

New Antibodies and Small Modular Immune Pharmaceuticals for Chronic Lymphocytic Leukemia

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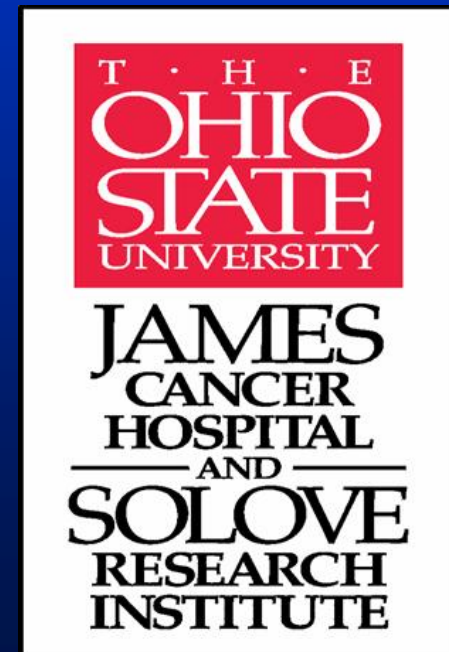
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Chronic Lymphocytic Leukemia

- One of the most common types of leukemia in adults with median age at diagnosis of 72
- While most patients are asymptomatic at diagnosis, majority eventually develop symptoms and require therapy for CLL; these patients ultimately will die of disease
- Even in absence of CLL progression, complications of CLL (infections, autoimmune, Richter's transformation, and 2nd cancers) eventually develop in most patients
- Unlike other types of leukemia, no therapy outside of possibly allogeneic stem cell transplant that cures or prolongs survival of this disease; therapy is therefore initiated at time of symptoms

CLL Therapy: The Problem

- Chemotherapy based treatments of CLL are palliative and do not extend survival
- Chemotherapy based treatments of CLL do not effectively treat del(17p13.1) disease
- Chemotherapy-based regimens have unacceptable short and long term toxicities
 - « Infection
 - « Cytopenias
 - « Autoimmune complications
 - « Impairment of future immune-based therapies
 - « Secondary cancers and leukemia

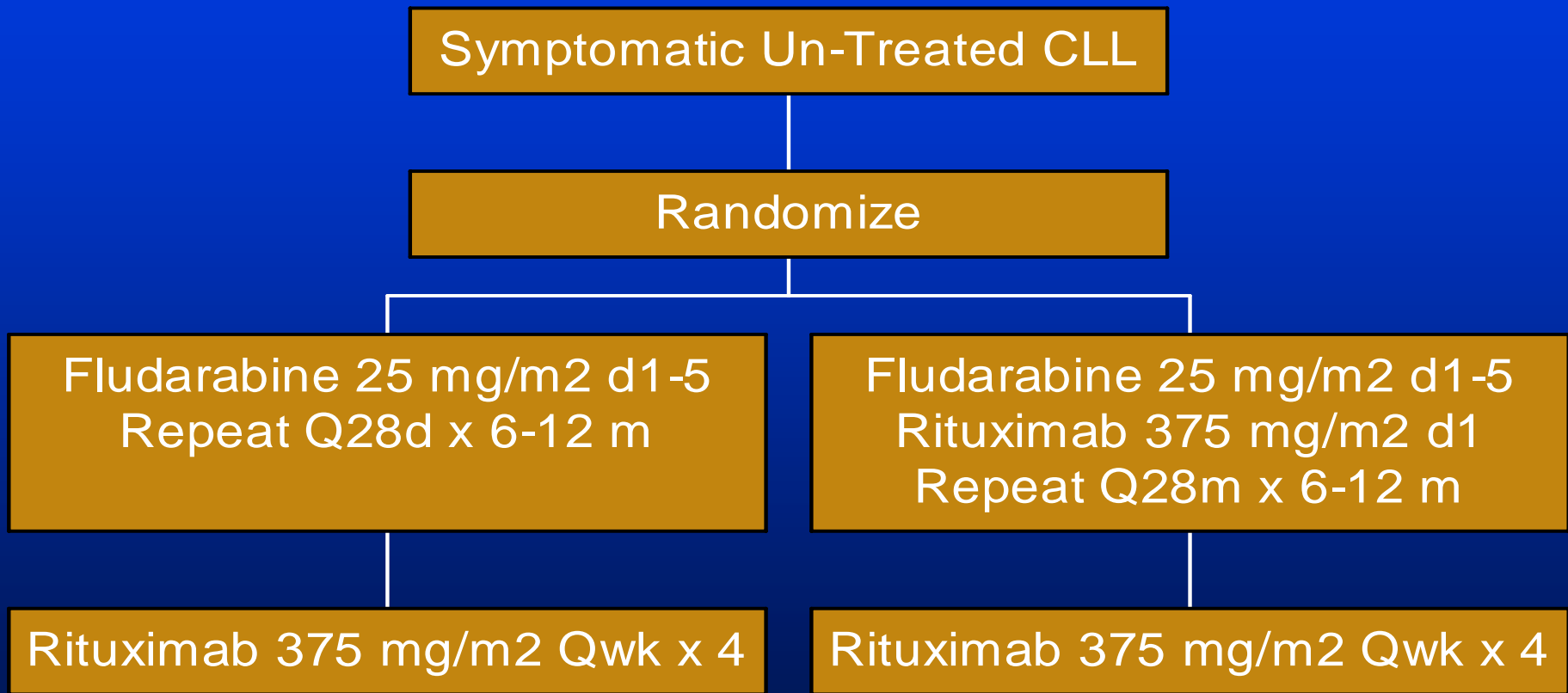
**Discussion of a problem occurs best in
the context of a potential solution**

**Could antibody and peptide-based therapies for
CLL represent at least a partial solution?**

Rituximab

- Chimeric anti-CD20 monoclonal antibody approved by FDA in 12/97 for relapsed, low-grade NHL
- Due to B-cell selectivity, toxicity profile of rituximab notable only for initial infusion reactions with minimal myelosuppression or infections
- Initial trials in SLL/CLL demonstrated very modest activity that was partially overcome with dose/schedule intensification
- Mechanism of action of rituximab in CLL possibly different as compared to other types of lymphoma (less ADCC and CDC)
- Greatest application has been in combination-based regimens

CALGB 9712 Design



104 pts enrolled with toxicity similar between arms except for more myelosuppression in combination arm

Treatment Outcome: CALGB 9011 to 9712

Trial	Fludarabine CALGB 9011	Fludarabine + Rituximab CALGB 9712	P=value
No Pts	179	104	
% CR Rate	20	38	0.002
% Overall Response	63	84	0.0003
% 2-year DFS (95%CI)	45 (37,52)	67 (58,76)	<0.0001
% 2-year OS (95%CI)	81 (75,87)	93 (88,98)	0.0009

Shorter PFS in pts with del(11q22.3) and del(17p13.1)

Byrd JC, et al: Blood 105:49, 2005

Byrd JC, et al: J Clin Oncol 24: 437, 2006

Fludarabine, Cyclophosphamide , and Rituximab In Previously Untreated CLL

- Three day MDA FC regimen with addition of rituximab repeated q 28 days for 6 cycles of therapy
- Three hundred patients previously untreated enrolled on this study with median follow-up of 6 years
- Responses noted in 95% of patients, including 72% CR rate and extended PFS as compared to historical FC controls
- 6-year failure-free survival 51% whereas survival was 77%
- Poor response duration in patients > 70 yrs, β_2 M or LDH > 2 x ULN, del(17p13.1), WBC > 150 x 10⁹/L

Alemtuzumab

- Humanized anti-CD52 antibody introduced in 1980's as immune suppressive agent
- Toxicity led to abandonment in autoimmune diseases but found to be active in CLL and PLL
- Clinical development rocky due to profound immune suppression and toxicity profile however FDA approved for fludarabine-refractory CLL in 2001
- Trials to date reveal improved efficacy in initial therapy and MRD; infectious toxicity from immune suppression will limit use in these areas

Status of Antibody Therapy in CLL

- Single agent rituximab has modest response with small proportion of complete remissions in previously treated CLL pts
- Combination therapy with rituximab appears to improve response, progression-free survival, and overall survival in CLL (no randomized data)
- Chemoimmunotherapy with rituximab does not overcome adverse outcome of del(17p13.1) CLL
- Alemtuzumab is effective against select types of CLL but is profoundly immunosuppressive and challenging to combine with other agents