

Therapy of Acute Lymphoblastic Leukemia in Adults

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- Otsuka – Research Funding

Presentation Objectives

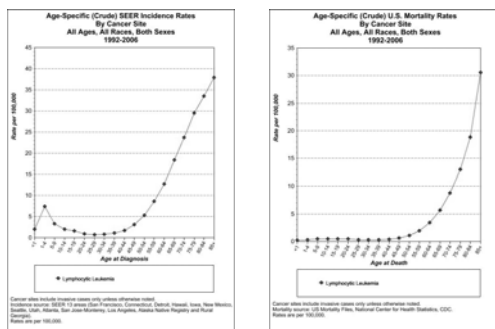
- Incidence, presentation, classification of ALL
- Standard therapy recommendations for adults with ALL
- Active areas of investigation in ALL therapy
- Emerging therapies in ALL

Incidence

- ALL accounts for approximately 20% of acute leukemias in adults, with incidence increasing above age 50
 - ~ 2 cases/100,000
 - 12% of all leukemias
 - 0.4% of all cancers
- Variable distribution by race
- Increased incidence
 - Radiation exposure
 - Toxic chemicals
 - Chromosomal abnormalities (+21, Fanconi, Bloom, AT, WA)

American Cancer Society

Incidence, Mortality in US



Clinical Presentation

- Signs/symptoms of anemia, neutropenia, thrombocytopenia
- Bone pain
- Organomegaly (liver, spleen, LN, SVC)
- CNS disease
- Metabolic abnormalities
- Rare: eosinophilia, ARF, pulmonary nodules, BM necrosis, pericardial effusion, skin nodules, cyclic neutropenia

- World Health Organization (WHO)¹ classification
 - Based on cytogenetic, molecular characteristics
 - Precursor lymphoid neoplasm
 - B-lymphoblastic leukemia/lymphoma (80%)
 - 7 distinct entities defined by specific recurring chromosomal abnormalities; cases of B-ALL lacking these abnormalities are considered as "not otherwise specified."
 - T-lymphoblastic leukemia/lymphoma (20%)
 - Leukemia vs. Lymphoma
 - Lymphoma preferred when mass lesions with <25% marrow involvement.
- French-American British (FAB) historic classification based on morphology

1. Vardiman et al, Blood 114:937, 2009

Immunophenotype of B-ALL

Subtype	Characteristics
Early Pre-B	CD19, cCD79a, cCD22, TdT
Pre-B	CD19, cCD79a, cCD22, TdT, CD10 (CALLA)
Mature B	clg μ

Mature B or Burkitt-type ALL

- TdT- negative
- Higher median age
- Male predominance
- Abdominal mass
- Lymphadenopathy
- Renal or bone involvement
- \uparrow CNS disease
- Early relapse

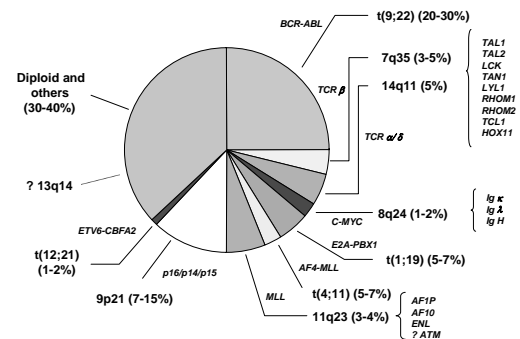
Immunophenotype of T-ALL

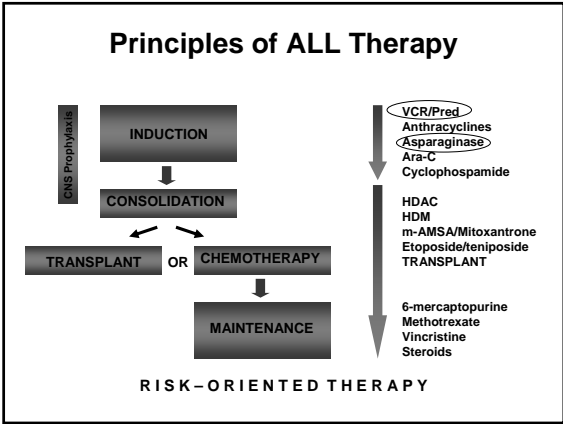
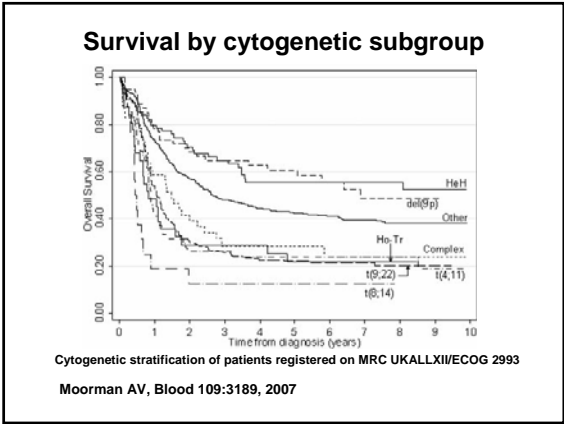
Subtype	Characteristics
Pro-T (T-I)	cCD3+, CD7+
Pre-T (T-II)	CD2+ and/or CD5+ and/or CD8+
Cortical T (T-III)	CD1a+
Mature T (T-IV)	CD1a-, sCD3+
α/β + T-ALL	Anti-TCR α/β +
γ/δ + T-ALL	Anti-TCR γ/δ +

T- ALL

- Higher median age than average
- Higher proportion males
- High WBC; 50% chromosomal aberrations
- Mediastinal disease
- \uparrow incidence CNS relapse
- Formerly poor outcome (mCRD ~ 10mo)
 - Current CR ~ 90%, LFS 45-60%
 - Cyclophosphamide, ara-C, asparaginase
 - Mediastinal irradiation
- Late relapses up to 3 yrs post remission

Cytogenetic Abnormalities in Adult ALL





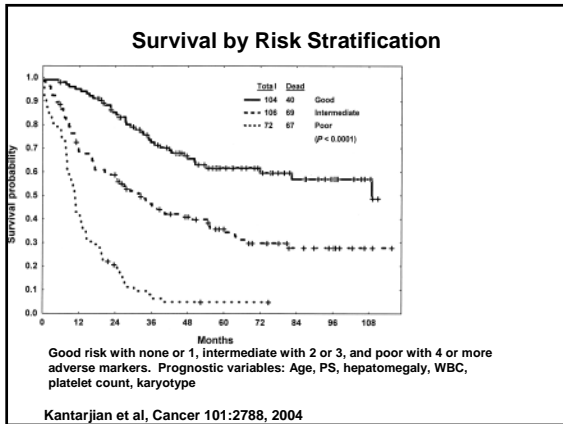
- ### CNS Prophylaxis in Adult ALL
- Dual prophylaxis needed:
 - IT chemotherapy (Ara-C, MTX, steroids)
 - HD systemic chemotherapy
 - XRT (Decreasing role)
 - 4 to 8 IT doses; Burkitt 16 IT doses
 - Triple therapy: improved CNS relapse rate but not EFS or OS (vs. IT MTX alone)
 - CNS disease: 2 IT/wk until CR, weekly x 8, monthly x 12
 - Cranial nerve palsies ⇒ immediate XRT
- Omura et al. Blood 1980; 55:199
Kantarjian et al, Blood 1988; 72:1784
Matloub et al, Blood 2006; 108:1165

- ### Maintenance Therapy in Adult ALL
- Traditional 2-3 year maintenance with POMP
 - Administration to limits of tolerance has improved outcome
 - Pediatric studies with 1,2,3 years of maintenance → more = better
 - Exceptions
 - Mature B ALL
 - Ph-positive ALL (combined with imatinib)
 - ? Role of maintenance in T ALL and LL

- ### Hyper-CVAD Regimen for ALL
- Hyper-CVAD x 4
 - CTX 300 mg/m² q 12h days 1-3
 - Doxorubicin 50 mg/m² day 4
 - VCR, Dexamethasone days 1-4, 11-14
- Alternating every 21 days with:
- MTX and Ara-C x 4
 - MTX 1 g/m² day 1 (leucovorin rescue)
 - Ara-C 3 g/m² q 12h x 4 days 2, 3
- Kantarjian et al, JCO 18:547, 2000
Kantarjian et al, Cancer 101:2788, 2004

- ### Hyper-CVAD, 1992-2000 (n=288)
- Overall response rate 92%
 - Induction mortality 5%
 - 2% if <60 yrs vs 16% if ≥60 yrs
 - Median follow-up 63 months
 - 5-yr CR duration 38%, survival rate 30%
 - Adverse factors for CR duration (MVA): age ≥45 yrs, WBC ≥ 50 x 10⁹/L, PS 3-4, Ph+, FAB L2, >1 course to CR, and Day 14 BM blasts >5%

Group	Score	5-yr CR
Low	0-1	52%
Int	2-3	37%
High	≥4	10%
- Kantarjian et al, Cancer 2004; 101:2788



- ### Adverse Prognostic Factors in Adult ALL
- Age (> 30 yrs)
 - Leukocyte count
 - >100 x 10⁹/L for T-lineage
 - >30 x 10⁹/L for B-lineage
 - Karyotype
 - t(9;22)(q34;q11)
 - t(4;11)(q21;q23) involving the *MLL* gene
 - Hypodiploidy
 - Complex
 - Poor response to therapy
 - Delayed time to complete remission, >4 weeks
 - Persistent MRD positivity

Contemporary Treatment

Study	Year	N	Med Age (Range)	CR (%)	SCT	Survival (%)
CALGB 8811	1995	197	32 (16-80)	85	-	50, 3 yrs
CALGB 9111	1998	198	35 (16-83)	82	HR	43, 3 yrs
GMALL 05/93	2001	1163	35 (15-65)	83	HR	35, 5 yrs
GIMEMA 0288	2002	778	28 (12-60)	82	-	27, 9 yrs
CALGB 19802	2003	163	41 (16-82)	78	-	35, 3 yrs
HyperCVAD, MDACC	2004	288	40 (15-92)	92	Ph+	38, 5 yrs
LALA-94	2004	922	33 (15-55)	84	HR	36, 5 yrs
PETHEMA ALL-93	2005	222	27 (15-50)	82	HR	34, 5 yrs

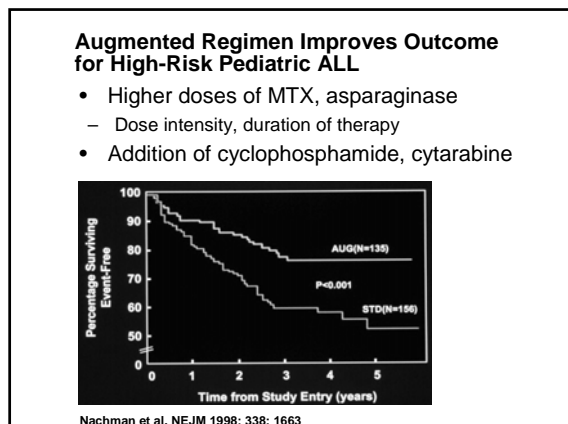
HR, high risk

SCT vs Chemo/auto: Comparative trials

Study	Year	N	Med Age (Range)	TRM % D vs No D	Survival %,(yrs) D vs No D
LALA-87	1994	257	26 (15-40)	16 vs 3	HR: 44 vs 20 SR: 51 vs 45, (5)
JALSG-ALL93	2002	263	31 (15-59)	Not stated	46 vs 40 Ph+: 44 vs 7, (6)
GOELAMS 02*	2004	198	33 (15-59)	15 vs 7	75 vs 40, (6)
MRC/ECOG E2993	2008	1913	31 (15-65)	HR: 36 vs 14 SR: 20 vs 7	HR: 41 vs 35 SR: 62 vs 52, (5)
HOVON-18, -37 ALL	2009	433	31 (16-55)D 26 (15-54) No	HR: 15 vs 4 SR: 16 vs 2	HR: 53 vs 41 SR: 69 vs 49, (5)

* All patients high risk

- ### Questions in Adult ALL Therapy
- Value of treatment intensification
 - Role of SCT in first CR
 - Use of MRD in risk-oriented therapy
 - Incorporation of targeted therapies



Retrospective Comparisons of Adult v. Pediatric Regimen Outcomes

Trial Comparison	AYA Patients/ Median age, y	CR Rate	Survival Rate
United States ¹¹ CALGB (Adult) CCG (Pediatric)	124 / 19 197 / 16	90% 90%	(7 year OS) 46% 67%
France ¹² LALA-94 (Adult) FRALLE-93 (Pediatric)	100 / 18 77 / 16	83% 94%	(5 year EFS) 41% 67%
The Netherlands ¹³ HOVON (Adult) DCOG (Pediatric)	73 / 20 47 / 12	91% 98%	(5 year EFS) 38% 71%
Italy ¹⁴ GIMEMA (Adult) AIEOP (Pediatric)	95 / 16 150 / 15	89% 94%	(2 year OS) 71% 80%
United Kingdom ¹⁵ UKALL XII/E2993 (Adult) ALL97 (Pediatric)	67 / 15-17 61 / NA	94% 98%	(5 year OS) 56% 71%
Sweden ¹⁶ Adult ALL Grp (Adult) NOPHO-92 (Pediatric)	99 / 18 36 / 16	90% 99%	(5 year OS) 39% 74%
Finland ¹⁷ Finnish Leukemia (Adult) NOPHO (Pediatric)	97 / 19 128 / 13	97% 96%	(5 year OS) 60% 67%

Stock W, Hematology, Am Soc Hematology 2010

Pediatric approach in adults: GRAALL-2003

- Median age 31 years (range 15-60)
- 8.6 fold prednisone, 3.7 fold VCR, 16 fold L-asparaginase compared with LALA-94
- 225 pts Ph-neg ALL
- Questionable benefit for > 45 years
 - TRM 23% vs. 5%

	GRAALL-2003	LALA-94	p
CR	93	88	.02
Induction death	6	5	NS
EFS, 42 mo	55	41	<.001
OS, 42 mo	60	54	<.001

Huguet F et al, JCO 27:911, 2009

Questions in Adult ALL Therapy

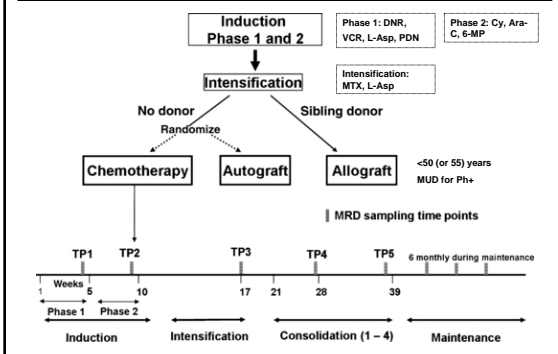
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MRC UKALL XII/ECOG 2993

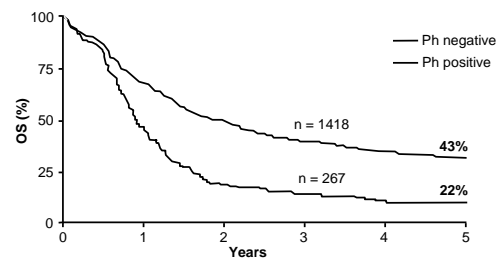
- Initiated 1993, international study group
- Prospective allocation to allo-SCT in CR1 for pts < 55 yrs-old if sibling donor
- > 55 yrs or no donor randomized to auto-SCT or chemotherapy
- 1913 patients
 - 1418 Ph neg
 - 267 Ph+, pre-imatinib use
- MRD assessment
 - Non T-lineage, Ph neg, clonal Ig/TCR rearrangement present: n=161 patients

Goldstone AH, et al. Blood. 2008;111:1827-1833

MRC UKALL XII/ECOG E2993: Study Design



MRC UKALL XII/ECOG E2993



Goldstone AH, et al. Blood. 2008;111:1827-1833

MRC UKALL XII/ECOG 2993, Ph Negative, n=1646

Risk Group, %	OS at 5 Yrs		Relapse		Death From Nonrelapse Causes at 2 Yrs	
	Donor	No Donor	Donor	No Donor	Donor	No Donor
High risk	41	35	37	63	36	14
	P = .20		P < .00005		P < .05	
Standard risk	62	52	24	49	20	7
	P = .02		P < .00005		P < .05	

- High risk: >35 years, WBC >30,000
- Standard risk: All others

Goldstone AH, et al. Blood. 2008;111:1827-1833

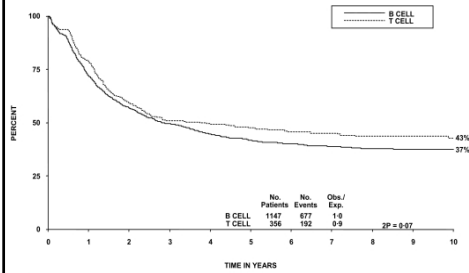
MRC UKALL XII/ECOG 2993, Ph Negative, n=1646

TRM (%)	3 months	6 months	1 year	2 years
High Risk				
Donor	1.5	7.3	26.0	35.8
No donor	1.2	2.0	10.3	13.6
Standard Risk				
Donor	0.4	3.4	17.6	19.5
No donor	0.3	1.2	5.3	6.9

- Non-relapse deaths similar between donor vs no donor groups at 3 months but significantly higher at later time points in *both* groups
 - Increased age significant predictor for toxicity
- Most deaths due to infection and GVHD

Goldstone AH, et al. Blood. 2008;111:1827-1833

MRC UKALL XII/ECOG 2993: OS, B- vs. T-lineage



M risk:
 B CELL: 1147 817 634 518 418 241 202 248 207 171 143
 T CELL: 156 278 207 168 138 123 102 99 76 64 51

Marks D, et al. Blood. 2009;114:5136

Auto SCT in Standard Risk Ph neg ALL

Percent (5-yr)	Chemo	Autologous	P
EFS	42	33	.02
Overall survival	47	37	.06
High risk	40	32	.2
Standard risk	49	41	.2
Nonrelapse mortality	13	19	.3

- MRD after induction and HD MTX in no donor group
 - RFS 29% for MRD pos vs 76% MRD neg (p=.01)

Goldstone AH, et al. Blood. 2008;111:1827-1833
 Patel, et al, BJH, 2009, 148:80

Reduced-Intensity Conditioning (RIC)

- Designed to have less TRM
- Usually fludarabine-based regimen
- High relapse rate in pts transplanted beyond CR1

Study	Year	N	Med Age (Range)	CR1 (%)	2-yr TRM (%)	2-yr Survival (%)
Martino ¹	2003	27	50 (18-63)	15	23	31
Hamaki ²	2005	33	55 (17-68)	39	21	30
Mohty ³	2008	97	38 (17-65)	29	18	CR1 52; >CR1 27
dePadua ⁴	2008	30	44 (23-64)	17	33	32
Stein ⁵	2009	24	48 (23-68)	46	21	CR1 70; >CR1 50

1. Martino R. Haematologica. 2003;88:555. 2. Hamaki T. Bone Marrow Transplant. 2005;35:549.
 3. Mohty M. Haematologica. 2008;93:303. 4. de Padua ASH 2008. 5. Stein A. BBMT 2009;15:1407.

Current SCT Guidelines

- Risk adapted strategy
 - Cytogenetic profile
 - Presence of MRD
- Transplant in CR1
 - High risk patients
 - Intermediate risk patients controversial
 - No benefit for autologous SCT
- Transplant > CR1
 - All risk groups
 - Alternative cell sources (haplo-, cord)

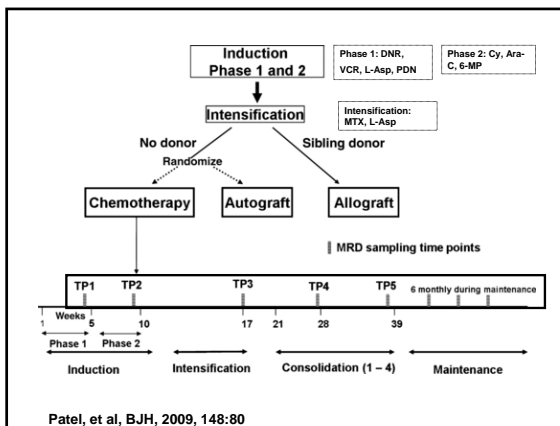
Hahn et al, BBMT, 2006, 12:1-30

Questions in Adult ALL Therapy

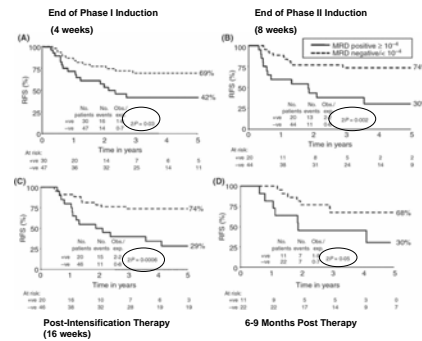
- Value of treatment intensification
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Clinical Implications of MRD in Adult ALL

- Based on studies in childhood ALL
- Requires homogenous therapy to determine kinetics and relevance
- Particularly relevant to standard risk ALL
 - Subsets potentially over- or undertreated
 - Relapse in 40-55% without identifiable factors
 - Role of stem cell transplant in 1st CR
- MRD-based risk group stratification
 - Low risk: Treatment reduction
 - High risk: Treatment intensification



Kaplan-Meier estimates of RFS at 4 time-points in auto-SCT/chemo patients



Questions in Adult ALL Therapy

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Targeted Therapies: TKI for Ph+ ALL

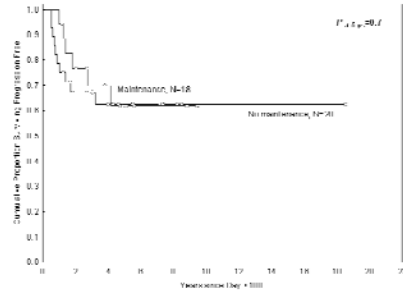
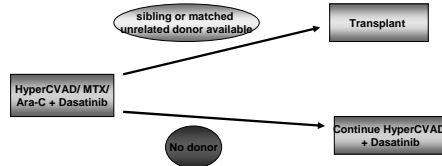
- Pre-TKI era
 - OS <10% without SCT
 - OS 25-45% with SCT
- Post-TKI era
 - Higher CR rates, more SCT-eligible pts
 - Increased survivors without SCT

Study (historic vs current + imatinib)	CR %	Survival % (Years)
Lee ¹	82 vs 79	39 vs 78 (3)
JALSG 93 vs 202, Yanada ²	51 vs 96	44 vs 76 (1)
LALA 94 vs GRAAPH 2003, de Labarthe ³	71 vs 96	39 vs 65 (1.5)
HyperCVAD vs HyperCVAD+IM, Thomas ⁴	92 vs 93	15 vs 55 (3)

1. Lee et al, Blood 105:3449, 2005 2. Yanada et al, JCO 24:460, 2006
3. de Labarthe et al, Blood 109:1408, 2007 4. Thomas et al, Blood 112:a2931, 2008

SWOG Protocol S0805 (Intergroup)

- Newly diagnosed Ph⁺ or BCR-ABL⁺ ALL
 - Untreated
 - Received one course of chemo before CG is known
- Age ≤ 50 years
- Adequate renal, hepatic and cardiac function
- PS 0 - 2



Progression-free survival by TKI maintenance post SCT using a landmark analysis at 6 months.

Kebriaei et al, BBMT 2011, Aug 22 Epub

Hyper-CVAD + Rituximab in BL & B-ALL

- Strong expression CD20, associated with worse outcome
 - GRAALL 2003, 143 adults, Ph⁻, higher risk of relapse and lower EFS (15% vs. 59% at 42 mo, p=.003)¹
- In vitro synergy with chemotherapy
- Hyper-CVAD+rituximab if CD20 ≥20%²
 - Rituximab 375 mg/m² on days 1,11 of CVAD; days 1, 8 of lipo-DNR/Ara-C MTX/Ara-C, 8 doses over the first four courses
 - Given with early, late intensifications during months 6 and 18 of maintenance therapy.
 - CR 95%, 3-yr OS 50%
 - Age < 60 years, OS 75% v 47%, p=.003 with addition of rituximab
 - No benefit to older patients, OS 28% v 32%, related in part to deaths in CR.

1. Maury S, Haematologica 95:324, 2010 2. Thomas D, J Clin Oncol 28:3880, 2010

Nelarabine in T-ALL

- Ara-G toxic to T-lymphoblastoid cells
- Nelarabine (Compound 506U78): prodrug ara-G
- Phase I¹:
 - MTD: 60 mg/kg/d x5; DLT: Neurotoxicity
- Phase II²
 - 1.5 gm/m²/d, days 1,3,5 (Initial dose of 2.2 decreased after 3 patients due to neurotoxicity)
 - N=26, median age 34 years
 - CR 31%, median DFS and OS 20 weeks, 1 yr OS 28%
 - Toxicity grade 3 or 4 neutropenia (37%) and thrombocytopenia (26%); 1 grade 4 CNS
- Phase II³
 - 36% CR, III-IV neurotox 7%
 - 80% of CR pts went to SCT; 3-yr OS 31%

1. Berg et al, JCO 23:3376-82, 2005
 2. DeAngelo et al, Blood 109:5136, 2007
 3. Gokbuget N, Blood Epub June 2011

Emerging Therapies for ALL

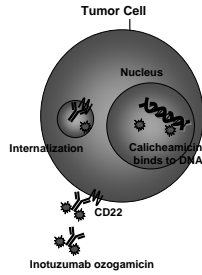
- Newer agents
 - Clofarabine
 - Others: lipo VCR, pegylated asparaginase
- Monoclonal antibodies
 - Inotuzumab
- Immunomodulation
 - Bi-specific antibody
 - CAR therapy

Recent FDA Approvals for ALL Therapy

- Liposomal vincristine (Marqibo)
 - FDA approval: Adults with ALL
- Pegylated asparaginase (Oncaspar)
 - FDA approval: Newly diagnosed children and adults with ALL
- Clofarabine
 - Novel nucleoside analog
 - FDA approval: Relapsed or refractory pediatric ALL after 2 regimens
- Nelarabine
 - Pro-drug of deoxyguanosine analogue 9-β-D-arabino-furanosylguanine (ara-G)
 - FDA approval: Relapsed T-cell ALL or LL or treatment failure after > 2 regimens

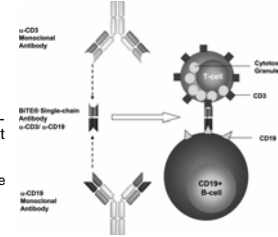
Inotuzumab Ozogamycin

- Humanized CD22 Ab conjugated to calicheamicin
 - Ab-Ag complex internalized upon binding CD22 (90% of ALL)
 - Calicheamicin released inside tumor cell, binds DNA inducing double-stranded DNA breaks
 - 49 pts with refractory ALL Rx with IO 1.3-1.8 mg/m² IV Q 3wks¹
 - 46 evaluable: 9 CR, 19 marrow CR, OR 61%; 20 underwent SCT in CR; VOD post SCT
1. Jabbour et al. ASCO 2011



Blinatumomab: Bi-specific Antibody

- Bi-specific, single-chain antibody that redirects CD3p T cells toward lysis of cells expressing the CD19 antigen
- Blinatumomab used as single agent in precursor B-ALL patients with persistent MRD¹
 - 16 evaluable: 13 molecular CR after 1 cycle treatment
 - AEs: lymphopenia, fever, hypogammaglobulinemia



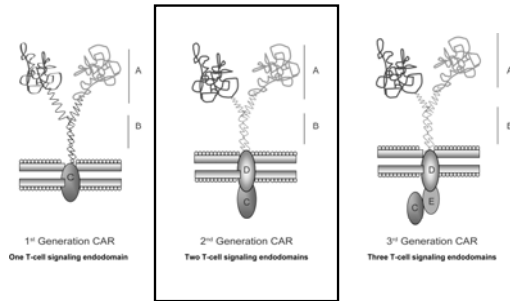
1. Topp MS et al. Blood. Abstract 840, 2009

Cellular Therapy: CAR Technology

- Chimeric antigen receptors (CARs) consist of an extracellular single chain antibody fused to intracellular signaling domains, and when expressed in T cells, redirect antigen recognition toward specified monoclonal antibody¹⁻³.
- CAR strategy does not rely on pre-existing anti-tumor immunity to generate anti-tumor immune effector cells.
- Receptors are “universal” in that they bind antigen in a MHC independent fashion.
- Animal models have demonstrated the capacity of adoptively transferred CAR T cells to eradicate established tumors.

1. Singh et al, Cancer Res 67(6):2872, 2007 2. Kowolik et al, Cancer Res 66(22):10995, 2006
3. Cooper et al, Blood 101(4):1637, 2003

Directing T cells for CD19 using chimeric antigen receptors



CD19 CAR as DLI in SCT

- Conventional DLI given after relapse in ALL results in long-term disease control 0-13%¹.
 - ALL cells may lack needed co-stimulatory molecules for T cell activation.
 - ALL blasts rapidly proliferate; may overwhelm DLI effect.
- Pre-emptive DLI
 - Used in ALL patients with decreasing chimerism; 46 pts with mixed chimerism, 31 pre-emptive DLI, 3 yr EFS 37% vs 0% for 15 pts without DLI.²
- “Targeted DLI”, redirecting T cells to CD19-expressing B cells.

1. Collins et al, BMT 2000, 26:511 2. Bader et al JCO 2004, 22:1696

Thank You

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