10th ANNUAL CHC 2020

IMMUNOTHERAPY
SESSION SUMMARIES

PRESENTED BY: DR. RONAN FOLEY,
DR. JOHN KURUVILLA & DR. ROB LAISTER

Content in this report is drawn from the presentations made by the respective speakers during the CHC 2020 virtual stream on October 2nd, 2020.

CELL THERAPY

DR. RONAN FOLEY / JURAVINSKI CANCER CENTRE

Immunotherapy is evolving rapidly with remarkable results, changing the landscape of cancer therapy.

- Cell-based therapies are emerging in the clinic
  - A current limitation is that the patient's cells must be individually collected/process
  - **Creating capacity and timely delivery of products are critical immediate goals**
    - Efforts with autologous and "off the shelf" products are in progress
- Recent Trial Updates:
  - **CARTITUDE-1-** A phase Ib/II study of JNJ-4528, a B-cell maturation antigen (BCMA)-directed CAR T therapy in RR MM *(Berdeja JG, et al. ASCO Virtual Abstract Presentation 2020, Abstract 8505)*
  - **PLATFORM-** Safety of lisocabtagene maraleucel (CAR T) given with durvalumab (checkpoint inhibitor) in patients with RR aggressive B-Cell NHL *(Siddiqi T, et al. ICML 2019, Abstract 122.)*

Looking Forward:

- Modifications of current successful approaches for 'greater efficacy and safety' have created a new modality of cancer therapy
- **Key themes/strategies for the future of cell therapy** that have shown promise include:
  - Novel combinations (in early phase studies)
  - CAR-transduced natural killer (NK) cells in CD19-positive lymphoid tumours
  - Use of dasatinib as on/off switch for CAR T cells (dasatinib pauses activated CAR T cells in a function-off state in vivo)
  - Other methodologies for gene transfer (i.e. highly soluble sleeping beauty transposase to improve control of gene insertion)
  - iPSC reprogramming

Click here to access the slides presented by Dr. Ronan Foley

CARE™
COMMUNITY • ACADEMIC • RESEARCH • EDUCATION
COMMUNAUTÉ • ACADÉMIQUE • RECHERCHE • ÉDUCATION

ANTIBODY BASED THERAPY

DR. JOHN KURUVILLA / PRINCESS MARGARET CANCER CENTRE

Antibody therapies have become standard tools in lymphoma. Established agents and new therapies in development are reviewed below.

- *Monoclonal antibodies against CD20*- the original target
  - **Rituximab- an incredibly positive 20-year story**
    - Toxicity low and easy to combine with chemotherapy
    - Major improvements in ORR, PFS and OS
    - Optimization via sub-cutaneous (sub-Q) administration and cost savings with biosimilar options
  - **Obinutuzumab- the first type II, glycoengineered, humanised anti-CD20 mAb designed to provide an advancement in antibody technology**
    - Showed increased direct cell death induction and enhanced ADCC in preclinical studies (compared with rituximab)
    - Practice changing in CLL and rituximab-refractory FL. Additional studies are ongoing
  - Other anti-CD20 antibodies: ofatumumab and ublituximab
- *Antibodies as a delivery system*- antibodies bind to a target antigen to 'deliver' a variety of effectors to the target
  - Anti-CD20 radioimmunoconjugates- targeted radiation
    - **Zevalin and Bexxar** had single agent activity but **practical issues largely outweighed any clinical benefits**
    - Ongoing studies with novel compounds (i.e. Betalutin) and targets are being evaluated
  - Antibody-drug conjugates (ADC)- targeted cytotoxicity
    - **Brentuximab vedotin- CD30- directed ADC**
      - Multiple positive RCTs for consolidation post-ASCT for cHL (AETHERA), frontline HL (ECHELON-1), previously treated CD30+ cutaneous T cell lymphoma (ALCANZA), and frontline CD30+ PTCL (ECHELON-2)
    - **Moxetumomab Pasudotox-tdfk- immunotoxin that targets CD22**
      - Approved for hairy cell leukemia, however toxicity is a challenge
- *Antibodies to manipulate the immune system*- agents with specific mechanisms that interfere with the immune system to make it recognize cancers more effectively or help bring immune effectors directly to the tumor
  - Immune checkpoints
    - **Nivolumab and pembrolizumab** are programmed cell death 1 (PD-1) immune checkpoint inhibitors that are **well established in RR-cHL** (signal in NHL less impressive but some positives with PMBCL and some T and NK cell lymphoma subtypes)
      - Phase III trials are underway (including frontline trials)
    - Hu5F9-G4 is a **macrophage checkpoint inhibitor** still early days but shows promise in combination with rituximab in NHL
  - Bispecific T-Cell Engagers (BiTEs)
    - Blinatumomab- first approved BiTE that targets CD3/CD19
      - Excellent preliminary activity in lymphoma, challenges with toxicity, and administration led to development of multiple new CD3/CD19 targeting BiTEs currently in early phase trials
  - NK-engaging therapeutic antibodies
    - AFM13 (CD30/CD16A TandAb) is the most advanced NK-cell engaging antibody in clinical development that may be effective in HL and T-Cell lymphoma

Looking Forward:

- **Antibody-based therapies will continue to be a key component of lymphoma care in Canada**
  - Exciting new agents in development are expected to build on the clear improvements in patient care already achieved with currently available antibody-based therapies

Click here to access the slides presented by Dr. John Kuruvilla

THE CHALLENGES AHEAD: A TRANSLATIONAL SCIENCE PERSPECTIVE ON IMMUNOTHERAPY

ROB LAISTER, PhD / PRINCESS MARGARET CANCER CENTRE

Cancer Immunotherapy has provided a new arsenal of treatments for many different hematological malignancies (modalities include cell therapy, monoclonal antibodies, BiTES, cytokines, IMiDs, and cancer vaccines).

- **Immunotherapy is complicated and there is a lot that we still don't know**
  - Current preclinical models used to assess cell therapies do not adequately capture how the human immune system responds to cancer immunotherapies nor the multicellular complexity of the tumour microenvironment
- Tumour microenvironment and CAR T
  - **Baseline characteristics both in the periphery and in the tumour are associated with poor response to CD19 CAR-T.** Factors include *(Jain et al. ASH 2019 Abstract 627)*:
    - Circulating factors related to systemic inflammation (CRP, IL-6, Ferritin)
    - Tumour microenvironment signature related to inflammation (interferon activated genes) and macrophages
    - Circulating myeloid derived suppressor cells can inhibit T-cell proliferation
  - What happens within the tumour microenvironment following CAR T-cell therapy? *(Chen et al, JCI Insight, 2020)*
    - Small numbers of exogenous, CAR T-cells appear to result in the recruitment and activation of an endogenous (non-CAR T) immune infiltrate
- Immunometabolism and immunotherapy- metabolic reprogramming during T-cell activation is critical
  - Introduction of **additional proteins that further reprogram immune effector metabolism may be beneficial**
- Immunotherapy and the competition for nutrients *(i.e. Arginine- Fultang, et al, Blood Adv. 2020)*
  - **Engineering CAR T-cells to overcome arginine deficiency may help achieve optimal tumour control and durable responses** in the nutrient limited space that is the tumour microenvironment

Looking Forward:

- Future efforts in immunotherapy translational research will need to better define the interplay between cell subsets that confer anti- and pro-tumour activity in different hematological malignancies and their respective tumour microenvironments

Click here to access the slides presented by Dr. Rob Laister

TO ACCESS THE ENTIRE CHC NATIONAL ON-DEMAND VIDEO SESSIONS

CLICK HERE TO REGISTER

IF YOU ARE REGISTERED,

CLICK HERE TO LOGIN & VIEW ONLINE

Immunotherapy On-Demand Video Sessions

CONNECT WITH CARE™

17 - 1400 Cornwall Road, Oakville, ON L6J 7W5

www.CAREeducation.ca

info@careeducation.ca

Community Academic Research Education

CARE Education

@weareCARE

www.facebook.com/weareCARE