

Infection in Patients Receiving Immunomodulatory Agents

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การประชุมวิชาการประจำปี ครั้งที่ 41 - สหประชาชาติแห่งประเทศไทย
กรุงเทพฯ, 22-23 กรกฎาคม 2565 ณ โรงแรมดิเอ็มโพเรียม (The Emporium Hotel)

Disclosure

- I have no actual or potential conflict of interest in relation to this presentation.



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Immunomodulators

- Immunomodulator: A chemical agent that modifies the immune response or function of the immune system (as by stimulation or inhibition)
- Association between infections and conventional immunomodulators or immunosuppressive agents such as steroids and chemotherapeutics is well known



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Biologic Immunomodulators

- Vast expansion in diversity and number of available immunomodulatory agents in the last 2 decades
 - Rheumatologic diseases
 - Hematologic malignancies
 - Neurologic diseases
 - Dermatologic diseases
 - Gastrointestinal diseases
 - Solid organ transplantation
- Characteristics of biologic agents
 - More targeted in their effect
 - Impact potential infectious complications



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Mechanism of Action Does Matter

- Mechanism of a biologic agent – “KEY” to predict host susceptibility to infection
 - Eculizumab (C5 complement inhibitor)
 - Susceptible to meningococemia
 - Similar to congenital terminal complement deficiency
- Indication for biologic agents
 - Rituximab (anti CD-20) in lymphoma targets tumor cells
 - Rituximab in rheumatoid arthritis targets B cells
- Dose and duration
 - Effects of Rituximab: 6 months
 - Effects of Eculizumab: weeks

Infection in Biologic Agent Therapy – It’s Complicated

- **Based on case series and case reports**
 - Interpret based on overall immunosuppressive state

Example;

- Autoimmune diseases
 - Presumed immune dysregulation
 - Previous treatment or concurrent use of immunosuppressive
 - Joint prosthesis
- Hematologic malignancies
 - Abnormal immune cells function and number
 - Other immunosuppressive agents
 - Central venous catheter

Immunomodulating Agents

- **Monoclonal Antibodies**
 - TNF- α inhibitors
 - Infliximab
 - Adalimumab
 - Certolizumab pegol
 - Golimumab
 - Anti CD-20 Antibodies
 - Rituximab
 - Ofatumumab
 - Obinutuzumab
 - Anti CD-52 Antibody
 - Alemtuzumab
 - Anti IL Anitbodies
 - Ustekinumab (IL12 and IL23)
 - Tocilizumab (IL6)
 - Complement Inhibitor
 - Eculizumab
- **Immune Activating Agents**
 - Ipilimumab (CTLA-4 inhibitor)
 - Pembrolizumab (PD-1 inhibitors)
- **Biologic Agents**
 - TNF- α inhibitor
 - Eternacept
 - IL-1 inhibitor
 - Anakinra
 - CTLA-4 fusion protein
 - Abatacept
 - Belatacept
 - JAK inhibitors
 - Ruxolitinib (JAK 1/2)
 - Tofacitinib (JAK 3)
 - Tyrosine Kinase Inhibitors (TKI)
 - Imatinib, Dasatinib, Nilotinib
 - Sorafenib, Sunitinib, Pazopanib
 - Proteosome inhibitors
 - Bortezomib
 - Carfilzomib

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Anti CD-20 Antibodies

- **Rituximab**, Ofatumumab, Obinutuzumab
- Monoclonal antibodies to CD-20, a B lymphocyte marker
- Practical impact
 - Profoundly impaired vaccine response to new and recall antigens
 - Rituximab linked to hypogammaglobulinemia (esp. repeated doses over months or years)
 - Associate with hepatitis B virus reactivation (black box warning on all agents!)

Van der Kolk LE, et al. Blood 2002;100:2257-9, Ljungman P, et al. Br J Haematol 2005; 103: 96-8, Casulo C., et al. Clin Lymphom Myeloma Leuk 2013;13:106-11, Makatsori M., et al. QJM 2014;107: 821-8

Case Scenario

- A 59-year-old male
- Diagnosed diffused large B cell lymphoma (19 June 2014) presented with tonsil enlargement and cervical lymphadenopathy
- Lymph node biopsy showed positive CD-20
- Received R-CHOP 6 cycles (21 Aug 2014 - 16 Dec 2014)
- HBsAg-negative, antiHCV-negative
- June 2015 (10 months after CMT)
 - Fever with malaise and jaundice
 - TB 12.8 mg/dL, DB 9.4 mg/dL, AST 874 U/L, ALT 1491 U/L

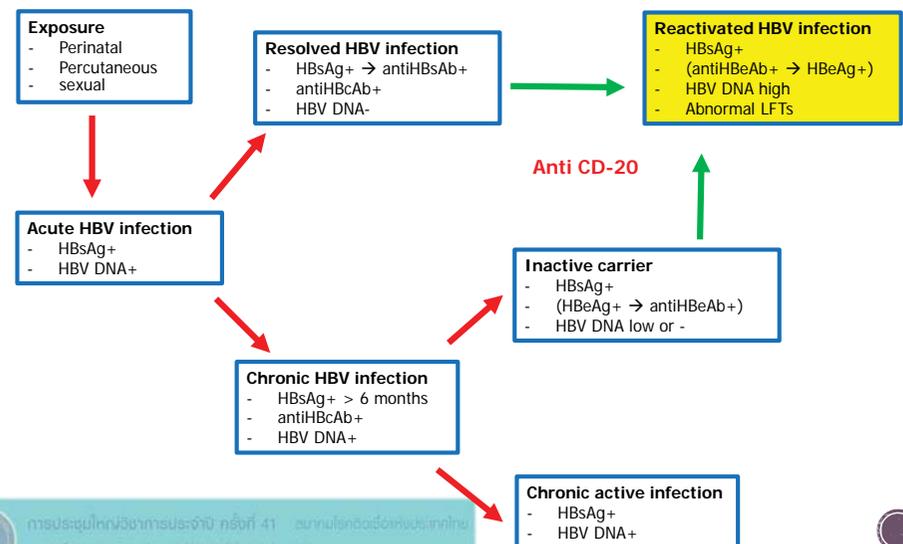
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Case Scenario

- At admission
 - TB 30.2 mg/dL, DB 25.5 mg/dL, AST 1462 U/L, ALT 1982 U/L
 - HBsAg positive, antiHBsAb negative
 - AntiHBcAb positive, antiHBcAb IgM-negative
 - antiHAV IgG positive, antiHAV IgM negative
 - antiHCV negative
 - HBV viral load 26,374 IU/mL
- Treatment
 - Entecavir (0.5) 1 tab OD
 - Supportive treatment: ursolin, NAC
 - Candidate for orthotropic liver transplantation

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HBV Reactivation



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Anti CD-20 and HBV Reactivation: HBsAg+

- Rise in HBV DNA +/- abnormal liver test
 - Can progress to fulminant hepatic failure and death
- Higher risk in inactive carrier > patients with resolved HBV
 - In non-Hodgkin's lymphoma with HBsAg+ carriers
 - RCHOP: 80% reactivation
 - CHOP: 55% reactivation
 - EARLY reactivation in HBV carriers without antiviral prophylaxis (can occur within days)



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Pei S., et al. Ann Hematol 2010; 89:255-62



Anti CD-20 and HBV Reactivation: anti-HBcAb+

- Loss of anti-HBsAb and reappearance of HBsAg
- Detectable HBV DNA
- Pattern
 - HBV DNA detectable weeks to months before reverse seroconversion or clinical hepatitis
 - Potential window for intervention – DNA monitoring
 - Some patients with detectable DNA → spontaneously clear



Kusumoto S., et al. CID 2015; 61:719-29, Huang Y-H., et al. JCO 013; 31: 2765-72,
Hsiao L-T., et al. Medicine 2015; 94:e1321, Yeo W., et al. JCO 2009; 27:605-11,
Niitsu N., et al. JCO 2010;28:5097-100



Anti CD-20 and HBV Reactivation: anti-HBcAb+

- Lymphoma
 - 24% reactivation with RCHOP
 - 8-12% if using detectable DNA as a criteria for reactivation
 - 0% reactivation with CHOP
- Reactivation occurs later than inactive carrier
 - 2-6 cycles of R-containing regimens and up to 12 months later
- Risk factors
 - HBsAb < 10 IU/L
 - HBV DNA detected at baseline
 - More than 6 cycles of Rituximab



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Prevention of HBV Reactivation

- ALL received anti CD-20; **SCREEN** for HBV
 - Also TNF- α inhibitors, abatacept, high dose steroid, etc...
- If HBsAg+ → antiviral prophylaxis
 - Most data on "lamivudine"
 - Other drug are emerging; TDF
- Management for anti-HBcAb+ : varies
 - Guidelines recommend antiviral prophylaxis
 - Recent studies showed excellent outcomes with careful monthly monitoring of HBV DNA for up to 1 year after receiving anti CD-20 therapy



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Niitsu N., et al. JCO 2010;28:5097-100, Reddy KR., et al. Gastroenterol 2015; 148:215-9



Anti-CD20 and Herpes Zoster

- A study in RA: 29,129 biologic agent treatment episodes
- Received HZ vaccine 0.4% in 2007 to 4.1% in 2011
- 423 HZ episodes
 - Certolizumab 2.45 per 100 PYs (anti-TNF)
 - Rituximab 2.27 per 100 PYs
 - Golimumab 1.61 per 100 PYs (anti-TNF)



PML and Biologics

- Increased incidence of PML in rheumatologic patients
- Association: efalizumab, adalimumab, natalizumab, fludarabine, rituximab, mycophenolate, steroids, MTX
- Rates per 100,000 discharge:
 - SLE 4, RA 0.4, others CTD 2 (average 1 in 100,000)
- 0.2% with natalizumab for multiple sclerosis or Crohn's
- 1 in 500 with efalizumab for psoriasis
- 57 reported cases after rituximab



Anti CD-52 Antibody

- Alemtuzumab
- Monoclonal antibodies to CD-52, a marker on B, T and NK lymphocytes
- Use in lymphoproliferative disorders and solid organ transplant
- Practical impact
 - Depletion of all lymphocyte cell lines (esp. CD4⁺-T lymphocytes)
 - Vulnerable to broad range of infections
 - When use in hematologic diseases → CMV reactivation
 - Solid organ transplantation → fungal diseases



Alemtuzumab in lymphoproliferative disorders

- Chronic lymphocytic leukemia
 - 43% infection
 - Most common – CMV reactivation/CMV diseases
 - Others – Adenovirus, PML, VZV, fungal infection, toxoplasmosis
- Hematopoietic Stem cell Transplant
 - CMV reactivation 66.7% (37% in non-alemtuzumab)
 - Opportunistic infections 44.4% (29.6% in non-alemtuzumab)



Alemtuzumab in Transplant Recipients

Infection rate in kidney transplant recipients

- Alemtuzumab – 33%
- Basiliximab (anti-CD25) – 40%
- Antithymocyte globulin – 36%

Fungal infection (most common – candidiasis)

- Alemtuzumab – 10%
- Basiliximab – 9%

Disseminated fungal infection

- Alemtuzumab – 68%*
- Basiliximab – 30%

Pancreas transplant – 6.6% (cryptococcosis, histoplasmosis, aspergillosis and candidiasis)



Blood Stream Infections in Transplant Recipients Receiving Alemtuzumab

Bacteremia 69/449 episodes(15%)

Organism	Percent
<i>S. aureus</i>	18
CoNS	12
<i>E. faecium</i>	9.5
<i>E. faecalis</i>	7.5
<i>P. aeruginosa</i>	8.5
<i>K. pneumoniae</i>	10
<i>E. coli</i>	6
<i>E. cloacae</i>	3.5
<i>S. marcescen</i>	2
others	27



Thank You

Q & A

