Canadian Hematology Today @ ASH 2024

Event Summary

San Diego, California • December 6, 2024

catalytic health
communications • advertising • strategy
15 years

In this report...

Acronyms

ABVD	DOXORUBICIN, BLEOMYCIN, VINBLASTINE, AND DACARBAZINE
AE	ADVERSE EVENT
AL amyloidosis	IMMUNOGLOBULIN LIGHT CHAIN AMYLOIDOSIS
ALL	ACUTE LYMPHOBLASTIC LEUKEMIA
alloSCT	ALLOGENEIC STEM CELL TRANSPLANTATION
AML	ACUTE MYELOID LEUKEMIA
ASCT	AUTOLOGOUS STEM CELL TRANSPLANT
ASH	AMERICAN SOCIETY OF HEMATOLOGY
AV	ACALABRUTINIB AND VENETOCLAX
AVO	ACALABRUTINIB, VENETOCLAX, AND OBINUTUZUMAB
B-ALL	B-CELL ACUTE LYMPHOBLASTIC LEUKEMIA
BCMA	B-CELL MATURATION ANTIGEN
BR	BENDAMUSTINE RITUXIMAB
BTKi	BRUTON TYROSINE KINASE INHIBITOR
CAR	CHIMERIC ANTIGEN RECEPTOR
CLL	CHRONIC LYMPHOCYTIC LEUKEMIA
CR	CYTARABINE AND RITUXIMAB
CRS	CYTOKINE RELEASE SYNDROME
DFS	DISEASE-FREE SURVIVAL
DLBCL	DIFFUSE LARGE B-CELL LYMPHOMA
DRD	DARATUMUMAB, LENALIDOMIDE, AND DEXAMETHASONE
DVCD	DARATUMUMAB, BORTEZOMIB, CYCLOPHOSPHAMIDE, AND DEXAMETHASONE
DVRD	DARATUMUMAB, BORTEZOMIB, LENALIDOMIDE, AND DEXAMETHASONE
EFS	EVENT-FREE SURVIVAL
HbSC	HEMOGLOBIN SC DISEASE

Acronyms continued

HbSS	HEMOGLOBIN SS
ICER	INCREMENTAL COST EFFECTIVENESS RATIO
ITP	IMMUNE THROMBOCYTOPENIA
IVIG	INTRAVENOUS IMMUNOGLOBULIN
IVRD	ISATUXIMAB, BORTEZOMIB, LENALIDOMIDE, AND DEXAMETHASONE
IxaRd	IXAZOMIB, RITUXIMAB, AND DEXAMETHASONE
MCL	MANTLE CELL LYMPHOMA
MDS	MYELODYSPLASTIC SYNDROMES
MPN	MYELOPROLIFERATIVE NEOPLASMS
MRD	MINIMAL RESIDUAL DISEASE
NCI SR	NATIONAL CANCER INSTITUTE STANDARD RISK
ORR	OVERALL RESPONSE RATE
OS	OVERALL SURVIVAL
PFS	PROGRESSION-FREE SURVIVAL
Pola-R-CHP	POLATUZUMAB VEDOTIN WITH RITUXIMAB, CYCLOPHOSPHAMIDE, DOXORUBICIN, AND PREDNISONE
QALY	QUALITY ADJUSTED LIFE YEAR
R-chemo	RITUXIMAB AND CHEMOTHERAPY
R-CHOP	RITUXIMAB, CYCLOPHOSPHAMIDE, DOXORUBICIN, VINCRISTINE, AND PREDNISOLONE
RD	RITUXIMAB AND DEXAMETHASONE
R/R	RELAPSED/REFRACTORY
R2	RITUXIMAB PLUS LENALIDOMIDE
TEAE	TREATMENT-EMERGENT ADVERSE EVENT
TRAE	TREATMENT-RELATED ADVERSE EVENT
VCD	BORTEZOMIB, CYCLOPHOSPHAMIDE, AND DEXAMETHASONE
VRD	BORTEZOMIB, LENALIDOMIDE, AND DEXAMETHASONE

Objectives

SCIENTIFIC STEERING COMMITTEE:

DIEGO VILLA, MD
BC CANCER – VANCOUVER CANCER CENTER

ERIC TSENG, MD
ST. MICHAEL'S HOSPITAL

- Provide current and high-quality information on the latest developments in the management of hematologic disease
- Create collegial learning opportunities that enable clinicians to directly apply new insights to their practice
- Respond to emerging professional needs for specific and in-depth information on the latest therapies and approaches to disease management in the Canadian market

Key Lessons and Reflections Emerging from the COVID-19 Pandemic, as a Practicing Hematologist in Canada

MENAKA PAI, MD
MCMASTER UNIVERSITY

Dr. Pai reflected on the lessons learned throughout the COVID-19 pandemic. She recalled the first year of the pandemic, when hospitals cancelled non-essential care and deployed specialists to unfamiliar roles, including in the ICU. Emphasizing the importance of adapting to uncertainty, Dr. Pai pointed out that clinical hematologists are often required to apply their clinical judgement to evolving and unclear situations. Indeed, many guideline recommendations in hematology are conditional, due to lower-quality evidence. Communicating uncertainty is an important skill, and Dr. Pai emphasized that the public and patients don't expect physicians to have all the answers. However, strong statements without strong evidence – such as the World Health Organization's initial messaging that COVID was not airborne – erode public trust and feed misinformation. She encouraged her colleagues to practice clinical humility and communicate honestly.

The ability to adapt and work with multidisciplinary teams is essential in a crisis like COVID-19. Dr. Pai is an experienced GRADE methodologist. However, GRADE guidelines often take 2 years to create. As cochair of the clinical guideline working group for the Ontario COVID-19 Science Advisory Table, Dr. Pai was required to lead the creation of guidelines that could be disseminated to various specialties as quickly as possible. Rather than using the GRADE methodology of finding high-quality evidence, the working group adapted to the situation and found ways to interpret large amounts of low-quality evidence in a rapid fashion. At one point, they were updating some guidelines every few days. To adapt to worldwide drug shortages, the team released guidance on the minimum effective dose for various medications.

Dr. Pai also saw engagement with the public as essential during COVID-19 and underwent media training. As a South Asian mother and physician, her voice resonated with diverse communities as she addressed vaccine hesitancy with empathy and evidence. Dr. Pai encouraged her peers to use their positions as health care professionals to shape public discourse on a wide range of health care and scientific matters.

The Ontario Science Table Guideline Working Group: **Our Collective Pandemic Output**

2 years of weekly meetings

11 major guideline updates

26 white papers on drugs & therapeutics

Key impacts on healthcare policy and delivery

Finally, Dr. Pai candidly discussed the psychological toll of the pandemic, including the early fear of becoming very ill or infecting family members and the misplaced guilt many physicians experienced after watching so many patients suffer. Dr. Pai explained that during the pandemic, she educated learners, cared for patients, parented and homeschooled her children, contributed to 24 peer-reviewed papers, was promoted to full professor, and made numerous media appearances. By the end of the pandemic, however, she recalled, "I felt very empty and very unhappy and so did everyone around me." By the end of the pandemic, the burnout rate of Canadian physicians had risen to 50% and physician burnout continues to remain above the pre-pandemic rate of 36%. Burnout is especially pronounced among women and early-career physicians, with implications for career decisions.

Dr. Pai encouraged her fellow hematologists to gain insight into their own psychological challenges, noting that "if you don't know you're not okay, you can't do anything about it." She encouraged her colleagues to model vulnerability and self-care by letting their trainees and peers know when they are struggling and to put as much effort into their well-being as their clinical and research endeavours. She stressed that physicians must take care of themselves so that they can take care of others.

Thrombosis at ASH 2024

PETER GROSS, MD
UNIVERSITY HEALTH NETWORK

Dr. Gross summarized the most important abstracts in thrombosis at ASH 2024, as well as abstracts he recommended due to their innovative research methodology. He began by discussing the late-breaking abstract on the RENOVE study, which evaluated the extended treatment of venous thromboembolism with reduced- versus full-dose direct oral anticoagulants in patients at a high risk of recurrence. He highlighted that venous thromboembolism is a common, potentially fatal disease. While guidelines recommend indefinite anticoagulation in patients at a high risk of recurrence, continued anticoagulation exposes patients to bleeding risks that compound over time. The trial enrolled adults after their initial treatment for venous thromboembolism. The patients either had indications for long-term anticoagulation or long-term anticoagulation was deemed warranted by their physician. Patients were randomized to extended anticoagulation with reduced-dose or full-dose direct oral anticoagulants. Recurrent venous thromboembolism occurred at 2.2% in the low-dose group and 1.8% in the full-dose group. Clinically relevant bleeding was 15.2% in the full-dose group versus 9.9% in the low-dose group. The composite endpoint of recurrent venous thromboembolism or clinically relevant bleeding was lower in the reduced-dose group than in the full-dose group. All-cause mortality was slightly lower in the reduced-dose group, suggesting reduced-dose anticoagulation therapy did not increase the risk of death or arterial thromboembolic events.

Comparing RENOVE to AMPLIFY-EXT and EINSTEIN-CHOICE, Dr. Gross explained that the trials enrolled different patient populations. RENOVE followed patients for 3 years while the other two trials followed patients for 1 year. Dr. Gross highlighted the dramatic increase in bleeding when patients are followed for 3 years, compared to 1 year.

Dr. Gross identified additional important ASH 2024 sessions for the treatment of thrombosis, including abstract 851. In the study, patients with with isolated sub-segmental pulmonary embolism, who were not given anticoagulation treatment, were followed over many years. The rate of venous thromboembolism was 3.09 per 100 patient-years, while the bleeding rate was 1.88 per 100 patient-years.

Dr. Gross also recommended abstract 296, showing mechanical prophylaxis doesn't work in children; abstract 300, comparing various regimens to improve pregnancy outcomes in those with protein S deficiency; and abstract 813, a database study assessing lower limb injuries and the risk of venous thromboembolism.

Dr. Gross also drew attention to abstract 1236, on extracellular vesicles in antiphospholipid antibody syndrome; abstract 0135, which focusses on a new FVIII mutation that is procoagulant; and abstract 0701, a health care database study on the potential role of a GLP-1 receptor agonist in the prevention of venous thromboembolism.

In context of previous RCTs

	Amplify-Ext	Einstein-Choice	RENOVE
Number of pts	2486	3365	2768
patients	90% unprovoked	Equipoise	different
Follow-up	1 year	1 year	3 years
Recurrent VTE/VTE death	3.8 v 4.2%	1.3 v 2.1%	2.2% v 1.8%
MB and Clin relevant NMB	3.2 v 4.3%	2.4% v 3.3%	9.9% v 15.2%

Low dose v Regular dose

Q&A

Do you think the late-breaking abstract comparing low- and full-dose anticoagulation is practice changing?

I think we will need to examine the inclusion criteria. I would like to understand why the bleeding rate is higher than I would expect, and if it is because the population followed in this study was more chronically ill.

Benign Hematology at ASH 2024

SIRAJ MITHOOWANI, MD
ST. JOSEPH'S HEALTHCARE, HAMILTON

Dr. Mithoowani provided context to help ASH attendees better understand the key abstracts in benign hematology. He began with a study showing etavopivat reduced the incidence of vaso-occlusive crises in patients with sickle cell disease (abstract 179). In this phase 2 study, 60 patients aged 12 to 65 with sickle cell disease of any genotype were randomized to take etavopivat at 200 mg, 400 mg, or placebo for 52 weeks. At baseline, the patients had an average of 3.3 vaso-occlusive crises per year. Results demonstrated that the rates of vaso-occlusive crises were 1.07 and 1.06 in the etavopivat 200 mg and 400 mg groups, and 1.97 in the placebo arm. The investigational drug also improved the hemoglobin response rate at week 24 (25%, 38%, and 11% in the 200 mg, 400 mg, and placebo groups respectively).

While hydroxyurea is the standard of care for treatment of sickle cell anemia (HbSS or hemoglobin S-beta-thalassemia), there are no clear treatment indications for the HbSC form of the disease. A phase 2 study enrolled children and adults with HbSC sickle cell disease in a hospital in Ghana (abstract 3). Out of 212 randomized patients (approximately 50% of whom were adults), hydroxyurea led to more dose-related toxicities, compared to placebo (32.7% versus 10.5%), which were mostly grade 2 cytopenia. Hydroxyurea was associated with fewer vaso-occlusive crises (incidence ratio 0.38), and a lower composite endpoint of any sickle-cell-disease-related complication (37 versus 69). HbSC disease is the second-most common genotype for sickle cell disease, affecting 55,000 children annually. The study could therefore have profound implications.

Dr. Mithoowani then described a study assessing the benefits of widespread screening for iron deficiency (abstract 277). He explained that iron deficiency is very prevalent, disproportionately affects persons with the capacity to menstruate, and is underdiagnosed. Using a Markov simulation model, the study examined the cost-effectiveness of screening all adult women in the U.S. for iron deficiency with different thresholds: ferritin below 25µg/L, ferritin below 15µg/L, or no screening (the latter being the status quo). The willingness to pay threshold was set at $100,000 USD per QALY. Screening all U.S. women of childbearing age with a ferritin threshold of less than 25µg/L was extremely cost effective. Accruing $212,000 in costs, the screening strategy generated 24.3 QALYs and the ICER (compared to no screening) was $940/QALY. If patients were treated with IV iron, the ICER remained low, at $1700/QALY. In addition to demonstrating the value of liberal screening, the study could have important implications for health equity.

Moving on to ITP, a retrospective cohort study presented at ASH followed ITP patients at seven centers in the U.S. and Canada between 2010 and 2020 (abstract 547). Out of 1226 patients who met the study criteria (296 adults, 930 children), 28 (2.2%) had critical bleeding (15 adults, 13 children), which was defined as a bleed in a critical anatomical site or an ongoing bleed resulting in hemodynamic instability or respiratory compromise. The study demonstrated that critical bleeding in ITP has a very high mortality; 10 patients died, including three children, and four patients developed a neurological disability. The range in time to first treatment was 3.2 to 9.5 hours. Dr. Mithoowani explained that this study emphasizes the importance of rapid and standardized care for ITP bleeding emergencies.

Another important ITP study presented at ASH is a phase 3 study that enrolled adults and children (10 years and above) with primary persistent/chronic ITP after IVIG, corticosteroids, or anti-D immunoglobulin failure. The participants were randomized 2:1 to rilzabrutinib or placebo for 24 weeks, followed by an open-label 28-week trial of rilzabrutinib. Among the 202 adults enrolled, 46% had previously received five or more ITP therapies and 28% had received splenectomies. A durable platelet count response occurred in 23% of patients in the treatment arm, compared to 0% in the placebo arm. Based on this study, rilzabrutinib could be one of many future therapeutic options for ITP.

Another important study at ASH 2024 is the ENERGIZE-T trial (abstract 409), which randomized 258 transfusion-dependent alpha- or beta-thalassemia patients 2:1 to mitapivat at 100 mg twice daily or placebo twice daily for 48 weeks. Most of the patients enrolled (71%) had more than 12 red blood cell units transfused over 24 weeks before the trial began. The transfusion reduction response, defined as a 50% decrease in transfused red blood cells in any consecutive 12-week period, was 30.4% in the treatment arm versus 12.6% in the placebo arm. The medication was well tolerated. Dr. Mithoowani

recognized that an effective oral drug could revolutionize care in low- and middle-income countries where thalassemia is most prevalent.

Finally, Dr. Mithoowani highlighted a late-breaking abstract on a qualitative problem with erythropoietin that leads to erythrocytosis and the definition of a new disease entity: hepatic-like erythropoietin polycythemia. Dr. Mithoowani explained that erythropoietin is the primary regulator of erythropoiesis. It is produced in the fetal liver, and then in the kidney, shortly after birth. Researchers identified six unrelated families with hereditary erythrocytosis associated with normal circulating erythropoietin levels. Next-generation sequencing suggested a qualitative change in erythropoietin, a "liver type" glycosylation pattern that is distinct from the classic kidney-type glycosylation pattern seen in adulthood. The "liver type" form of erythropoietin was more potent in activating erythrocytosis. The authors concluded it is essential to consider quantitative and qualitative erythropoietin screening as part of the biological tests for the diagnosis of idiopathic and hereditary erythrocytosis.

Q&A

Regarding abstract 547, was there any discussion in the abstract about predictors of critical bleeding?
Bleeding predictors weren't discussed in the abstract. I'm very interested to see if any risk factors were identified, because the large study offers the potential for a tremendous amount of datamining.

Sex, lies, and iron deficiency in 2024 cost-effectiveness of screening ferritin thresholds for the treatment of iron deficiency in women of reproductive age.

Interval	Number iron deficient	Number not iron deficient	Likelihood ratio
Ferritin			
>100	8	108	0.13
>45 ≤100	7	27	0.46
>18 ≤45	23	13	3.12
≤18	47	2	41.47
Total	**85**	**150**	
Transferrin saturation			
>0.21	9	55	0.28
>0.8 ≤0.21	23	70	0.57
>0.05 <0.08	14	17	1.43
≤0.05	38	4	16.51
Total	**84**	**146**	
Mean cell volume			
>95	2	32	0.11
>91 - ≤95	5	26	0.34
>85 - ≤91	16	44	0.64
>74 - ≤85	32	42	1.35
≤74	30	6	8.82
Total	**85**	**150**	

- Ferritin is the single best test for diagnosing iron deficiency
- Yet, the optimal cutoff is still being debated
- This paper has important implications for health equity, and demonstrates the value of *screening* with a *ferritin cutoff* of <25µg/L for women of reproductive age

Important Sessions on Non-Hodgkin's Lymphoma at ASH 2024

MARY-MARGARET KEATING, MD
QEII HEALTH SCIENCES CENTRE

Dr. Keating began by discussing updates from the landmark phase 3 ENRICH (abstract 235) and ECOG-ACRIN EA4181 (abstract 236) trials. ENRICH followed older MCL patients and examined ibrutinib and rituximab compared to R-chemo (R-CHOP or BR). The trial demonstrated the superiority of ibrutinib and rituximab, with a median PFS that was 23 months higher than the R-chemo arms. Interestingly, R-CHOP was not superior to BR within the R-chemo arms of the study. ECOG-ACRIN EA4181 randomized patients to three cycles of BR followed by three cycles of CR, BR/CR with acalabrutinib, or BR and acalabrutinib. Comparing molecular remission rates at the end of induction, acalabrutinib provided added benefit.

An updated analysis of the TRIANGLE study (abstract 240) revealed that after a median follow-up of 53 months, the 3-year failure-free survival was 75% in patients who received ASCT alone, 85% in patients who received ibrutinib alone and 86% in patients who received ASCT and ibrutinib. While longer follow-up data is needed, this study is likely to prompt debate about whether MCL patients should receive ASCT.

Moving on to follicular lymphoma, Dr. Keating highlighted the MITHIC-FL1 trial (abstract 340), evaluating mosunetuzumab in the frontline setting. The early phase study of 77 patients could be hypothesis-generating for larger studies in the future. Dr. Keating also summarized the EPCORE NHL-2 study (abstract 342), a phase 1b/2 study of epcoritamab plus R2. In 111 R/R follicular lymphoma patients, the combination led to an ORR of 96%, a complete response rate of 87% at 24 months and PFS of 70% at 24 months, representing improvement from R2 alone. Not surprisingly, high rates of neutropenia (62%) were observed.

In Hodgkin lymphoma, Dr. Keating discussed abstract 457, an update on the RAPID Trial assessing ABVD followed by PET-directed radiation therapy. With 16 years of follow-up, there were no differences in OS between those who had negative PET scans after ABVD and were randomized to radiation therapy or no further therapy.

Dr. Keating then discussed updates from the phase 3 POLARIX trial (abstracts 469–474) evaluating Pola-R-CHP versus R-CHOP in previously untreated DLBCL patients. The 5-year PFS in the Pola-R-CHP arm was 64.2% versus 59.1% in the R-CHOP arm; 5-year OS was 82.2% in the Pola-R-CHP arm compared to 79.6% in the R-CHOP arm. Dr. Keating noted the trial may lead the DLCBL-treating community to advocate for funding for the new regimen.

Dr. Keating also recommended the late-breaking abstract on the inMIND trial, a phase 3 trial evaluating tafasitamab and R2 versus R2 in R/R follicular lymphoma. The median PFS was 22.4 months in the tafasitamab arm, compared to 13.9 months in the placebo arm. These results suggest a potential new standard of care for patients with R/R follicular lymphoma, although Dr. Keating noted that funding for R2 is currently very limited across Canada.

Another late-breaking abstract, an update of ECOG-ACRIN EA4151, shows there is no OS benefit of ASCT in MCL patients with undetectable MRD after their initial treatment.

TRIANGLE trial results

A+I Arm
- 3-year FFS: 86%
- Overall survival: 90%
- Superior FFS vs A arm

I Arm
- 3-year FFS: 85%
- Overall survival: 91%
- No FFS superiority vs A+I

A Arm
- 3-year FFS: 75%
- Overall survival: 85%
- Inferior FFS vs other arms

Median follow-up: 53 months
Key finding: Both A+I and I arms demonstrated prolonged overall survival compared to A arm.
Ibrutinib + RCHOP/RDHAP induction and maintenance is a new standard of care… **is this the end of the ASCT era?**


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Leukemia at ASH 2024: What You Need to Know

MICHELLE GEDDES, MD
TOM BAKER CANCER CENTER

Dr. Geddes summarized studies presented at ASH that may change AML management in the Canadian treatment landscape. She noted that, in recent years, AML treatment has shifted toward treatment decision-making based on molecular mutations. She highlighted abstract 219, a phase 1b/2 study that evaluated ivosidenib, plus azacitidine and venetoclax in patients with *IDH1*-mutated AML, MDS, or MPN. About 70% of those enrolled were newly diagnosed, and 30% were R/R. At a median follow-up of 36 months, patients had undergone a median number of four cycles (with a range of 1 to 75) and 16 patients (29%) were still on the investigational combination treatment. The most common reasons for stopping treatment were ASCT (22 patients, 55%) and relapse (10 patients, 25%). Dr. Geddes highlighted that the low relapse rate at 3 years was impressive for upfront AML therapy. The ORR was 94%, 77% of patients were MRD-negative by flow cytometry, and the median EFS was 50.4 months.

Another important ASH update comes from the AUGMENT-101 phase 2 study of revumenib in patients with R/R *KMT2AR*-mutated AML (abstract 211). Dr. Geddes explained that *KMT2A* gene rearrangements, which occur in no more than 10% of patients with AML, are associated with a poor prognosis. In the study, 97 heavily pretreated patients were treated with revumenib, an oral selective menin inhibitor, combined with an azole. The ORR was 64% and 22 patients (23%) achieved a complete response. The median response duration was 6.4 months and a third of patients went on to ASCT. For context, Dr. Geddes noted that patients with *KMT2A*-mutated AML who have had two or more prior treatments have a median prognosis at time of relapse of 2.4 months with currently available treatments.

Dr. Geddes also drew attention to the phase 1b study of bleximenib in combination with intensive chemotherapy in newly diagnosed AML with *KMT2A* rearrangements or *NPM1* alterations (abstract 215). The ORR was 83% in patients with KMT2A rearrangements and 100% in patients with *NPM1* alterations. TRAEs attributed to bleximenib alone occurred in 18% of patients, with thrombocytopenia and neutropenia the most common bleximenib-related AE.

A key question is how MRD results should guide subsequent treatments. A retrospective review (abstract 58) followed 72 patients with *NPM1*-mutated AML (94% of patients) or core-binding factor AML (6% of patients) who had achieved a complete response following induction chemotherapy, and then had molecular relapse on regular MRD monitoring. The patients received at least one cycle of azacitidine and venetoclax. By cycle two, 49% were peripheral blood MRD negative and 33% had low-level MRD. Approximately 73% of the patients proceeded to alloSCT after a median of two cycles. Those who did not go on to transplant received a median of seven cycles of azacitidine and venetoclax. At a median follow-up of 20 months after molecular relapse, the median OS was not reached and 84% of patients remained in molecular remission. In Dr. Geddes's view, the study demonstrates that it is reasonable to offer azacitidine and venetoclax after a molecular relapse to bridge patients to curative therapy.

In closing, Dr. Geddes highlighted one ALL study, the highest rated abstract at the ASH meeting (abstract 1). The practice-changing trial shows blinatumomab added to chemotherapy improves disease-free survival in B-ALL. In the study, patients with a median age of 4.3 years were randomized to chemotherapy alone or blinatumomab and chemotherapy. At a median follow-up of 2.5 years, in the NCI SR-average group, the 3-year DFS for the blinatumomab and chemotherapy arm was 97.5% versus 90.2% for the chemotherapy alone arm. In the NCI SR-high group, the 3-year DFS was 94.1% for chemotherapy plus blinatumomab arm versus 84.8% for the chemotherapy alone arm; toxicities were low. Dr. Geddes suggested that, based on this study, blinatumomab will become part of the standard of care for intermediate-and high-risk pediatric ALL patients, and likely adult patients as well.


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What's New in Multiple Myeloma at ASH 2024

ALISSA VISRAM, MD
THE OTTAWA HOSPITAL

Outlining the Canadian treatment algorithm for newly diagnosed multiple myeloma, Dr. Visram explained that fit, transplant-ineligible patients are currently offered DRD, while RD is recommended for frail patients. For those who are transplant-eligible, the standard of care is now VRD, followed by ASCT, followed by lenalidomide until progression. Recent updates are likely to change this algorithm, however.

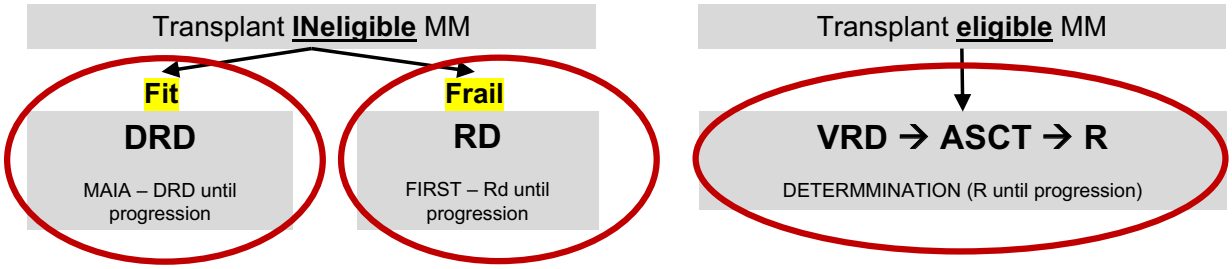
Starting with frail patients, an update from the UK Fitness trial (Abstract 673) followed patients who were randomized to receive lower doses of IxaRD, based on frailty scores, or standard-dose IxaRD. Despite the attempt to improve tolerability, frailty-adjusted dosing did not lead to improved discontinuation rates. Interestingly, however, the 1-year OS was better in the frailty-adjusted arm, due to fewer deaths from infections. Dr. Visram said the study is reassuring that "starting low and going slow" is a good approach for frail multiple myeloma patients.

Abstract 774 describes the utility of a dexamethasone-sparing regimen in frail patients. In the study, patients were randomized to lenalidomide and dexamethasone or lenalidomide and daratumumab. At 40 months of follow-up, the median PFS was significantly longer in the daratumumab arm, compared to the dexamethasone arm. Grade 3 infections were comparable between the two groups. This trial suggests that, if patients have a good response, discontinuing dexamethasone is not likely to compromise treatment effectiveness.

Describing 2024, as the "year of the quad," Dr. Visram identified key trials that show the benefit of quadruplet therapy in both transplant-eligible and ineligible patients. She began by presenting the IMROZ and CEPHEUS trials, which showed improved outcomes with quadruplet therapy (IVRD and DVRD) in transplant-ineligible patients, compared to triplet therapy in the MAIA trial. Importantly, patients in the quadruplet trials were generally much fitter, compared to the MAIA trial.

Assessing the question of whether anti-BCMA-based quadruplets can improve outcomes in newly diagnosed, transplant-ineligible multiple myeloma patients, Dr. Visram pointed to a phase 1 trial assessing belantamab mafodotin and VRD (abstract 497). This combination will be important to watch as the research advances.

Recent updates that may challenge this algorithm...



QUADRUPLETS
- **DVRD** (CEPHEUS)
- **IsaVRD** (IMROZ)
- **BelaVRD** (DREAMM-9)

De-escalation studies
(MY13, iFIT UK)

- **Frailty adapted therapy**
(UK FITNESS; HOVON 143)
- **Dex sparing regimen**
(IFM 2017-03)

QUADRUPLETS
- **DVRD → ASCT → DR** (PERSEUS)
- **IsaVRD → ASCT → IR/R** (GMMG HD7)

Optimizing Maintenance
- **Dara/R or R** (GMMG-HD7; AURIGA)
- **Teclistamab/Len vs Len** (MajesTEC-4)

Regarding quadruplet therapy in the transplant-eligible setting, Dr. Visram highlighted the GMMG-HD7 trial (abstract 769) evaluating IVRD induction therapy versus VRD. The 3-year PFS rate was 83% for IVRD versus 75% for VRD.

On the question of how to optimize maintenance therapy, abstract 675 reports on the AURIGA study, which randomized post-transplant, MRD-positive patients to doublet maintenance (lenalidomide and daratumumab) versus lenalidomide alone. The results showed that doublet maintenance improved MRD conversion, compared to lenalidomide (50.5% versus 1.8%). PFS was also improved. The effect was higher in high-risk patients, suggesting that doublet maintenance therapy should be prioritized for these patients.

Looking at BiTEs, two abstracts presented at ASH shed light on the outcomes of teclistamab, one in fit versus frail patients (abstract 704) and one in younger versus older patients (abstract 934). Surprisingly, the safety and effectiveness of teclistamab was comparable across fit and frail patients, as well as younger and older cohorts.

Noting that the rates of severe infections, including opportunistic infections, are high with BiTEs, Dr. Visram highlighted a study evaluating the real-world impact of IVIG prophylaxis in patients receiving teclistamab (abstract 256). Grade ≥3 infections were significantly lower in patients who received primary IVIG prophylaxis compared to secondary IVIG prophylaxis (9.8% versus 38%).

On the topic of AL amyloidosis, Dr. Visram recommended the 5-year follow-up of the ANDROMEDA trial (abstract 891), which showed that overall heme complete response rates were higher with DVCD, compared to VCD (59.5% versus 19.2%). The 7-year OS rate was 76% with DVCD compared to 65% with VCD, and cardiac and renal response rates were two times higher with DVCD, versus VCD. The results showed the median time to heme complete response was 67.5 days with DVCD, which will be helpful information when counselling patients.

Q&A

Would you recommend lenalidomide and daratumumab as a dexamethasone-sparing regimen for frail patients, based on the study summarized in abstract 774?

Patient preference and logistical challenges are key factors in this decision. Lenalidomide and low-dose dexamethasone is an oral regimen. However, lenalidomide and daratumumab is more effective. If patients are willing to come into the clinic for the therapy, I would recommend the latter.

Chronic Lymphocytic Leukemia: Important Updates at ASH 2024

CHRISTOPHER HILLIS, MD
JURAVINSKI CANCER CENTRE

Dr. Hillis began with the good news that, in the targeted therapy era, CLL patients' life expectancy is nearing that of age-matched controls. However, the unmet need remains high for young patients with CLL. In double-refractory patients, the median OS is 2.2 years. Abstract 1870 reveals that outcomes of non-covalent BTKis are not satisfactory in this double-refractory population, with a median duration of response of 10.5 months.

Dr. Hillis pointed to two ASH abstracts attempting to inform a new prognostic scoring system in the targeted treatment era. Abstract 587 demonstrates that low (<10%) variant allele frequency of the *TP53* mutation is not a poor prognostic marker in CLL patients treated with targeted therapy. However, abstract 583 shows that complex karyotype, but not an isolated *TP53* mutation, is associated with inferior OS in CLL patients in the targeted therapy era. Importantly, this study also found that the leading cause of death in the study cohort was infection, followed by secondary primary malignancies.

Treaters are currently struggling with the question of whether to use continuous BTKi or a venetoclax-based combination. While abstract 4625 demonstrates that patients who received venetoclax and obinutuzumab had a higher 18-month PFS rate, compared to the cBTKi cohort (92.2% versus 84.3%), abstract 1864 demonstrates no significant OS difference between BTKi and BCL2i therapy. Dr. Hillis also highlighted a meta-analysis on the prevalence of *BTK* and *PLCG2* mutations in BTKi-treated CLL patients who experience disease progression (abstract 4630). This study found similar rates of *BTK* and *PLCG2* mutations across all three BTKi options.

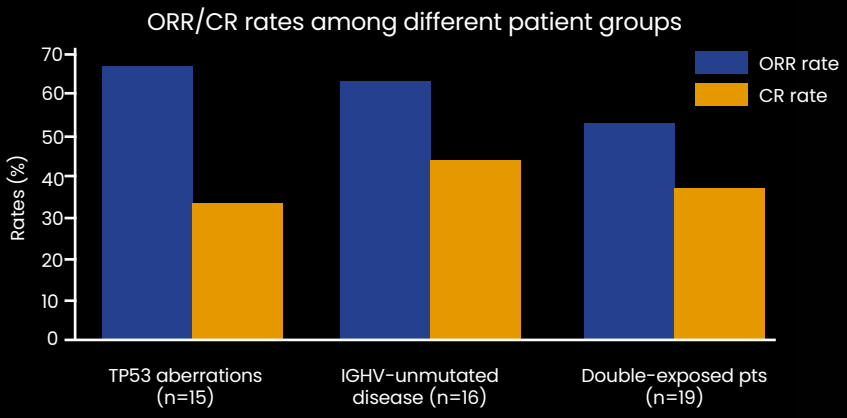
Highlighting new treatment strategies in CLL, Dr. Hillis pointed to the AMPLIFY trial (abstract 1009), which randomized patients without del(17p)/TP53 mutations to either AV, AVO, or chemoimmunotherapy. Dr. Hillis noted the trial was designed at a time when chemoimmunotherapy in the frontline was a reasonable treatment choice. The 36-month PFS was 76.5% for the AV regimen, 83.1% for the AVO arm, and 66.5% for the chemoimmunotherapy arm. However, Dr. Hillis noted that 38.4% of patients in the AVO arm had a serious AE, compared to 24.7% of patients in the AV arm.

Dr. Hillis also pointed to the phase 1/1b study (abstract 1012) of sonrotoclax and zanubrutinib in first-line CLL therapy. Despite high rate of contusion (38%), the ORR was 100%, suggesting this combination is worth watching in further studies.

On the topic of T-cell mediated treatment, Dr. Hillis pointed to a study of epcoritamab monotherapy in R/R CLL (abstract 883). In 40 patients, who had received at least two previous treatments, the ORR was 61%. Nonhematologic TEAEs were CRS (96%), diarrhea (48%), peripheral edema (48%).

Lastly, Dr. Hillis recommended a study showing

883 Epcoritamab monotherapy in R/R CLL: Results from CLL expansion and optimization cohorts of EPCORE CLL-1



- 40 pts enrolled in two cohorts
- Received at least 2 previous treatments
- Nonhematologic tx-emergent AEs were CRS (96%), diarrhea (48%), peripheral edema (48%)

that 90 days of ibrutinib in combination with CAR T-cell therapy improved complete response rates to 45% (versus 18% without ibrutinib). This underlines the importance of addressing immune system function before therapies that rely on functional T cells.

Closing Remarks & Adjournment

DIEGO VILLA, MD
ERIC TSENG, MD

Dr. Tseng concluded by recognizing that many new treatments are becoming available in lymphoma and leukemia, noting it is an incredible time to be a hematologist in Canada. Dr. Villa thanked everyone for their passionate and informative presentations. He also thanked the sponsors for making the event possible.

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