Optimizing Transfusion Support In MDS Patients

Rena Buckstein MD FRCPC
Associate Professor, Dept of Medicine, University of Toronto
Chair, Hematology Site Group, Odette Cancer Center
Director of MDS-CAN
Toronto, Ontario
Disclosures

• Research funding and honoraria Celgene
• Research funding Takeda
• Research funding Otsuka
Agenda

• Burden, prognosis and risks of anemia and RBC Transfusion dependence
• How patients are currently transfused
• ‘Restrictive’ vs. ‘Liberal Transfusions’
• Bleeding and Platelet Transfusions in MDS

Recently Diagnosed: n=670

**EL-Net Lower Risk:**
29% TD at Diagnosis-18 months

Sekeres M et al. JNCI 2008
Probability of non-Leukemic Death Increases with Anemia in Men (A) and Women (B)

Probability of Developing Cardiac Disease and Death Increases with Anemia and TD (> 1 units/8 weeks x 16 weeks)

HR 3.85, P < .0001

(HR 2.88, P<0.001)

Malcovati L et al. Haematologica 2011
Dynamic assessment of RBC-transfusion dependency improves the prognostic value of the IPSS-R in MDS patients.

Transfusion dependence upstages lower risk disease.
EL-NET: RBC transfusion dose density influences PFS in lower risk MDS: landmark year 1, 516/1267 transfused

Low: < 0.87 u/m
High: ≥ 0.87 u/m

Low: >0-0.75 u/m
Mid: 0.75-1.75 u/m
High: > 1.75 u/m

IWG 2006: TI
IWG 2018: LTB
IWG 2018: HTB
EL-NET: 1683 patients
QOL by Transfusion Dependence

MVT Analysis:
- TD
- Age > 75
- Female sex
- MDS CI
- Hgb < 10 g/L

Stauder, R. Leukemia 2018
Risks of Red Blood Cell Transfusions

• Cost/convenience
• Iron overload
• TACO and TRALI
• Infections
• Alloimmunization (15-20%)
South Australia: n=817
11% alloimmunized
70% after 20 units
50% by 6 months

65% vs 18% auto antibodies

Lower rates of allo immunization:
Disease modifying therapy (HDC/ALLO>HMA)
Higher risk disease

Singhal D et al. Haematologica 2017
Prophylactic RH/Kell matching decreased allo-immunization by 68% (19 to 6%) and 100% for RH/Kell (0 vs 18%)

Lin, Y. et al Vox Sang, 2017,112:79-86
# Impact of red blood cell transfusion strategies in haematological patients: a systematic review and meta-analysis: Favors Restrictive

<table>
<thead>
<tr>
<th>Mortality</th>
<th>RBC Use</th>
<th>Plt use</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study</strong></td>
<td><strong>Year</strong></td>
<td><strong>n</strong></td>
</tr>
<tr>
<td>Observational study</td>
<td>2004</td>
<td>84</td>
</tr>
<tr>
<td>Jansen</td>
<td>2004</td>
<td>84</td>
</tr>
<tr>
<td>Berger</td>
<td>2012</td>
<td>372</td>
</tr>
<tr>
<td>Lightdale</td>
<td>2012</td>
<td>141</td>
</tr>
<tr>
<td>Hoek</td>
<td>2013</td>
<td>158</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>RCT</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Delma</td>
<td>2016</td>
<td>89</td>
</tr>
<tr>
<td>Subtotal (I² = 0%, P = 0.995)</td>
<td>-0.75 (-1.06, 0.30)</td>
<td>12.14</td>
</tr>
<tr>
<td>Overall (I² = 0%, P = 0.995)</td>
<td>-0.75 (-1.06, 0.30)</td>
<td>12.14</td>
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</tbody>
</table>

### Notes

- **Mortality:** Weights are from random effects analysis.
- **RBC Use:** Weights are from random effects analysis.
- **Plt use:** Weights are from random effects analysis.

**Mainly cohort studies**

**Mainly in patients receiving chemotherapy/ASCT**

**Hoeks M et al. British Journal of Haematology 2017**
PROS and CONS of Liberal Transfusions

**Pros:**
- Improved QOL: Fatigue and Physical function
- Decreased Dyspnea
- Less Cardiac Morbidity/mortality?

**Cons:**
- Iron Overload
- Frequent Visits, $$
- TACO, TRALI, ATR
- More Infections
Audit of RBC Transfusions: US, Canada, UK

• Questions?
  • How are MDS patients being transfused?
  • How can we best meet our patients needs?

• Dissemination:
  ❑ MDS Foundation, AAMAC
  ❑ Leukemia Lymphoma Society Canada,
  ❑ MDS-CAN registry,
  ❑ University of York and the UK MDS patient forum

• 712 respondents (475 TD); 75% US

Starkman, Buckstein et al. *Blood* 132(Suppl_1):3092-3092
Audit results (n=475)

• Risk: Lower 45%, Higher 27%, not known: 27%
• Became TD at or within 6 months of diagnosis: 51%
• Visited transfusion clinic/4 weeks: 1-2 x: 63%
• # units/4 weeks: median 2
• Felt better after 1-2 days: 53%
  • Never felt better: 7%
• Felt worse for 1-2 days: 20%
• Time to organize transfusion: 65% 1-2 days, same day 24%
  • Of 75% non same day, 30% wished for same day X match

Starkman, Buckstein et al. Blood 132(Suppl_1):3092-3092
Audit results: Median Hgb Threshold 80 g/L

Starkman, Buckstein et al. Blood 132(Suppl_1):3092-3092
Q55: I would prefer to get my blood transfused at a higher threshold than my physician currently uses.

- Answered: 351    Skipped: 360

40% What Threshold?
66% chose Hgb < 85 or higher
24% chose Hgb of < 95-100

Starkman, Buckstein et al. *Blood* 132(Suppl_1):3092-3092
Q52: The ability to check blood counts with a machine at home to determine when another transfusion is needed before experiencing symptoms due to low blood levels would improve my quality of life.
Do transfusions improve QOL (FACT-AN)?

Fig. 1. The total FACT-An score for 15 patients before and after blood transfusion (day 0–7). Scores at day 3 (median 59) and day 7 (median 58) were compared with scores at day 0 (median 50). Data are presented as medians with 25th and 75th percentile ranges in the boxes. The whiskers represent the 10th and 90th percentiles and dots are outliers.

Fig. 2. The association between increments in the FACT-An score and the Hb value (day 0 to 3) as analyzed by Spearman’s rank-order correlation ($n = 14$). The correlation coefficient was large ($r_s 0.66, p 0.02$).
Therapeutic impact of red blood cell transfusion on anemic outpatients: the REDDS-III RETRO study

85% Hematologic cancers, n=208
Pre Tx Hgb 77 g/L (74-79 IQR)
1 week post transfusion:87 g/L (81-94)

70% had clinical improvement in either fatigue, walk distance or both
6 minute walk test improved median of 20 m (significant)
Fatigue (FACIT-F) improved 3 points (significant)
Dyspnea did not improve

Most predictive of benefit:
Not being on chemotherapy
Worst levels of fatigue and dyspnea
Receiving 2 units instead of 1
Post transfusion Hgb of > 80 g/L (6 minute walk)

Lezin E. et al. Transfusion 2019
Does it take more blood to remain at higher baseline?

- N=36 (19 TI and 17 TD)
- All treated with DARB 300 ug/week +/- GCSF until 16 weeks to target hgb 120 g/L
  - Not at target: transfused
- 56% responded (75% TI and 50% TD)
- 13 were transfused to target hgb at week 16 and maintained for 8 weeks at this level
- Transfusion rate in previously transfused did not exceed pre-study

Red blood cell transfusion thresholds and QoL in myelo
dysplastic syndromes: a pilot, feasibility study (REDDS-1)

**Inclusion:**
- MDS > 18 yrs
- < 20% marrow blasts
- TD (1 u/8 weeks)
- LE > 6 months

**Exclusion:**
- ESAs
- Disease modifying agents
- Active bleeding or hemolysis

**Test:** liberal strategy

- Feasibility
- HrQoL
- Outcomes

**Standard:** restrictive strategy

Stanworth S et al. BJH 2019
Outcomes

Primary
To evaluate protocol adherence when implementing a restrictive and a liberal red cell transfusion strategy

- % of pre-transfusion Hb concentrations being below the target range of the assigned red cell transfusion strategy

- Achievement of at least a 20g/L difference between the mean pre-transfusion Hb in the liberal and restrictive strategy groups

Secondary

- Number of patients ineligible due to screening failure or workload of department
- Enrolment rates
- % compliance with completing QoL
- Ability of patients to remain blinded to the treatment arm
- Proportion of transfusions and patients with all transfusions given correctly, according to the algorithm
- Magnitude of change in physical functioning, fatigue, dyspnoea and global health scores on the EORTC QLQ-C30 and in descriptive part EQ-5D-5L
- Numbers of adverse events (cardiac and thromboembolic events) and transfusion reactions
- Overall utilisation of blood during study period
**Study transfusion algorithm**

Consent & Enrol

*6 week run-in period*

Hb level target $\geq 100$ g/L

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Randomise: Hb $\geq 100$g/L achieved?

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Yes: **Randomise**, then

Continue allocated RBC transfusion policy until end of week 12

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Restrictive arm: Target Hb 85-100g/L

Next clinic, measure pre-transfusion Hb:

- Hb $< 70$g/L, transfuse 2○, return 1/52,
- Hb 70-79g/L, transfuse 2○, return 2/52
- Hb 80 – 85g/L, transfuse 1○, return 2/52
- Hb $> 85$ no transfusion, return 2/52

---

Liberal arm: Target Hb 110-125g/L

Next clinic, measure pre-transfusion Hb:

- Hb $< 95$ g/L, transfuse 2○, return 1/52,
- Hb 95 - 104g/L, transfuse 2○, return 2/52
- Hb 105-110 g/L, transfuse 1○, return 2/52
- Hb $> 110$ g/l no transfusion, return 2/52

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No

Patient not randomised

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Stanworth S et al. BJH 2019
As compliance is $\geq 70\%$ in both arms, the study was declared feasible.

4 patients in restrictive arm did not get transfused.

### Primary Outcome Results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Restrictive (n=20)</th>
<th>Liberal (n=18)</th>
<th>Overall (n=38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of participants with at least 1 transfusion</td>
<td>16</td>
<td>18</td>
<td>34</td>
</tr>
<tr>
<td>Proportion of pre-transfusion haemoglobin concentrations being below the target range of the assigned red cell transfusion strategy % (exact 95% CI)</td>
<td>86 (75-94)</td>
<td>99 (95-100)</td>
<td>94 (90-97)</td>
</tr>
</tbody>
</table>
## Primary Outcome Results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Restrictive (n=20)</th>
<th>Liberal (n=18)</th>
<th>Overall (n=38)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-transfusion haemoglobin concentration (g/L)(^1) Mean (standard deviation)</td>
<td>80 (6)</td>
<td>97 (7)</td>
<td>91 (10)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Difference in mean pre-transfusion haemoglobin concentrations (liberal – restrictive) (g/L) Difference (95% CI)</td>
<td>16.7 (14.6-18.8)</td>
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</table>

\(^1\) t-test for equality of means
### Some Secondary Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Restrictive (n=20)</th>
<th>Liberal (n=18)</th>
<th>Overall (n=38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of RBC transfusions after randomisation</td>
<td>58</td>
<td>105</td>
<td>163</td>
</tr>
<tr>
<td>Total number of occasions RBC transfusion indicated by algorithm</td>
<td>38</td>
<td>94</td>
<td>132</td>
</tr>
<tr>
<td>Number of RBC units transfused</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per participant Median (IQR)</td>
<td>6 (4-7)</td>
<td>11 (8-14)</td>
<td>8 (5-11)</td>
</tr>
<tr>
<td>Per participant per 4 weeks Median (IQR)</td>
<td>3 (2-3)</td>
<td>4 (3-5)</td>
<td>3 (3-4)</td>
</tr>
<tr>
<td>Number of days between transfusions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>14 (11-21)</td>
<td>14 (7-14)</td>
<td>14 (7-15)</td>
</tr>
</tbody>
</table>
Amplitude of variation in haemoglobin concentration (post-hoc)

<table>
<thead>
<tr>
<th></th>
<th>Restrictive (n=20)</th>
<th>Liberal (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (IQR) adjusted sum of squares per participant</td>
<td>72 (47-116)</td>
<td>34 (32-58)</td>
</tr>
</tbody>
</table>
Patient reported outcome parameters (post-hoc): standardised area under the curve - median and IQR

- 72-75% successfully blinded
- 50% Liberal vs 30% restrictive reported improved fatigue

<table>
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<th>Restrictive (n=20)</th>
<th>Liberal (n=18)</th>
<th>Overall (n=38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EQ-5D-5L: Descriptive part</td>
<td>0.76 (0.51-0.81)</td>
<td>0.83 (0.69-0.86)</td>
<td>0.78 (0.68-0.86)</td>
</tr>
<tr>
<td>(Higher=better)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EORTC: Physical functioning</td>
<td>61 (50-86)</td>
<td>69 (48-94)</td>
<td>68 (50-86)</td>
</tr>
<tr>
<td>(Higher=better)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EORTC: Global health scores</td>
<td>63 (60-75)</td>
<td>70 (53-87)</td>
<td>68 (56-76)</td>
</tr>
<tr>
<td>(Higher=better)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EORTC: Fatigue</td>
<td>38 (33-54)</td>
<td>34 (14-66)</td>
<td>37 (21-63)</td>
</tr>
<tr>
<td>(Lower=better)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EORTC: Dyspnoea</td>
<td>42 (31-64)</td>
<td>25 (1-77)</td>
<td>40 (12-67)</td>
</tr>
<tr>
<td>(Lower=better)</td>
<td></td>
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</tr>
</tbody>
</table>
Thrombocytopenia in MDS

- < 100 x 10⁹/L: 40-65%
- < 20 x 10⁹/L: 17% (increased bleeding and IPSS-R scores)
- Bleeding COD: 13-24% of patients
  - MDS CAN: 30/581: 5%
- Correlation between actual plt counts and bleeding non-linear (n=2924, 10 y)
  - 12% patient days grade 2 bleeds
  - 1.3% patient days grade 3+ bleeds

From where does the practice of prophylactic plt transfusions originate? Inpatients!

<table>
<thead>
<tr>
<th>Source</th>
<th>n</th>
<th>Age</th>
<th>Scenario</th>
<th>Intervention</th>
<th>Results</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wandt H Lancet 2012 Open label RCT Germany</td>
<td>397</td>
<td>16-80</td>
<td>AML and ASCT</td>
<td>Therapeutic Versus Prophylactic (Plt &lt; 10 x 10^9/L)</td>
<td>WHO bleeding 2+: 42 vs 19%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>WHO bleeding 4+: 5 vs 1%</td>
<td>.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Effect only in AML not ASCT</td>
<td></td>
</tr>
<tr>
<td>Stanworth S NEJM 2013 Open label non inferiority RCT UK and Australia TOPPS</td>
<td>600</td>
<td>16+</td>
<td>AML and ASCT</td>
<td>Therapeutic Versus Prophylactic (Plt &lt; 10 x 10^9/L)</td>
<td>WHO bleeding 2+: 50 vs 43%</td>
<td>.06 for non-inferiority</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>WHO bleeding 3 or 4 2 vs 1%</td>
<td>0.13</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>WHO bleeding 2+ ASCT 45 vs 47%</td>
<td>NS</td>
</tr>
</tbody>
</table>
Risks and disadvantages of platelet transfusions

• Allo-immunization and refractoriness: 5-11%
• Bacterial contamination 1/1000-3000
• Febrile reactions and urticaria
• Cost
• Time/inconvenience
• Lack of donors!
Retrospective cohort study of thrombocytopenia management and outcomes...

- Retrospective audit Sunnybrook MDS patients enrolled in MDS-CAN
- Persistent severe thrombocytopenia (PST)
  - Plt count < 20 x 10⁹/L for minimum of 50% lab tests over 8 weeks
- Prophylactic platelets (PROPH) if given within a recurrent interval of 2 weeks
- Therapeutic platelets (THERA) given less frequently
- WHO bleeding scale highest grade assigned once per visit/hospitalization
- Patients assigned to one of 4 groups based on maximal treatment strategy to prevent bleeding

Vijenthura A et al. Leuk Res 2019
<table>
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</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>71</td>
<td>72</td>
<td>74</td>
<td>72</td>
<td>.97</td>
</tr>
<tr>
<td>OS (95% CI)</td>
<td>1.2 (0.7-2.4)</td>
<td>0.7 (0.5-1.2)</td>
<td>0.6 (0.3-1.3)</td>
<td>2.5 (0.9-7.4)</td>
<td>.04</td>
</tr>
<tr>
<td>IPSSR-H/VH</td>
<td>44%</td>
<td>68%</td>
<td>77%</td>
<td>50%</td>
<td>0.13</td>
</tr>
<tr>
<td>Time from dx to DST (y)</td>
<td>1.2</td>
<td>0.5</td>
<td>1.2</td>
<td>1.0</td>
<td>0.8</td>
</tr>
<tr>
<td>Median plt</td>
<td>13</td>
<td>10</td>
<td>13</td>
<td>13</td>
<td>0.3</td>
</tr>
<tr>
<td>% plt &lt; 10 x 10^9/L</td>
<td>36%</td>
<td>50%</td>
<td>36%</td>
<td>23%</td>
<td>0.2</td>
</tr>
<tr>
<td>Time to 1st bleed</td>
<td>10 w</td>
<td>5 w</td>
<td>3 w</td>
<td>5 w</td>
<td>.04</td>
</tr>
<tr>
<td>Therapeutic plts</td>
<td>32%</td>
<td>-</td>
<td>-</td>
<td>23%</td>
<td>.01</td>
</tr>
<tr>
<td>#plt tx/4w (IQR)</td>
<td>0 (0-0.1)</td>
<td>2.2 (1.4-3)</td>
<td>3.1(2.2-5)</td>
<td>0 (0-0.3)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

- Median duration of PST was 27 weeks; median plt 12 (IQR 9-16)
- 71% in groups 1 and 4 received no plt transfusions

Vijenthura A et al. Leuk Res 2019
Bleeding grades according to treatment group

- Trend to more grades 1-2 bleeding in groups 1 and 2

- Of 12 patients with grades 3-4 bleeding, 6/8 in groups 2 and 3 were plt refractory

- 9% overall died of hemorrhage (n=9)
  - Alloimmunized/refractory
  - Plts > 10
  - Prophylactic treatment
Patients with chronic, stable, severe thrombocytopenia, such as individuals with myelodysplasia or aplastic anemia, who are not receiving active treatment may be observed without prophylactic transfusion, reserving platelet transfusions for episodes of hemorrhage or during times of active treatment (Type of recommendation: informal consensus; Evidence quality: intermediate; Strength of recommendation: moderate).

Schiffer A et al. JCO 2018
• A no prophylaxis platelet transfusion strategy should be used for patients with asymptomatic chronic bone marrow failure (including those taking low dose oral chemotherapy or azacitidine) (2B)

• Prophylactic platelet transfusion should be given to patients with chronic bone marrow failure receiving intensive treatment (1B)

• Patients with chronic bleeding of WHO grade 2 or above require individual management according to the severity of their symptoms and signs. A strategy of prophylaxis (e.g. twice a week) should be considered (2C)
Summary

• Anemia is common in MDS and more than 50% become TD
• Anemia and TD are associated with decreased OS, LFS, impaired QOL
• The link between plt count and bleeding in stable outpatients is poorly established
  • Rates of severe or fatal bleeding are low
• We may be *undertransfusing* RBC
• We may be *overtransfusing* Plts
• Randomized trials are feasible and needed
Thank You

MDS-CAN

Our Patients

Crashley Estate

<table>
<thead>
<tr>
<th>Location</th>
<th>PI Name</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancouver</td>
<td>Dr. Thomas Nevill</td>
<td>Vancouver General Hospital</td>
</tr>
<tr>
<td></td>
<td>Dr. Heather Leitch</td>
<td>St. Paul’s Hospital</td>
</tr>
<tr>
<td>Edmonton</td>
<td>Dr. Nancy Zhu</td>
<td>University of Alberta Hospital</td>
</tr>
<tr>
<td>Calgary</td>
<td>Dr. Michelle Geddes</td>
<td>Tom Baker Cancer Centre</td>
</tr>
<tr>
<td>Saskatoon</td>
<td>Dr. Mohammed Elemary</td>
<td>Saskatchewan Cancer Agency</td>
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<tr>
<td>Winnipeg</td>
<td>Dr. Versha Banerji</td>
<td>CancerCare Manitoba</td>
</tr>
<tr>
<td>Montreal</td>
<td>Dr. John M. Storring</td>
<td>McGill University Health Centre</td>
</tr>
<tr>
<td>Ottawa</td>
<td>Dr. Mitchell Sabloff &amp;</td>
<td>The Ottawa Hospital</td>
</tr>
<tr>
<td></td>
<td>Dr. Grace Christou</td>
<td></td>
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<tr>
<td>Quebec City</td>
<td>Dr. Robert Delage</td>
<td>CHU de Québec</td>
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<tr>
<td>Hamilton</td>
<td>Dr. Brian Leber</td>
<td>Juravinski Cancer Centre</td>
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<tr>
<td>Toronto</td>
<td>Dr. Karen Yee</td>
<td>Princess Margaret Hospital</td>
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<td>Dr. Shabbir Alibhai</td>
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<td>Halifax</td>
<td>Dr. Mary-Margaret Keating</td>
<td>QEII Health Sciences Centre</td>
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<tr>
<td>Moncton</td>
<td>Dr. Eve St-Hillaire &amp;</td>
<td>Dr. Georges-L. Dumont Regional Hospital</td>
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<td></td>
<td>Dr. Nicholas Finn</td>
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**Hematology Site Group @ Sunnybrook Health Sciences/OCC**

<table>
<thead>
<tr>
<th>Kevin Imrie MD</th>
<th>Signy Chow MD</th>
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<tbody>
<tr>
<td>David Spaner MD PhD</td>
<td>Lisa Chodirker MD</td>
</tr>
<tr>
<td>Richard Wells MD DPhil</td>
<td>Eugenia Piliotis MD</td>
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<tr>
<td>Matthew Cheung MD</td>
<td>Neil Berinstein MD</td>
</tr>
<tr>
<td>Lee Mozessohn MD</td>
<td>Jeannie Callum MD and Yulia Lin MD</td>
</tr>
</tbody>
</table>