BioCanRx Conference
Summit for Cancer Immunotherapy (Summit4CI)

June 25th – 28th, 2017 - Gatineau, Quebec

Below is a report back of major themes gleaned from the BioCanRx Summit for Cancer and some recommendations for consideration.

Background and Disclaimer

This is the second year for this conference focused on immuno-oncology research, clinical care, research investment, treatment access, health economics and health policy from the perspective of most of the relevant stakeholders. I found it to be stimulating, positive, inclusive, information-rich and exhausting.

I am not a scientist, allied health care professional or health economist. I am a layperson and it is from that lens that I provide this report back. I can neither confirm nor deny the validity of research methodology or reported outcomes. This is not intended to suggest that I doubt either but merely that I am not in a position to comment on them except as a layperson. I will not attempt to explain any of the science at a granular level but to give you a general sense of where it is going and how far it has come.

I will also include some recommendations from a health policy perspective.

I will also describe the Learning Institute, a pilot we introduced this year, matching young researchers with patient attendees intended to share knowledge and enhance the conference experience for both.

Sunday June 25, 2017

Opening Evening Plenaries

The two opening plenaries set the stage with basic information about immuno-therapy. Simply put, it is a process of engineering T-cells to target cancer cells and not healthy cells. Because we have many different types of T-cells, it is very important which ones we decide to engineer because the outcome will not necessarily be the same.

Traditional therapies have included chemotherapy, radiation and surgery. Immuno-therapies are the 4th pillar in therapy. It is a maturing and evolving area and refers to therapies including combinations of checkpoint inhibitors and oncolytic viruses.

One type of immuno-therapy, chimeric antigen receptor T-cells, or CAR-T-cells, targets B cell malignancies. The optimum outcome is to develop such a therapy with a lasting CAR response, rather than a transient one. Research using this innovation has been very promising to date.

The second presenter spoke of research using these therapies in solid tumours which is apparently very challenging.

Monday June 26, 2017

The day began with an inspiring story of and by **Stacy Erholtz**, a cancer patient treated successfully for her rare cancer with the Mayo measles vaccine. Her story certainly underscored the importance of innovation research and for me a take home message was also the need for more support and particularly peer to peer support built into clinical trials.

Day One – Plenary Session 1

The **first plenary session** was a group of presentations about the **Microbiome.** In introduction**,** it was explained that are many organisms that live on us from bacteria to viruses to fungi and protozoa. Every surface on our body has a distinct microbiome and every individual has a distinct microbiome. A very important immune system of the body, often underappreciated, is the gut. (**N.B**. For a very good layperson's discussion of the gut I recommend Guilia Enders book "The Gut").

Gut microbiome produce vitamins and short chain fatty acids among other important activities for immune health. It is a first line of defense against pathogens entering the body. It is important, therefore, to train and maintain this system. While we generally maintain microbiome stability throughout life, diseases, antibiotics, infections, diet and even birth by caesarean section will create instability. As we age it also loses some stability.

We study the microbiome through sequencing it, that is, by isolating DNA and sequencing it.

The second presentation moved from the gut to head and neck cancers and **oral cancers of the mouth**, which are not the same. Only 2-4% of oral cancers are related to human papilloma virus which is important to understand since treatment in HPV related cases is different than in other cases.

There has been a marked increase in oral cancers in women over 46 years old and in young white women and young white men generally. Periodontal disease increases the risk of oral cancer as does the combination of both drinking and smoking. It is thought that the increases in young people may be related to the use of tooth whitening products.

In a trial of 50 participants, the rate of recurrence of oral cancer was high. Metastasis is a major factor in outcomes. 50% of oral cancers are on the tongue.

She hypothesized that fusobacterium, rod-shaped bacteria found as normal flora in the mouth and large bowel and often in necrotic tissue, probably as secondary invaders, is implicated in cancer, either as a contributor or an opportunistic pathogen.

This is also hypothesized in colorectal cancer. In addition, it is hypothesized that other bacteria that are associated with colorectal cancer are piggybacking on fusobacterium, which is sticky, to exacerbate cancer proliferation.

A presentation about lung cancer described the value of checkpoint inhibitors, including CTLA-4 and PD-L1, in treatment. One study of 140 people suggested that the use of antibiotics was an independent factor in blunting the response of checkpoint inhibitor PD-L1, although that the infection itself may be limiting a good response to it.

Day One – Plenary Session 2

Plenary Session 2 dealt with a number of **clinical, social and economic impacts** of the cancer landscape.

First, there was a discussion of the impact of four (4) recent U.S. Supreme Court decisions that have had the effect of limiting patent protection and potentially having a chilling effect on innovation. This was followed by a presentation about the patent trends in CAR-T therapies.

There was a discussion of the importance of education for researchers to ensure that pre- clinical trial implementation could be validated.

Lastly, there was a very interesting presentation about the value of public/private partnerships in advancing immunotherapy research including a multi-stakeholder approach to clinical trial design involving health economists, patient representatives as well as private and public investors and researchers.

Day One – Plenary Session 3

Plenary Session 3 delved into novel preclinical models including zebrafish, next generation mouse models as well as in vitro screening platforms using cytotoxic CD 8 killer cells. This was definitely beyond my comprehension.

Tuesday June 27, 2017

Day Two – Plenary Session 4

Plenary Session 4 dealt with **antibodies and anti-body like molecules**. Wikipedia defines an **antibody** (**Ab**), also known as an **immunoglobulin** (**Ig**), as a large, Y-shaped protein produced mainly by plasma cells that is used by the immune system to neutralize pathogens such as bacteria and viruses. The antibody recognizes a unique molecule of the harmful agent, called an antigen, via the Fab's variable region. Each tip of the "Y" of an antibody contains a paratope (analogous to a lock) that is specific for one particular epitope (similarly analogous to a key) on an antigen, allowing these two structures to bind together with precision. Using this binding mechanism, an antibody can *tag* a microbe or an infected cell for attack by other parts of the immune system, or can neutralize its target directly (for example, by blocking a part of a microbe that is essential for its invasion and survival). Depending on the antigen, the binding may impede the biological process causing the disease or may activate macrophages to destroy the foreign substance. The ability of an antibody to communicate with the other components of the immune system is mediated via its Fc region (located at the base of the "Y"), which contains a conserved glycosylation site involved in these interactions.

Conventional natural killer cells have receptors called CD16 receptors that can be adapted and repurposed to make antibodies. Another antibody, ZW25, which is bispecific for the HER2 biomarker expressing cancers including breast, gastric and ovarian appears to be effective in pre-clinical research and is now in Phase I human safety trials of heavily pretreated breast and gastric/esophageal cancer trial participants. Reported on at ASCO this year, it appears that in this small sample of 10 people with advanced disease and prior HER2 therapy, the ZW25 antibody was well tolerated. Another antibody in clinical development for ling cancer, L-DOS47, seems to bind well to cancer cells but not to normal cells. It has been shown to act in concert with

chemotherapy. There is presently a 3 centre Phase I trial in the U.S. with 50 participants combining this antibody therapy with checkpoint inhibitors.

Day Two – Plenary Session 5

The topic of **Plenary Session 5** was **innate immunity.** The first presentation described a pediatric trial using the body's natural killer cells as a treatment. In a small trial of 8 participants, 3 of the 5 still in the trial were in remission. It is starting to be used on brain tumours. It may also have potential in ovarian cancer. It is being considered for combination therapy as well.

The next presentation looked at the impact of surgery on cancer progression. Surgery is known to cause immune suppression, blood coagulation and other surgical stress. These can help people heal but can also enhance cancer recurrence. Within the first 24 hours after surgery there is an inflammatory cytokine response and then switches to a non-inflammatory cytokine response. Tissue damage inversely correlates with disease free progression and directly with disease increase. It appears that post-operative natural killer cells are defective. There is a tumour-associated antigen cancer vaccine that can stop this damage to the natural killer cells.

Another issue discussed is what is called immune reconstitution syndrome. This may occur as one is being treated because the immune system may be revved up as it is reconstituting and actually cause disease proliferation. It has been found *in vitro* that pDendritic (pDC) cells increase natural killer cell anti-leukemia activity and overcome resistance to treatment. Thus, using pDC as post-transplant immunotherapy may prevent relapse due to immune reconstitution therapy. This may also be effective in AML. Presently research is being conducted to find a clinical trial grade of pDC to start a trial in humans.

Another puzzle is how circulating cancer cells determine where they will attach themselves. If we can stop them from metastasizing there is a greater chance of successful therapy. *In vitro* a peptide called the LT peptide appears to block breast cancer from metastasizing. Whether this will work *in vivo* and for people who have metastasized breast cancer at diagnosed needs further research.

Wikipedia defines **peptides** in part as natural biological or artificially manufactured short chains of amino acid monomers linked by peptide (amide) bonds. Peptides are distinguished from proteins on the basis of size, and as an arbitrary benchmark can be understood to contain approximately 50 or fewer amino acids.[Proteins consist of one or more polypeptides arranged in a biologically functional way, often bound to ligands such as coenzymes and cofactors, or to another protein or other macromolecule (DNA, RNA, etc.), or to complex macromolecular assemblies. Finally, while aspects of the lab techniques applied to peptides versus polypeptides and proteins differ (e.g., the specifics of electrophoresis, chromatography, etc.), the size boundaries that distinguish peptides from polypeptides and proteins are not absolute: long peptides such as amyloid beta have been referred to as proteins, and smaller proteins like insulin have been considered peptides. Amino acids that have been incorporated into peptides are termed "residues" due to the release of either a hydrogen ion from the amine end or a hydroxyl ion from the carboxyl end, or both, as a water molecule is released during formation of each amide bond. All peptides except cyclic peptides have an N-terminal and C-terminal residue at the end of the peptide (as shown for the tetrapeptide in the image).

Day Two – Lunch Panel

Establishing Effective Patient Partnerships in Translational Research explored opportunities and barriers for involving patients and patient representatives into the research process. Patient representatives from Canada and the U.S. joined researchers from Canada and England to explore this topic. The consensus strongly supported the involvement of multiple stakeholders including health economists and patients in all aspects of research from design, implementation, dissemination and knowledge translation. In the Canadian context, with its mixture of public and private reimbursement systems and the division of federal and provincial/territorial jurisdiction in health policy, the advice and information and experience of these diverse groups is particularly important to ensure that good research actually reaches people who need access to treatments. Education of researchers and patients about the basics of each other's discipline, experience, opportunities and challenges is important.

Day Two – Plenary Session 6

Plenary Session 6 continued the discussion of oncolytic viruses and viral vaccines. Generally, the consensus is that one treatment will probably not be enough to knock out most cancers. The use of two or more vaccines and/or oncolytic viruses will be needed to kick start the immune system. A number of such combination trials are in pre-clinical development and some are already in early clinical trials.

Wednesday June 28, 2017

Day Three – Plenary Session 7

Plenary Session 7 dealt with **adoptive cell therapy, beyond melanoma.** I found the presentations to be very technical but I took away the message that this work is important because it is looking for new immunosuppressive signals in the tumour environment to activate.

Day Three – Plenary Session 8

Plenary Session 8 dealt with **biomarkers and immune profiling.** The first presenter explained the potential for CAR-T cells in paediatrics. Because of the relatively small size of the population it will be important that there are partnerships between several institutions to find a predictive biomarkers. This was followed by an excellent presentation describing the details of the steps in conducting a clinical trial. There was also a good discussion of the different type of CAR-T cells. The toxicity of each and functionality are different. In addition, each area in the body handles these cells differently and the vector site you use is relevant to toxicity. The question is how to identify people who are at risk of cytokine release syndrome (CRS). The hypothesis is that we may be able to follow people over time to determine when to intervene to avoid toxicity. Animal modelling does not always predict clinical outcomes. A trial is underway using IL6 as a prophylaxis against CRS but no results are yet available.

Day Three – Luncheon Companion Diagnostics

LUNCHEON COMPANION DIAGNOSTICS (CDs) discussion featured a multi-stakeholder panel that reviewed many aspects of the issues with regulating companion diagnostics that are used to determine genetic biomarkers people have that may be predictive of success for some treatments as well as a signal of propensity for disease. There are numerous problems including the lack of a formal process at the Health Canada level to evaluate CDs and particularly in conjunction with treatments in trials. CADTH has at least started to develop a pan-Canadian process on both the oncology and non-oncology side to do health technology assessment of the CD and the treatment for which it is used together. Patient and clinician submissions are invited.

KEYNOTE SESSIONS

The two closing keynote sessions addressed potentially exciting future directions in immuno-therapy and a very engaging presentation by Jeff Hoch, a health economist about the relationship between research and what health care payers wish to know from the research to help them determine which treatments to fund. The gap between the acceleration of research knowledge and the pace of change in health systems planning is a huge and growing problem that requires a multi-stakeholder, objective approach to resolve.

LEARNING INSTITUTE

The Learning Institute is a process adapted from the HIV community to which we are grateful for sharing so generously. We piloted it at the Conference with the amazing leadership of Patrick Sullivan, an inspiration patient representative on many organizations from Vancouver and the resourceful, infinitely patient Stephanie Michaud and Renee Leduc of BioCanRx. The process is to pair a patient attendee with at least one young researcher attendee at the Conference. We had 15 researchers and 7 patient group attendees. Each pairing was assigned certain sessions about which they were required to report. The entire group met each morning before the sessions and reported in after which others commented on the sessions. There will be a full report out of our findings and a more detailed description of the event in a forthcoming BioCanRx newsletter. We also hope to publish some abstracts about it if feasible. It was such a big success that several young researchers expressed an interest in an Advocacy Boot Camp just for them which we hope to organize. Let me know if you are interested.

In his closing remarks Dr. John Bell announced that it would become a permanent feature of the Conference. Thank you John!

Congratulations to all of the award-winning researchers !

CONCLUSIONS AND RECOMMENDATIONS

1. The pace of research and innovation in many areas of cancer is startling. We have reason for optimism that for many cancers may become a chronic manageable disease or even be cured. Education for all stakeholders as the research evolves is essential, including knowledge translation to patients and patient groups. Partnerships and collaborations between groups stakeholders is essential.
2. It is evident from the way public and private insurance review and reimbursement systems are changing or devolving that they are not prepared for the rapid change from population health style medicine to personalized, precision medicine and that researchers, clinicians, allied health professionals, caregivers, patients and patient groups are going to need to work together to ensure that messages are delivered to these reimbursers about the importance to moving to a health outcomes based health care model from a pay for outputs model including a move away from siloed health budgets.
3. There is a need for more involvement of patients and patient representatives as research is being developed to enhance recruitment and retention in trials.
4. In order for researchers to understand the basics of the access environment and for patients and patient representatives to understand top line information about their disciplines we need a joint information and training session developed jointly.
5. CADTH should develop a training programme to assist both patient and clinician representatives doing CDs to understand how to do them to ensure they include information of interest and relevance to CADTH.
6. All government stakeholders with responsibility for approval, regulation, recommendation and payment for CDs should develop a joint multi-stakeholder informed process for doing this work and a consensus set of guidelines coming out of their work that should be reviewed and updated regularly as new information becomes available.
7. Patient representatives need to collaborate to work with the provinces to ensure additional funding for laboratory testing that pathology laboratories need to do as a result of CDS. New indications require laboratories to do new biomarker testing without provision of additional human or financial resources to cope with the additional volume of work.
8. Because the gap between the acceleration of research knowledge and the pace of change in health systems planning is huge and growing problem, stakeholders must find an objective, trusted convener of a multi-stakeholder think tank/ brainstorm to have this discussion candidly and constructively with real decision makers at the table willing to make the necessary reasonable concessions to reach consensus. The vision must be a system that values health outcomes not just siloed outputs.
9. The Learning Institute concept should be considered by other stakeholder groups as a model to adapt to get to work together more and learn about others' challenges, areas of work, expertise and skills with a view to future synergies and collaborations and most of all better decision making outcomes for patients.

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