Evolution of Lymphoma Therapy: What can we expect for the rest of the millennium decade?

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disclaimers

- Served on advisory boards for Millenium, Roche Canada, Celgene, Lundbeck, Pfizer, Seattle Genetics
- Own no stock in biotech
Canadian Cancer Statistics 2011
(incidence, women)

Breast 27.6
Lung 14.4
Colorectal 11.4
Body of Uterus 5.6
Thyroid 5.3
Non-Hodgkin Lymphoma 4.1
Ovary 3.0
Melanoma 2.9
Pancreas 2.4
Leukemia 2.4
Kidney 2.3
Bladder 2.1
Cervix 1.5
Oral 1.4
Brain 1.4
Stomach 1.2
Multiple Myeloma 1.2
Liver 0.5
Hodgkin Lymphoma 0.5
Esophagus 0.5
Larynx 0.2
All Other Cancers 8.0

New Cases
N = 84,800

Canadian Cancer Statistics 2011
(mortality, women)

6th most common cause of cancer death

- Lung: 26.7
- Breast: 14.4
- Colorectal: 11.1
- Pancreas: 5.6
- Ovary: 4.9
- Non-Hodgkin Lymphoma: 3.8
- Leukemia: 2.8
- Body of Uterus: 2.1
- Brain: 2.1
- Stomach: 1.9
- Multiple Myeloma: 1.8
- Kidney: 1.7
- Bladder: 1.5
- Esophagus: 1.2
- Oral: 1.1
- Melanoma: 1.0
- Cervix: 1.0
- Liver: 0.5
- Larynx: 0.3
- All Other Cancers: 14.5

Deaths
N = 35,100
Change in 5-year Survival Rates by Age and Treatment Era

Veal, JCO 2010
definitions for this talk

• Progression-free survival
  – Measure of cancer/lymphoma control: length of time from start of treatment until disease starts to grow again (ie relapse)

• Overall survival
  – Time from start of treatment to death from any cause (lymphoma, toxicity, other…)

How Oncologists Look at Data

% of pts alive or in remission

Kaplan-Meier Curve

Is the difference between these curves/treatments significant?

time from end of treatment
Clinical trials in aggressive/curable lymphomas: The past

Classical Recipe Comparison

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CHOP became standard for aggressive lymphoma after U.S. Intergroup Trial

Fisher et al NEJM 1992
The Rituximab success story

- Target: CD20 protein on surface of (virtually) all B cell lymphomas
  - 90% of lymphomas are B cell
- Humanized antibody: very few side effects
- Combined easily with chemotherapy
  - Results of all regimens improved with addition of rituximab
  - No added toxicity
Improved survival of patients with follicular lymphoma on clinical trials after addition of antibody therapy.
Rituximab added to CHOP improves survival in patients age >60 with DLBCL

Median survival: 8 yrs vs 3 yrs

Coiffier et al, Blood 2010
Case 1
50 yo male, lawyer

- Presents with cough, chest pain
- Found to have huge mass in mediastinum invading into lung
  - Adrenal glands involved, bone marrow
- Has 4 high-risk features: >1 extranodal site of disease, high LDH, poor performance status, stage IV
  - Despite treatment with R-CHOP and radiation, overall survival at 5 years ... 30%?
Three Certainties in Life

1) death
2) taxes
3) lymphoma classification will change
   (3 times so far for me)

Working Formulation 1982
- low, intermediate, high-grade

→ WHO Classification
- 30-40 different entities
- treatments - less similar
- prognosis - very different biology
Gene expression profiling: 40,000 genes → 2 groups of diffuse large B cell lymphoma

Outcome of germinal centre DLBCL is superior to ABC subtype
Protein Kinase C beta: a new target?

- Identified through gene expression profiling work as associated with worse outcome
- Increased expression in lymphoma cells at time of relapse

PKCβ at diagnosis at relapse
Understanding signalling pathways is important in developing new therapy for DLBCL.

Friedberg, Clin Cancer Res 2011
Enzastaurin

• Small molecule inhibitor of PKCβ
  – Active in vitro; in combination with other agents
• Oral drug, well tolerated
• Active in phase II testing in relapsed DLBCL

• Opportunity: interfere with B cell signaling pathway critical to cell survival
How to best test enzastaurin?

R-CHOP x 6-8 → placebo

→ R-CHOP x 6-8 → enzastaurin daily x 36 mon

completed

R-CHOP + enzastaurin x 6-8

→ R-CHOP x 6-8
Case 2: 37 yo male, father of 2

- Diagnosed Stage II Hodgkin lymphoma, with 15 cm mediasinal mass
- Initial response to chemotherapy (ABVD) but progressed after last cycle
- No response to second-line chemotherapy
- Proceeded to mediastinal radiation, followed by high-dose chemo and ASCT → relapsed 4 months post-transplant
Decline in mortality rate from HL in North America

Introduction of chemotherapy: MOPP + ABVD

Aisenberg, Blood, 1999; Reprinted from Ries; NIH Publ 97-2789, 1997
HL Outcomes – Continued Improvement


Relative survival: 5 y 73% 85%
10 y 62% 80%

1980-84 2000-04

all 25-34y >60y
Second-line treatment for HL is autologous stem cell transplantation:

- ~50% of patients will experience relapse after autotransplant
- survival after 2\textsuperscript{nd} relapse depends on lymphoma biology:
  - Median time: 27 months
- New treatments needed
Development of SGN-35

- Malignant B cells in Hodgkin Lymphoma express CD30
- Antibodies to CD 30 (eg SGN-30) were ineffective: no responses despite binding of Ab to tumour cells
- Technology developed to couple antibody (delivery vehicle) with chemotherapy (payload)
Brentuximab Vedotin (SGN35): Mechanism of Action

Brentuximab vedotin (SGN-35) monomethyl auristatin E (MMAE), potent antitubulin agent

protease-cleavable linker

anti-CD30 monoclonal antibody

ADC binds to CD30

ADC-CD30 complex traffics to lysosome

MMAE is released

MMAE disrupts Microtubule network

G2/M cell cycle arrest

Apoptosis
Evaluation of SGN-35 in patients with HL in relapse after autologous stem cell transplantation

94% (96 of 102) of patients achieved tumor reduction

Chen et al., ASH 2010
Progression-free and overall survival

% Patients Free of PD or Death vs Time (Weeks)

Median (range) cycles of treatment = 9 (1–16)

Chen et al., ASH 2010
Case 3
38 yo female

- Diagnosed with follicular lymphoma in Slovakia: treated with CVP chemotherapy ~ 2002
- Emigrated to Canada; well x 1 year → back pain, huge (20cm) abd mass
Treated with CVP + rituximab (8 cycles) followed by maintenance rituximab x 2 years…
At end of maintenance Rx: asymptomatic relapse
An old drug is new again - Bendamustine

- First synthesized in the 1960s in Jena, in the former East Germany
  Limited data published during the initial period of investigation

- Used in the treatment of NHL, CLL, multiple myeloma, Hodgkin´s disease and solid tumors, i.e. breast cancer and small cell lung cancer

- In a previous phase II study Bendamustine plus Rituximab showed high activity in relapsed indolent lymphomas whilst having a low toxicity profile
Significant activity of bendamustine in relapsed indolent lymphoma

Significant activity of bendamustine in relapsed indolent lymphoma
Bendamustine-Rituximab (B-R) vs CHOP-R

**StiL NHL 1-2003**

- Follicular
- Waldenströms
- Marginal zone
- Small lymphocytic
- Mantle cell

- Bendamustine-Rituximab
- CHOP-Rituximab

Bendamustine 90 mg/m² day 1+2 + R day 1, max 6 cycles, q 4 wks.
CHOP-R, max 6 cycles, q 3 wks.
Progression-free Survival

B-R: 54.9 vs CHOP-R: 34.8 months (median)

HR = 0.57 (95% CI: 0.43 - 0.76)

p = 0.00012

Rummel et al.: Blood 114: 168 (abstr #405), 2009
Time To Next Treatment

B-R: not reached vs CHOP-R: 37.5 months (median)

HR = 0.52 (95% CI: 0.38 - 0.70)

p = 0.00002

Rummel et al.: Blood 114: 168 (abstr #405), 2009
Rituximab + bendamustine is superior to R + CHOP

- Progression-free survival 55 months vs 35 months
- Improved PFS in follicular lymphoma as well as other indolent lymphomas (mantle cell, lymphoplasmacytic)
- Better tolerated: less significant bone marrow suppression, neuropathy and alopecia (hair loss) and fewer infectious episodes
- More skin rashes in those receiving bendamustine
- No difference yet in overall survival
Future developments in therapy for lymphoma

• First decade of this millennium: 2 “great leaps forward”
  – Bench: dissection of multiple signaling pathways important in lymphoma biology (and potential therapeutic targets)
  – Bedside: rituximab as paradigm for targeted therapy

• It is critical that therapeutic clinical trials build on this success
Future developments in therapy for lymphoma

• Next decade of this millenium: many small steps
  – Multiple defined clinical/biological entities
  – One therapy not likely to “fit all” in the future
  – Steps will be smaller (no more leaps… maybe one or two) and more numerous
Questions?