Non-Hodgkin’s and Hodgkin lymphoma: using and disease characteristics as a guide to treatment selection

Arnold Freedman, M.D.
Therapy for B cell lymphomas

- Follicular lymphoma
- Diffuse large B cell lymphoma
- Mantle cell lymphoma
- Hodgkin lymphoma
Treatment of follicular NHL

- Observation or treatment
- Chemoimmunotherapy
- Chemoimmunotherapy + maintenance
- Rituximab monotherapy
- New agents
Overall survival of asymptomatic patients with indolent follicular NHL not impacted by early chemotherapy.

Ardeshna et al, Lancet 2003
Follicular lymphoma: Impact of rituximab therapy

New Rx

PFS

OS

HT

Ardeshna et al, Lancet Onc 2013
Follicular lymphoma: Initial approach

For low volume, asymptomatic patient:

No survival advantage for early chemotherapy or rituximab monotherapy.

No advantage for maintenance rituximab in patients not needing of treatment (RESORT Trial).
How effective is current initial therapy?

- Chemoimmunotherapy (what is the best 1st therapy?)
- Chemoimmunotherapy + antibody maintenance
- Rituximab monotherapy
- Rituximab + something new
Which regimen for follicular lymphoma?  
R-CVP vs R-CHOP vs R-FM

R-CHOP and R-FM superior to R-CVP (3-year TTF and PFS). R-CVP less toxic. No difference in OS

Federico et al. JCO 2013
Bendamustine-R v R-CHOP follicular lymphoma

No difference in overall survival
BR less toxic than CHOP-R

Rummel et al. Lancet 2013
PRIMA Trial: maintenance R v observation after R-chemo (95% R-CHOP/R-CVP), FL all grades

EFS

OS

Salles et al. Lancet 2011
Rituximab maintenance after R-FND

R-FND x 4, R x 4, then R maintenance (1 dose q 2 m x 4 doses) or no maintenance.

abbreviated R maintenance **without** benefit

Vitolo et al, JCO 2013
Rituximab monotherapy (SAKK)

Previously untreated FL (42% mass > 5cm, 23% elevated LDH, FLIPI not available).

R x 4, followed by abbreviated maintenance
(1 dose q 2 m x4) or none.
5 y of maintenance, has no advantage in EFS, OS.

Martinelli et al, JCO 2010
Taverna et al, JCO 2016
Obinutuzumab-based induction and maintenance in patients with previously untreated follicular lymphoma. Phase III GALLIUM study

**Previously untreated CD20-positive iNHL**
- Age ≥18 years
- FL (grade 1–3a) or splenic/nodal/extranodal MZL
- Stage III/IV or stage II bulky disease (≥7cm) requiring treatment
- ECOG PS 0–2
- Target FL enrolment: 1200

**Induction**

**G-chemo**
- G 1000mg IV on D1, D8, D15 of C1 and D1 of C2–8 (q3w) or C2–6 (q4w) plus CHOP, CVP, or bendamustine†

**R-chemo**
- R 375mg/m² IV on D1 of C1–8 (q3w) or C1–6 (q4w) plus CHOP, CVP, or bendamustine†

**Maintenance**

**G**
- G 1000mg IV q2mo for 2 years or until PD

**R**
- R 375mg/m² IV q2mo for 2 years or until PD

*Randomized 1:1*  
CR or PR‡ at EOI visit
INV-assessed PFS (FL; primary endpoint)

**R-chemo, n=601**

- Pts with event, n (%): 144 (24.0)
- 3-yr PFS, % (95% CI): 73.3 (68.8, 77.2)
- HR (95% CI), p-value*: 0.66 (0.51, 0.85), p=0.0012

**G-chemo, n=601**

- Pts with event, n (%): 101 (16.8)
- 3-yr PFS, % (95% CI): 80.0 (75.9, 83.6)

Median follow-up: 34.5 months

*Stratified analysis; stratification factors: chemotherapy regimen, FLIPI risk group, geographic region
Overall survival (FL): R-chemo vs G-chemo

- Stratified analysis; stratification factors: chemotherapy regimen, FLIPI risk group, geographic region

<table>
<thead>
<tr>
<th></th>
<th>R-chemo, n=601</th>
<th>G-chemo, n=601</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pts with event, n (%)</td>
<td>46 (7.7)</td>
<td>35 (5.8)</td>
</tr>
<tr>
<td>3-yr OS, % (95% CI)</td>
<td>92.1 (89.5, 94.1)</td>
<td>94.0 (91.6, 95.7)</td>
</tr>
<tr>
<td>HR (95% CI), p-value*</td>
<td>0.75 (0.49, 1.17), p=0.21</td>
<td></td>
</tr>
</tbody>
</table>

Median follow-up: 34.5 months
Initial therapy for follicular NHL

B-R better and less toxic that CHOP-R, CVP-R.

Chemotherapy-R + R maintenance (PRIMA) beneficial, but is R maintenance necessary after B-R?

Rituximab monotherapy appropriate for the right patient (SAKK regimen – short term maintenance).

Obinutuzumab-chemo + maintenance superior to R-chemo + R maintenance, for PFS.
  Non-fatal AEs higher in the G arm (infections, cytopenias)
  Fatal AEs more common with bendamustine in both arms.
Options for relapsed follicular lymphoma

New anti-CD20 mAbs (+ chemotherapy)

Lenalidomide + R

Oral kinase inhibitors (Idelalisib 47% RR, median duration 18 m. Ibrutinib less effective 28% RR)

Immunotherapies (CAR T, anti-PD1)
Obinutuzumab + bendamustine and O maintenance vs bendamustine for rituximab refractory follicular lymphoma

PFS

OS

Lenalidomide + R for follicular lymphoma

Relapsed FL - ORR 76%, median time to progression 2 y.
Untreated FL (72% FLIPI 0-2)
  ORR 98%, CR 87%, 3 y PFS 79%

Phase III trial vs chemoimmunotherapy with R maintenance.

Fowler et al, Lancet Oncol 2014
Diffuse large B cell lymphoma

Prognosis

Treatment
2016 WHO Classification

DLBCL NOS (not otherwise specified)
    Germinal center B-cell type (IHC defined)*
    Activated B-cell type (IHC defined)*

*Large B-cell lymphoma with IRF4 rearrangement*
T cell/histiocyte-rich large B cell lymphoma
Primary mediastinal large B-cell lymphoma
Intravascular large B cell lymphoma
Lymphomatoid granulomatosis, an Epstein-Barr virus (EBV) positive large B-cell lymphoma
Primary cutaneous DLBCL, leg type
EBV positive DLBCL NOS*
Alk+ Large B-cell lymphoma

HHV-8 DLBCL NOS^*

DLBCL associated with chronic inflammation
Primary effusion lymphoma
High-grade B-cell lymphoma NOS*

High-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements*
B cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma

Swerdlow et al. Blood 2016
Prognosis of DLBCL

International Prognostic Index (IPI) and “Cell of origin” (GC v non GCB/ABC) are valid with chemoimmunotherapy.

Interim PET scans not predictive of overall survival following R-CHOP.

C-Myc translocations associated with poor outcome.
5-10% of DLBCL have c-myc rearrangements.

Up to 74% also bcl-2, 26% bcl-6 rearrangements.

High-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements (2016 WHO) by FISH or karyotype.

Immunohistochemistry for myc and bcl2 overexpression (double expressors), still controversial.

Best therapy unknown.

Barrans et al. JCO 28:3360, 2010
c-myc, bcl-2 translocations and DLBCL

myc translocation (11%) = poor OS
myc + bcl-2 translocation (6%) = worst OS

Green et al. JCO 30:3460, 2012
DA-EPOCH-R in c-myc rearranged DLBCL/BCL-U

Progression-free survival – All patients

Dunleavy et al. ASH, 2014
What regimen for “DH” DLBCL?

Meta-analysis, 11 studies, 394 patients

R-CHOP, EPOCH-R, R-HyperCVAD, R-CODOX-M/IVAC

For PFS: R-CHOP inferior; R-EPOCH better.

Howlett et al. BJ Heme, 2015
Early stage DLBCL: continuous risk of relapse

CHOP x 3 + RT or CHOP x 8

R-CHOP x 3 + RT

PFS

OS

Stephens et al. JCO, 2016
Treatment of DLBCL

Advanced stage

R-CHOP 21 x 6 = excellent outcome (MiNT trial).

R-CHOP 14  x 6 = R-CHOP 21 x 8.

R-CHOP 21 x 6 not directly compared to 8 cycles.
Can we do better than R-CHOP (non-GCB subtype, high IPI, “DH”)?

Is there any role for autologous stem cell transplantation in first remission?

What is the best approach for treatment of elderly patients?
Treatment of DLBCL: Can we do better than R-CHOP?

R2CHOP (R-CHOP + lenalidomide)

Non-GCB may benefit from R2CHOP

JCO 33:251, 2015
Phase III Randomized Study of R-CHOP vs. DA-EPOCH-R and Molecular Analysis of Untreated Large B-Cell Lymphoma: CALGB/Alliance 50303


Abstract 469, American Society of Hematology, Dec 4, 2016
50303 Event Free Survival

<table>
<thead>
<tr>
<th>Arm</th>
<th>N</th>
<th>Events</th>
<th>3 Y (95% CI)</th>
<th>5 Y (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-CHOP</td>
<td>233</td>
<td>64</td>
<td>0.81 (0.75-0.85)</td>
<td>0.69 (0.62-0.75)</td>
</tr>
<tr>
<td>DA-EPOCH-R</td>
<td>232</td>
<td>70</td>
<td>0.79 (0.73-0.84)</td>
<td>0.66 (0.59-0.72)</td>
</tr>
</tbody>
</table>

Median follow-up 5.0 y
HR=1.14 (0.82-1.61)
p = 0.4386
50303 Overall Survival

<table>
<thead>
<tr>
<th>Arm</th>
<th>N</th>
<th>Events</th>
<th>3 Y (95% CI)</th>
<th>5 Y (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-CHOP</td>
<td>233</td>
<td>44</td>
<td>0.85 (0.80-0.89)</td>
<td>0.80 (0.74-0.85)</td>
</tr>
<tr>
<td>DA-EPOCH-R</td>
<td>232</td>
<td>50</td>
<td>0.85 (0.79-0.89)</td>
<td>0.76 (0.70-0.71)</td>
</tr>
</tbody>
</table>

Median follow-up 5.0 y
HR=1.18 (0.79-1.77)
p = 0.42
ASCT in 1st remission

Meta-analysis 3,079 pts conventional Rx or ASCT in CR1, no difference in EFS or OS.

Italian (Gruppo Italiano Terapie Innovative Linfomi)
High intermediate and high IPI
8 cycles R-CHOP vs HD sequential therapy and ASCT.

Cortelazzo et al JCO 2016
8 cycles R-CHOP vs HD sequential therapy and ASCT

DFS

All patients

High Int IPI

High IPI

OS

Cortelazzo et al JCO 2016
R-CHOP should be used if possible. (Cancer 121:1800, 2015).

Mini-R-CHOP (1/2 doses of CTX, ADR, VCR)

- 2 yr OS and PFS: 59% and 47%.

R-CHOP + lenalidomide (d1-14, 15 mg)

Treatment of DLBCL in Elderly Patients

R-gemcitabine CVP: 2 y OS 56%, PFS 50%


Bendamustine + R, median OS/PFS 7.7 m.
Treatment of relapsed DLBCL

R-ICE = R-DHAP (JCO 28:4184, 2010)

R-DHAP = R-GDP (JCO 32:3490, 2014)
  R-GDP - outpatient, less toxic, less admissions, similar RR and percent
going to ASCT.

AutoSCT still useful for chemosensitive relapse.

For others, new agents.
ZUMA-1: Phase 2 CD19 CAR T cells

Enrolled & Leukapheresed (n=111)

Conditioning
Cy 500 mg/m²
Flu 30mg/m² × 3 days

KTE-C19
2 × 10⁶ /kg (n=101)

No bridging therapy allowed

Pre-specified interim analysis (*)
• ≥3 month follow-up (n=51 DLBCL, * n=11 TFL/PMBCL)
• ≥1 month follow-up (n=93 DLBCL, TFL, PMBCL)
ZUMA-1 Pivotal Trial Met Primary Endpoint of ORR At the Interim Analysis (P<0.0001)*

Response at 3 months

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>N</th>
<th>ORR</th>
<th>CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>DLBCL</td>
<td>51</td>
<td>39%</td>
<td>33%</td>
</tr>
<tr>
<td>TFL / PMBCL</td>
<td>11</td>
<td>64%</td>
<td>64%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>62</strong></td>
<td><strong>44%</strong></td>
<td><strong>39%</strong></td>
</tr>
</tbody>
</table>

- CR rate in refractory to 2nd line or greater = 47%
- CR rate in relapsed post-ASCT=75%
- 7 patients relapsed from a CR
- 6 patients converted from PR to CR, follow-up ongoing
- 1 patient converted from SD to CR
R-CHOP needs improvement for high risk (high IPI, ABC, DH) and elderly patients.

c-myc + (double hit) DLBCL - poor prognosis, DA-EPOCH-R may be the best regimen.

AutoSCT still useful for chemosensitive relapse, not in CR1.

For others, new agents, CAR T cells look very promising.
Treatment of mantle cell lymphoma

R-Chemotherapy: which regimen?

R-Chemotherapy + maintenance

R-Hyper-CVAD (no ASCT)

ASCT in first remission

Management of relapse
R-CHOP vs R-FC for MCL

• Age >60, stage II-IV MCL

• Initial randomization:
  – 8 cycles R-CHOP
  – 6 cycles R-FC

• 2nd randomization: maintenance IFN v R

• OS better for R-CHOP compared to R-FC

Kluin-Nelemans et al. NEJM 2012
R-CHOP +/- maintenance R for MCL

Overall survival benefit for R maintenance following R-CHOP.
Initial treatment of MCL

Bendamustine-R is better than R-CHOP

Rummel et al, Lancet, 2013
Hyper CVAD/cytarabine-methotrexate + rituximab (no ASCT)

63 patients registered
- 3 patients off protocol
- 1 did not receive study treatment
- 1 unconfirmed diagnosis
- 1 consent withdrawn

60 patients cycle 1
- 4 patients
- 3 with unacceptable toxicity
- 1 death

56 patients cycle 2
- 11 patients
- 1 with unacceptable toxicity
- 1 NR
- 4 PR
- 5 CR

45 patients cycle 3
- 23 patients
- 19 CR/CRu
- 1 PR
- 3 with unacceptable toxicity
- 2 PR
- 19 CR
- 1 NA due to grade 5 infection

22 patients cycle 4

(A) Cumulative probability

Follow-up, months

Number at risk
- OS
- PFS
- FFS

Br J Heme 158:346, 2012
Auto SCT for MCL in 1st remission

Only 1 randomized trial in CR1 following CHOP induction (no rituximab), PFS no OS benefit.

Many phase II studies showing excellent PFS/OS, especially for low risk patients.

Inclusion of cytarabine in induction and with conditioning improves PFS, but not overall survival.
When to consider SCT for MCL (CIBMTR)
R-CHOP vs R-CHOP/R-DHAP+HiDAC conditioning

Time to treatment failure

OS

Hermine et al. Lancet 2016
Treatment naïve mantle cell lymphoma lenalidomide-rituximab (N=38)

34% low risk, 34% intermediate risk, 32% high risk
ORR 92%, 64% CR

Ruan et al. NEJM 2015
Relapsed mantle cell lymphoma

Other chemotherapies (bortezomib) – limited benefit.

Lenalidomide: ORR 28%, 7% CR,
   med. duration 16.6 m.

Ibrutinib: ORR 67%, CR 21%,
   med. duration 17.5 m. (I + R promising).

Auto SCT – limited benefit

Allo SCT – ~ 40% DFS but highly selected
For young, fit patients: clinical trial (auto vs maintenance R), chemoimmunotherapy + ASCT.

Chemoimmunotherapy (CHOP-R or B-R) followed by maintenance R, reasonable option.

Ibrutinib/lenalidomide look promising, non-cytotoxic drug regimens maybe the future.
Initial treatment of Hodgkin lymphoma

Early stage

Advanced stage
Prognostic factors early stage HL

<table>
<thead>
<tr>
<th>EORTC</th>
<th>Age &lt; 50</th>
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<tr>
<td></td>
<td>No LMA (&lt; 1/3 max intrathoracic diameter)</td>
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<tr>
<td></td>
<td>ESR &lt; 50 without B sx</td>
</tr>
<tr>
<td></td>
<td>ESR &lt; 30 with B sx</td>
</tr>
<tr>
<td></td>
<td>&lt; 4 lymph node groups</td>
</tr>
<tr>
<td>GHSG</td>
<td>No LMA (&lt; 1/3 max intrathoracic diameter)</td>
</tr>
<tr>
<td></td>
<td>ESR &lt; 50 without B sx</td>
</tr>
<tr>
<td></td>
<td>ESR &lt; 30 with B sx</td>
</tr>
<tr>
<td></td>
<td>No extranodal extension</td>
</tr>
<tr>
<td></td>
<td>&lt; 3 lymph node groups</td>
</tr>
</tbody>
</table>
HD10 Trial GHSG

CS I–II without risk factors

n=1370

- ABVD
- 30 Gy IF
- ABVD
- 20 Gy IF
- ABVD
- 30 Gy IF
- ABVD
- 20 Gy IF

5 yr PFS 91-94%, 8 yr PFS 85-90%

Engert A et al. NEJM 2010
HD-6: Design

Patients with Stage I-IIA non-bulky Hodgkin lymphoma

Standard Arm
Treatment by Strata
Favorable: STNI (35Gy)

Unfavorable * : ABVD x 2 + STNI

*Unfavorable:
- Age > 40
- ESR > 50
- MC / LD histology
- > 4 sites

Experimental Arm:
Both Strata: ABVD x 2
If CR: x 2 more = 4
If PR: x 4 more = 6

Primary Outcome: 12 yr OS

Meyer RM et al. NEJM 2012
HD-6 Trial
Stage 1A or 2A non-bulky HL

All patients

Unfavorable risk patients
Randomized Phase III Trial to Determine the Role of FDG–PET Imaging in Clinical Stages IA/IIA Hodgkin’s Disease [RAPID]

Is radiation necessary in early stage HL after ABVD x 3 if PET is negative?

Overall survival

Progression-free survival

Radford et al. NEJM 2015
Approximate cumulative risks: Early stage Hodgkin Lymphoma.

- Recurrent Hodgkin’s lymphoma
- Second malignant condition
- Cardiovascular events

Armitage JO. NEJM 2010
Initial treatment of early stage favorable Hodgkin lymphoma

ABVD x 2 + 20 Gy in GSHG (HD10) favorable patients.

ABVD alone based on HD6 study.

Omitting radiation a reasonable option (RAPID Trial).

Balance risk of recurrence with late toxicities.
Initial treatment of early stage unfavorable Hodgkin lymphoma

– ABVD x 4 + 30 Gy involved site RT.

– ABVD x 6, no RT, if PET negative (BC Vancouver group).

– Eliminating radiotherapy may be associated with increased risk of relapse.
BCCA management of advanced stage HL

Advanced stage * HL > 16 y

Restaging FDG-PET scan following completion of ABVD chemotherapy for residual mass > 2cm on CT imaging

End PET positive

*IFRT (30-35Gy) *If feasible

End PET negative

Observation (planned RT) (no)

*- Stage 3 or 4 or
- Stage 1 or 2 bulky (> 10cm) or
- Stage 2B
FFTFT Advanced stage cHL end PET-neg: Bulky vs non-bulky (BCCA) median f/u 4.6 y

Bulky (N=113) 5 y FFTF 89%
Non-bulky (N=148) 5 y FFTF 88%

P=.458

Savage et al ASH 2015
Advanced stage Hodgkin lymphoma: IPS in modern treatment era with ABVD

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>IPS</th>
<th>Original 5 y OS</th>
<th>Current 5 y OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alb &lt; 40 g/L</td>
<td>0</td>
<td>89 ± 2</td>
<td>98 ± 2</td>
</tr>
<tr>
<td>Hgb &lt; 105 g/L</td>
<td>1</td>
<td>90 ± 2</td>
<td>97 ± 2</td>
</tr>
<tr>
<td>male</td>
<td>2</td>
<td>81 ± 2</td>
<td>92 ± 2</td>
</tr>
<tr>
<td>Stage IV</td>
<td>3</td>
<td>78 ± 4</td>
<td>87 ± 3</td>
</tr>
<tr>
<td>Age ≥ 45</td>
<td>4</td>
<td>61 ± 5</td>
<td>85 ± 4</td>
</tr>
<tr>
<td>WBC ≥ 15 x 10^9/L</td>
<td>≥5</td>
<td>56 ± 8</td>
<td>74 ± 5</td>
</tr>
<tr>
<td>Lymph &lt; 0.6 x 10^9/L or 8%</td>
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</table>

Moccia et al JCO 2012
Stage IIB-IV or IPS $\geq 3$
n=549

EORTC - BEACOPP v ABVD
high-risk (IPS $\geq 3$) advanced stage HL

ABVD x 8

No difference in EFS/OS

BEACOPP esc x4 –
BEACOPP std x 4

Median age 35y, stage 4: 59%, IPS $> 4$: 74%

Carde et al. JCO 2016
Can bleomycin be eliminated if PET negative after 2 cycles ABVD in stages IIA unfavorable, IIB-IV Hodgkin lymphoma?

Johnson et al. NEJM 2016
Treatment of relapsed Hodgkin lymphoma

Brentuximab

Checkpoint blockade
Five-year survival and durability results of brentuximab vedotin in patients with relapsed or refractory Hodgkin lymphoma

Chen et al. Blood 2016, 128:1562
Phase I study of Brentuximab vedotin + ABVD or AVD

- Stage II bulky, IIB, III/IV
- 95% CR
- Pulmonary toxicity in 24% of ABVD + brentuximab patients
- Completed phase III trial of ABVD v AVD + brentuximab

Lancet Oncology 14:1348, 2013
PD-1 and Hodgkin lymphoma

• Classical HL (cHL) is characterized pathologically by a failed immune response

• cHL frequently harbors amplification at 9p24.1 leading to overexpression of PD-L1 and PD-L2

• cHL may have a genetically driven vulnerability to PD-1 blockade

PD-L1 expression in cHL

Copy Gain

Amplification

Response Characteristics and Changes in Tumor Burden in Patients with Hodgkin's Lymphoma Receiving Nivolumab.

Initial treatment of advanced stage Hodgkin lymphoma

• ABVD is first choice in early and advanced stage.

• BEACOPP: PFS advantage in some studies but NO survival benefit and more toxicity.

• Stanford V = ABVD in early and advanced stage (FFS and OS).

• PET directed therapy in early stage favorable and unfavorable.
Brentuximab and anti-PD1

- Brentuximab + AVD - very active in early stage disease.

- Await results of phase III A-AVD vs ABVD for advanced stage patients.

- Maintenance brentuximab after ASCT, PFS but no survival benefit.

- Nivolumab/pembrolizumab are highly active in relapsed/refractory disease.

- Future role for anti-PD1 pending many studies.