Update on Chemotherapy-Induced Anemia and Neutropenia Therapies
ASCO 2007: Update on Chemotherapy-Induced Anemia and Neutropenia Therapies

Safety and efficacy of intravenous iron in patients with chemotherapy-induced anemia receiving darbepoetin alfa

- Effects of intravenous (IV) iron supplementation on responses to every-three-week (Q3W) darbepoetin alfa (DA) by baseline hemoglobin in patients (pts) with chemotherapy-induced anemia (CIA)\(^1\)
- A phase III randomized controlled study comparing iron sucrose intravenously (IV) to no iron treatment of anemia in cancer patients undergoing chemotherapy and erythropoietin stimulating agent (ESA) therapy\(^2\)

Improvement in quality of life precedes increase in hemoglobin levels upon treatment with intravenous iron and epoetin alfa

Identifying patients at high risk for neutropenic complications during chemotherapy: development of prediction models

- Risk assessment model for first-cycle chemotherapy-induced neutropenia among lung cancer (LC) patients: the DELFOS study\(^3\)
- Identifying patients at high risk for neutropenia complications during chemotherapy for metastatic breast cancer (MBC) with doxorubicin or pegylated liposomal doxorubicin: development of a prediction mode\(^4\)
- Predictors of febrile neutropenia among medicare patients with breast, lung and colorectal cancer\(^5\)

Safety and efficacy of intravenous iron in patients with chemotherapy-induced anemia receiving darbepoetin alfa
Background

- Anemia:
  - common complication of myelosuppressive chemotherapy
  - results in decreased functional capacity and quality of life

- Therapies to ameliorate chemotherapy-induced anemia include
  - ESAs
  - Supplemental iron therapy
  - Blood transfusions

- Two ESAs currently available in Canada, darbepoetin alfa (DA) and epoetin alfa (EA), differ in receptor-binding affinity and serum half-life, allowing for alternative dosing and scheduling strategies

- Cancer patients treated with ESAs experience improved HRQoL

- DA and EA can be administered at extended intervals (once every three weeks for DA and weekly for EA) without loss of efficacy

ESA = erythropoietic-stimulating agent  HRQoL = health-related quality of life
Mounting evidence indicates that chemotherapy-induced patients with anemia given ESA respond better when parenteral iron administered\(^1\)

- Intravenous iron extremely underutilized as an adjunct to ESA therapy
- Three relatively safe intravenous iron preparations, all associated with fewer serious adverse events than the high-molecular-weight dextran, include
  - Low molecular weight iron dextran
  - Ferric gluconate
  - Iron sucrose At ASCO 2007, three studies investigated iron supplementation in combination with ESA administration in patients with cancer and chemotherapy-induced anemia\(^2-4\)

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ESA = erythopoietic-stimulating agent
Effects of intravenous (IV) iron supplementation on responses to every-three-week (Q3W) darbepoetin alfa (DA) by baseline hemoglobin in patients (pts) with chemotherapy-induced anemia (CIA)

Study design

- Phase IIIb, randomized, open-label, multicentre, 16-week trial
- Patients randomly assigned (1:1) to receive either
  - DA 500 mcg Q3W and IV iron (200 mg Q3W or 2 x 100 mg within 3 weeks, as required) or
  - DA 500 mcg Q3W and oral/no iron
- Inclusion criteria:
  - Nonmyeloid malignancy with at least 8 weeks planned cyclic cytotoxic chemotherapy
  - Chemotherapy-induced anemia (baseline Hb <110 g/L in 24 hours prior to randomization)
  - ECOG PS 0–2 and serum ferritin <800 ng/mL
- No RBC transfusions 14 days prior to randomization or
  - planned for period between randomization and day 1
- No ESA therapy in 4 weeks prior to randomization, and
  - No ESAs given in period between randomization and study day 1

ECOG = Eastern Cooperative Oncology Group  ESA = erythropoetin-stimulating agent  DA = darbepoetin alfa  Hb = hemoglobin  IV = intravenous  PS = performance study  Q3W = every 3 weeks  RBC = red blood cell
Study design (continued)

- A total of 396 patients randomized and received at least one dose of DA (IV iron arm: n = 200; oral iron/no iron arm: n = 196)
- Randomization stratified by tumour type (lung/gynecological vs. other tumours) and according to baseline Hb (Hb <100 g/L and ≥100 g/L), last Hb value obtained on or before first day of DA
- Intravenous iron administered as sodium ferric gluconate complex in sucrose or iron sucrose at equivalent dose of 200 mg elemental iron per application
- Iron dextran not used
- DA administered as fixed dose of 500 mcg

DA = darbepoetin alfa
IV = intravenous
Hb = hemoglobin
Study design (continued)

- Patients requiring dose reductions given fixed doses of 300 mcg or 150 mcg
- Dose increases not permitted in study
- DA withheld if Hb >130 g/L
- DA re-initiated with a 40% dose reduction when Hb <120 g/L
- Primary endpoint: hematopoietic response defined as Hb ≥120 g/L or increase of ≥20 g/L by end of treatment phase
- Safety endpoint: incidence of adverse events with at least 10% incidence
- Study treatment period: 13 weeks, with follow-up visit at week 16
- End of treatment phase: 31 days after last dose or end of study visit, whichever earliest

DA = darbepoetin alfa
Hb = hemoglobin
Key findings

- For each treatment arm, median number of days to achieve hematopoietic response was longer for patients with baseline Hb <100 g/L, vs. baseline of Hb ≥100 g/L (Table 1 below)

- For each treatment arm, median number of days to achieve Hb ≥110 g/L was longer for patients with baseline Hb <100 g/L vs. baseline Hb ≥100 g/L
  - IV iron: 45 days versus 22 days, respectively
  - Standard care: 65 days versus 22 days, respectively

| Table 1: Proportion of patients achieving a hematopoietic response by end of treatment phase |
|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|
|                                               | Darbepoetin alfa + IV iron                     | Darbepoetin alfa + oral/no iron               |
| Number of patients achieving a hematopoietic response by EOTP | Hb <100 g/L (n = 93) | Hb ≥100 g/L (n = 107) | Hb <100 g/L (n = 85) | Hb ≥100 g/L (n = 111) |
| Crude percentage (95% CI)*                    | 62 (56, 76)                                   | 69                                           | 52                                           | 72                                           |
| K-M percentage (95% CI)*                      | 67 (56, 76)                                   | 64 (55, 73)                                  | 61 (50, 72)                                  | 65 (55, 74)                                  |
| Time to hematopoietic response (days)         | 56 (43, 65)                                   | 44 (40, 64)                                  | 65 (55, 94)                                  | 51 (43, 71)                                  |

*Unstratified binomial percentage with exact 95% CI; \(^a\) Determined from the unadjusted K-M estimate: 100*(1-S(5)) at the last non-censored timepoint.

K-M = Kaplan-Meier; EOTP = end of treatment phase

Hb = hemoglobin
Key findings (continued)

- Fewer patients receiving iron supplementation required blood transfusions (Figure 1 below)

![Graph showing K-M percentage (95% CI) of patients achieving a RBC or whole blood transfusion from week 5 (day 29 to EOTP)]

- Darbepoetin alfa + IV iron
- Darbepoetin alfa + oral/no iron

K-M = Kaplan-Meier
Baseline Hb <100 g/L
Baseline Hb ≥100 g/L

n = 9
n = 23
n = 7
n = 13

11%
31%
8%
14%

CI = confidence interval   DA = darbepoetin alfa   EOTP = end of treatment phase   Hb = hemoglobin

Key findings (continued)

- Combination of DA and IV iron well tolerated with no unexpected safety concerns
- Adverse events related to treatment with intravenous iron manageable in these patients (Table 2 below)

<table>
<thead>
<tr>
<th>Table 2: Adverse events with at least 10% incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Darbepoetin alfa + IV Iron</td>
</tr>
<tr>
<td>Darbepoetin alfa + oral/no iron</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Hb &lt;100 g/L</strong></td>
</tr>
<tr>
<td>(n = 94) n (%)</td>
</tr>
<tr>
<td>Number of patients reporting AEs</td>
</tr>
<tr>
<td>Nausea</td>
</tr>
<tr>
<td>Dyspnea</td>
</tr>
<tr>
<td>Fatigue</td>
</tr>
<tr>
<td>Vomiting</td>
</tr>
<tr>
<td>Pyrexia</td>
</tr>
<tr>
<td>Asthenia</td>
</tr>
<tr>
<td>Anorexia</td>
</tr>
<tr>
<td>Neutropenia</td>
</tr>
<tr>
<td>Diarrhea</td>
</tr>
</tbody>
</table>

Note: Includes all AEs within 21 days of last study drug (except serious AEs [including deaths] which are reported within 30 days of last study drug)

AEs = adverse events

Hb = hemoglobin  DA = darbepoetin alfa  IV = intravenous

Key conclusions

- Patients given darbepoetin alfa with intravenous iron supplementation appeared to have improved clinical outcomes:
  - More patients achieved hematopoietic response
  - More patients achieved target Hb ($\geq 110$ g/L) in shorter time
  - Fewer patients received transfusions

- In both treatment arms, better clinical outcomes for patients who received on-time treatment (baseline Hb $\geq 100$ g/L) than late treatment (baseline Hb <100 g/L)
A phase III randomized controlled study comparing iron sucrose intravenously (IV) to no iron treatment of anemia in cancer patients undergoing chemotherapy and erythropoietin stimulating agent (ESA) therapy

Study design

- Prospective, randomized, open-label, phase III clinical trial (n = 375)

- Stage I
  - Patients with chemotherapy-induced anemia (Hb levels ≤ 100 g/L) received treatment with ESA alone (100 mcg DA or 40,000 units EA weekly or 200 mcg DA every other week) for 8 weeks

- Stage II
  - Patients classified as ESA responders (≥ 10 g/L increase in Hb) or ESA non-responders randomized to receive either
    - Fixed doses of ESA plus up to 1,500 mg of IV iron sucrose (given in 3 divided doses of up to 500 mg) for 12 weeks or
    - Fixed doses of ESA alone for 12 weeks

- Primary endpoint: change in Hb in responders

- Secondary endpoints: Hb change among non-responders, start and duration of Hb response, adverse events, and change in Hb in all patients


DA = darbepoetin alfa   EA = epoetin alfa   ESA = erythropoietin-stimulating agent   Hb = hemoglobin   IV = intravenous
Key findings

- Baseline iron status did not predict responsiveness to iron sucrose therapy
- Adding iron sucrose to ESA resulted in greater mean maximum Hb levels and greater number of patients who achieved Hb increase >20 and >30 g/L in both prior ESA responders and non-responders (Table 3 below)

### Table 3: Maximum improvement in Hb levels over baseline after IV iron sucrose compared to no iron in ESA-treated patient

<table>
<thead>
<tr>
<th>Maximum Hb change</th>
<th>Iron sucrose plus ESA</th>
<th>ESA only</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group A (R)</td>
<td>Group C (NR)</td>
</tr>
<tr>
<td>Intent-to-treat population</td>
<td>n = 59</td>
<td>n = 40</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>2.6 (1.6)</td>
<td>2.5 (1.9)</td>
</tr>
<tr>
<td>Median</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Minimum – maximum</td>
<td>0 – 7</td>
<td>0 – 7</td>
</tr>
<tr>
<td>p-value (A+C) vs. (B+D)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>p-value (A) vs. (B)</td>
<td>0.004*</td>
<td></td>
</tr>
<tr>
<td>p-value (C) vs. (D)</td>
<td>0.027</td>
<td></td>
</tr>
</tbody>
</table>

| Evaluable population | n = 41 | n = 31 | n = 53 | n = 32 |
| Mean (SD)            | 2.9 (1.7)  | 2.6 (2.0)  | 2.1 (1.4)  | 1.6 (2.0)  |
| Median               | 3          | 2          | 2          | 1          |
| Minimum – maximum    | 0 – 7      | 0 – 7      | 0 – 6      | 0 – 7      |
| p-value (A+C) vs. (B+D) | 0.0021  |          |            |            |
| p-value (A) vs. (B)  | 0.0081*    |          |            |            |
| p-value (C) vs. (D)  | 0.0819     |          |            |            |

**Abbreviations:** SD = standard deviation; R = responders and NR = non-responders based on response to ESA during Stage 1

*All p-values are from the ANCOVA analysis

* *Primary endpoint*
Safety

- There were no grade 4 adverse events
- Serious, but non–life-threatening, iron sucrose–related adverse events (grade 3) observed were:

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>2 (1 serious)</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (1 serious)</td>
</tr>
<tr>
<td>Chest Pain</td>
<td>1 (serious)</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>1 (serious)</td>
</tr>
</tbody>
</table>

Key conclusions

- Intravenous iron sucrose increased Hb levels and iron stores significantly
  - Well tolerated in doses up to 500 mg increments in ESA-treated patients with chemotherapy-related anemia
  - Prior response to ESA therapy did not significantly influence response to IV iron

- Intravenous iron sucrose should be considered in combination with erythropoietic therapy in anemic cancer patients receiving chemotherapy


ESA = erythropoetin-stimulating agent
Hb = hemoglobin
IV = intravenous
Improvement in quality of life precedes increase in hemoglobin levels upon treatment with intravenous iron and epoetin alfa

Quality of life improvement precedes anemia correction in patients with chemotherapy induced anemia treated with intravenous iron.

Background

- Henry et al. evaluated effects of intravenous iron, oral iron, and no iron on patient-reported health-related quality of life in anemic cancer patients receiving chemotherapy and epoetin alfa

Study design

- Open-label, randomized, controlled multicentre prospective trial
- Patients (n = 187) randomly assigned in 1:1:1 ratio to receive either IV iron, oral iron, or no iron supplementation
- Drug regimen was as follows:
  - Ferric gluconate: 125 mg intravenous once weekly for 8 weeks
  - Ferrous sulfate: 325 mg PO TID for 8 weeks
  - EA administration: 40,000 IU SC weekly for weeks 1–4
  - Dosing of EA adjusted according to Hb levels per protocol until end of study

EA = epoetin alfa   Hb = hemoglobin
IU = international units
IV = intravenous   SC = subcutaneously
Study design (continued)

- Primary endpoint: mean change in Hb level from baseline to last value (week 10, first whole blood or RBC transfusion, or study withdrawal, whichever came first)

- Secondary endpoints: comparisons among Hb response (defined as ≥20 g/L change from baseline to last value), change from baseline in other laboratory parameters, and HRQoL

- Quality of life (QoL) assessed at screening, week 5, and week 10 with Functional Assessment of Cancer Therapy (FACT)-Anemia screening tool\(^1\)

- Inclusion criteria:
  - Diagnosis of nonmyeloid malignancy
  - ECOG performance status 0–2
  - Hb levels <110 g/L
  - Serum ferritin levels >100 ng/mL and/or transferrin saturation levels >15%

- Exclusion criteria: recent WBC or RBC transfusions and/or EA or IV iron use within 30 days of start of study

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EA = epoetin alfa; IV = intravenous  ECOG = Eastern Cooperative Oncology Group  ESA = erythropoetin-stimulating agent  Hb = hemoglobin  HRQoL = health-related quality of life  RBC = red blood cell  WBC = white blood cell

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Key findings

- Hemoglobin responses significantly greater by end of study in evaluable patients receiving IV ferric gluconate (FG) vs. oral iron or no iron (Figures 1 and 2 below)

**Figure 1: Hemoglobin change from baseline**

**Figure 2: Patients with change in Hb of ≥20 g/L from baseline**

\[ p = 0.0092, \text{ Oral vs IV ferric gluconate} \]

\[ p = 0.0044, \text{ No iron vs ferric gluconate} \]

\[ p = 0.7695, \text{ Oral vs no iron (ANOVA)} \]

IV = intravenous; Hb = hemoglobin
Key findings (continued)

- Significant improvement in FACT-Fatigue subscale at 4 weeks observed only in FG group
- Hb response still similar between all three groups at this time point
- Intravenous iron demonstrated positive changes in Hb, CHr, and serum ferritin
- Transferrin saturation levels in this group dropped by end of study
- Percentage of hypochromic red cells increased in the IV iron group, although less than in oral iron and ESA-alone groups (Table 1 below)

<table>
<thead>
<tr>
<th>Table 1: Changes from baseline to end of study in iron indices</th>
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<tbody>
<tr>
<td></td>
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<tr>
<td>Transferrin Saturation (%)</td>
</tr>
<tr>
<td>Reticulocyte Hemoglobin Content (pg)</td>
</tr>
<tr>
<td>Hypochromic Red Blood Cells (%)</td>
</tr>
<tr>
<td>Serum Ferritin (mcg/L)</td>
</tr>
</tbody>
</table>

CHr = reticulocyte hemoglobin content  
ESA = erythropoetin-stimulating agent  
FACT = Functional Assessment of Cancer Therapy  
FG = ferric gluconate  
Hb = hemoglobin  
IV = intravenous
Key findings (continued)

- No differences in any Hb efficacy outcome parameters between oral iron and no iron groups, despite oral iron compliance of 93.3%

- Incidence of SAEs
  - In the IV FG group 15 (23.8%)
  - In the oral iron group 18 (29.5%)
  - In the no iron group 16 (25.4%)

- Drug-related SAEs
  - In the IV FG 8 (12.7%)
  - In the oral iron groups 19 (31.1%)

- Overall incidence and severity of AEs similar in all three groups

- Most common AEs in ≥20% patients were asthenia, nausea, constipation, pain, vomiting, diarrhea, and leucopenia


AE = adverse event; FG = ferric gluconate
Hb = hemoglobin; IV = intravenous; SAE = serious adverse event
Key conclusions

- Combining intravenous iron with ESA therapy led to early and clinically significant (≥3) improvement in fatigue score, which preceded the improvement in hemoglobin response.

- Hemoglobin increased in response to epoetin alfa therapy in all three groups.
  - Responses significantly greater in patients given intravenous ferric gluconate vs. oral iron or no iron.

- Intravenous ferric gluconate well tolerated; drug-related adverse events more common in oral iron group vs. intravenous iron group.
Key conclusions (continued)

- Treatment with intravenous iron should be considered in patients with chemotherapy-induced anemia to
  - Maximize response to, and efficiency of, ESA treatment and
  - Improve quality of life
- Result consistent with studies in different populations, including chronic kidney disease and non-anemic iron-deficient women. Independent of changes in hemoglobin levels,\(^1\)\(^-\)\(^3\) improvements resulted in
  - Quality of life
  - Fatigue, and
  - Cognitive function scores in patients receiving iron therapy


**ESA** = erythropoetin-stimulating agent
Canadian perspective by Dr. Jose Chang

- Canadian practice guidelines for treating chemotherapy-induced anemic patients recommend use of iron
- Form of iron preparation has changed, as more efficacy data become available; data suggest intravenous iron is preferred form
- IV iron results in increased Hgb levels, improvement in quality of life, and decreased transfusion rates
- Study by Henry, et al.\(^1\) was well conducted and demonstrated statistically significant results in favour IV iron
- Pintér, et al.\(^2\) and Bellet, et al.\(^3\) provided further evidence that IV iron improves efficiency of erythropoietin-stimulating agents (ESAs) in treatment of chemotherapy-induced anemia
- Data by Pintér, et al. also indicate that patients achieve higher quality of life with use of intravenous iron in combination with darbepoetin alfa
- Results in line with Canadian practice guidelines; further encourage expanded use of intravenous iron with ESAs

Identifying patients at high risk for neutropenic complications during chemotherapy: development of prediction models
Background

- Neutropenia and associated impaired immunity is the major dose-limiting toxicity for systemic chemotherapy administration
- Febrile neutropenia associated with significant morbidity, mortality, and health care costs\(^1\)
- Current guidelines recommend prophylactic use of G-CSF when risk of FN is approximately 20%, to decrease duration and risk of FN\(^2,3\)
- Patients undergoing first-cycle CT are at highest risk of developing FN\(^4-6\)
- No reliable clinical tools available to estimate which patients at high risk of developing FN
- Several studies at ASCO addressed development of cycle-based risk prediction models for febrile neutropenia complications

CT = chemotherapy
FN = febrile neutropenia
G-CSF = granulocyte colony-stimulating factor
Risk assessment model for first-cycle chemotherapy-induced neutropenia among lung cancer (LC) patients: the DELFOS study

Study design

- Objective of research study: determine a predictive model for first-cycle (CIN) in patients with lung cancer
- Data obtained from DELFOS Study (n = 210), a multicentre non-interventional prospective-cohort study in Spain
- Authors assessed hematological toxicity during the first three cycles of CT in these patients
- Hierarchical principle used to obtain predictive LRM, as a way to enable results replication
- Model implemented for CIN defined as neutropenia grade = 3 (with or without body temperature 38 C°)
- ROC curve used to determine sensitivity and specificity of model

CIN = chemotherapy-induced neutropenia
CT = chemotherapy
LRM = logistic regression model
ROC = receiver operating characteristics
Key findings and conclusions

- LRM predicted CIN at first-cycle ($p < 0.0005$) through the following factors
  - Baseline platelet count
  - Baseline hemoglobin, and
  - Type of chemotherapy treatment
- Baseline platelet count and baseline hemoglobin inversely associated with CIN
- CIN increased among patients treated with platinum-based CT regimens in the absence of taxanes ($p = 0.027$; OR = 5.5; 95% CI [1.2, 24.9])
- Model may help guide CT dose and/or frequency of administration, as well as need to introduce supportive treatment such as G-CSF

CIN = chemotherapy-induced neutropenia
CT = chemotherapy
G-CSF = granulocyte-colony stimulating factor
LRM = logistic regression model
Identifying patients at high risk for neutropenia complications during chemotherapy for metastatic breast cancer (MBC) with doxorubicin or pegylated liposomal doxorubicin: Development of a prediction model

Study design

- Authors developed cycle-based risk prediction model for neutropenic complications (NC) during chemotherapy with traditional DOX or PLD for MBC.
- Study was randomized clinical trial of MBC patients (n = 509) who received chemotherapy with
  - DOX (60 mg/m2 Q3W) or
  - PLD (50mg/m2 Q4W)
- Patient treatment and hematological factors potentially associated with NC were evaluated.

DOX = doxorubicin
MBC = metastatic breast cancer
NC = neutropenic complications
PLD = pegylated liposomal formulation
Q3W = every 3 weeks
Q4W = every 4 weeks
Study design (continued)

- NCs were defined as
  - Febrile neutropenia
  - Neutropenia with infection, or
  - Absolute neutrophil count (ANC) = 1.5 x 10^6 cells/L
- Risk-scoring algorithm (range 0–63) derived from final reduced model
- Risk factors retained in the model included
  - Poor performance status
  - ANC = 2.0 x 10^6
  - First cycle of chemotherapy
  - Older age of patient, and
  - DOX vs. PLD

DOX = doxorubicin   NC = neutropenic complications
PLD = pegylated liposomal formulation
Key findings and conclusions

- Authors concluded for sensitivity (58%) and specificity (78.7%) predict the following probability risk of NC for risk scores below, within, or above optimal threshold
  - Below 0.3%–2%
  - Within 3%–8% and
  - Above 9%–45%

- This risk prediction model tool demonstrated acceptable internal validity and can be readily applied by clinician prior to first cycle of chemotherapy

NC = neutropenic complications
Predictors of febrile neutropenia among medicare patients with breast, lung and colorectal cancer

Hosmer WD, et al. ASCO 2007: Abstract 9120
Study design

- Authors created a prediction rule to estimate risk of FN with first chemotherapy cycle prior to initiation of chemotherapy based on readily available clinical information.
- Study mainly focused on elderly population of patients.
- Elderly patients often underrepresented in evaluation of neutropenic complications, but receive increasingly aggressive chemotherapy (Table 1).

FN = febrile neutropenia

Table 1: Patient characteristics according to type of cancer

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cancer type</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Breast</td>
</tr>
<tr>
<td>n</td>
<td>4,278</td>
</tr>
<tr>
<td>Female (%)</td>
<td>100</td>
</tr>
<tr>
<td>Race (%)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>89</td>
</tr>
<tr>
<td>Black</td>
<td>5</td>
</tr>
<tr>
<td>Latino</td>
<td>2</td>
</tr>
<tr>
<td>Asian</td>
<td>2</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
</tr>
<tr>
<td>Age (%)</td>
<td></td>
</tr>
<tr>
<td>65–69</td>
<td>29</td>
</tr>
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<td>70–74</td>
<td>36</td>
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<td>75–79</td>
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<tr>
<td>80–84</td>
<td>9</td>
</tr>
<tr>
<td>85+</td>
<td>3</td>
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<tr>
<td>Stage at diagnosis (%)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>23</td>
</tr>
<tr>
<td>2</td>
<td>53</td>
</tr>
<tr>
<td>3</td>
<td>15</td>
</tr>
<tr>
<td>4</td>
<td>9</td>
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<tr>
<td>History of blood disorder (%)</td>
<td>14</td>
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<td>History of CVD (%)</td>
<td>7</td>
</tr>
<tr>
<td>History of COPD (%)</td>
<td>7</td>
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<tr>
<td>Charlson Comorbidity Index (%)</td>
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</tr>
<tr>
<td>0</td>
<td>57</td>
</tr>
<tr>
<td>1</td>
<td>17</td>
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<td>2</td>
<td>11</td>
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<tr>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Months from diagnosis to first chemotherapy</td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>5</td>
</tr>
<tr>
<td>1–3</td>
<td>52</td>
</tr>
<tr>
<td>3 or more</td>
<td>43</td>
</tr>
<tr>
<td>Chemotherapy interval (%)</td>
<td></td>
</tr>
<tr>
<td>No Interval</td>
<td>21</td>
</tr>
<tr>
<td>1 week</td>
<td>16</td>
</tr>
<tr>
<td>2 weeks</td>
<td>18</td>
</tr>
<tr>
<td>3 weeks</td>
<td>22</td>
</tr>
<tr>
<td>4 weeks</td>
<td>23</td>
</tr>
<tr>
<td>Number of myelosuppressive drugs (%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>62</td>
</tr>
<tr>
<td>3 or more</td>
<td>2</td>
</tr>
</tbody>
</table>

CVD = cardiovascular disease; COPD = chronic obstructive disease

Study design (continued)

- SEER medicare data analyzed in patients (n = 313,356)
  - Diagnosed between 1995 and 2000
  - With breast, colorectal, prostate, and lung cancer, and
  - Received chemotherapy within 11 months of diagnosis

- Using this dataset, authors able to examine predictors of FN in large population of elderly patients with common malignancies

- A logistic regression model used to define multivariate relationships with FN after first cycle of chemotherapy

- Performance evaluated by ROC analysis (Table 2)

COPD = chronic obstructive pulmonary disease

<table>
<thead>
<tr>
<th>Predictor (reference)</th>
<th>Relative risk</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female (male)</td>
<td>1.13</td>
<td>0.04</td>
</tr>
<tr>
<td># of myelosuppressive chemotherapy agents (none)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1.62</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2</td>
<td>1.06</td>
<td>0.64</td>
</tr>
<tr>
<td>3</td>
<td>1.72</td>
<td>0.16</td>
</tr>
<tr>
<td>Stage at diagnosis (Stage 1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 2</td>
<td>0.88</td>
<td>0.27</td>
</tr>
<tr>
<td>Stage 3</td>
<td>1.82</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stage 4</td>
<td>2.06</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of blood disorder</td>
<td>1.29</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of COPD</td>
<td>1.39</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Charlson Comorbidity Index (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.96</td>
<td>0.57</td>
</tr>
<tr>
<td>2</td>
<td>1.15</td>
<td>0.10</td>
</tr>
<tr>
<td>3</td>
<td>1.17</td>
<td>0.16</td>
</tr>
<tr>
<td>4 or more</td>
<td>1.38</td>
<td>0.03</td>
</tr>
<tr>
<td>Time from diagnosis and first chemotherapy (&gt;3 months)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 month</td>
<td>1.78</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1–3 months</td>
<td>1.34</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Variables tested, but excluded because not statistically significant: age, race/ethnicity and history of cardiovascular disease.

ROC = 0.66 in derivation set and 0.69 in validation set
Key findings and conclusions

- Higher predicted risk of FN found in first cycle in elderly patients associated with
  - Advanced disease stage
  - History of COPD or blood disorders
  - Charlson Comorbidity Index ≥4, and
  - Initiating chemotherapy <1 month from diagnoses (Figure 1)
  - In dataset for patients with breast, lung, and colorectal cancers, this model predicts risk of FN after first cycle of chemotherapy moderately well

COPD = chronic obstructive pulmonary disease
FN = febrile neutropenia
Figure 1: Predicted versus actual risk of FN in cycle 1 by cancer type

Canadian perspective by Dr. Jose Chang

- All predictive models used in above studies to identify patients at high risk of neutropenic complications operate within Canadian practice restrictions and guidelines
- These models need to be validated further to prove usefulness in predicting patients at high risk of developing febrile neutropenia
- Use of colony-stimulating factors (CSFs) improves white blood cell recovery from chemotherapy exposure and reduces the risk of dose delay and reductions
- Use of CSFs most important in dose-dense protocols and chemotherapy regimens with high risk of neutropenia as outlined in these several abstracts
- Improved dosing and convenience with longer-acting, pegylated agent, effective in achieving neutrophil recovery
- Evolving role for G-CSF, both in standard and pegylated forms, to prevent FN and associated complications; these abstracts have helped define treatment populations at risk.