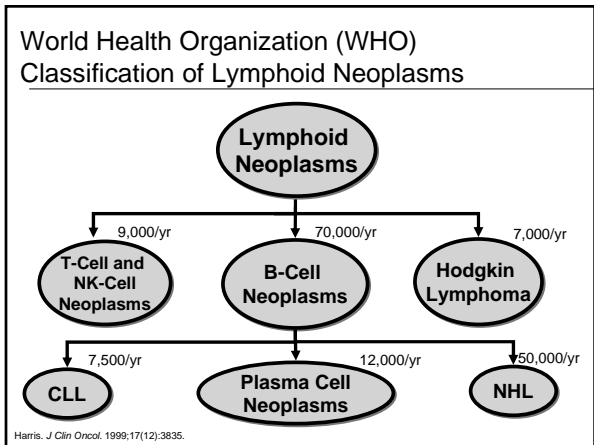
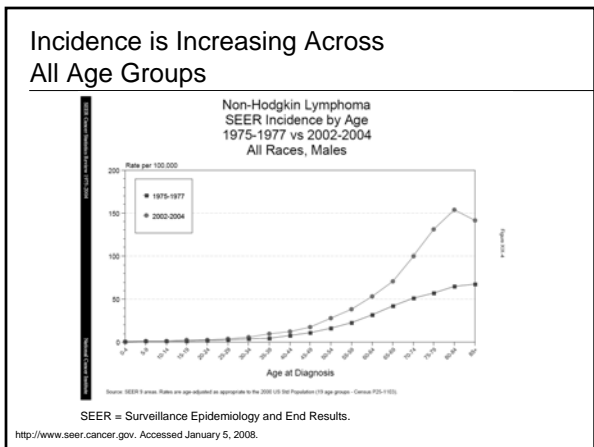


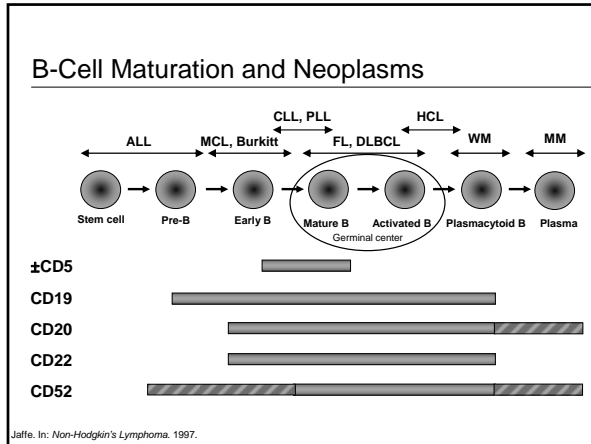
**Emerging Strategies
 for the Treatment of
 Lymphoma and Myeloma**

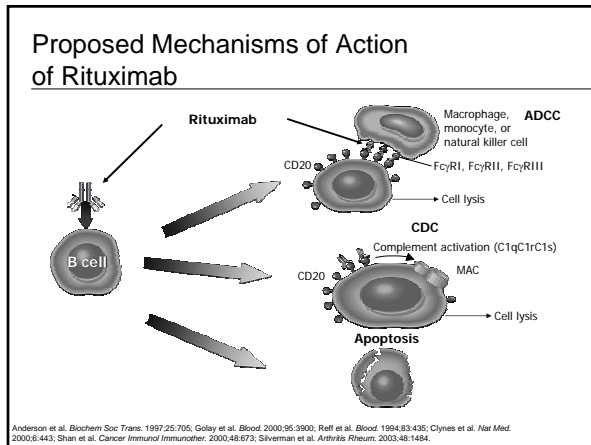
Mitchell R. Smith, MD, PhD
*Director, Lymphoma Service
 Fox Chase Cancer Center
 Philadelphia, Pennsylvania*





Tomorrow's Therapies Today: Clinical Trials for Leukemia, Lymphoma & Myeloma

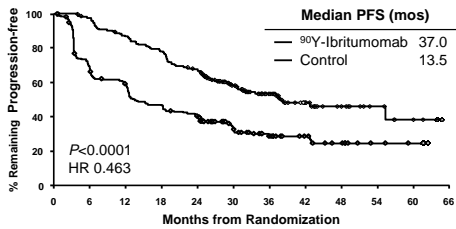




Radioimmunotherapy (RIT): Advantages in Treating NHL

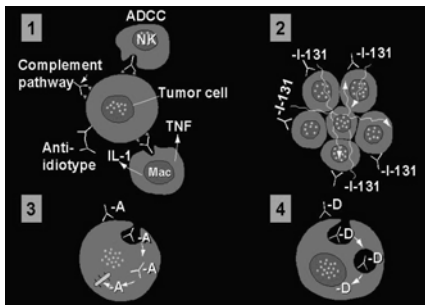
- **Advantages of radiolabeled antibodies in treating NHL**
 - Lymphoma cells are inherently sensitive to radiotherapy
 - Crossfire effect—tumor cells distant from the bound antibody can be killed by ionizing radiation from β -emitting isotopes, important in bulky or poorly vascularized tumors

Randomized Phase 3 Trial of Zevalin® (⁹⁰Y-Ibritumomab Tiuxetan) Consolidation of First Remission in Advanced Stage FL: PFS



Median observation period was 3.5 years.
FL = follicular lymphoma; HR = hazard ratio; PFS = progression-free survival
Hagenbeek et al. ASH, 2007, Abstract 643.

Antibody-Based Cancer Therapy

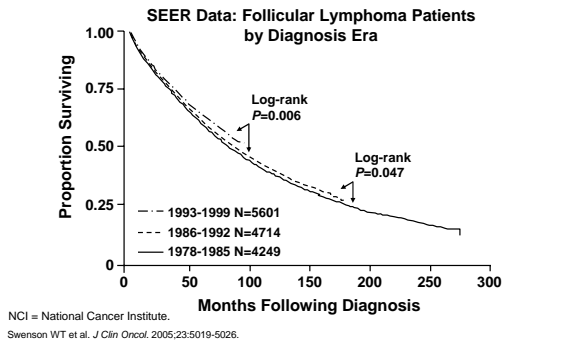


Press et al. *Biologic Therapy of Cancer Updates*. JB Lippincott; 1994;4:1-13.

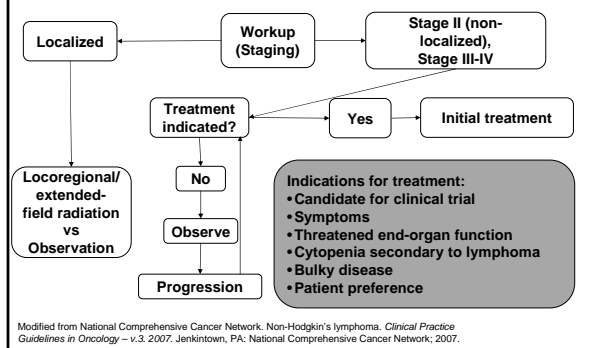
Goals of Therapy: "Cure" vs Control of Disease?

- Examples of potentially curable lymphomas
 - Hodgkin Lymphoma
 - Diffuse large B-cell lymphoma
 - Peripheral T-cell lymphoma
 - RESEARCH GOALS:
 - Increase % of cures
 - Decrease toxicity of therapy
 - Better treatments for patients who are not cured with current therapy
- Examples of lymphomas currently felt to be treatable, not curable
 - Follicular grades 1 and 2
 - CLL/small lymphocytic lymphoma
 - Marginal zone lymphoma
 - Mantle cell lymphoma
 - RESEARCH GOALS:
 - CURE
 - Longer survival
 - Decrease toxicity of therapy

NCI/SEER Data Showed Improved Survival in Follicular Lymphoma Patients in the U.S.



Treatment of Low-Grade Lymphoma



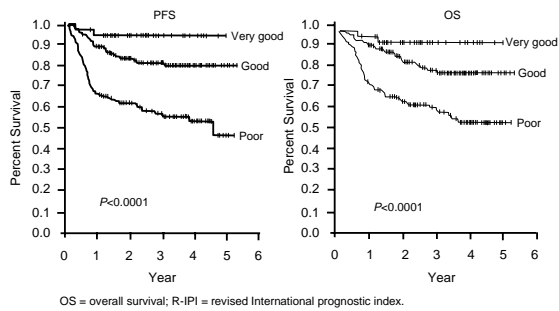
Management Strategies for Indolent NHL: Most Common Treatments in U.S.

- Rituximab alone (ECOG RESORT trial)
- Rituximab + CVP
- Rituximab + CHOP
- Alkylating agents (chlorambucil)
- Intensive chemo-radio-immuno-therapy + stem cell transplantation
- PREFER CLINICAL TRIAL
 - At FCCC today: rituximab + bortezomib

Diffuse Large B-Cell Lymphoma (DLBCL)

- 1975: lymphoma is curable
 - de Vita et al NCI
- 1979: doxorubicin-containing regimens better
 - Jones et al SWOG
- 1993: CHOP is the standard of care
 - Fisher et al (5-year overall survival 45%)
- 1997: Does rituximab add benefit to CHOP?
 - 2 studies started: GELA (Coiffer et al); E4494 (Habermann et al)
- 2000s: Rituximab + CHOP is better than CHOP alone
 - 5-year overall survival 50%–90% depending on prognostic factors
- Now What?
 - **Need better therapy for high-risk and relapsed disease**
 - **Less toxicity for all patients**

Outcome According to R-IPI of R-CHOP in Patients With DLBCL: PFS and OS



Sehn et al. *Blood*. 2006;109:1857.

Management Options for DLBCL: Summary

- Stage I and localized II: R-CHOP + radiation therapy
- Stage III and IV
 - Low/low-intermediate risk: R-CHOP
 - High-intermediate/high-risk: R-CHOP or clinical trial
 - R-CHOP + drug/antibody
 - R-CHOP followed by consolidation of remission
- Relapsed or refractory disease
 - Candidate for high-dose therapy (ASCT)
 - New non-crossresistant regimen followed by ASCT and/or clinical trial
 - Noncandidate for high-dose therapy (due to age, other illnesses)
 - Clinical trial or individual approach
 - CMC-544 (anti-CD22 antibody-drug conjugate) + rituximab
 - ⁹⁰Y-ibritumomab tiuxetan + gemcitabine
 - YM155 (anti-survivin)
 - Anti-CD40 antibody + rituximab + gemcitabine

National Comprehensive Cancer Network. *Practice Guidelines in Oncology*. v2. 2006.

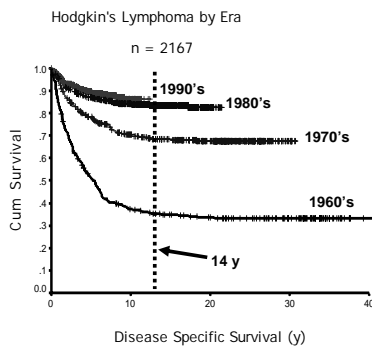
Tomorrow's Therapies Today:

Clinical Trials for Leukemia, Lymphoma & Myeloma

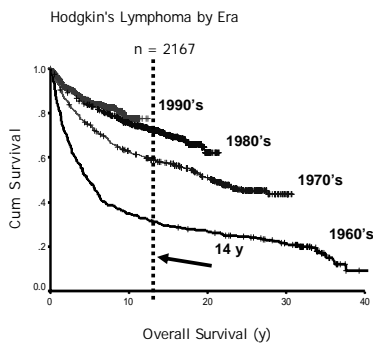
T-cell NHL

- Standard therapy = CHOP
- Can we find a biologic agent to add to CHOP for better results?
 - (analogous to rituximab in B-cell NHL)
- Denileukin diftitox (Ontak®) recently completed, encouraging
- Bevacizumab (Avastin®) in ECOG trial
- Examples of new agents under study:
 - Pralatrexate
 - Histone deacetylase (HDAC) inhibitors
 - Romedepsin

Hodgkin Lymphoma by Era: Disease-Specific Survival



Hodgkin Lymphoma by Era: Overall Survival



Tomorrow's Therapies Today:

Clinical Trials for **Leukemia, Lymphoma & Myeloma**

Advances in Management of Hodgkin Lymphoma Since 1960

- B-cell disease
- No laparotomy-splenectomy
- No maintenance therapy
- Change from MOPP → ABVD, → ? BEACOPP
- Less or no RT: reduction in dose-field
- Growth factors allow dose-intense/dose-dense regimens
- Risk-adapted therapy
- Moving to response-adapted therapy
- Individualized therapy

Hodgkin Lymphoma: Early Stage

- Standard therapy = ABVD x 4 cycles followed by involved field radiation (IF-RT)
- RESEARCH QUESTIONS
 - Can we omit 1 to 2 drugs from ABVD, especially bleomycin?
 - How many cycles of ABVD are necessary?
 - Can we tailor # of cycles to risk and/or response, ie, PET scan results?
 - Do we need IF-RT if PET is negative?
 - Do we need more intensive therapy if PET remains positive?
- GOALS:
 - To define risk-adapted and response-adapted treatment plans that
 - Maintain excellent outcomes
 - Minimize toxicity

Hodgkin Lymphoma: Advanced Stage

- **Standard therapy = ABVD x 6–8 cycles**
- **Research Questions**
 - ABVD: is it gold standard or are new regimens such as Stanford V and/or BEACOPP better?
 - When is there a need for RT after chemotherapy?
 - Is PET accurate enough to tailor therapy?
 - Does PET add anything to pre-treatment risk prediction (IPS)?

IPS = International prognostic score.

Tomorrow's Therapies Today:

Clinical Trials for **Leukemia, Lymphoma & Myeloma**

Front-line Therapy: New Paradigm

Induction therapy with novel agents
 Thalidomide + Dexamethasone (DEX)
 Lenalidomide + DEX
 Bortezomib + DEX
 Aim for CR or PR
 Optimize stem cell transplant?
 Stem cell transplant optional?
 Improve efficacy in non-transplant candidates?

Ongoing/Completed Phase 3 Trials for Newly Diagnosed Multiple Myeloma

No SCT:

- MP-T = melphalan, prednisone, thalidomide
- MP-R = melphalan, prednisone, lenalidomide
- MP-V = melphalan, prednisone, bortezomib

Combinations of alkylators + these newer agents increases response rates compared with the newer agents alone

Followed by SCT (avoid melphalan):
VAD vs Bortezomib + DEX
VAD vs Bortezomib-AD

Planned Phase 3 Trials for Newly Diagnosed Multiple Myeloma

No SCT:
MP-Lenalidomide vs MP-Thalidomide
Lenalidomide-dex vs MP-Thalidomide
Lenalidomide-dex ± bortezomib

Followed by SCT:
Bortezomib-dex ± lenalidomide

Tomorrow's Therapies Today:

Clinical Trials for **Leukemia, Lymphoma & Myeloma**

Novel Agents for Front-line MM Therapy: Conclusions

- Thalidomide/Dex
 - ORR 63%–72% (CR 4%–8%)
- Bortezomib based therapies
 - ORR 66%–95% (CR 10%–43%)
- Lenalidomide/Dex
 - ORR: 91% (CR 18%)
 - 1-yr survival 96%
- Treatment tolerable
 - Challenges include blood clots (DVT; pulmonary embolism)
 - Peripheral neuropathy
- Optimal sequences under study

A Key Challenge for the Future: Risk-Adapted Myeloma Therapy

Standard Risk	High Risk
• t(11;14), t(6;14)	• t(4;14), t(14;16)
• Hyperdiploid	• Deletion 17
• Low β_2 -microglobulin	• Deletion 13
• Normal serum albumin	• High β_2 -microglobulin
	• Light chain, IgA MM
	• Renal failure
(Expected median OS 7 yr)	(Expected median OS 4 yr)
Induction?	
Role of SCT?	
Maintenance?	
Specific New Agents?	

Lenalidomide (CC-5013; Revlimid®): Development Summary in Relapsed/Refractory MM

- Preclinical (2000): targets MM and microenvironment
- Phase I trial (2001): MTD 25 mg PO; 71% MR or better (n=24)
- Phase II trial (2003): 25% CR + PR + MR (n=102)
- Phase II trial (2004): Lenalidomide in relapsed and refractory MM, 225 pts, 30 sites; 27% CR + PR + MR
- Phase III trials (2005): Lenalidomide/Dex vs Dex/placebo in relapsed MM, 705 pts, 97 sites
- FDA approval 2006

CR = complete response; MR = minor response; MTD = maximum tolerated dose; PR = partial response.

Hideshima et al. *Blood* 2000; Richardson et al. *Blood* 2002; Zangari et al. *Blood* 2001 (abst); Richardson et al. *Blood* 2006; Weber et al. *NEJM* 2007; Dimopoulos et al. *NEJM* 2007

Tomorrow's Therapies Today: *Clinical Trials for* Leukemia, Lymphoma & Myeloma

Bortezomib: Development Summary in Relapsed/ Refractory MM

- 2000: preclinical studies, phase 1 trials
- 2001: phase 2 trials, 256 patients
- SUMMIT Study: 35% CR + PR + MR
– 10% CR/nCR
- 2002–2003: APEX Phase 3 study, 669 patients
- Accelerated approval (FDA) 2003
- EMEA approval 2004
- Approval (FDA) 2005

Hideshima T et al. Clin Cancer Res. 2001;6:13071; LeBlanc R et al. Cancer Res. 2002;62:4996; Orlowski RZ et al. J Clin Oncol. 2002;20:4420; Richardson PG et al. N Engl J Med. 2003;348:2608; Jagannath S et al. Br J Haematol. 2004;127:165; Richardson PG et al. N Engl J Med. 2005;352:2487.

Rationally Based Combination Therapies

Bortezomib +:

- Hsp 90 inhibitor
- Doxil
- NPI-0052
- Perifosine
- LBH 589
- Smac peptides
- Bcl 2 inhibitor
- p38 MAPK inhibitor
- HuLuc63

Lenalidomide +:

- mTOR inhibitor
- Anti-CD40 antibody
- Doxil
- HuLuc63
- LBH 589
- Perifosine
- Bevacizumab
- Vaccine

Courtesy of Paul Richardson.

Novel Therapies Targeting Myeloma Cells in the BM Microenvironment

