allogeneic HSCT & continued through day 100 post-transplantation; the dose should be reduced to 240 mg daily if coadministered with cyclosporine.
- Metabolized primarily by **Hepatic**
- Renal dosage adjustments are not warranted until a creatinine clearance (CrCl) of < 10 mL/min
- **Letermovir is active against DNA polymerase inhibitor-resistant viral strains**.

Drugs Today 2018, 54(6): 361

LETERMOVIR FOR SECONDARY CYTOMEGALOVIRUS (CMV) PROPHYLAXIS IN A PEDIATRIC STEM CELL TRANSPLANT PATIENT. CLEVELAND, OH

- An 11-year old male who had undergone a 4/6 HLA-matched cord blood transplant
- CMV resistance to treatment
- Letermovir could be useful in **secondary prophylaxis** in pediatric patients with ganciclovir-resistant CMV who are at risk of recurrences.

Jennifer Le. Biology of Blood and marrow TRANSPLANTTAION.2019

USE OF LETERMOVIR FOR SALVAGE THERAPY FOR RESISTANT CYTOMEGALOVIRUS IN A PEDIATRIC HEMATOPOIETIC STEM CELL TRANSPLANT RECIPIENT

- First publishe -use of Letermovir for the treatment of resistant cytomegalovirus (CMV) in a pediatric patient.
- 14-year-old girl underwent a **double unrelated umbilical cord UCB -HSCT /** sickle cell disease (hemoglobin SS)
- Ganciclovir-resistant CMV DNAemia with end-organ involvement that was treated successfully with a combination of **Foscarnet and letermovir**
- After she was transitioned to letermovir monotherapy for **secondary prophylaxis**,
- she developed **recurrent DNAemia** with laboratory-confirmed ganciclovir, foscarnet, and letermovir resistance

Jacob T Kilgore.2019. Pediatric infectious diseases society

STUDY: AUG 2019- 2023 PHASE 2

- 60 participants
- primary objective study evaluate the pharmacokinetics (PK) of letermovir (LET) in pediatric participants. (Prevention)
- 3 age groups:
- Group 1: From 12 to <18 years of age (adolescents)
- Age Group 2: From 2 to <12 years of age (children
- Age Group 3: From birth to <2 years of age (neonates, infants and toddlers)
- All participants will receive open label LET for 14 weeks (~100 days) post-transplant, with doses based on body weight and age.
  L etermovir Tab , Cap, IV

1902. A SURVEY OF PEDIATRIC BMT CENTERS REGARDING LOCAL CMV PROPHYLAXIS MANAGEMENT PRACTICES AND INTEREST IN A FUTURE RANDOMIZED TRIAL.

- **Survey :**
- (40%) of pediatric BMT centers /US administer CMV prophylaxis to at least a subset of their HCT recipients.
- The variation in prophylaxis regimens highlights the lack of comparative effectiveness data to guide clinical decisions
- 51 (89%) :interest in a randomized trial to assess the efficacy of Letermovir **prophylaxis against** CMV reactivation.
- **The preferred comparator for such a trial was placebo/nothing (55%) followed by high dose Acyclovir (24%).**

Brian T. Fisher .2018.USA

CMV TREAMENI IN CMV PHSCT: LEFLUNOMIDE AND MARIBAVIR

- **Maribavir:** orally availab
- Inhibition Protein kinase enzyme U197 –PU197 :Anti CMV DNA synthesis, viral gene expression
- **Resistant CMV.**
- (FDA) Approved ,**only For children aged12 years or older .**

- **Leflunomide (Arava) Orall, inhibitor of pyrimidine synthesis Inhibiting virion**
- **Effective in clearance of CMV when copy numbers are low.**
  $<2 \times 10^3$ copies/mL

- Papanicolaou GA.Clin Infect Dis.2019 Apr 8;68(8):1255-1264.
- **Gokarn. Biol blood Marrow Transplant. 2019**

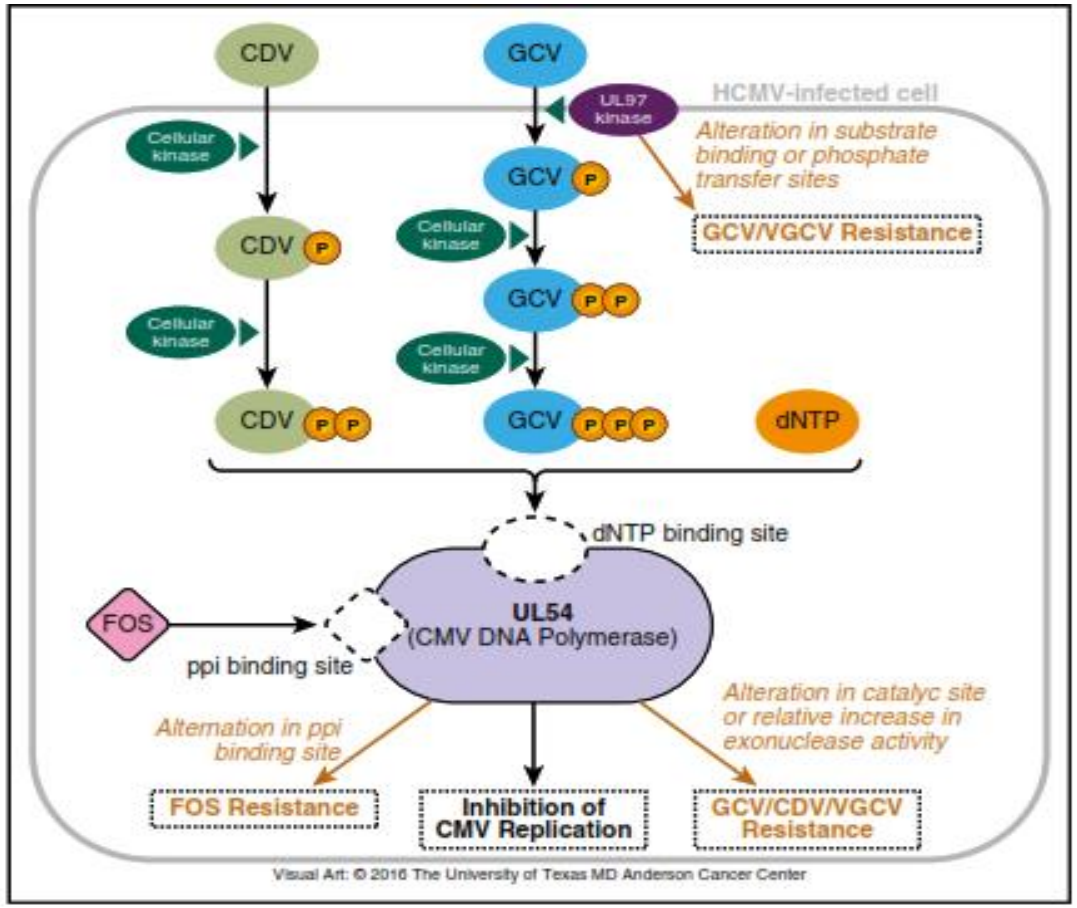
HOW I TREAT RESISTANT CMV INFECTION IN HEMATOPOIETIC CELL TRANSPLANTATION RECIPIENTS.

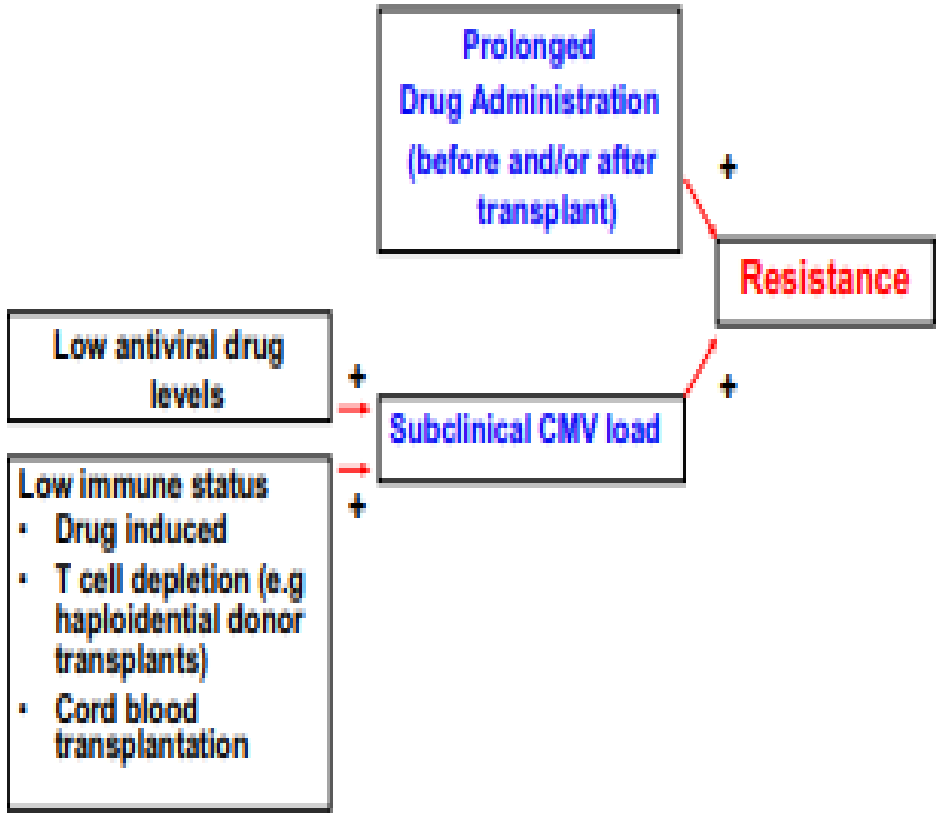
- **Viremia Fails to improve or continue to increase after 2 weeks** of appropriatedly dosed Resistance is rare after pediatric HSCT (10% in 1 study)
- Incidence :vary from 0% to 7.9% in HSCT recipients (HLA-matched donors)
- 14.5% :Haploidentical donors
- Diagnisis: specific genetic mutations.
- **UL97 mutations ;resistance to Ganciclovir & Valganciclovir,**
- **UL 54 mutation ; multidrug resistance.**
- **Risk factors for resistance include :**
- prolonged or previous anti-CMV drug exposure or inadequate dosing, absorption, or bioavailability.
- Type of HCT and degree of immunosuppression

BLOOD, 8 DECEMBER 2016 x VOLUME 128, NUMBER 23

BLOOD, 4 JUNE 2009 VOLUME 113, NUMBER 23

MECHANISM OF ACTION OF ANTIVIRAL DRUGS FOR CMV
FIRAS EL CHAER BLOOD, 2016
BLOOD, 4 JUNE 2009 VOLUME 113, NUMBER 23





HOW I TREAT RESISTANT CYTOMEGALOVIRUS INFECTION IN HEMATOPOIETIC CELL TRANSPLANTATION RECIPIENTS. FIRAS EL CHAER BLOOD 2016.TX 2016.

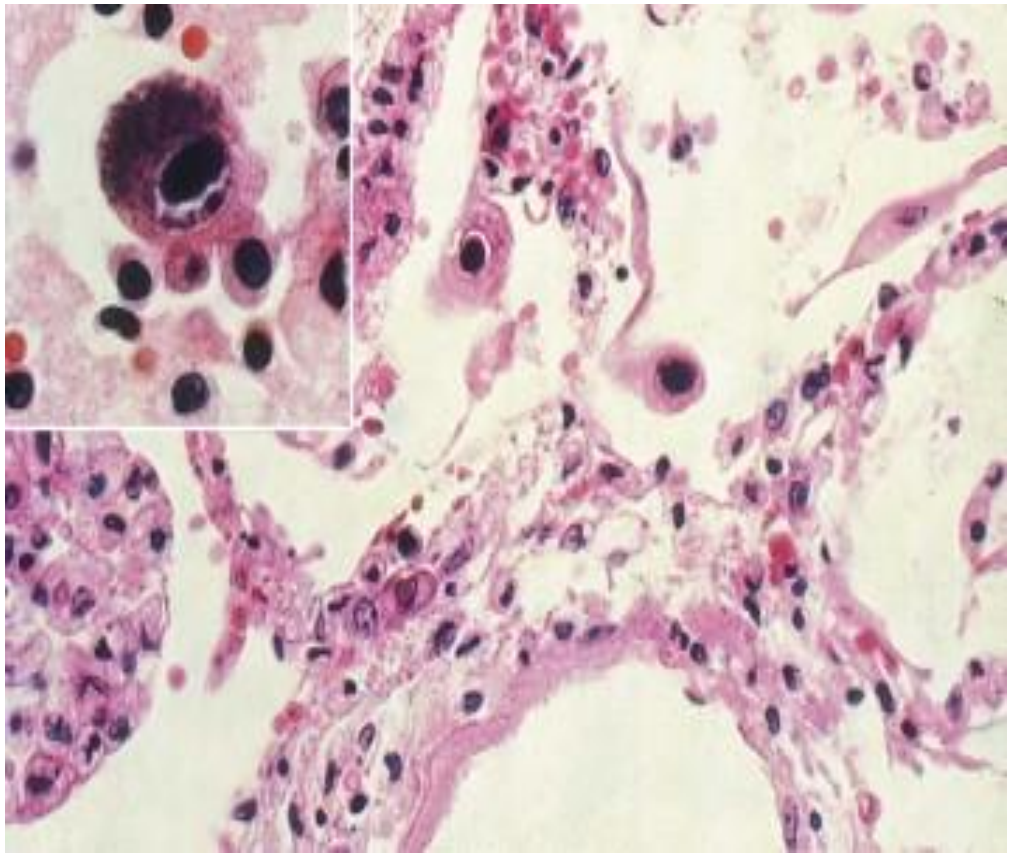
- **Treatment**
- Reducing immunosuppression (if possible)
- Ganciclovir dose escalation,
- Gaganciclovir & Foscarnet combination
- Adjunct therapy such as CMV-specific cytotoxic T-lymphocyte infusions.
- Novel therapies such as **Maribavir, Brin cidofovir, and Letermovir**

BLOOD, 8 DECEMBER 2016 x VOLUME 128, NUMBER 23

CONCLUSION

- CMV Seropositivity & Reactivation continue to influence Allogeneic HCT outcomes in the current era.
- Although significant progress has been made in prevention of CMV disease,
- More effective and better-tolerated antivirals are urgently needed.
- **Immune reconstitution** following HCT is a major determinant of the risk of CMV.
- **It will require careful correlation of clinical and immunological analyse**

A large (cytomegalic), 25- to 35-µm cell containing a large central, basophilic intranuclear inclusion (referred to as an owl's eye. (owl’s eye inclusions)



Thank You