Primer 03

2013 Antiviral (Non HIV) Resistance Primer

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DISCLOSURES

Financial Relationships with Relevant Commercial Interests
  • None
Herpes Viruses
Herpes Viruses

• Selective pressure contributes to the development of resistance

• Risk of resistance related to
  – Selective antiviral drug pressure (therapy/prophylaxis)
  – Viral load
    • (higher VL, more likely for resistance to develop)
Herpesvirus Resistance Testing

• Susceptibility testing is available for some Herpes viruses at certain commercial and reference labs
  – Phenotypic testing
    • Plaque reduction assay in cell culture (esp for HSV)
  – Genotypic testing
    • PCR and sequencing of target genes with report of mutations associated with resistance
    • Examples: Sequences of UL97 phosphotransferase gene and UL 54 DNA polymerase gene for CMV
Acyclovir
(Valacyclovir and Famciclovir)

- Acyclic guanosine analog
- Uses:
  - HSV-1, HSV-2, VZV but NOT CMV or EBV
- Resistance occurs almost exclusively in immunosuppressed hosts
  - More common in HSV than VZV
  - When an acyclovir resistant HSV or VZV is successfully treated, if recurrent disease occurs the recurrent isolate is characteristically wild type, ie acyclovir sensitive
  - Secondary (drug pressure) is more common than primary (the acquired virus is resistant)
  - Acyclovir resistance confers resistance to valacyclovir, famciclovir
- Mechanisms of resistance
  - Thymidine kinase deficient viral mutants (absent TK-UL 97 mutation)
    - Acyclovir and ganciclovir resistant but sensitive to foscarnet, cidofovir
  - Thymidine kinase alterations
    - Same as above
  - DNA Polymerase mutations (UL 54 mutation)
    - Acyclovir resistant: may also be resistant to ganciclovir or foscarnet or cidofovir
Acyclovir Mechanism of Action
Mechanism of Resistance Within Virus

Acyclovir

TK

ACV-MP

Cellular Kinases

ACV-DP

Cellular Kinases

ACV-TP

dNTPs

DNA

Altered Specificity

Viral DNA Polymerase Resistant to Acyclovir and Ganciclovir +/- Foscarnet +/- Cidofovir

ACV-TP inhibitor

TK Deletion or Altered Specificity
Acyclovir resistance

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Ganciclovir

- Guanosine analog
- Active against CMV, HSV-1, HSV-2, VZV
- Requires initial phosphorylation by CMV UL97 ser/thr kinase
- Inhibits viral DNA polymerase
- Resistance occurs due to drug pressure
  - Usually due to drug pressure (secondary resistance) rather than primary (transmitted virus is resistant)
  - UL 97-only resistant to ganciclovir
    - Sensitive to foscarnet, cidofovir
  - UL 54-resistant to ganciclovir and often to foscarnet and/or cidofovir
Mechanism of Action of Ganciclovir

Mechanism of Resistance Within Virus

Ganciclovir

GCV-MP

Altered Specificity
UL97 protein kinase mutation
Resistant to GCV but not Foscarnet, Cidofovir

Cellular Kinases

GCV-DP

GCV-TP

Cellular Kinases

Viral DNA Polymerase Mutation
Resistant to GCV + often Foscarnet and Cidofovir

dNTPs → DNA

GCV-TP inhibitor
Foscarnet

• **Activity**
  - Binds to DNA polymerase
  - Activity: HSV, VZV, CMV

• **Resistance**
  - DNA Polymerase mutations
  - (UL54 and others, but not UL 97)
Cidofovir

• Mechanism of action
  – Inhibitor of phosphorylation by viral DNA Polymerase

• Activity
  – Herpes virus, pox viruses, adenovirus, polyoma virus
  – Seldom used due to high toxicity, unclear efficacy

• Resistance
  – Viral DNA polymerase mutations (not UL 97)
Hepatitis B
Therapy for Hepatitis B

- Lamivudine
  - Activity: HIV and HBV
  - Resistance:
    - most common: YMDD motif in viral DNA polymerase, most often in patients chronically treated with lamivudine monotherapy

- Tenofovir
  - Activity: HIV and HBV
  - Nothing testable about mechanism of resistance

- Telbivudine
  - Active against HBV only
  - Nothing testable about mechanism of resistance
  - Not active against HIV

- Adefovir, Tenofovir, Entecavir
  - Active against HBV and has some anti HIV activity
  - Nothing testable about mechanism of resistance
HBV Therapy
Resistance Concerns if Patient Has HBV/HIV Coinfection

• Because emtricitabine (FTC), lamivudine (3TC), and tenofovir (TDF) have activity against both HIV and HBV, if HBV or HIV treatment is needed, ART should be initiated with the combination of TDF + FTC or TDF + 3TC as the nucleoside reverse transcriptase inhibitor (NRTI) backbone of a fully suppressive antiretroviral (ARV) regimen.

• If HBV treatment is needed and TDF cannot safely be used, the alternative recommended HBV therapy is entecavir in addition to a fully suppressive ARV regimen.

• Entecavir has activity against HIV; its use for HBV treatment without ART in patients with dual infection may result in the selection of the M184V mutation that confers HIV resistance to 3TC and FTC. Therefore, entecavir must be used in addition to a fully suppressive ARV regimen when used in HIV/HBV-coinfected patients.

• If ART needs to be modified due to HIV virologic failure and the patient has adequate HBV suppression, the ARV drugs active against HBV should be continued for HBV treatment in combination with other suitable ARV agents to achieve HIV suppression.
Influenza
Summary of Influenza Resistance 2013
This is non testable since it changes with time!

• **Neuraminidase Inhibitor Resistance**
  (Oseltamivir)
  – Seasonal H3N2 = sensitive
  – Seasonal H1N1 = resistant
  – 2009/Pandemic H1N1 = sensitive

• **Adamantine Resistance**
  (Rimantidine)
  – Seasonal H3N2 = resistant
  – Seasonal H1N1 = sensitive
  – 2009/Pandemic H1N1 = resistant

• **Current Therapy of Choice…..but subject to change**
  – Pandemic H1N1 = Oseltamivir
  – Seasonal H3N2 = Oseltamivir
  – Seasonal H1N1 = Rimantidine
Influenza Therapy

• Neuraminidase Inhibitors (Oseltamivir, Zanamavir)
  — Activity
    • Influenza A and B
  — Resistance:
    • H274Y mutation is most common (oseltamivir only, not zanamavir) which occurs mostly in Influenza A

• Adamantanes (Rimantidine, Amantadine)
  — Activity
    • Influenza A only
  — Mechanisms of action
    • M2 protein