HIGH-DOSE MELPHALAN & TRANSPLANT: Historic And New Perspectives

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The George & Edith Richman Professor and Distinguished Scientist in Cancer Research
Director of Novel Cell Therapy
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Case Western Reserve University
One Millionth Blood Stem Cell Transplant Marks Major Medical Milestone: International Cooperation Among Physicians, Scientists Credited for Landmark Achievement

Dietger Niederwieser
Geoffrey Herzig, MD: 1941-2013

“Friend and Colleague”
MY RECOLLECTIONS

• An honor to be chosen to speak at this conference

• One of smartest persons I ever met

• One of most unique persons I ever met

• “Ode To An Athlete Dying Young”: AE Housman

• Grateful for opportunities to collaborate & pursue studies

MY RECOLLECTIONS (con’t)

• Stories about “Yellow Berets”, who’s who, etc
MY RECOLLECTIONS (con’t)

- Uncanny knack to anticipate issues, i.e. “1/3 the alcohol” in high dose BCNU
- Often knew the answer for potential randomized trials
- Hence fewer publications
- Not bother with the “paperwork”
- On the other hand:
- Genius for trial design and to undertake new initiatives
? Luck ?
Right place at the right time
CYTARABINE

- Anti-metabolite chemotherapeutic agent
- Intravenous
- Most commonly used agent for therapy of leukemia
ACUTE LEUKEMIA THERAPY
High-dose Cytarabine

**Central Nervous System Toxicity of High-Dose Systemic Cytosine Arabinoside**

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GORDON L. PHILLIPS, MD,†† URIOS FROISMAN, MD§ and DAVID J. FISHMAN, MD*

Forty-nine adult patients with acute leukemia in relapse, refractory to conventional therapy, were studied. Increasing quantities of i.v. bolus high-dose cytosine arabinoside (cytarabine) were administered using the following schedules: 3 g/m² every 12 hrs for 4-16 consecutive doses, or 4.5 g/m² every 12 hrs for 12 consecutive doses. Patients ages ranged 16-76 years (median: 38). Thirty-seven patients had previously received either induction or maintenance therapy with conventional doses of cytarabine. Cerebral or cerebellar dysfunction attributable to cytarabine was observed in eight patients and appeared 6-8 days (mean: 6.6) after the first dose and lasted 3-7 days (mean: 4.7). None of 12 patients receiving up to 24 g/m² total dose exhibited CNS toxicity; three of 19 receiving a total dose of 36 g/m² and one of 12 patients given a total dose of 48 g/m² developed reversible neurologic dysfunction. Four of six patients receiving 54 g/m² developed CNS toxicity (irreversible in two cases), a significantly greater incidence compared to toxicity in patients receiving ≤48 g/m² total dose (P < 0.01). CNS toxicity was dose-related since patients treated for 12 consecutive doses of 4.5 g/m² had significantly greater CNS toxicity than 12 consecutive doses at 3 g/m² (P < 0.04). Systemic cytarabine doses less than 54 g/m² can be administered with minimal CNS side-effects.


**High-Dose Cytosine Arabinoside Therapy for Refractory Leukemia**


Fifty-seven patients with refractory acute leukemia were treated with high-dose cytosine arabinoside to establish the maximum tolerated dose and duration and to determine the antileukemic activity. The maximum tolerated regimen was found to be 3 g/m² every 12 hr for 6 days. At this dose, nonhematologic toxicity was limited to conjunctivitis in approximately half of the patients, and liver toxicity (transient elevations in transaminase, alkaline phosphatase, or bilirubin) was frequently observed, but neither was dose-limiting. Extending the duration of treatment to 8 days resulted in excessive diarrhea and skin toxicity (painful erythema with bullae), while increasing the dose to 4.5 g/m² q. 12 hr for 6 days resulted in severe cerebellar toxicity. Myelosuppression was severe, but was not related to the intensity of treatment; granulocyte bone marrow recovery usually occurred 10-15 days (range 2-40 days) after initiating therapy, and platelet recovery occurred after a median of 26 days (range 16-41 days). Anti-leukemic activity was evident in the 46 patients who survived at least 3 wk. Complete remissions were obtained in 1 of 8 patients with chronic myelogenous leukemia (CML) in accelerated phase and 1 of 3 acute lymphocytic leukemia (ALL) patients. A more detailed analysis of response was possible for the 37 evaluable patients with acute nonlymphoblastic leukemia: 20% of these patients responded, with 61% complete remissions. The median unmaintained response was 4 mo (range 2-26 -mo). The complete response rate was higher in patients who received at least 12 doses of high-dose cytosine arabinoside compared to shorter regimens [17/28 (61%) versus 3/9 (33%). p < 0.05]. Resistance to cytosine arabinoside in conventional doses was documented in 11 patients, 6 of whom responded (2 complete remissions) to high-dose regimens. We conclude that high-dose cytosine arabinoside in the maximally tolerated regimen of 3 g/m² every 12 hr for 8 days has substantial antileukemic activity in patients refractory to standard therapy. Durable unmaintained remissions can be achieved, even in patients who fail to respond to cytosine arabinoside in conventional doses.

AUTOLOGOUS BONE MARROW TRANSPLANT
One of Earliest Transplant Trials: Lymphoma

N=27 relapsed & refractory lymphoma pts
Paved way for ROUTINE use of this approach

MELPHALAN

• Bifunctional alkylating chemotherapeutic agent
• Intravenous
MELPHALAN
History and Properties

• 1st synthesized 1953:

• L-phenylalanine added for CH₃ group on nitrogen mustard
• levo isomer - MELPHALAN
• racemic mixture - MERPHALAN
• dextro isomer - MEDPHALAN
• Not cell-cycle specific
• 60% bound to albumin
• Transported into cells by amino acid transport systems
• Elimination:
  • spontaneous chemical hydrolysis
  • active renal tubular secretion & glomerular filtration

• Clearance influenced by:
  • CrCl;
  • fat free mass;
  • hematocrit
• Toxic effects:
  • Early cytopenias, mucositis, alopecia, GI toxicity, pneumonitis, t-MN (t-AML/t-MDS), atrial arrhythmias, transaminitis
• Broad anti-tumor activity: AML, lymphoma, myeloma, neuroblastoma, other
HIGH-DOSE MELPHALAN AND HCT Multi-Center Phase I Study

8-times prior dose;
Much greater efficacy;
Most common HCT regimen

J Clin Oncol 1: 359-367, 1983
HIGH-DOSE MELPHALAN AND HCT
Multi-Center Phase I Study

- 120-225 mg/m² IV divided dose administration over 3 days
- Autologous bone marrow re-infusion
- N=33 relapsed or refractory cancer patients
  - N= 4 @ 120 mg/m²
  - N=20 @ 180 mg/m²
  - N= 5 @ 225 mg/m²
  - N= 4 @ 225 mg/m² plus cyclophosphamide priming
    300 mg/m² IV 7 d before melphalan; sheep model
- PK in blood and CSF (N=4 Omaya reservoir) using HPLC

HIGH-DOSE MELPHALAN AND HCT Multi-Center Phase I Study

- Peak serum conc achieved immediately: 4.8-11.5 µg/mL
- PK two-compartment open model system
- Plasma disappearance: $\alpha = 40$ min; $\beta = 2$ hr
- 3 of 4 had detectable CSF conc, peak at 30-60 min after IV
- 10% corresponding serum conc: 0.15-0.20 µg/mL

- Early and severe cytopenias:
  - 5 severe (3 fatal) infections
  - 1 fatal hemorrhage
- Transient LFTs, palmar erythema, rash, alopecia
- GI toxicity dose-limiting: CY-priming no effect
- Severe diarrhea, stomatitis, esophagitis
- “Optimal” dose 180 mg/m²

### Table 6. Tumor Responses After High-Dose Melphalan Treatment

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. of Patients</th>
<th>CR</th>
<th>PR</th>
<th>NR</th>
<th>ED</th>
<th>Duration of Response† (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma</td>
<td>13</td>
<td>5</td>
<td>4</td>
<td>1</td>
<td>3</td>
<td>5 (2–12+)</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>6</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>7.5 (5–10)</td>
</tr>
<tr>
<td>Ewing’s</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>6, 7</td>
</tr>
<tr>
<td>Breast</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>3, 14</td>
</tr>
<tr>
<td>Ovary‡</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0 5, 6.5</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>7</td>
<td>1§</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>5§, 3</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>33</strong></td>
<td><strong>10</strong></td>
<td><strong>9</strong></td>
<td><strong>7</strong></td>
<td><strong>5</strong></td>
<td></td>
</tr>
</tbody>
</table>

HIGH-DOSE MELPHALAN AND HCT
Observations

- Most commonly used transplant regimen
- Activity: many adult/pediatric malignancies & amyloidosis
- Predictable early toxic effects; rare late or cumulative
- Repeated cycles high-dose melphalan well-tolerated & effective
- Incorporated into many regimens:
  - Autologous: BEAM, BuMELT
  - Allogeneic: Flu-MEL
Figure 1. 100-day TRM and year of high-dose procedure for neuroblastoma (with permission, from Ladenstein et al.\textsuperscript{60}).
HIGH-DOSE MELPHALAN AND HCT
Phase I-II Plus Amifostine

• N=58 multi-center trial
• Melphalan dose escalation starting at 200 mg/m²
• 20 mg/m² increments to 300 mg/m²
• Incorporation amifostine
• Thiol prodrug (WR2721); protects organ mucosa
• Pharmacokinetic features well-matched with melphalan
• Demonstrated tolerance to 280 mg/m²
• Demonstrated activity in Hodgkin and NHL
• Cardiac toxicity (atrial fibrillation), not GI, dose-limiting

GL Phillips, et al. BMT 33, 781-787, 2004
Mucosal RRT: N=53

- **220**: 6, 0, 0, 3, 1, 10
- **240**: 0, 0, 0, 11, 3, 24
- **260**: 2, 3, 0, 12, 2, 19
- **280**: 0, 0, 0, 0, 0, 0
- **300**: 0, 0, 0, 0, 0, 6
- **Total**: 10, 5, 6, 26, 6, 53

HIGH-DOSE MELPHALAN AND HCT
Phase I-II Plus Amifostine

Non-mucosal RRT: N=53

<table>
<thead>
<tr>
<th>Melphalan Dose (mg/m²)</th>
<th>Total No. Patients</th>
<th>Affected Patients</th>
<th>Organ System</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>220</td>
<td>11</td>
<td>1</td>
<td>Cardiac</td>
<td>IV</td>
</tr>
<tr>
<td>240</td>
<td>5</td>
<td>0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>260</td>
<td>6</td>
<td>0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>280</td>
<td>27</td>
<td>1</td>
<td>Hepatic</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cardiac</td>
<td>II</td>
</tr>
<tr>
<td>300</td>
<td>9</td>
<td>2</td>
<td>Cardiac</td>
<td>II, IV</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>Hepatic</td>
<td>IV</td>
</tr>
<tr>
<td>All doses</td>
<td>58</td>
<td>6</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

HIGH-DOSE MELPHALAN AND HCT Amifostine

- N=126 consecutive autologous HCT (2007-2014)
- Single center
- Amifostine 740 mg/m\(^2\) IV at:
  - 24 hr & 30 min before melphalan
- Melphalan 200 mg/m\(^2\) IV

<table>
<thead>
<tr>
<th>GI Toxicity</th>
<th>Grade 1-4</th>
<th>Grade 3-4</th>
<th>Median Grade</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>mucositis</td>
<td>55%</td>
<td>14%</td>
<td>2</td>
<td>2d</td>
</tr>
<tr>
<td>diarrhea</td>
<td>92%</td>
<td>12%</td>
<td>2</td>
<td>7d</td>
</tr>
<tr>
<td>nausea</td>
<td>85%</td>
<td>4%</td>
<td>1</td>
<td>8d</td>
</tr>
<tr>
<td>vomiting</td>
<td>67%</td>
<td>3%</td>
<td>1</td>
<td>2d</td>
</tr>
</tbody>
</table>

Negotiations underway for prospective, randomized trial

HIGH-DOSE MELPHALAN AND HCT Use in Tandem Transplants

- Enhance anti-tumor effect
- High-dose melphalan:
  - efficacy without overlapping or long-term toxicities
- Ideal for tandem transplants

EP Smith, P Stiff, SWOG, BMT CTN. *Blood* 2014 (ASH abstract #676)
HIGH-DOSE MELPHALAN AND HCT
Tandem Transplant Hodgkin Lymphoma

N=89 pts: primary refractory, refractory relapsed

↓

Progenitor cell collection for 2 HCT procedures
(≥ 3.0 x 10⁶ CD34/kg)

↓

Melphalan 150 mg/m² x 1 and autologous HCT

↓

Assess response

↓

If at least stable disease: BCNU or 12 Gy TBI plus etoposide & cyclophosphamide and auto HCT
SWOG S0410/BMT CTN 0703
Primary Refractory or Refractory Relapse HL

Tandem Transplant Hodgkin Lymphoma
Overall Survival

At Risk: 89
Deaths: 15
2-Year Estimate: 91%
5-Year Estimate: 83%

EP Smith, P Stiff, SWOG, BMT CTN. Blood 2014 (ASH abstract #676)
SWOG S0410/BMT CTN 0703
Primary Refractory or Refractory Relapse HL

Tandem Transplant Hodgkin Lymphoma Progression-Free Survival

2-yr PFS of 63% exceeded (>15% improvement)
S9011 2-yr PFS of 45% (single autologous HCT)

EP Smith, P Stiff, SWOG, BMT CTN. Blood 2014 (ASH abstract #676)
HIGH-DOSE MELPHALAN AND HCT Optimization

- Dose increase
- Modify formulation
Can melphalan dose be optimized to improve depth of response, response duration and OS, while maintaining acceptable toxicity?

Is extent of melphalan exposure a significant predictor of outcome in patients with multiple myeloma?

HIGH-DOSE MELPHALAN AND HCT Optimization

- N=115 myeloma autologous HCT pts; 6 centers
- Median (range) age 58 (35-73) yr
- Median (range) melphalan dose 192 (89-216) mg/m²
- Gender: 66 males, 49 females
- At diagnosis:
  - serum albumin (mean ± s.d): 38 ± 7 g/L
  - serum β₂ microglobulin (mean ± s.d): 4.8 ± 5.3 µg/ml

HIGH-DOSE MELPHALAN AND HCT
AUC Variability

Mass spectroscopy and enzymatic method

AUC range: 5-25 mg/L.h
Median: 12.85 mg/L.h

HIGH-DOSE MELPHALAN AND HCT
Response To Melphalan

Paraprotein changes from diagnosis to pre to post HCT

Mean: 32 g/L
Mean: 12 g/L
Mean: 5 g/L

Treatment stage: 1= diagnosis, 2= pre HCT, 3=post HCT

### HIGH-DOSE MELPHALAN AND HCT

#### Incidence > Grade 3 Toxicity

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>No. patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mucositis</strong></td>
<td></td>
</tr>
<tr>
<td>- clinical</td>
<td>14 (12%)</td>
</tr>
<tr>
<td>- functional</td>
<td>23 (20%)</td>
</tr>
<tr>
<td><strong>Gastrointestinal toxicity</strong></td>
<td></td>
</tr>
<tr>
<td>- Nausea</td>
<td>15 (13%)</td>
</tr>
<tr>
<td>- Vomiting</td>
<td>6 (5%)</td>
</tr>
<tr>
<td>- Diarrhoea</td>
<td>24 (21%)</td>
</tr>
<tr>
<td>- colitis</td>
<td>3 (3%)</td>
</tr>
<tr>
<td><strong>CNS (seizures, loss of consciousness)</strong></td>
<td>4 (3%)</td>
</tr>
<tr>
<td><strong>Cardiovascular/pulmonary</strong></td>
<td>3 (3%)</td>
</tr>
<tr>
<td><strong>Renal failure</strong></td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>

Multivariate logistic regression analysis

Only risk factor for mucositis > gr 3:

- Melphalan AUC (continuous), HR 1.2, p = 0.004
Improved survival probability
• Melphalan AUC > 12.85 mg/L.h (HR 0.56, \( p = 0.02 \))

Lower survival probability
• Relapsed or progressive disease (HR 2.53, \( p = 0.002 \))

Multivariate Cox regression analysis

Improved survival probability
Melphalan AUC > median
(HR=0.35, p =0.006)
First autograft (HR=0.25,
p = 0.002)

Lower survival probability
Disease stage 3 (HR=2.71,
p = 0.006)

Multivariate Cox regression analysis
Using pharmacokinetics:

- Higher range melphalan exposure associated with:
  - a small acceptable increase in severe mucositis
  - improved time to progression & overall survival
- Targeting higher melphalan exposure warranted

HIGH-DOSE MELPHALAN AND HCT
200 mg/m² In Renal Failure

- Single center retrospective report
- N=149 first autograft myeloma patients 2001-2012
- Given melphalan 200 mg/m² in divided dose IV over 2 days
- Renal insufficiency definition: < 60 mL/min
- Excluded if
  - received melphalan < 200 mg/m²
  - underwent hemodialysis at any time
- N=103 CrCl > 60 mL/min: median 58 yr
- N= 46 CrCl < 60 mL/min: median 61 yr

K Sweiss, et al. Bone Marrow Transplant 2016
HIGH-DOSE MELPHALAN AND HCT 200 mg/m² In Renal Failure

Median Duration TPN
10 vs 6 days (p=0.02)

Median duration diarrhea
8 vs 5 days (p=0.0001)

K Sweiss, et al. Bone Marrow Transplant 2016
HIGH-DOSE MELPHALAN AND HCT
200 mg/m² In Renal Failure

K Sweiss, et al. Bone Marrow Transplant 2016
HIGH-DOSE MELPHALAN AND HCT
200 mg/m² In Renal Failure

K Sweiss, et al. Bone Marrow Transplant 2016
HIGH-DOSE MELPHALAN AND HCT
200 mg/m² in Renal Failure

37 vs 17 mo, p=0.0025

K Sweiss, et al. Bone Marrow Transplant 2016
HIGH-DOSE MELPHALAN AND HCT
200 mg/m² in Renal Failure

- < 60 mL/min: Median (range) F/U 35 (2-132) mo
- > 60 mL/min: Median (range) F/U 47 (1-45) mo
- Comparable overall survival
- Longer median treatment-free survival (TFS) in CrCl < 60
  - 37 mo vs 17 mo (p=0.0025)
- Multivariate analysis predicted longer TFS for:
  - CrCl < 60 mL/min (HR 3.5)
  - prior proteasome inhibitor therapy (HR 2.441)
- Melphalan 200 mg/m² safe & effective in CrCl 30-60 mL/min
**HIGH-DOSE MELPHALAN AND HCT**
Prospective, Multi-Center: 280 vs 200 mg/m²

<table>
<thead>
<tr>
<th>Patient number</th>
<th>N=65</th>
<th>N=66</th>
<th>P value</th>
</tr>
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<tbody>
<tr>
<td>Melphalan dose mg/m²</td>
<td>200</td>
<td>280</td>
<td></td>
</tr>
<tr>
<td>Timing: Up-front HCT</td>
<td>50</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>At relapse</td>
<td>15</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Mucositis gr 2-3</td>
<td>33%</td>
<td>12%</td>
<td>0.004</td>
</tr>
<tr>
<td>Any gr 2-3 toxicity</td>
<td>36%</td>
<td>22%</td>
<td>0.06</td>
</tr>
<tr>
<td>nCR + CR</td>
<td>39.4%</td>
<td>21.5%</td>
<td></td>
</tr>
<tr>
<td>nCR + CR + PR</td>
<td>74.2%</td>
<td>56.9%</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Amifostine 740 mg/m² @ 24 hr & 30 min before single IV bolus melphalan: use of oral ice chips

HIGH-DOSE MELPHALAN AND HCT
280 vs 200 mg/m²

Median PFS 3.5 yr
N=66

Median PFS 2.7 yr
N=65
HIGH-DOSE MELPHALAN AND HCT
280 vs 200 mg/m²

Median OS 6.2 yr
N=66

Median OS 5.3 yr
N=65

THE END IS NEAR
HIGH-DOSE MELPHALAN AND HCT

Better Understanding Toxicity & New formulations
## HIGH-DOSE MELPHALAN AND HCT Optimization: Pharmacokinetic Interactions

<table>
<thead>
<tr>
<th>Agent</th>
<th>Effect on Melphalan</th>
<th>Mechanism</th>
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<tbody>
<tr>
<td>Carboplatin</td>
<td>Increases plasma concentration</td>
<td>Reduces renal clearance</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>Increases plasma concentration</td>
<td>Reduces renal clearance</td>
</tr>
<tr>
<td>Furosemide</td>
<td>Decreases plasma concentration</td>
<td>Increases renal clearance</td>
</tr>
</tbody>
</table>


- Melphalan covalently bound to red cell membranes
- Anemia means higher non-red blood cell fraction binding
- Higher plasma & ultrafiltrate conc; lower clearance

HIGH-DOSE MELPHALAN AND HCT
Anemia and Toxicity

Total melphalan plasma clearance

Unbound melphalan plasma clearance

HIGH-DOSE MELPHALAN AND HCT
Dosing In Obesity

3-arm BMT CTN 0702 autologous HCT trial:

H Lazarus, N Berger, L Metheny: prospective waist:hip ratio
Archived blood samples for adipokines
Correlate with toxicity


HIGH-DOSE MELPHALAN AND HCT GI Toxicity: Retrospective Study

Melphalan 200 mg/m²: 1-day N=185 vs 2-day (N=93) dosing

<table>
<thead>
<tr>
<th>Toxicity profile</th>
<th>2-Day dosing melphalan (N = 185)</th>
<th>1-Day dosing melphalan (N = 93)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral mucositis</td>
<td>118 (64%)</td>
<td>56 (60%)</td>
<td>0.7</td>
</tr>
<tr>
<td>Grade 0–2: 160 (87%)</td>
<td>Grade 0–2: 88 (95%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3–4: 25 (13%)</td>
<td>Grade 3–4: 5 (5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Grade 0–2: 166 (90%)</td>
<td>Grade 0–2: 84 (90%)</td>
<td>0.9</td>
</tr>
<tr>
<td>Grade 3–4: 19 (10%)</td>
<td>Grade 3–4: 9 (10%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>Grade 2: 7 (4%)</td>
<td>Grade 2: 1 (1%)</td>
<td>0.5</td>
</tr>
<tr>
<td>Grade 3–4: 2 (1%)</td>
<td>Grade 3–4: 0 (0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic dysfunction</td>
<td>Grade 2: 13 (7%)</td>
<td>Grade 2: 3 (3%)</td>
<td>0.3</td>
</tr>
<tr>
<td>Grade 3–4: 1 (1%)</td>
<td>Grade 3–4: 0 (0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supportive care during hospitalization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opioid medication use</td>
<td>160 (87%)</td>
<td>75 (81%)</td>
<td>0.1</td>
</tr>
<tr>
<td>PCA use</td>
<td>44 (24%)</td>
<td>18 (19%)</td>
<td>0.3</td>
</tr>
<tr>
<td>TPN use</td>
<td>14 (8%)</td>
<td>2 (2%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Additional antiemetic medication use^a</td>
<td>180 (97%)</td>
<td>92 (99%)</td>
<td>0.5</td>
</tr>
<tr>
<td>Median days to platelet engraftment (range)</td>
<td>13 (8–31)</td>
<td>13 (9–30)</td>
<td>0.6</td>
</tr>
<tr>
<td>Median days to neutrophil engraftment (range)</td>
<td>12 (11–19)</td>
<td>12 (11–14)</td>
<td>0.7</td>
</tr>
</tbody>
</table>

SR Parmar, et al. BMT 49: 761-6, 2014
HIGH-DOSE MELPHALAN AND HCT GI Toxicity

One Day vs Two Day Dosing

Progression-Free Survival

Overall Survival

P-value by a stratified log-rank test = 0.348

P-value by a stratified log-rank test = 0.101

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HIGH-DOSE MELPHALAN AND HCT
GI Toxicity: Pharmacogenetics

• Amino acid transporters principal mediators cell uptake
• LAT1 encoded by SLC7A5 gene; LAT2 encoded by SLC7A8
• N=135 myeloma autologous HCT
• Analyzed SNPs: N=7 SLC7A5 and N=20 SLC7A8 genotyped
• SNP in first intron of SLC7A5, rs4240803
• Significant association TPN (OR=.45, 95%CI .25-.79; p=.007)
• LAT1 protein on endothelial cells contributes to blood-brain barrier; ? transport into CNS & nausea/ anorexia
• Variability in melphalan transport affects mucosal injury
• Individualize melphalan dose
HIGH-DOSE MELPHALAN AND HCT
Propylene Glycol-Free Melphalan

Conventional melphalan formulations
• marginal solubility; difficult to prepare
• limited chemical stability after reconstitution
• required administration within 1 hr
• propylene glycol as co-solvent
  • attendant problems
  • metabolic acidosis, renal dysfunction & arrhythmias

Propylene glycol-free melphalan
• incorporates Captisol
  • specially modified cyclodextrin
  • improves solubility and stability of melphalan
  • 8-10 hr stability; up to 24 hr if refrigerated
• eliminates propylene glycol toxicities
HIGH-DOSE MELPHALAN AND HCT Propylene Glycol-Free Melphalan (Evomela)

- N=61 myeloma autograft phase lib study
- EVOMELA 200 mg/m² as 2 doses 100 mg/m² each
- all subjects engrafted
- median: neutrophil day 12; platelet day 13
- day 100 TRM 0%
- CR rate 21% (13% stringent CR; 8% CR)
- PR rate 79% (61% VGPR; 18% PR)
- gr 3 mucositis 10%; stomatitis 5%;
  - no gr 4 mucositis or stomatitis
"If I have seen farther than others, it is because I was standing on the shoulders of giants."

Isaac Newton