SAVE THE DATE RESEARCH EXPERT SPEAKERS HOPE NETWORKING AID FORUM SUPPORT CAREGIVERS EDUCATION SURVIVORS THERAPIES SIDE EFFECTS

NATIONAL CONFERENCE ON LYMPHOMA

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AGGRESSIVE LYMPHOMAS - FUTURE

Dr Stéphane Doucet
CHUM
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
Importance of Clinical Trials

Preclinical Studies

Phase I
- Few patients
- What’s the highest/best dose that we can achieve
- Outcome: Toxicities

Phase II
- Slightly more patients
- What’s the effect at the best dose
- Outcomes: Efficacy & Toxicity

Phase III
- Large number of patients
- Comparative trial – 2 or more treatments
- Outcomes: Survival, disease control

Phase IV
- Post marketing surveillance
- Huge numbers
- Outcomes: Unusual toxicities
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: 2-5 years
Pre-clinical efficacy (in vitro in vivo demonstration of anti-cancer drug activity): 1-3 years
Formulation and manufacturing: 1-2 years
Clinical Trials
FDA Approval

Many targets...
Genetic Characterization of NHLs
Cell surface targets

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

Obinutuzumab (GA101)
Mechanisms of Action

Increased Direct Cell Death
Type II versus Type I antibody

Enhanced ADCC
Glycoengineering for increased affinity to FcyRIIIa

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.
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.
PI3K inhibitor

- The PI3K pathway is important in regulating the cell cycle
- It is directly related to cellular inactivity, proliferation, cancer, and longevity.
- Combination therapies for DLBCL? Trials underway.
Idelalisib
Umbralisib (TGR-1202)

• Unique structure and improved tolerability
• Monotherapy, oral
• June 2017: combination of TG-1101 (ublituximab) and TGR-1202 (umbralisib), ‘U2 regimen’, with bendamustine is a highly active and well tolerated treatment for patients with aggressive lymphomas. Combination being bought forward in the DLBCL arm of the UNITY-NHL program.
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
• 210 adult cHL patients enrolled in a multicenter, non-randomized, open-label clinical trial. Patients had refractory or relapsed disease after autologous stem cell transplantation and/or brentuximab vedotin (175 patients)
  ➢ With a median follow-up of 9.4 months (range: 1-15), the overall response rate was 69%, including partial responses in 47% of patients and complete responses in 22%
• Demonstrated antitumor activity in recurrent/refractory primary mediastinal large B-cell lymphoma (phase II KEYNOTE-170 trial)
  ➢ Objective response rate (ORR) was 41% based on 29 patients (95% CI, 24–61). Four patients (14%) showed complete response (CR) and 28% a partial response (PR).
Nivolumab

- PD-1 inhibitor
- Phase II CheckMate-205 trial, patients with relapsed/refractory Hodgkin lymphoma after autologous stem-cell transplant (ASCT)
  - Overall response rate was 65% in brentuximab vedotin (BV)-naïve patients, 68% in patients BV after ASCT, and 73% in patients BV before and/or after ASC
- 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.
  - 11 patients with DLBCL, ORR 36%; 23 patients with T-cell lymphoma, ORR 17%
Chimeric antigen receptor gene therapy (CAR-T)

Adoptive Immuno-Gene Therapy using CAR-T-cells for Refractory B Cell Non-Hodgkin Lymphoma

Lymphoma

Blood drawing
PBL
Ex vivo culture
gene transfer
Retrovirus vector SFG-1928z
Infusion
CD19-CAR-T cell processin & quality test

CD19-CAR-T cell

Lymphoma

CD19
scFv
CD28
CD3ζ
Cytotoxic activation

Clinical
Differences between small molecules and biologics

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

- 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
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.

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

Tailored approach
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
