12 - Core Concepts: Antiviral Drugs

Speaker: Andrew Pavia, MD

Core Concepts: Antiviral Drugs

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Disclosures of Financial Relationships with Relevant Commercial Interests

- Antimicrobial Therapy Inc, WebMD, Merck and Company

What you need to know

- Common basic mechanism e.g. target and drug type
  - Target: Polymerases (including reverse transcriptase
    - Types: nucleoside/nucleotide analogs, NNRTI's
  - Target: Entry
  - Target: Uncoating
  - Target: Integration
  - Target: Budding or release
- Clinically important resistance mechanisms

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, such as in severely immunocompromised hosts, more likely for resistance to develop)

Herpes Virus Resistance Testing

- Susceptibility testing is available for some herpes viruses at certain commercial and reference labs
  - Phenotypic testing
    - Plaque reduction assay in cell culture (especially 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

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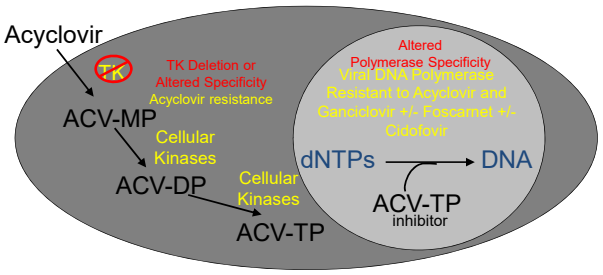
Acyclovir and Valacyclovir

- Acyclic guanosine analogs
- Therapeutic uses:
  - HSV-1, HSV-2, VZV but NOT CMV or EBV
- Resistance occurs almost exclusively in immunosuppressed hosts (especially HSCT recipients and advanced HIV)
  - More common with HSV than VZV
  - When acyclovir resistant HSV or VZV disease is successfully treated, if recurrent disease occurs, the recurrent isolate is characteristically wild type, i.e. acyclovir sensitive
  - Secondary resistance (due to drug pressure) is more common than primary (the acquired virus is resistant)
  - Acyclovir resistance also confers resistance to valacyclovir (and famciclovir which is not available in US)
  - Mechanisms of resistance
    - Thymidine kinase deficient viral mutants (absent TK)
      - Acyclovir and ganciclovir resistant viruses remain 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 foscarent or cidofovir

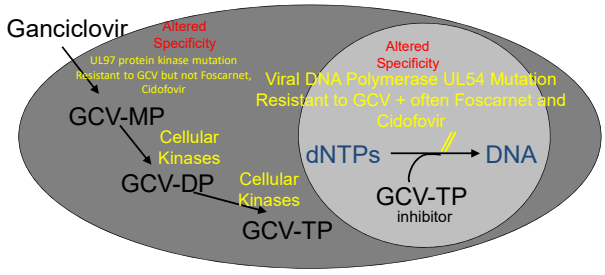
Acyclovir Mechanism of Action Mechanism of Resistance Within Virus



Ganciclovir and Valganciclovir

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

Mechanism of Action of Ganciclovir Mechanism of Resistance Within Virus



Foscarnet

- Activity
  - Binds to DNA polymerase
  - Active against HSV, VZV, CMV
- Resistance
  - DNA Polymerase mutations
  - (UL54 and others, but not UL 97)

Cidofovir

- Mechanism of action
  - Acyclic phosphonate nucleotide analog
  - Inhibitor of phosphorylation by viral DNA Polymerase
- Activity
  - HSV-1, HSV-2, CMV
  - pox viruses, adenovirus, polyoma virus, papillomavirus
- Use with caution
  - Significant renal toxicity
  - Unclear efficacy for adenovirus, polyoma viruses
- Resistance
  - Viral DNA polymerase mutations (not UL 97)

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Letermovir

- Mechanism of action
  - Inhibitor of viral terminase subunit pUL56, a component of the terminase complex involved in DNA cleavage and packaging
- Activity
  - CMV
  - NOT HSV, VZV
- Use for prophylaxis approved
  - Little data on treatment
- Drug Interactions
  - Cytochrome p450 3A inhibitor: increases cyclosporine, tacrolimus, sirolimus and decreases voriconazole
- Toxicity
  - Not myelosuppressive
- Resistance
  - Not likely testable: UL56 gene of terminase complex

Hepatitis B

Therapy for Hepatitis B

- Lamivudine
  - Active against both HIV and HBV
  - Resistance:
    - most common: YMDD motif in viral DNA polymerase, (similar to M184V in HIV)
    - 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 – DNA polymerase inhibitor
  - Nothing testable about mechanism of resistance
  - Not active against HIV
- Adefovir, 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.
- TAF has activity against HBV similar to TDF but not likely to be tested
- 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

Influenza Therapy

- Adamantanes (Rimantidine, Amantadine)
  - Not recommended because resistance is widespread and stable
  - Activity
    - Influenza A only
  - Mechanisms of action
    - M2 protein
- Neuraminidase Inhibitors (Oseltamivir, Zanamivir, Peramivir)
  - Activity
    - Influenza A and B
  - Mechanisms of action
    - Inhibits release of new virions from surface of infected cell
  - Resistance:
    - H274Y mutation is most common (oseltamivir only, not zanamavir) which occurs mostly in Influenza A, confers partial resistance to peramivir
    - Occasionally emerges in HSCT patients on prolonged treatment or with prophylaxis

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Influenza Therapy

- Baloxavir Single dose active against Influenza A and B
  - Mechanisms of action
    - Inhibits replication of viral RNA by interfering with polymerase complex via Cap-Dependent Endonuclease
  - Resistance
    - Several mutations (don't memorize) predominantly changes to I38X (Thr, Phe or Met)
    - Treatment emergent resistance in 5% to as high as 20% in children
    - Resistance more common in H3N2 than H1N1 and rare in influenza B
    - Do date, only limited transmission of resistant variants

Summary of Influenza Resistance 2020-2021 Much is Non Testable Since It Changes With Time!

- Neuraminidase Inhibitor Resistance
  (Oseltamivir, Zanamavir, Peramivir)
  - Seasonal H3N2 = sensitive
  - 2009/Pandemic H1N1 = sensitive (Current H1N1 are closely related)
  - Influenza B – sensitive but higher IC50
  - Seasonal H1N1 2008 = resistant (These strains have not circulated since 2009)
- Adamantine Resistance
  (Rimantidine)
  - Essentially all circulating viruses resistant
- Baloxavir
  - 2 isolates with resistance detected in nationwide surveillance in Japan

SARS-CoV-2

SARS-CoV-2

- Remdesivir
  - Mechanism
    - Acts as nucleoside analog
    - Inhibits RNA-dependent RNA polymerase
  - Resistance
    - Resistant mutant selected for by serial passage in vitro, but none detected in clinical samples (with very limited data)
  - Not testable yet
- Molnupiravir
  - Mechanism
    - Acts as nucleoside analog
    - Causes "catastrophic errors" in replication

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