INDOLENT LYMPHOMAS - FUTURE

Presenter?
Treatment Decision: Standard of Care versus Clinical Trial

**Standard of care**
- Treatment decision usually based on a prior large trial comparing the old standard to new standard
- Offered in most hospitals
- Less testing/scans

**Clinical trial**
- Access to new options or new drugs
- Can be high risk/high gain
- More rigorous testing
What are clinical trials?

Clinical trials are carefully planned research studies where the most-promising discoveries and results from laboratory studies are tested with patients.

Trials may look at:
- new treatments, tests or procedures
- lifestyle choices
- the impact of cancer on you and your family
New & Improved Treatments

A clinical trial can test many aspects of treatment:

• The safety and effectiveness of new medications;
• The addition of new medications to standard treatments;
• Potential new methods of administering standard treatments (e.g. oral versus IV, inpatient versus outpatient).
Clinical Trial Safety

• Clinical trials are carefully examined and approved by ethics committees and must meet rigorous Health Canada and medical standards.
• A large amount of detailed research is conducted on any new treatment or procedure before it reaches the stage where it is tested on patients.
• Healthcare professionals work very hard to minimize the risks of participating in a clinical trial.
Clinical Trial Phases

**Preclinical**
- Lab & animal studies

**Phase I**
- Safety study
- 20-80 people

**Phase II**
- Safety study
- Identify side effects
- Measure effectiveness
- 100-300 people

**Phase III**
- Measure effectiveness
- Monitor side effects
- 1,000-3,000 people

**Phase IV**
- Monitor long-term side effects
Timeline for new drug discovery

Drug synthesis or discovery
Pre-clinical efficacy: (in vitro in vivo demonstration of anti-cancer drug activity)
Chemical optimization
ADME and Toxicology
Formulation and manufacturing
Clinical Trials
FDA Approval

3-5 years
2-3 years 1-2 years 1-2 years
7-12 years

Timeline for drug repurposing

- Observation of novel activity
- Pre-clinical efficacy (in vitro in vivo demonstration of anti-cancer drug activity)
- Formulation and manufacturing
- Clinical Trials
- FDA Approval

1-3 years
1-2 years
2-5 years

Many targets...
Cell surface targets

- CD20 is a good target
- Expressed on >90% B cell lymphomas

www.myelomacinderella.net
Immuno-oncology

"Immuno" in Immuno-Oncology (I-O) refers to your immune system.
I-O uses drugs known as immunotherapies that target your body's immune system to help fight cancer.
“Immunotherapy is revolutionizing cancer care. We are now using completely new approaches in the treatment of the disease. It took a long time to get here, although it seems so logical to try stimulating and manipulating the immune system to attack cancer cells. The potential in oncology right now is enormous and seemingly limitless. Some of the issues we are grappling with are how to control the immune system and how to target it to go after specific types of tumors.”

Jodi Fisher Horowitz Professor in Leukemia Care Excellence and Director of Blood and Marrow Transplantation at the Abramson Cancer Center of the University of Pennsylvania
Monoclonal antibodies

- Mimicking the immune system
- Rituxan
- Development of novel anti-CD20 MAbs with activity in rituximab-resistant disease
Obinutuzumab (GA101) Mechanisms of Action

Increased Direct Cell Death
Type II versus Type I antibody

Enhanced ADCC
Glycoengineering for increased affinity to FcγRIIIa

Lower CDC
Type II versus Type I antibody

ADCC = antibody-dependent cell-mediated cytotoxicity
CDC = complement-dependent cytotoxicity

With permission from Goede V et al. Proc ASCO 2013;Abstract 7004.

Phase III GALLIUM trial: 40 months+ follow-up, obinutuzumab (Gazyva) plus chemotherapy in the first-line setting reduced the risk of disease progression or death by 32% versus rituximab (Rituxan) plus chemotherapy in patients with follicular lymphoma.
Ublituximab (TG-1101)

Type I, chimeric, glycoengineered anti-CD20 recombinant IgG1 MAb that targets CD20 antigen, with enhanced clinical activity and potency.

Targeted Therapies

Targeted therapies are drugs or other substances that block the growth and spread of cancer by interfering with specific molecules ("molecular targets") that are involved in the growth, progression, and spread of cancer.

➢ B cell focus in lymphoma
➢ T cells largely unaffected by targeted therapies so patients stay healthier during treatment
Bruton's Tyrosine Kinase (BTK) Inhibitors

• BTK is a protein that plays a critical role in the growth and survival of B-cells
• New therapies stops BTK from working, killing the malignant B-cells
  ➢ Ibrutinib
• More selective and potent BTK inhibitors are being investigated.
  ➢ ACP-196
  ➢ ONO/GS-4059
  ➢ BGB-3111, CC-292
Ibrutinib

- First in class, potent, irreversible BTK inhibitor
- Many trials in combination with other drugs
Ibrutinib

Ongoing studies as monotherapy and in combination for B cell lymphomas.
Acalabrutinib

- Second generation BTK inhibitor
- More potent, fewer side effects
- 61 patients with CLL demonstrated safety and efficacy. At a median follow-up of 14.3 months, patients exhibited an overall response rate of 95%.
- FDA breakthrough designation for MCL – trial results expected soon
- Designated as an orphan medicinal product by the EMA for CLL/SLL, MCL, and lymphoplasmacytic lymphoma (Waldenström's macroglobulinaemia)
- Multiple trials underway as single agent and in combination
Tirabrutinib ONO/GS4059

- Highly potent & selective oral therapy
- Phase I: 90 patients enrolled with CLL & NHL
- MCL patients ORR 92%, 11/12 patients
- 75% AE grade 1 or 2; grade 3 & 4 mainly hematological & spontaneously recovered during treatment
- Less bleed risk; no clinically significant diarrhea, cardiac dysrhythmias or arthralgia were observed
BGB-3111

• Highly specific BTK inhibitor
• Active in patients with Waldenström macroglobulinemia (WM)

➢ 42 patients in the efficacy population demonstrated a best objective response rate (ORR) of 90%.
  ➢ 18 (43%) patients showed very good partial response
  ➢ 14 (33%) patients achieved partial response
  ➢ 6 (14%) patients showed minor response
  ➢ Stable disease was demonstrated by the remaining 4 (10%) patients

PI3K inhibitor

• The PI3K pathway is important in regulating the cell cycle
• It is directly related to cellular inactivity, proliferation, cancer, and longevity.
Idelalisib
Umbralisib (TGR-1202)

• Unique structure and improved tolerability
• Monotherapy, oral
• Combined ublituximab (TG-1101), ibrutinib, and umbralisib (TGR-1202) showed that the combination was well tolerated and had activity across heavily pretreated patients with high-risk B-cell malignancies
  ➢ 4 patients with MCL ORR of 100%
  ➢ ORR of 100% was also demonstrated in 2 patients with MZL
  ➢ 80% in 5 patients with follicular lymphoma
Copanlisib

- CHRONOS-1 study Copanlisib showed an objective response rate (ORR) of 59.2% without inducing major colitis events or elevation of hepatic transaminases in patients with relapsed or refractory indolent B-cell lymphoma
  - 17 patients (12%) with complete response
  - 67 patients (47.2%) showing partial response
  - Stable disease attained by 42 patients (29.6)
  - 3 patients (2.1%) experienced progressive disease
Bcl-2 Inhibitor: Venetoclax

1. An Increase in BCL-2 Expression Allows the Cancer Cell to Survive
   - Pro-apoptotic Proteins (BAX, BAK)
   - Anti-apoptotic Proteins (BCL-2)
   - Mitochondria

2. Venetoclax Binds to and Inhibits Overexpressed BCL-2
   - BH3-only
   - Mitochondria

3. Apoptosis is Initiated
   - Apoptosome
   - APAF-1
   - Cytochrome c
   - Active Caspase
   - Procaspsate
   - Mitochondria
Immune checkpoint inhibitors

- PD = Programmed Cell Death protein
- PD-1 and PD-L1 turn off T-cell activation, preventing T cells from attacking the cancer.
- PD-1/PD-L1 inhibitors achieve anticancer effects in the form of durable responses, improvements in survival, and less toxicity for patients.
- Binding of T-cells to PD-L1/2 inhibits T-cell function and blunts the normal immune response.
Pembrolizumab

- PD-1 inhibitor, used for many types of cancer
- Relapsed follicular lymphoma Phase II trial in combination with rituximab, overall response rate (ORR) was 65%, including a complete response rate of 50%
- 20 patients evaluated to date; the best response was stable disease in 3 patients and 4 patients had progressive disease

Nivolumab

- PD-1 inhibitor
- Phase 1 study (CA209-039), nivolumab well tolerated and exhibited antitumor activity in extensively pretreated patients with relapsed or refractory B- and T-cell lymphomas.
  - Patients with FL, ORR 40%
  - 2 patients with cutaneous T-cell lymphoma (CTCL) responded
  - 1 of 2 patients with peripheral T-cell lymphoma (PTCL) continued to have an ongoing response at 79 weeks.
Chimeric antigen receptor gene therapy (CAR-T)
Differences between small molecules and biologics

- Small Molecules:
  - made via chemical synthesis *in vitro*
  - potentially made via different synthetic routes

  **Synthetic route A**

  **Synthetic route B**

  **Synthetic route C**

  *Atorvastatin: lipid lowering agent*
  Reference compound = Lipitor

- Irrespective of the synthetic route, all compounds have the same chemistry/molecular weight \( \text{C}_{33}\text{H}_{35}\text{O}_{5}\text{N}_{2}\text{F} : 558.62\text{g/mol} \)
  - all generic small molecules have identical chemical formulas and structures
Differences between small molecules and biologics

- **Proteins**
  - made *in vivo* using a host organisms’ cellular machinery
  - template encoded by DNA-RNA and all molecules are synthesized identically by the ribosome
  
The final protein product may be subject to numerous post-translational modifications that can alter the chemistry of the molecule

*These modifications can have a number of important implications*
Biologics and their inherent complexity

- A crucial difference between small molecules and biologics is that an increase in complexity and heterogeneity make it more difficult to accurately characterize the active pharmaceutical mixture.
The manufacturing processes influence biologics

- Details of the manufacturing process will affect the final product
- Manufacturing details and quality control are often proprietary and closely guarded company secrets
Biosimilars in lymphoma

- SEBs currently used in supportive care (G-CSF, EPOs)
- Currently no approved SEB for lymphoma treatment in Canada
- ~13 SEBs in development for rituximab
- Market authorization for rituximab SEBs expected in Europe in 2017; expected to enter Canadian market in 2020
- Very limited awareness of SEBs in Canadian lymphoma patient community
Precision Medicine

Patient population

Standard approach

Tailored approach

Treatment

Treatment A (effective in 20% of target population; 80% is waste)

Treatment A
Treatment B
Treatment C
Treatment D
Personalized medicine

• Personalized treatments
  ➢ Not all people are the same
  ➢ Match treatment to the patient’s genetic profile

• Not all tumors are the same
  ➢ Match treatment to the tumour’s genetic profile

• Re-educate the patient’s own immune system to attack the tumour
Is research working?

- Yes!!!!
- Improved depth of remissions, longer remissions and improved survivals since introduction of rituximab
  - In combination with chemotherapy
  - As maintenance therapy
- Better understanding of cancer cell signaling and pathways
- Newer targeted agents
Is research working?

Lymphoma
5-Year Relative Survival 1960-2011
