Case Presentation

Student

APPE GENERAL MEDICINE ROTATION
ABC UNIVERSITY MEDICAL CENTER
OCTOBER 2015

THIS EXAMPLE IS TO BE USED FOR INSTRUCTION ON AN EXAMPLE FORMAT, BUT NOT FOR CLINICAL CONTENT. PLEASE CONSULT YOUR PRECEPTOR REGARDING SPECIFIC EXPECTATIONS AT YOUR ROTATION SITE.

Case Presentation

Patient Case: LB

- **CC**
  - Presented to ER with vision changes x 2 weeks

- **HPI**
  - 53 yo African American female
  - Normal vision with sudden and rapid deterioration
  - "I feel blind"
  - Could not come to the hospital sooner due to financial reasons.
  - Lost 60 lbs due to poor appetite over the last several months
  - Non-adherent to HIV medications and has not seen a doctor

Patient Case

- **PMH**
  - Cryptococcal meningitis (2012)
  - CNS lymphoma (2014)
  - H/o Focal seizures
  - H/o Pneumocystis Jiroveci Pneumonia (PJP)

- **Prior to Admission (PTA)**
  - levetiracetam (Keppra®) 500 mg PO BID

- **FH:** Non-contributory

- **SH**
  - (-) EtOH, tobacco, illicit drugs
  - Single
  - Caregiver: daughter

- **Allergies**
  - NKDA

- **General Information**
  - HT: 5’6”
  - WT: 43 kg (6/2), 36 kg (6/12)
  - Lost 7 kg
  - IBW: 59.3 kg
  - BP: 129/74 mmHg
  - Pulse: 77 bpm
  - Resp: 18 breaths/min
  - Temp: 97.4°F
  - Pneumovax 23® (9/30/12)

Laboratory Results (Labs)

- **BMP**
  - Random BG (mg/dL) 91 (70-139)
  - BUN (mg/dL) 10 (7-23)
  - Creatinine (mg/dL) 0.72 (0.66-1.25)
  - Cl- (mmol/L) 122 (98-107)
  - Na+ (mEq/L) 142 (136-145)
  - K+ (mEq/L) 5.4 (3.5-5.1)
  - CO2 (mmol/L) 23 (21-32)

- **CBC**
  - WBC (billion/L) 4 (3.7-10.4)
  - Hgb (g/dL) 11.7 (12.1-15.1)
  - MCV (mg/dL) 88.5 (81.2-96.7)
  - MCH (pg/cell) 29.1 (27.5-33.1)
  - Platelets (billion/L) 319 (131-340)

- **Review of Systems (ROS)**

  | General       | Weight loss: 60 lbs from baseline
  |               | No fever, chills, sweating
  | HEENT         | Recent changes in vision
  |               | No headache, sore throat
  | Neuro         | Weakness
  | Lungs         | No SOB, wheezing, cough, sputum
  | CV            | No chest pain
  | GI            | No nausea, vomiting, diarrhea
  | GU            | No dysuria, hematuria, urgency

- **Physical Exam (PE)**

  | General       | Thin, cachectic
  | Ocular        | Pupils dilated 7 mm, minimally reactive to light, retina diffusely erythematous
  |               | Acuity:
  |               | - OD: 20/400 vision (severe impairment)
  |               | - OS: 20 light perception (optic nerve)
  | HEENT         | White plaques on tongue
  | Lungs         | Poor air movement, clear
  | Circulatory   | RRR, normal heart sounds
  | Abdomen       | Soft, non-tender, non-distended, bowel sounds
  | Neurologic    | Alert and oriented x 3
  | Extremities   | 3/5 strength in arms and legs
**Hospital Course: Labs**

- CD4 (cells/mm³): 1  
  - 2/2014: 3  
  - 1/2014: 2  
  - 9/2012: 1

- HIV (copies/mL): 17,503  
  - 2/2014: 119,486  
  - 1/2014: 118,649  
  - 9/2012: 579,665

**Hospital Course: Medical Management**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Medication</th>
<th>Dose</th>
</tr>
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</table>
| Cytomegalovirus (CMV) retinitis | Ganciclovir/Valganciclovir | 250 mg IV x 1 dose  
  450 mg → 900 mg PO BID |
| HIV/AIDS                    | Atripla® (efavirenz/  
  emtricitabine/tenofovir) | 600 mg/200 mg/300 mg 1  
  tab PO daily |
| Mycobacterium avium complex (MAC)  
  CD4 < 50 cells/mm³ | Azithromycin              | 1200 mg PO weekly  
  400 mg → 200 mg PO daily |
| Cryptococcus CD4 ≤ 100 cells/mm³ | Fluconazole                | 800 mg/160 mg PO daily |
| PJP CD4 ≤ 200 cells/mm³ | Trimethoprim/sulfamethoxazole (Bactrim DS®) | 800 mg/160 mg PO daily |
| Oral candidiasis            | Nystatin                 | 5 mL S/S QID x 3 days |

**Hospital Course: Diagnostic Tests**

- MRI  
  - Normal enhancement of optic nerve  
    - R/O neurological cause or lymphoma  
    - Stroke  
    - Likely old

- Polymerase Chain Reaction (PCR)  
  - Blood: CMV detected  
  - CSF: Varicella zoster virus (VZV) detected

- CMV retinitis & VZV meningitis  
  - Ganciclovir 100 mg → 200 mg IV q 12h

**Hospital Course**

- Genotype Testing  
  - Resistance (NNRTIs): delavirdine, efavirenz, nevirapine

- HIV/AIDS  
  - Start Stribild® (elvitegravir/cobicistat/emtricitabine/tenofovir) 150 mg/150 mg/200 mg/300 mg 1 tab PO daily

- CMV retinitis  
  - Ganciclovir 15 mg intravitreal injection  
    - 1 dose before discharge

**CMV Retinitis**

- Epidemiology  
  - Cytomegalovirus: DNA virus in herpes family  
  - Severely immunosuppressed individuals  
    - CD4 < 50 cells/mm³  
      - Not receiving or failed antiretroviral therapy  
      - Before ART: 30% of AIDS patients  
      - CMV infection increases mortality by 60%  
      - HAART: CMV decreased by 80–90%

- Pathophysiology  
  - Disseminated infection or localized end-organ disease  
  - Retinitis: 2/3 of CMV infected patients  
  - Retinal necrosis → scar tissue formation → scar tissue can tear → retinal detachment  
  - Retina affected by CMV cannot regenerate  
  - Progresses to bilateral if untreated (10-21 days)
**CMV Retinitis**

**Risk Factors**
- CD4 < 50 cells/mm$^3$
- Previous opportunistic infections
- HIV viral load > 100,000 copies/mL
- High CMV viral load

**Signs & Symptoms**
- Peripheral: asymptomatic, floaters, decreased peripheral vision
- Central retinitis: decreased visual clarity

**Prophylaxis**
- Latex condoms, hand-washing
- Maintain CD4 > 100 cells/mm$^3$, adherence to HAART
- Valganciclovir failed to show a benefit in high-risk patients (CD4 < 100 cells/mm$^3$, CMV viremia)

**Diagnosis**
- Retinal Exam: fluffy yellow-white lesions
- CMV PCR:
  - Detected in the vitreous fluid 80% of the time
  - Detected in the blood 70% of the time
- Negative blood test does not rule out CMV retinitis

**Treatment**
- Goal: stabilize vision by inhibiting CMV replication within 1-2 weeks
- Lesion location, severity, level of immunosuppression

**Clinical Pearls**
- Avoid in sulfa allergy (probenecid)
- C/I in renal dysfunction
- Requires hydration and PO probenecid before and after administration

### Table: Treatment, Dosing, ADRs, Monitoring

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dosing</th>
<th>ADRs</th>
<th>Monitoring</th>
</tr>
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<tbody>
<tr>
<td>Foscarnet</td>
<td>60 mg/kg IV q12h or 90 mg/kg IV q24h for 14-21d then 90-120 mg/kg IV q24h</td>
<td>Nephrotoxicity, electrolyte abnormalities, seizures, anemia</td>
<td>CBC, Chem-7, K, Mg, Ca, Phos, SCr, BUN</td>
</tr>
<tr>
<td></td>
<td><strong>Preferred</strong></td>
<td></td>
<td>Monitor renal function twice weekly during induction and once weekly during maintenance</td>
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<td>Cidofovir (Vistide)</td>
<td>5 mg/kg/week for 2 weeks, then 5 mg/kg every other week</td>
<td>Dose-related nephrotoxicity, neutropenia, uveitis, low intraocular pressure</td>
<td>BUN, S/Cr, urinalysis before each infusion, eye exams</td>
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<td>5 mg/kg IV q12h x 2-3 days then Valganciclovir 900 mg PO daily</td>
<td>Anemia, neutropenia, thrombocytopenia, nausea, diarrhea, renal dysfunction</td>
<td>CBC + differential, BMP</td>
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<td>Ganciclovir + Valganciclovir</td>
<td>Ganciclovir 5 mg/kg IV q12h x 14-21d then Valganciclovir 900 mg PO daily</td>
<td></td>
<td>*Requires dose adjustment if GCV &lt; 70 mL/min</td>
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<td>Bacterial or fungal infections, hemorrhage, retinal detachment</td>
<td>Vision changes, pain, irritation</td>
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<td>Foscarnet</td>
<td>2.4 mg/injection 1-4 doses over 7-10 days</td>
<td>Bacterial or fungal infections, hemorrhage, retinal detachment</td>
<td>Vision changes, pain, irritation</td>
</tr>
</tbody>
</table>
CMV Retinitis

- Monitoring
  - Regular eye exams because may relapse
    - Treatment
      - 2 weeks after initiation, then monthly
    - Post-treatment
      - Every 3 months, up to once per year

Literature Review

REFERENCE:

Clinical Trial #1

- Objective
  - PO valganciclovir vs IV ganciclovir for CMV retinitis induction therapy
- Study Design
  - 42 sites
  - Randomized, non-inferiority study
- Primary Outcome
  - Progression of CMV retinitis at 4 weeks
    - Retinal photographs
- Secondary Outcomes
  - Satisfactory response to induction treatment
  - Time to progression of retinitis

Study Design

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>≤ 3 months PO ganciclovir prophylaxis</th>
</tr>
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<tr>
<td>Exclusion Criteria</td>
<td>- H/O treated CMV retinitis</td>
</tr>
<tr>
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<td>- Severe diarrhea</td>
</tr>
<tr>
<td></td>
<td>- Neutrophils &lt; 750 cells/mm³</td>
</tr>
<tr>
<td></td>
<td>- Platelets &lt; 75,000 per mm³</td>
</tr>
<tr>
<td></td>
<td>- CrCl &lt; 70 mL/min</td>
</tr>
<tr>
<td>Duration</td>
<td>Assess q 2 weeks until progression, then monthly</td>
</tr>
<tr>
<td>Statistical analysis</td>
<td>Efficacy: CI &gt; -0.25</td>
</tr>
</tbody>
</table>

Study Population

N = 160
N = 80
N = 80

Ganciclovir
5 mg/kg IV q12h x 3 weeks
5 mg/kg q24 h x 1 week

Valganciclovir
900 mg PO BID x 3 weeks
900 mg PO daily x 1 week

Week 4
Valganciclovir 900 mg PO daily

Progression CI Satisfactory Response CI Median time to progression CI
Valganclovir 7 of 71 patients (9.9%) -9.7 ± 10 46 of 64 patients (71.9%) -20.4 ± 10.1 160 days > 74
Ganciclovir 7 of 70 patients (10%) -9.7 ± 10 47 of 61 patients (77%) -20.4 ± 10.1 125 days 5 99
ADRs & PK

- **Adverse effects**
  - Diarrhea: valganciclovir 19% > ganciclovir 10% (p = 0.11)
  - Catheter-related events: ganciclovir 9% > valganciclovir 4%

- **Pharmacokinetics (PK)**
  - Systemic exposure similar with both treatments
    - **AUC at week 4**
      - Ganciclovir: 30.7 ± 7.7 (μg·hr/ml)
      - Valganciclovir: 34.9 ± 13.3 (μg·hr/ml)

Author’s Conclusion

- Valganciclovir is as effective as ganciclovir for retinitis induction and has a similar safety profile.
- CMV retinitis progression, satisfactory response, and PK parameters were similar among the two regimens.

Critique

- **Strengths**
  - Retinal photographs readers were blinded
    - Protects against bias
  - PK data helps support the author’s conclusion

- **Weaknesses**
  - Large confidence intervals that included zero
    - Not statistically significant
  - Patients may have received prophylaxis with ganciclovir before enrollment
    - No longer the standard of care

Application To LB

- Due to the non-inferiority of valganciclovir, it was appropriate to switch the patient from IV to PO
- Valganciclovir 900 mg BID for induction therapy is appropriate per guideline recommendations.
- There is no PK advantage to using the IV route.

Clinical Trial #2

- **Objective**
  - IV/PO therapy vs intraocular therapy to treat CMV retinitis
- **Study Design**
  - Prospective cohort study
- **Inclusion criteria**
  - Diagnosis of CMV retinitis
  - CD4 < 100 cells/mm³
- **Primary Outcome**
  - Retinitis progression
- **Secondary Outcomes**
  - Visual acuity and field loss

**REFERENCE:**
**JABS DA, AHUJA A, NATTA MV, ET AL. COMPARISON OF TREATMENT REGIMENS FOR CYTOMEGALOVIRUS RETINITIS IN PATIENTS WITH AIDS IN THE ERA OF HIGHLY ACTIVE ANTIRETROVIRAL THERAPY. OPHTHALMOLOGY. 2013 JUNE;120(6):1262–1270.**
Study Design

- Study Duration: 5 years, visit every 3 months
- Statistical Analysis: Results adjusted for CD4, HIV load, and HAART use

<table>
<thead>
<tr>
<th>Study Population (N = 250)</th>
</tr>
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<tbody>
<tr>
<td><strong>Systemic Therapy</strong></td>
</tr>
<tr>
<td>Intravitreal Injection</td>
</tr>
<tr>
<td>Ganciclovir Implant</td>
</tr>
<tr>
<td>PO: ganciclovir (50%), valganciclovir (70%)</td>
</tr>
<tr>
<td>IV: ganciclovir</td>
</tr>
</tbody>
</table>

- Characteristics
  - Injection group: more active lesions and optic nerve involvement
  - 35.2% - bilateral disease
  - 12.4% - vision 20/200 or worse
  - 44.8% - switched among treatment groups

Results

<table>
<thead>
<tr>
<th>Systemic therapy vs. Intravitreal alone</th>
<th>Injections vs. Systemic therapy alone</th>
<th>Implants vs. Systemic therapy alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>50% reduction in mortality</td>
<td>p = 0.006</td>
<td></td>
</tr>
<tr>
<td>More retinitis progression, HR = 3.4</td>
<td>p = 0.004</td>
<td></td>
</tr>
<tr>
<td>50% reduction in new visceral CMV</td>
<td>p = 0.004</td>
<td></td>
</tr>
<tr>
<td>Greater visual field loss, HR = 5.5</td>
<td>p &lt; 0.01</td>
<td>50% reduction in loss of visual field</td>
</tr>
<tr>
<td>80% reduction in contralateral disease</td>
<td>p = 0.0005</td>
<td></td>
</tr>
</tbody>
</table>

Adverse Effects

- Neutropenia, anemia, thrombocytopenia, and elevated creatinine did not differ significantly among treatment groups.
- There was one case of endophthalmitis after intravitreal injection and two cases after implant placement.

Author’s Conclusions

- Patients who received intravitreal injections appeared to do worse.
  - Confounding factors - more severe retinitis or resistant CMV

Critique

- **Strengths**
  - The study attempted to control for confounding variables including CD4 counts, HIV load, and HAART use.
  - Better comparison of outcomes
- **Weaknesses**
  - Cohort study and not a clinical trial
    - Confounding variables
  - Not available: ganciclovir implant and PO ganciclovir
  - Patients received a variety of treatments
    - Mimics the real world setting, but limits ability to identify treatment benefit

Application To LB

- Current guidelines extrapolate implant clinical trial data to intravitreal injections.
- LB’s vision (20/400) is worse than study subjects (12.4% < 20/200)
- Do not recommend treating with intravitreal injections.
  - Extrapolated data
  - Quality of life
  - Cost standpoint
  - Poor prognosis: will not improve vision
  - Higher risk of eye infections
# Problem List

- CMV Retinitis
- VZV Meningitis
- HIV/AIDS
- Stroke
- Seizures

## CMV Retinitis

**Goals**
- Stabilize vision
- Minimize ADRs

**Assessment**
- Severe retinitis, uncontrolled
- Ganciclovir intravitreal injection dose
  - Guidelines: 2 mg per injection (max total: 8 mg)
  - 15 mg is inappropriate

**Plan**
- Continue ganciclovir 200 mg IV q12h x 2 wks
- Valganciclovir 900 mg PO BID for maintenance
- Discontinue ganciclovir intravitreal injections
  - Risk of infection > benefit

**Education**
- Valganciclovir
  - Side effects: nausea, diarrhea, vomiting
    - take with food
  - Hydrate for renal protection

**Monitor**
- CBC and BMP once weekly
- Evidence of bone marrow suppression
  - Ganciclovir: 450 mg PO BID
  - Consider a different agent
- Follow-up with ophthalmologist in 3 days
- Repeat CMV PCR in 1 week

## VZV Meningitis

**Goals**
- Eradicate infection
- Prevent neurological signs and symptoms

**Assessment**
- Asymptomatic, uncontrolled
- Acyclovir, famciclovir, and valacyclovir are preferred
- Ganciclovir has activity against both VZV and CMV
  - Penetrates the blood-brain barrier

**Plan**
- Continue ganciclovir 200 mg IV q12h x 2 wks

**Monitor**
- Mental status

## Stroke

**Goals**
- Prevent recurrence of stroke

**Assessment**
- Old infarct on MRI
- Secondary prevention indicated

**Plan**
- Initiate atorvastatin 40 mg daily and aspirin 81 mg daily
  - Atorvastatin > pravastatin: no protease inhibitors in regimen

**Education**
- Report muscle pain or dark urine

**Monitoring**
- Liver function tests as clinically warranted
Seizures

- **Goals**
  - Prevent seizures

- **Assessment**
  - Controlled
  - History of seizures likely secondary to CNS lymphoma

- **Plan**
  - Continue home levetiracetam (Keppra®) 500 mg PO BID

- **Education**
  - Emphasize adherence

- **Monitoring**
  - Renal function

---

References