10th ANNUAL CHC 2020

PLASMA CELL DYSCRASIAS SESSION SUMMARIES

PRESENTED BY: DR. KEVIN SONG, DR. CHRIS VENNER & DR. KEITH STEWART

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

TREATMENT OF RELAPSED REFRACTORY (R/R) MULTIPLE MYELOMA IN THE CANADIAN LANDSCAPE

DR. KEVIN SONG / BC CANCER

There has been significant improvement in survival for MM patients over the last 30 years (Kristinsson et al. Leukemia 2014). We expect to see this continue with the growing armamentarium of therapies available for relapsed/refractory myeloma.

- *Classes of medications currently available for R/R MM*
  - Alkylators: Cyclophosphamide, Melphalan
  - Corticosteroids: Dexamethasone, Prednisone
  - Immunomodulatory Drugs: Lenalidomide, Pomalidomide
  - Proteosome inhibitors: Bortezomib, Carfilzomib, Ixazomib
  - Monoclonal Antibodies: Daratumumab, Isatuximab
- Important concepts with MM relapse:
  - **Achieving a complete response (CR) Does Not Eliminate All Myeloma Clonese**
    - Even in a CR, patients still have residual clonal disease that will lead to relapse
  - Depth of response is important- Combination therapies can achieve deeper CRs
    - Daratumumab (first mAB approved for MM in Canada) is particularly appealing due to the direct on-tumour actions resulting in a rapid response and immunomodulatory actions that contribute to deep and durable response.
  - Applying long-term pressure on myeloma cells with continuous therapy (i.e. LEN Maintenance After ASCT) also has the potential to improve survival and has become very prevalent in practice
- *Firmly established backbones for combination therapy include:*
  - **Lenalidomide (len), dexamethasone (dex) + 3rd drug:** daratumumab *(Dimopoulos NEJM 2016)*, carfilzomib *(Stewart NEJM 2015)*, ixazomib *(Moreau NEJM 2016)*, Elotuzumab- not readily available in Canada *(Lonial NEJM 2015)*
  - **Bortezomib (bort), dex +/- 3rd drug:** carfilzomib *(Dimopoulos MA Lancet Oncol 2016)*, daratumumab *(Palumbo N Engl J Med 2016)*, panobinostat- not readily available in Canada *(San Miguel J Lancet Oncol 2014)*

- Novel agents that may become the backbone for future combinations:
  - Many novel drugs have improved tolerability compared to current standards so are very appealing for use in combination
  - With so many agents and potential combinations, **sequencing has become quite complex**
  - *Notable clinical trial updates for patients exposed to or refractory to len and bort in early-RRMM:*
  - OPTIMISMM: Pomalidomide (Pom) Vd versus Vd *(Richardson et al. ASCO Annual Meeting, Oral 8001; 2018)*
    - MM014- Daratumumab + Pom/Dex *(Siegel Leukemia 2019)*
      - Phase III Apollo trial ongoing
    - ICARIA- Isatuximab + Pom/Dex *(Attal Lancet 2019)*
      - Note: Isatuximab recently received HC approval and can be obtained through private insurance. Provincial funding decisions pending.
    - CANDOR- Carfilzomib plus Daratumumab *(Usmani ASH 2019)*
- Poor outcomes in patients refractory to CD38-mAbs
  - The success of dara has led to many patients being exposed earlier in their disease course- **what to do when a patient becomes refractory to dara is becoming a more prevalent challenge.**

Looking Forward:

- Newer therapies with **novel mechanisms of action** to watch for:
  - Venetoclax- BCL-2 inhibitor
  - Selinexor- first-in-class XPO1 inhibitor
  - Balantamab (GSK2857916)- humanized, afucosylated IgG1 anti-BCMA antibody
  - Teclistamab (JNJ-64007957)- humanized IgG-4 bispecific DuoBody® antibody that binds to BCMA and CD3
  - Idecabtagene vicleucel- BCMA CAR T
  - bb21217- next-generation anti-BCMA CAR T
  - JNJ-4528- BCMA CAR-T
  - CC-92480- Novel CELMoD agent
- **Current literature does not guide for all situations**
  - An individualized approach is needed
  - **Drug funding will play a huge role**

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NEW DEVELOPMENTS IN AMYLOIDOSIS

DR. CHRIS VENNER / CROSS CANCER INSTITUTE

Available treatments in AL amyloidosis have expanded based on advancements in MM.

- *Importance of staging in trial populations*
  - In early Mayo cardiac patients, early death is unlikely thus the goal is preventing further fibril deposition and maintaining/improving organ function
  - In advanced Mayo cardiac patients, the big problem is overcoming severe vital organ dysfunction which drives early death (largely cardiac)
  - Of Note: early death is a problem in frontline thus the impact of Mayo stage in the relapse setting is less clear
- *Response Criteria*- measuring impact on clone, impact of organs, and disease related organ failure or death
  - It is important to study response criteria to understand and interpret trial results properly
- Major advances in 3 phase III clinical trials:
  - *Bortezomib + Alkylator + steroid:* **Cyclophosphamide, Bortezomib, Dexamethasone** (CyBorD) *(Venner et al, Blood 2012, Mikhael et al, Blood 2012, Jaccard et al, Haematologica 2014)*, **Bortezomib-Mdex** *(Efstathios Kastritis et al, JCO 2020)*
    - Became the standard of care in Canada with trials demonstrating deeper response and better survival
  - **Ixazomib-Dexamethasone:** Tourmaline-AL1 Study *(Dispenziari et al, ASH 2019)*
    - Built upon success of PI's in AL amyloidosis with oral mode of delivery, better neurologic toxicity profile, and reduced GI toxicity
    - Clearly active, however failed to meet primary endpoint (potentially a problem of trial design)
  - **Subcutaneous Daratumumab +** CyBorD: ANDROMEDA Study *(Efstathios Kastritis et al, EHA25 Virtal 2020)*
    - Responses with DARA-CyBorD were deeper and achieved more rapidly; Advances seen in virtually every sub-group examined
    - **Dara-CyBorD truly reflects the new standard of care**

Looking Forward:

- The addition of Daratumumab to the frontline Canadian SoC has led to unprecedented hematologic and organ responses as well as disease control over time
  - **Questions remain:**
    - Impact in Mayo stage IIIB?
    - Durability of responses (especially in those that achieve VGPR or CR) in comparison to ASCT
    - Feasibility and effectiveness of retreatment
    - Feasibility, effectiveness, and necessity of incorporating into ASCT paradigm
- **Anti-fibril therapy efforts continue** but remain elusive

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MYELOMA 2020 AND BEYOND

DR. KEITH STEWART / PRINCESS MARGARET CANCER CENTRE

Dr. Stewart recently returned to Toronto after spending 15 years at the Mayo Clinic. His review looks at differences in practice between the US and Canada with additional perspectives on where we are heading with MM care.

- Comparing Canadian MM practice to the US:

What is different?

- Molecular work up
- Triplet Including KR (now quads)
- Consolidation (more KR)
- Intensification (Dara/Pom) – first "relapse"
- MRD monitoring – NGS

What is slightly ahead?

- Advanced Molecular testing
- Mass Spec Immunofix, possibly MRD
- Venetoclax is readily available for t(11;14)
- Quads are becoming quite common (in academia, not community)
- Subcutaneous dara approved and being integrated
- Isatuximab approved and available
- BCMA ADC now approved
- CAR-T BCMA filed with approval expected (by end of year?)

- Some cool *new things in MM*:
  - **Utility of mass spectrometry-based testing**- saves time and cost, is much more sensitive, can probably be used for MRD testing, and has led to a more accurate estimate of the true prevalence of MGUS in the community *(Murray et al. Blood Cancer J. 2012)*
  - **FISH testing to (more simply) define risk in myeloma**- presence of HR abnormalities (t[4;14] or t[14;16], del17p/monosomy 17, and/or 1q gain/amplification) prognostic of outcomes
  - **Prognostic genetic testing will move to the genome**- important for defining risk (i.e. not all 17p13 deleted patients have poor outcome but would typically have been classified as high-risk)
  - Multivariate association of markers with PFS/OS led to defining a **new and distinct disease segment: Double hit MM with biallelic P53 and ISS III + amp CKS1B** *(Walker et al. Leukemia. 2019)*
  - **Detecting Drug Resistance**: Cereblon pathway mutations in 22% of relapsed patients *(Kortum et al. Blood. 2016)*
    - Mate pair sequencing outperforms FISH in the genomic characterization *(Smadbeck et al. Blood Cancer J. 2019)*

Looking Forward:

- Treatment considerations today:
  - **Daratumumab will become standard** in front line
  - **Treatment will be for longer**
  - **Transplant required for now** but will decline over time
  - Obtaining **MRD will become a standard** of care
  - Elephant in the room is acquisition cost of novel therapies
- *Future state of NDMM:*
  - Staging with genomics and advanced imaging
  - 4 drug combinations + consolidation until MRD
  - Targeted therapies in subsets
  - Clonal mutations tracked for evolving drug resistance
  - MRD stability as endpoint for therapy escalation/de-escalation
  - New targets exploited at relapse - Immune

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