Infectious Complications in Patients with Chronic Lymphocytic Leukemia – Pathogenesis, Spectrum, Treatment

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Areas to be covered...

- Pathogenesis
- Spectrum of infections
- Strategies for prevention and prophylaxis of infection
Pathogenesis of Infection
Hypogammaglobulinemia

- Disease duration, stage

- Related to functional abnormalities of T- and non-clonal CD5-negative B-cells

- No clear correlation with specific Ig class deficiency
Impact of Ig V<sub>H</sub> Mutational Status

- No difference in Ig levels, immune response to vaccination, infection rate<sup>1</sup>
- Unmutated gene status - shorter time to 1st infection, higher infection-related mortality<sup>2</sup>
  - No impact on recurrent infections
  - Immunoglobulin levels comparable
  - Shorter time to first infection - p53, CD38+
    - No impact by zap-70 expression

Mucosal Immunity

• Infections common at mucosal sites

• Salivary Ig levels
  – Salivary IgM levels decreased
  – No difference in salivary IgG and IgA levels
  – No correlation with infection

• Mucosal immunity - independent regulation, or part of the malignant B-cell clone?
Defects in Cell-Mediated Immunity and Complement

- No correlation with infectious complications
- Decreased CD4/CD8 ratio
- Excessive T-suppressor, deficient T-helper cell function
- Defects in NK-cell, LAK cell activity
- Impaired response to recall antigens

- Complement
  - Reductions in levels
  - Defects in activation and binding
Spectrum of Infections
Conventional Alkylator-Based Regimens

- Common bacterial pathogens
- Recurrent infections
- Infections originating at mucosal sites
- Fungal and viral infections
Fludarabine-Based Regimens

- Common bacterial, opportunistic infections

- Pathogenesis related to T-cell defects
  - Decline in T-cell counts occur early
  - CD4 > CD8, NK cells
  - Defects persist 1-2 yrs after therapy d/c’d
  - Variable impact on Ig levels
Risk Factors for Infection - Fludarabine Regimens

• Disease stage, prior therapy, response to therapy
• Risk factors for major infections¹
  – Prior therapy for CLL
  – Advanced stage disease
  – Elevated creatinine
• Intergroup trial (CALGB 9011)²
  – Baseline low IgG level
  – No correlation with disease stage, response to therapy
• Number of prior regimens, hemoglobin <12 g/dl³

Infections with Fludarabine- vs Alkylator-Based Regimens

- Meta-analysis, single agent fludarabine - more Gr 3/4 infections than with alkylators\(^1\)
- French trial - F vs CAP vs ChOP - no OI’s w/F\(^2\)
- Intergroup trial (CALGB 9011) - F vs C vs FC\(^3\)
  - More infections with FC
  - F vs C
    - More infections/month of follow-up
    - More major infections, herpesvirus infections
    - Few cases of *Pneumocystis*, no *Aspergillus* infections

Infections - Fludarabine / Cyclophosphamide

- German trials - F vs FC\(^1\)
  - Rate of severe infections/OI’s comparable (33%, 40%)
  - Dose reductions more common with FC
- Addition of oblimersan to FC\(^2\)
- Use of FC in previously treated patients\(^3\)
  - 57% with infections, FUO
    - 26% - herpesviruses
    - 7% - fungal pathogens
    - Incidence in 1st 3 cycles of therapy - 74%

\(^3\)Kowal M, et al. Leuk Lymphoma 2004; 45:1159-1165
Rituximab-Based Regimens

• Single agent rituximab - few infections$^1$

• FR (CALGB 9712) - 20% Gr 3/4 infections$^2$
  – OI’s - localized herpesvirus infections, PCP (2)

• FCR - infection rates$^3,^4$

<table>
<thead>
<tr>
<th></th>
<th>Major</th>
<th>Herpesvirus</th>
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</thead>
<tbody>
<tr>
<td>Treatment-naïve</td>
<td>2.6%</td>
<td>5%</td>
</tr>
<tr>
<td>Previously treated*</td>
<td>16%</td>
<td>1%</td>
</tr>
</tbody>
</table>

(*comparable in F-sensitive and F-refractory patients)

2-CDA Therapy

• T-cell abnormalities - may persist for 1-2 yrs after agent d/c’d

• Age ≤55 yrs - prior therapy (45% vs 26%)\(^1\)

• CALGB 9211 - Gr 3-5 infections in 43% F-refractory patients\(^2\)
  – Bacterial infections most common
  – HSV, HZ, cerebral toxo, candidal esophagitis

## 2-CDA Therapy

### 2-CDA +/- prednisone

<table>
<thead>
<tr>
<th></th>
<th>Infections/FUO</th>
<th>Herpesvirus infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior treatment</td>
<td>49%</td>
<td>38%</td>
</tr>
<tr>
<td>Treatment-naïve</td>
<td>25%</td>
<td>20%</td>
</tr>
</tbody>
</table>

### Treatment-naïve - 2CDA or Chlorambucil, + prednisone

<table>
<thead>
<tr>
<th></th>
<th>FN/FUO</th>
<th>Herpesvirus</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-CDA</td>
<td>23%</td>
<td>21%</td>
</tr>
<tr>
<td>Chlorambucil</td>
<td>11%</td>
<td>11%</td>
</tr>
</tbody>
</table>

Pentostatin Therapy

- Cellular immune defects may persist for several months after d/c of agent

- CALGB phase II trial\(^1\)
  - Infections in >50% of patients - occur early
  - More common with advanced stage disease, prior therapy
  - OI’s in 26% - HSV, HZ, *Candida, Pneumocystis*

- ECOG trial - pentostatin, chlorambucil, prednisone - treatment-naive\(^2\)
  - Gr 3 infections - 31%
  - Herpes zoster - 20%

- PCR - Gr 3/4 infections - 28%\(^3\)

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\(^3\) Lamanna N, et al. J Clin Oncol 2006; 24:1575-1581
Alemtuzumab Therapy

- Defects in cell-mediated immunity
  - Develop within 1-2 mos of treatment
  - Persist for at least 9 mos after therapy d/c’d

- No correlation of immunosuppression with:
  - Cumulative dose
  - Route of administration

- Infections may be more common in non-responding patients

- CMV reactivation
Alemtuzumab - Pivotal Trial

• n=93, failed fludarabine

• 27% - Gr 3/4 infections (10% - responders)
  – Aspergillosis, candidiasis, zygomycosis, cryptococcosis
  – *Listeria* meningitis
  – *Pneumocystis*
  – CMV reactivation

First-Line Therapy - Alemtuzumab vs Chlorambucil

- Alemtuzumab, 30 mg, 3 times wkly
- Chlorambucil, 40 mg/m² q 28 days
- Up to 12 wks therapy
- N=297
- Improved ORR/CR with alemtuzumab (83%/24%, vs 55%/2%), superior PFS
- More infusion-related AE’s, CMV events with alemtuzumab

Flu-Cam for Relapsed/Refractory CLL

- \( n=36 \), phase 2 trial
  - Flu - 30 mg/m\(^2\)/d X 3 d
  - Cam - 30 mg/d X 3 d
  - 28 day cycles - maximum 6 cycles

- Prophylaxis - TMP/SMX, valacyclovir
  - Continued 2 mos after completion of therapy

- 2 CMV reactivations
- 2 *Aspergillus* pneumonias
- 1 fatal *E. coli* sepsis

Alemtuzumab -
Lymphoproliferative Disorders

- DFCI/BWH - n=27 (21 CLL, 6 plasma cell disorder)
  - Mortality - 37% (7/10 deaths infection-related)
  - 15/27 (56%) - OI’s
    - CMV viremia (44%)
  - 9/21 (43%) CLL patients - 12 OI’s
    - Aspergillosis (3), pyomyositis/bacteremia (2), single cases of: PML, adenoviral pneumonia, disseminated histoplasmosis, disseminated cryptococcosis, cerebral toxoplasmosis, disseminated acanthamaebiasis, CMV pneumonitis/colitis
    - 4/12 - neutropenic infections
  - 22/27 (82%) - 30, non-OI infections
    - 3 deaths - enterococcal bacteremia (2-VRE)

Alemtuzumab - Lymphoproliferative Disorders

- Literature review - n=410, 262 infections
  - 167 (64%) OI’s
    - HSV most common (32%)
    - CMV reactivation (31%)
    - *Pneumocystis* (7%)
    - Invasive pulmonary aspergillosis (6%)
    - Herpes zoster (4%)
    - Others - TB, cutaneous non-TB mycobacterial infections, sinonasal zygomycosis, PML, pulmonary cryptococcosis
  - 95 non-OI infections
    - Sepsis (30%) (*E. coli*)
    - Pneumonia (28%)

Alemtuzumab + Rituximab

• Alemtuzumab + rituximab for relapsed/refractory B-cell disorders
  • 52% - infections
  • 27% - CMV antigenemia
    – 15% required therapy

Alemtuzumab as Consolidation Therapy

• MDACC, n=41
  – CR with MRD, PR, nPR
  – Alemtuzumab consolidation - median of 5 mos after completion of induction therapy
  – Gr 3/4 neutropenia - 30%
  – 15 infections
    • 9 - CMV reactivation
    • Viral myocarditis, *Listeria*, septicemia, influenza A pneumonia
    – EBV+ large cell NHL (3) - 2 resolved w/o treatment

• N=9, initial F, alemtuzumab consolidation, median of 5 (range, 2-11) mos after F
  – 3 - CMV reactivation without disease

2Montillo M, et al. *Haematologica* 2002; 87:695-700
Alemtuzumab as Consolidation Therapy

• German CLLSG - CLL 4B -
  – F or FC - alemtuzumab (2 mos after F/FC x 12 wks) vs observation\(^1\)
  – Terminated early - 7/11 Gr 3/4 infections
  – 4 CMV reactivation, pulm aspergillosis, pulmonary TB reactivation, herpes zoster

\(^1\)Wendtner CM, et al. *Leukemia* 2004; 18:1093-1101
Alemtuzumab as Consolidation Therapy

• CALGB 19901 - F x 4, alemtuzumab x 6 wks, 2 mos later\textsuperscript{1,2,3}
  – 12/57 - Gr 3/4 infections
  – CMV reactivation - 8/57
    • 1 - fatal
    • 6 - complete/partial resolution
    • 1 - persistent infection
  – Weekly qualitative CMV PCR testing
    • 3/18 - CMV reactivation, no disease

• CALGB 10101 - FR x 6, alemtuzumab consolidation 3 mos later\textsuperscript{4}

\textsuperscript{1,2}Rai KR, et al. \textit{Blood} 2002; 100:205-206a, \textit{Blood} 2003; 102:676-677a
\textsuperscript{3}Morrison VA, et al; \textsuperscript{4}Lin T, et al; Tues 12/11 CLL session
Alemtuzumab as Consolidation Therapy

- CALGB study: induction with FR, followed four months later by alemtuzumab consolidation
- Consolidation was associated with 5 infection-related deaths in patients achieving a CR after FR induction (Legionella, CMV, and Pneumocystis pneumonia; viral and Listeria meningitis)
Alemtuzumab as Consolidation Therapy

• What are the issues?
  – Cumulative alemtuzumab dose
  – Cumulative fludarabine dose
  – Immune impact from prior rituximab
  – Response to induction therapy
  – Timing of consolidation following induction therapy

• Prospective assessment of immune function following induction therapy, consolidation therapy, post-consolidation may be needed (treatment-naïve, relapsed/refractory)
Strategies for Prevention and Prophylaxis of Infection
Immunoglobulin Therapy

- Randomized, placebo-controlled trial of prophylactic IVIG\(^1\)
  - 400 mg/kg q 3 wks
  - Reduction in minor/moderate bacterial infections
  - No decrease in major infections, mortality
  - No quality of life benefit - not cost-effective

- Prophylactic low-dose IVIG
  - 250 - 500 mg/kg q 4 wks
  - Reduction of infections in some series, not others
  - Cost-effectiveness

- Optimal dose, schedule, subset of patients that will benefit not clear

Antimicrobial Prophylaxis Regimens for CLL Patients

- **Antibacterial**
  - Ciprofloxacin 500 mg po bid
  - Levofloxacin 500 mg po qd

- **Antifungal**
  - Fluconazole 200 or 400 mg po qd
  - Posaconazole 300 mg po bid x 1d, then 300 mg po qd
  - Voriconazole 200 mg po bid
Antimicrobial Prophylaxis Regimens for CLL Patients

- Antiviral - HSV / HZ
  - HSV: Acyclovir 400-800 mg po bid
  - HZ: Acyclovir 800 mg po bid
  - Valacyclovir 500 mg po bid-tid, with food
  - Famciclovir 250 mg po bid

- Antiviral – CMV
  - Valganciclovir 900 mg qd
  - Ganciclovir 5 mg/kg IV qd
Antimicrobial Prophylaxis Regimens for CLL Patients

• Pneumocystis
  – Trimethoprim-sulfamethoxazole - one SS po qd or one DS po qd, or 3x wkly
  – Dapsone 100 mg po qd
  – Pentamidine 300 mg by aerosol q 4 wks
  – Dapsone 200 mg po + pyrimethamine 50-75 mg po + leucovorin 25 mg po q wk
  – Atovaquone 1500 mg po qd with high-fat meal
## Recommended Antimicrobial Prophylaxis by CLL Treatment Regimen

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Antibacterial</th>
<th>Antifungal</th>
<th>PCP</th>
<th>HSV/VZV</th>
<th>CMV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkylating agents (eg, chlorambucil)</td>
<td>No</td>
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<tr>
<td>Purine analog monotherapy (eg, fludarabine)</td>
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<td>No</td>
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<tr>
<td>Purine analog + anti-CD20 monoclonal antibody</td>
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<tr>
<td>Purine analog + cyclophosphamide</td>
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<td>Purine analog + cyclophosphamide + anti-CD20</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
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<td>monoclonal antibody</td>
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<tr>
<td>Anti-CD20 monoclonal antibodies (rituximab, ofatumumab, obinutuzumab)</td>
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<tr>
<td>Alemtuzumab</td>
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<td>Yes</td>
<td>Wkly PCR Monitoring</td>
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<tr>
<td>Bendamustine</td>
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<td>Lenalidomide</td>
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<td>Ibritinib</td>
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<td>Idelalisib</td>
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Alemtuzumab Therapy and CMV Reactivation

- Incidence of 4 - 29% (symptomatic infection)
  - Presentation as FUO, cough

- Asymptomatic infections identified by + antigen assays, PCR testing
  - 67% (previously treated)
  - 46% (treatment-naïve)

- 4-6 wks after initiation of therapy
  - Lymphopenia
  - Neutrophil nadir

- Infections after completion of therapy, deaths uncommon
Monitoring of CMV Reactivation

- Phosphoprotein 65 (pp65) antigenemia assay (antigen)
  - Rapid, sensitive, limited with severe leukopenia

- Quantitative PCR assays (CMV DNA)\(^1\)
  - More sensitive, reliable
  - Cutoff for initiation of preemptive therapy

- Better than viral culture, qualitative PCR methods

CMV - Preemptive Therapy

• PCR testing, institution of therapy with CMV reactivation

• Initiate upon 2 consecutive + results, obtained a wk apart

• Treatment options - symptomatic infection
  – Ganciclovir, 5 mg/kg IV bid, or 1000 mg po tid
  – Valganciclovir, 900 mg po bid
  – Duration - 14-21 days
    • Until resolution of symptoms and negative test, or 2 consecutive negative results
  – Continue alemtuzumab unless persistently symptomatic

CMV - Preemptive Therapy

• Treatment options - asymptomatic infection
  – Ganciclovir, 5 mg/kg IV bid, or 1000 mg po tid
  – Duration - 7-14 days, or until 2 consecutive negative results
  – Continue alemtuzumab

• CMV surveillance/preemptive therapy decreases incidence of symptomatic reactivation from 30% to 9%

CMV Prophylaxis

• Valacyclovir (500 mg qd) vs valganciclovir (450 mg bid)\(^1\)

• Symptomatic CMV reactivation -
  – 7/20 (35%) valacyclovir
  – 0/20 valganciclovir

• CMV testing q 2 wks

• Duration - continue 2 mos after completion of therapy

\(^1\)O’Brien S, et al. Blood 2005;106:830a
Vaccination Strategies

• Responses to immunization suboptimal
  – Improved responses if IgG > 700 mg/dl

• Superior responses with:
  – Protein, conjugated vaccines than polysaccharide vaccines
  – Adjuvant ranitidine treatment

• No formal vaccine recommendations (ZostaVax)
Future Issues

• Significant impact of infectious complications

• With new therapeutic modalities, evaluate not only traditional outcome parameters, but also impact on infectious complications

• Utilize “real world” monitoring techniques

• Identification of discrete patient subsets at increased risk for infection