Autoimmune Cytopenias in CLL

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Disclosure of Potential for Conflict of Interest

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Learning Objectives

• Recognize the incidence of autoimmune complications in CLL.
• Identify and confirm autoimmune manifestations in CLL.
• Review the management of these complications.
Case # 1

- 72 F, CLL Rai Stage IV
- On Chlorambucil x 3 months
- Hb 85 → 104 → 67 after 1 week
- ? Cause
- No Bleeding
- Inv: Retics low, Bilirubin- increased, LDH marginal increase.
- DAT +ve
- BM: Increased erythroid precursors, no MDS
Prevalence of Autoimmune Cytopenias (AIC) in CLL

- Cumulative Risk: 5-10%
- Time of AIC
  - All stages of CLL
  - Precipitated by drugs: purine analogs or alkylating agents
Autoimmune cytopenia in chronic lymphocytic leukemia: prevalence, clinical associations, and prognostic significance

Carol Moreno, Kate Hodgson, Gerardo Ferrer, Montse Elena, Xavier Filella, Arturo Pereira, Tycho Baumann and Emili Montserrat
Prevalence of Autoimmune cytopenias (AIC)

- Study period: 28yr (1980-2008), Barcelona
- Patient No: 960
- Prevalence of AIC: 70 (7%)
  - At diagnosis -19
  - Before diagnosis -3
  - During disease -48
- Subtypes: AIHA-49; ITP-20, Both-1
- Association with:
  - High Lympho, Rapid L doubling, Increased B2M, High CD38 and ZAP 70

*Mareno C. Blood 2010; 116: 4771-4776*
Survival of CLL Pts according to modified Binet Staging

Mareno C. Blood 2010; 116: 4771-4776
Other Prevalence Studies
The prognostic significance of cytopenia in chronic lymphocytic leukaemia/small lymphocytic lymphoma

- **Mayo Clinic:** All CLL Pts from 01 Jan 1995-31 Dec 2004: 1750
- Cytopenias due to CLL: 303 (17.3%)
  - BM failure -75%
  - AIC-25%
- Survival from Onset of Cytopenis:
  - BM failure : 4.4yr
  - AIC : 9.4yr, \( p<0.001 \)
- Cytopenia due to Autoimmune disease not an adverse prognostic factor
- **Zent CS. Br J Haematol 2008; 141: 615-621**
Autoimmune Cytopenias in CLL Manitoba

- Total 72 (Of 609 patients) = 11.8%
- Frequency of different Cytopenias
  - AIHA : 60%
  - ITP  : 29%
  - PRCA : 7%
  - AIN  : 4%
Autoimmune Cytopenias (AIC): Problems and Lacuane

- Positive DAT (Comb’s test): considered essential for Auto Immune Hemolytic Anemia
  - May be +ve in 20-30% CLL at some point without AIHA
  - May be –ve with definite AIHA.

- Reticulocytes: May remain low due to chemotherapy or disease
Definitions of Autoimmune Cytopenias in CLL
Criteria for AIHA

- Criteria for AIHA:
  Unexplained Hb <100g/L + at least

  - (a) 1 marker of autoimmune mechanism (DAT or Cold agglutinins) AND 1 marker of hemolysis
    • increased indirect bilirubin or LDH or Retics or BM erythropoiesis without bleeding
  OR

  - (b) 2 markers of hemolysis and no other cause like bleeding or hypersplenism

Case # 2

- 54 M, CLL Rai Stage III, Hb 92
- On Fludarabine x 4th cycle, Hb 110
- After 4 weeks: Bruising +ve, Platelets 140 → 40 → 30
- Spleen not palpable
- Inv: Retics low, Bilirubin- normal, LDH normal
- BM: Adequate megakaryocytes
Criteria for other AIC

- **ITP**: platelets \(<100 \times 10^9/L\) with \(\geq 2\) of following:
  - normal or increased platelet production on BM biopsy or no reticulocytopenia if BM NA.
  - no hypersplenism
  - No chemo in last month

Criteria for other AIC

• **Pure Red cell Aplasia (PRCA):** Hb <100g/L + Bone Marrow
  – Low or absent Retics, erythroblast maturation defects
  – Preserved granulocyte and platelet precursors

• **Autoimmune neutropenia (AIN):** sustained neutropenia (< 0.5 x 10^9/L)
  – no chemotherapy in preceding 8 weeks
  – bone marrow: low or absent granulocytic precursors, maturation arrest

Types of AIC

• Spontaneous AIC:
  – No chemotherapy for > 3 months

• Drug-induced:
  – During chemo or < 3 months of chemotherapy
CLL + Immune Cytopenias

- **Simple**: No BM failure or progressive CLL
  - Rx $\rightarrow$ Immunosuppressive therapy

- **Complex**: steroid refractory immune cytopenias or progressive CLL
  - Rx $\rightarrow$ Immunosuppressive + chemotherapy
Therapies for Simple AIC in CLL

- Isolated or Simple Autoimmune Cytopenias
  - First line: corticosteroids
  - Second line:
    - Cyclosporine, MMF
    - IVIG
    - Rituximab
    - Splenectomy
    - Azathioprine
    - Alemtuzumab

- Folic acid, Blood transfusions
Therapy of Complex (Refractory) AIC in CLL

• Use drugs which are:
  – not myelosuppressive
  – not known to cause autoimmune phenomenon
Therapy for Refractory AIC
Rituximab-based chemotherapy for steroid-refractory autoimmune hemolytic anemia of chronic lymphocytic leukemia

N Gupta, S Kavuru, D Patel, D Janson, N Driscoll, S Ahmed and KR Rai

Division of Hematology/Oncology, Department of Medicine, Long Island Jewish Medical Center, New Hyde Park, New York, USA

- **RCD:**
  - Ritux 375mg/m² (D1), Cyclo 750mg/m² day 2, Dex 12 mg o.d. x 7. Rpt 4 weeks.
- **Steroid refractory AIHA:** 8 Pts
- **Results:** Remission in 8: Median Hb 8.3 → 14.3
  - Median cycles 3 (range 1-4)
  - Median duration of remission: 13 months
  - Coomb’s negative 5/8
- **Effective in relapse AIHA**
Rise in Hb on Re-treatment with RCD in relapse AIHA
ORIGINAL ARTICLE: CLINICAL

A combination of rituximab, cyclophosphamide and dexamethasone effectively treats immune cytopenias of chronic lymphocytic leukemia

MATTHEW KAUFMAN¹, SEWANTI A. LIMAYE¹, NANCY DRISCOLL¹, CHRISTINA JOHNSON¹, ANGELICA CARAMANICA¹, YEHUDA LEBOWICZ¹, DILIP PATEL¹, NINA KOHN², & KANTI RAI¹
ORIGINAL ARTICLE

Rituximab–cyclophosphamide–dexamethasone combination in management of autoimmune cytopenias associated with chronic lymphocytic leukemia

ANNE-SOPHIE MICHALLET¹, JULIEN ROSSIGNOL², BRUNO CAZIN², & LOIC YSEBAERT³,
Treatment of autoimmune cytopenia complicating progressive chronic lymphocytic leukemia/small lymphocytic lymphoma with rituximab, cyclophosphamide, vincristine, and prednisone

DEBORAH A. BOWEN¹, TIMOTHY G. CALL¹, TAIT D. SHANAFELT¹, NEIL E. KAY¹,

- No. of Pts: 20. Median cycles: 4.9 (range 2-6)
- AIC: response in 19
  - CR: 14, PR: 5
  - Median TTT: 21.7 months
- Progressive CLL: Response in 17
  - CR: 9, PR: 8
  - Median TTT 27.7 months
- Treatment effective for “complex autoimmune cytopenia in CLL”

Leuk Lymph 2010; 51: 620-627
Rituximab based therapy in AIHA in CLL: CancerCare Manitoba

• Outcome of AIHA in CLL Treated with Rituximab based therapy from January 2003 - December 2007
• Retrospective Analysis
• All cases of AIHA in CLL who received Rituximab alone or in combination over a 5 year period
Comparison of response to RCD in CLL-AIHA

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<tr>
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<th>CCMB, Winnipeg</th>
<th>Gupta et al 2002</th>
<th>Kauffman et al 2009</th>
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<tbody>
<tr>
<td>No of Pts</td>
<td>9</td>
<td>8</td>
<td>20</td>
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<tr>
<td>Median age (Range)</td>
<td>62 (57-80)</td>
<td>60 (46-70)</td>
<td>63 (48-78)</td>
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<td>Rai Stage</td>
<td>I-1; II-2; III-3; IV-3</td>
<td>III-4; IV-4</td>
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<td>Response</td>
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<td>Fatality</td>
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<td>Median dur. Response</td>
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<td>13M</td>
<td>22M</td>
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Summary

- Cytopenias in CLL may be autoimmune in nature
- Drugs implicated: chlorambucil, fludarabine
- Conventional tests for hemolysis may be non-contributory
- For cytopenias requiring treatment: bone marrow exam is indicated
- First line management
  - **Simple AIC**: Steroids
  - **Complex AIC**: Rituximab, Cyclophosphamide, Dexamethasone (RCD)
Thank You