Autologous Stem Cell Transplantation (ASCT) Using Busulphan, Melphalan And Cyclophosphamide Conditioning

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Introduction

- Radiotherapy based conditioning was the preferred myeloablative regimen in our centre for both allogeneic and autologous SCT.
- A severe shortage of radiotherapy staff has now limited slots to one every 6 weeks.
- Reserved radiotherapy for ALL and some lymphomas.
Introduction

- Initial regimen was Busulphan, Melphalan and Thiotepa – effective but with severe mucositis
- Thiotepa unavailable in SA 2002
- Busulphan, Melphalan and Cyclophosphamide used since 2003
- Rationale for the combination (as opposed to BU/CY) was a lower dose of Busulphan than usual (decreasing toxicity) with the addition of Melphalan both for dose intensity and as immunosuppression in the T-cell depleted allogeneic transplants.
Aim of study

A retrospective analysis of the outcome of patients undergoing ASCT for haematological malignancies following conditioning with Busulphan, Melphalan and Cyclophosphamide:
- Toxity
- Disease recurrence
- Treatment related mortality
Patients

- All patients with haematological malignancies eligible for autologous stem cell transplantation with chemotherapy based conditioning
- Patients with myeloma were excluded as conditioning was with melphalan alone
- Radiotherapy was the preferred conditioning for lymphoma – depending on availability of slots and previous radiotherapy.
Stem cell mobilisation

- The chemotherapy for mobilisation was Etoposide 2g/m² in divided doses over two days
- G-CSF was administered at 10ug/kg daily from day 5 post Etoposide
- Harvesting was with large volume apheresis on a Cobe Spectra
- The minimum stem cell dose aimed for was 2x10⁶ CD 34 cells /kg
- Cells were cryopreserved and stored in liquid nitrogen
Conditioning regimen

- Busulphan 12mg/kg (total) in divided dosis over 3 days (with Phenytoin)

- Melphalan 70mg/m² daily x 2 days

- Cyclophosphamide 60mg/kg daily x 2 days (with Mesna)
Supportive care

- Positive pressure rooms
- Reverse barrier isolation
- Antimicrobial prophylaxis
- Nasogastric or parenteral feeding depending on the degree of mucositis
- No routine use of growth factors
Results

34 patients

Males = 19  Females = 15

Median age 35 years range (15 - 56) years

Diagnosis

- AML 16
- HD 8
- T lymphoblast 3
- Diffuse large B cell 4
- T NHL 3
### Results

**AML (CR1) n=16**

- t(8;21) | 8
- inv 16  | 1
- M2 + N karyotype | 1
- M2 + failed cyto | 1
- M5 + N karyotype | 1
- M4 + multiple cyto abn | 2
- M2 with basophilia | 1
- Transf MDS trisom 6 | 1
Results

Hodgkin’s Lymphoma n=8
  CR1 post salvage 1
  CR2 6
  CR 4 1

T-cell lymphoma (CR1) n=6
  T-LL 3
  Peripheral T 2
  Angioimmunobbl 1
Results

Diffuse large B-cell lymphoma n=4

CR 1 (high IPI) 2
CR 1 (slow resp) 1
CR 2 1
Results

Toxicity during infusion of chemotherapy:
- mild nausea and diarrhea
- one case of convulsions on busulphan – Phenytoin therapeutic

Median stem cell dose:
2.9 range (1.33 - 99x 10^6) CD34 cells/kg
## Results

<table>
<thead>
<tr>
<th>Condition</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucositis</td>
<td></td>
</tr>
<tr>
<td>Grade 2-3</td>
<td>26</td>
</tr>
<tr>
<td>Grade 4</td>
<td>8</td>
</tr>
<tr>
<td>Patients requiring TPN</td>
<td>8</td>
</tr>
<tr>
<td>Median days on TPN</td>
<td>15 range (5-22)</td>
</tr>
<tr>
<td>Haemorrhagic cystitis</td>
<td>4</td>
</tr>
<tr>
<td>VOD</td>
<td>2 (both recovered)</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>2 (both recovered)</td>
</tr>
</tbody>
</table>
## Results

### Infections

<table>
<thead>
<tr>
<th>Category</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Early</strong></td>
<td></td>
</tr>
<tr>
<td>Neutropenic fever</td>
<td>34</td>
</tr>
<tr>
<td>Candidemia</td>
<td>3 (2 died)</td>
</tr>
<tr>
<td>Severe oral herpes</td>
<td>8 (24%)</td>
</tr>
<tr>
<td>ESBL gram neg</td>
<td>4</td>
</tr>
<tr>
<td>Septic shock</td>
<td>2</td>
</tr>
<tr>
<td>Aspiration pneum</td>
<td>1</td>
</tr>
<tr>
<td><strong>Late</strong></td>
<td></td>
</tr>
<tr>
<td>Hickman line infection</td>
<td>3</td>
</tr>
<tr>
<td>Pulmonary TB</td>
<td>2</td>
</tr>
</tbody>
</table>
Results

CNS complications
Subdural haemorrhage / hygroma
N= 3 patients
  AML  2
  HD   1

Outcome
  Deaths  2
    - aspiration pneumonia
    - candidemia
Results

All patients engrafted
Median time 13 (range 8-30) days post SCT

Discharge
Median time 20(range 12-52) days post SCT
Results

Disease recurrence

7 patients
At a median of 5 (range 2-34) months post SCT

AML  n=6 (CR 1)

- M2 with normal karyotype
- M2 with failed cytogenetics and high white cell count
- M5 with normal karyotype
- M2 with t(8;21) and del 9 (q22)
- M4 with trisomy 19 and 22
- Transformed MDS with trisomy 6

HD  n=1 (CR 2)
Results

Alive  n = 21 (62%)

At a median time of:
34 (range 13 -71) months post SCT
Results

Deaths  n = 13 (38%)

Disease recurrence
  AML  6

Infection
  Gram neg septic shock (day 7)  1
  Candidemia (day 14)  1
  Septicaemia (ITP on steroids)(day 120)  1

Subdural hygroma + infection
  subd hg + asp pneumonia (day 30)  1
  subd hg + candidemia (day 45)  1

Unknown cause at home (post day 100)  2
Results

Statistics
Predictors of survival

O/S related to stem cell dose (0.05)

TRM related to
- older age (0.02)
- organ dysfunction (0.02)
Survival According to Diagnosis

- **Died**
- **Censored**

AML
NHL
HD

Follow up (days)

Cumulative Proportion Surviving
All Patients: Overall Survival

Died
Censored

Follow up (days)

Cumulative Proportion Surviving
Discussion – subdural haematoma / hygroma

Subdural haemorrhage/hygroma in SCT

Incidence:
- 2-2.7% in retrospective analysis
- 13% in a post mortem study
- 18% in a prospective study
- <5% of total transplants – our centre

Associations:
- IT chemotherapy + prolonged headaches
- low platelets
- AML autografts
Discussion – subdural haematoma / hygroma

Management
- maintain optimal platelet count and coagulation
- surgery for cases with progression and neurological deterioration

Prevention
- ? IT for patients with ALL and monoblastic leukaemia
- ? CT head before IT
- high risk if prolonged headache post IT chemo - early CT
- keep platelets >50 post LP
Conclusion

- The regimen is well tolerated with minimal early toxicity and a low incidence of VOD with no deaths due to the VOD.
- The relapse rate is comparable to International findings.
- Infections including resistant gram negative bacteria, candida and late tuberculosis remain a significant problem in our setting.
- Routine herpes prophylaxis should be considered in ASCT – 24% incidence is high.
- The two deaths due to the complications of subdural haemorrhage/ hygromas are very unusual and have not been seen before or since in our unit.