

ACUTE LYMPHOBLASTIC LEUKEMIA

Richard M. Stone, MD
Director, Adult Leukemia Program
Dana-Farber Cancer Institute and Brigham and Women's Hospital
Professor of Medicine
Harvard Medical School
Boston, MA

**ASH 2009: Acute Lymphoblastic
Leukemia Review: Outline**

1. Pediatric ALL
2. Minimal Residual Disease
3. Pediatric-like therapy in adults
4. Philadelphia-positive ALL
5. Chemo-immunotherapy

Pediatric ALL: Still Teaching the Adult Doctors

- The great success story: 85-90% cure rate
 - More responsive disease: more TEL-AML1 and less PH+
 - Better tolerance of chemo c/w older adults
 - More familiar with how-to-treat (“that’s all pediatric oncologists do”)
 - More patients so many more randomized clinical trials with ‘tweaks’ that lead to gradual improvement in outcome
 - Better regimens: more non-myelosuppressive chemo
- ASH 2009
 - Not all HR children require SCT
 - There are biologically defined subgroups of children almost certain to be cured
 - More about use of steroids and L-asparaginase

HR Pediatric ALL: Is SCT a must?

- AEIOB-BFM ALL 2000, n=1999
 - Focus on 311 HR pts who had one or more of
 - t(4;11), poor prednisone response, no CR on d33, or high RRD at d 78
- RX; Dex ‘v’ Pred ind’n, 5-6 dose intensive consol, Cr ppx, 2 year maintenance
- Pred poor responders don’t do so badly (70% DFS), but pos MRD do poorly (40% DFS)
- Not randomized but the 80 who had alloSCT 5 yr EFS=52%, no diff than the 45% in chemo-rx pts

Conter, et al. *Blood*. 2009;114(22): Abstract 319.

Pediatric ALL: trisomy and TEL-AML1 are very good

- N=3054 on COG 1991 for NCI-SR ALL
- 24% pos for either trisomy 4 or 10; 41% for TEL-AML-1 translocation
- 6 yr EFS%, OS% (all differences significant)
 - Trisomy+ ‘v’ -: 94, 99 ‘v’ 86, 94
 - Tel-AML1 + ‘v’ -: 91, 97 ‘v’ 88, 94
 - Either+ ‘v’ both-: 92, 98 ‘v’ 85, 94

Matloub, et al. *Blood*. 2009;114(22): Abstract 320.

Pediatric ALL: Steroids and L-asparaginase

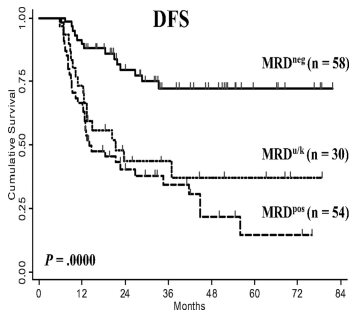
- DFCI-ALL Consortium 00-01; n=492 (282 SR); CR=96%
- Dex 'v' Pred used in post CR setting; 30 weeks of consolidation with full dose L-asparaginase 'v' individualized dosing based on nadir serum L-asparaginase level
- 5 year EFS%
 - Dex 'v' Pred: 90 'v' 81 (p=0.01)
 - Indiv L-asparaginase 'v' regular: 90 'v' 82 (p=0.04)
- However, in ages 10-18, osteonecrosis more common w dex: 23% 'v' 5% and at all ages fungal inf'n more common w dex: 19% 'v' 11%

Vrooman, et al. *Blood*. 2009;114(22): Abstract 321.

Minimal Residual Disease: Should we start using it in adults?

- Many pediatric protocols/regimens based intensity of subsequent therapy on post-treatment functional response
 - Prednisone early responders: look at day 7 or 'end-of window' marrow
 - Measure depth of remission by sensitive molecular or immunophenotypic techniques
- ASH 2009
 - More data that perhaps this is reasonable in adults, but we are limited by the lack of standardized assay, proof via randomized trial, and effective therapy, although it could be used to decide on need for allo SCT. The indications for SCT remain controversial.

MRD Detection does have Prognostic Value in Adult ALL



Bassan R, et al. *Blood* 2009;113:4153-4162.

PETHEMA LAL-AR-03.
Inclusion criteria

High-risk ALL. Any of the following:

- Age 30-60 yr.
- WBC count >30x10⁹/L.
- t(4;11) or *MLL/AF4* rearrangements
- Slow response to induction therapy (d 14 >10% marrow blasts or MRD in CR by multiparameter flow)

Exclusion criteria

- BCR-ABL* positive ALL → TKI+CHT+SCT
- Mature B-ALL (Burkitt's leukemia) → Specific TCHT+Ritux
- Biphenotypic AL
- Undifferentiated AL
- Lymphoblastic lymphoma without leukemic expression

Ribera, et al. ASH 2009, abst 322

PETHEMA LAL-AR-03.
(n = 235)

Day 14 marrow had > 10% blasts: intensified induction given (added mitoxantrone and high dose ara-C) (required by 32%)

86% achieved CR

All rec'd 3 consolidation modules

MRD assessment during CR positive: allo SCT (sibling, MUD or cord) (30% of CRs thus assigned; n = 47)

Ribera, et al. ASH 2009, abst 322

PETHEMA LAL-AR-03.
Results

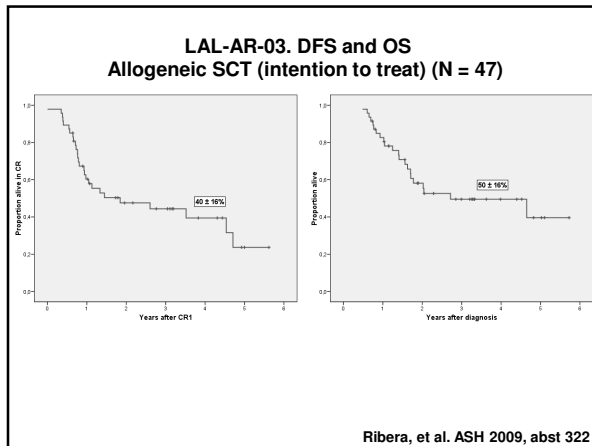
Advanced age, MRD and WBC have independent px significance on MRD analysis.

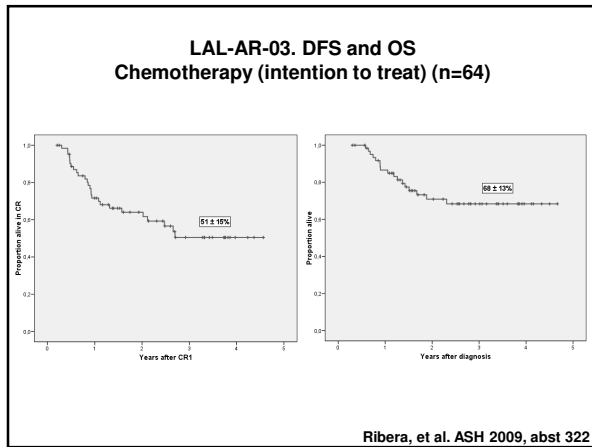
Those with negative MRD do well without transplant

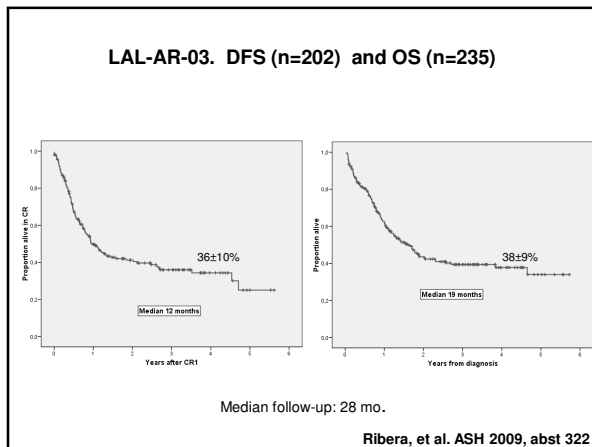
It is unclear if SCT can lead to better outcomes in those with MRD burden

Many are lost before the decision of allSct 'v' chemo can be made

Ribera, et al. ASH 2009, abst 322







More Evidence that Pediatric-Like Therapy in Adults is a Good Idea

- Cure of kids; 85% c/w 30% for adults (with multiple adult regimens, eg. CALGB, hyper CVAD, etc.)
- Adolescents and Young Adults (16-24 years old) who are treated by pediatric oncologists do better than if treated by adult oncologists
 - Different type kids who go to adult v pedi docs
 - Pedi docs have more experience with ALL
 - Pediatric regimens more suited for this disease
- ASH 2009
 - More data that the pediatric approach works
 - HOVON-70
 - MD Anderson: abstract 2037 (augmented BFM-2r OS=81%)
 - MD Anderson: abstract 3084 (hyperCVAD' 3yr EFS: 65-75%, possibly better with rituximab added)

Treatment of adolescents with ALL

| Cooperative Group | Age | EFS (%) |
|-----------------------------------|---------|----------|
| North America ¹ | | |
| CCG 1882/1901 | 16 - 21 | 63% (7y) |
| CALGB 8811-19802 | | 34% |
| French ² | | |
| FRALLE- 93 | 15 - 20 | 67% (5y) |
| LALA- 94 | | 41% |
| Dutch ³ | | |
| SKION ALL 6-9 | 15 - 21 | 69% (5y) |
| HOVON ALL 5 &18 | | 34% |
| English ⁴ | | |
| ALL97/rev99 | 15 - 17 | 65% (5y) |
| E2993 | | 49% |

1. Stock, et al. *Blood*. 2000;95(7):2364-71 2. Boissel, et al. *J Clin Oncol*. 2003;21(5): 774-780.
 3. de Bont, et al. *Leukemia*. 2004;18(12):2032-5. 4. Ramanujachar, et al. *Paed Blood Cancer*. 2007;48(3):254-61.

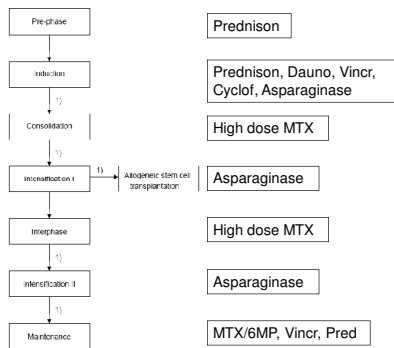
HOVON-70 study: intensification

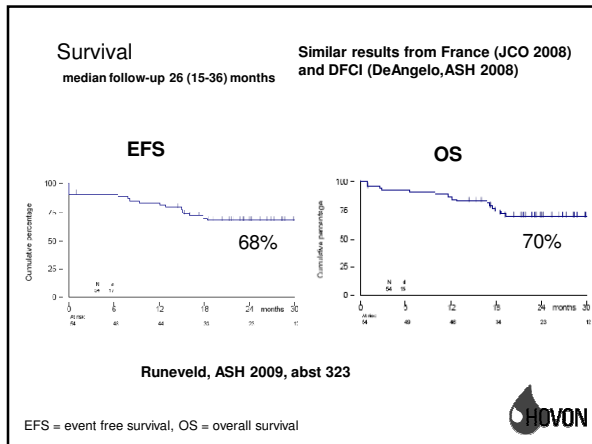
ALL, n=54,
age 17-39

Runeveld, ASH
2009, abst 323

Cum. dose:
ASP 126.000 IU/m²
MTX 30.000 g/m²

18x LP
t(9;22): + imatinib





Philadelphia-Positive ALL

- Philadelphia-positive ALL accounts for about 25% of adults with ALL and less than 5% of children with ALL
 - Increasing incidence with age
 - Considered a resistant leukemia requiring induction therapy followed by allogeneic stem cell transplant to yield any chance for long-term disease-free survival
- Advent of bcr-abl tyrosine kinase inhibitor (TKI) therapy plus chemotherapy has become the standard of care for non-elderly adults with Philadelphia-positive (Ph+) ALL
 - Single institution trials have suggested that the results with combination therapy might be as good as those obtained with allogeneic stem cell transplant
 - Still, the standard of care remains allogeneic stem cell transplant after remission has been achieved
- It may be appropriate to treat older adults with a TKI and minimal chemo

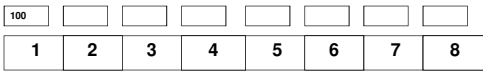
HyperCVAD + Dasatinib - Rationale

- Improved outcome with addition of imatinib to chemotherapy¹
- High incidence of imatinib resistant mutations at relapse^{2,3}
- Dasatinib ~ 300 x more potent than imatinib against BCR-ABL; active against imatinib resistant mutants⁴
- Dasatinib effective in patients resistant to imatinib⁵; crosses the blood-brain barrier⁶

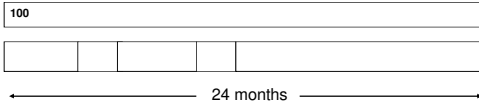
¹Thomas, Blood, 2004; ²Pfeifer, Blood, 2007; ³Jones, Cancer, 2008;
⁴Shah, Science, 2004; ⁵Ottmann, Blood, 2007; ⁶Porkka, Blood, 2008

HyperCVAD + Dasatinib - Regimen

Intensive phase



Maintenance phase



Risk-adapted intrathecal CNS prophylaxis

- Hyper-CVAD
- Dasatinib 50 mg po bid/ 100 mg daily
- MTX-cytarabine
- Vincristine + prednisone

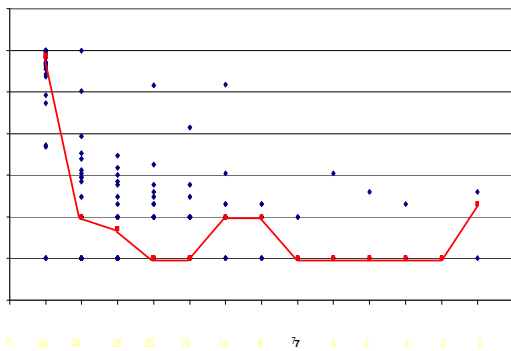
Ravandi, ASH 2009, abst 837.

HyperCVAD + Dasatinib – Induction Response

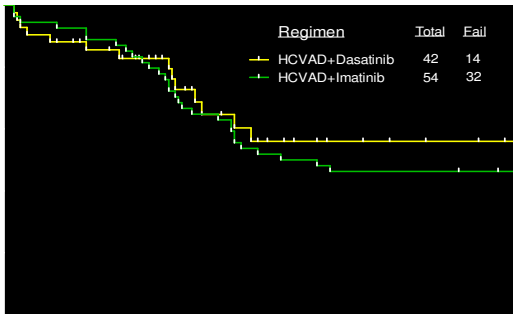
| Response | N/evaluable (%) |
|-------------------------------|-----------------|
| CHR | 33/35 (94) |
| Early Death | 2/35 (6) |
| Complete CG response | 27/33 (82) |
| Major Molecular Response (MR) | 13/31 (42) |
| Complete MR | 7/31 (23) |

Ravandi, ASH 2009, abst 837.

HyperCVAD + Dasatinib - Molecular Response over Time



HyperCVAD + Dasatinib – Event-Free Survival



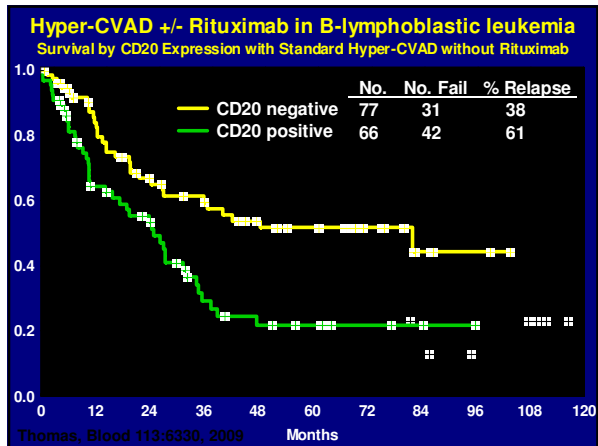
Ravandi, ASH 2009, abstr 837

Adding antibodies works in NHL, why not ALL?

- Novel approaches needed in Adults with ALL
 - Young adults could benefit from pediatric-like therapy
 - PH+ adults benefit from adding TKI
 - ? SCT for MRD pos pts
 - ? T-cell patients: add nelarabine (nucleoside analog approved in relapsed T-ALL)
- ASH 2009: Ab rx in ALL
 - Add rituximab to chemo in CR20+ ALL
 - Add alemtuzumab (anti CD52 Ab) in MRD setting in CD52+ ALL (both T and B)

Hyper-CVAD +/- Rituximab in B-lymphoblastic leukemia: Significance of CD20

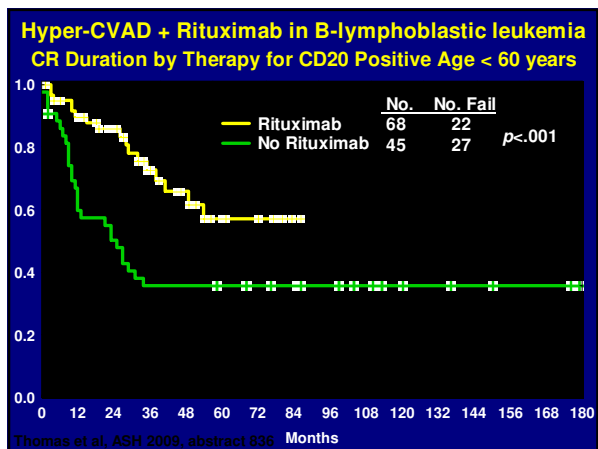
- B-lineage specific surface antigen
 - Heterogeneity in expression of CD20 ($\geq 20\%$)
 - 40% to 50% in B-lymphoblastic leukemia
- Role of CD20 in rituximab-resistant NHL lines
 - Pro-apoptotic Bax/Bak, constitutive activation of NF- κ B, overexpression anti-apoptotic Bcl-2
- Addition of rituximab to chemotherapy improves outcome in other B-lineage leukemias
 - Burkitt-type leukemia/lymphoma
 - Chronic lymphocytic leukemia



Hyper-CVAD +/- Rituximab in B-lymphoblastic leukemia: Study Group

- Ph negative B-lymphoblastic subset (n=282)
 - Treated with standard (n=109) and modified hyper-CVAD (n=173) regimens since 1992
 - Median age 41 yrs (13 – 83); 21% ≥ 60 yrs
 - Incidence CD20 expression 53%
 - Overall CR rate 95%, 5-yr CRD and OS rates 50% each

Thomas et al, ASH 2009, abstract 836



Hyper-CVAD +/- Rituximab in B-lymphoblastic leukemia: Summary

- Rituximab improves CRD & survival if younger (< 60 yrs)
 - Age, WBC, PLT, therapy with rituximab
 - Lower rate of MRD positivity at time of CR (compared with CD20 negative group)
 - Alternative regimens for older group
- No benefit of anthracycline intensification
- Novel anti-CD20 MoAbs (e.g. ofatumumab) and/or combinations with other MoAbs may further improve outcome
- Randomized clinical trials underway

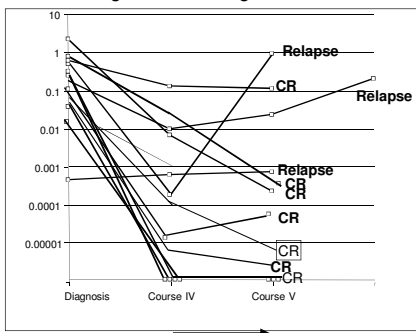
Thomas et al, ASH 2009, abstract 836

CALGB 10102: Treatment Schema: ABC repeated after module D, phase I alemtuzumab

| Module A | Module B | Module C | Module D* | Maintenance |
|--|--|--|---|--|
| Cytosin Daunorubicin Vincristine Dexamethasone L-asparaginase G-CSF Imatinib | Cytosin Cytarabine Vincristine L-asparaginase IT-Methotrexate G-CSF Imatinib | Methotrexate (IV, PO, IT) Vincristine 6-MP Imatinib | 10 mg* cohort 1 20 mg* cohort 2 30 mg* cohort 3 *Phase I dose escalation | Vincristine Dexamethasone Methotrexate 6-MP Imatinib |

Imatinib @ 400 mg/ day for Ph+ patients in Modules A,B,C
 Imatinib @ 600 mg/day for Ph+ patients during Maintenance therapy
 Stock, et al. ASH 2009, abst 838

MRD evaluation using Q-PCR of IgH/TCR:
 Median of 1-log decline during Alemtuzumab Rx



Stock, et al. ASH 2009, abst 838

CALGB 10102

- First report of feasibility of adding Alemtuzumab to front-line therapy for ALL
 - 22 of 24 Phase I patients received all 12 doses of Alemtuzumab

- Asymptomatic viremia occurred commonly but did not result in DLT in 30 mg cohort
 - Strict CMV prophylaxis and monitoring with pre-emptive therapy was effective in preventing symptomatic CMV infections
 - Late viral infections (zoster) quite common

- With median follow-up of 51 months, median DFS has not been reached

Stock, et al. ASH 2009, abst 838

Conclusions: ALL, ASH 2009

- Pediatric Oncologists are teaching us
 - Be mindful of risk status and MRD
 - Use their therapy in younger adults

- Perhaps better outcomes by adding antibodies (in the right setting) and tyrosine kinase inhibitors in PH+ ALL

ASH 2009: Acute Lymphoblastic Leukemia Review

- Thanks for your attention
- Acknowledgements
 - Dan DeAngelo, Martha Wadleigh, David Steensma, Ilene Galinsky, Susan Buchanan, Adriana Penicaud, Dara Stern, DFCI SCT team
 - Jose Ribera, Wendy Stock, Deb Thomas, Farhad Ravandi, A. Runeveld
