Conditioning for allos

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Internal Medicine II

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Agenda

• Rational for high dose chemotherapy
• What is a myeloablative conditioning regimen?
• Comparative trials of HD-therapy and ASCT vs conventional chemotherapy
• Dose-adapted high dose regimens in Auto SCT?
• Conditioning for allo SCT
  MAC-RIC-NMA
• Why do we need NMA/RIC?
• Comparative trials RIC vs MAC
Rational of High Dose Chemotherapy and Autologous Stem Cell Transplantation

- Intensification of the Chemo(radio)therapy

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Overcoming Resistance of Tumor cells

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Significant Increase in Response Rates
Scheme of an Autologous Stem Cell Transplantation

Chemotherapy ± Irradiation

Autologous Stem Cells

Regeneration of the Immune system

Regeneration of Hematopoiesis

1-2 Weeks

1-2 Months

Mobilisation

CD34+ Cryoconserved

P

P
What is a myeloablative Regimen?
HD - Chemotherapy for Multiple Myeloma

Melphalan 100 - 140 mg/m²

*Mc Elwain 1983*

Response Rate: > 70% (CR 20%)
TRM: 15 - 25%

Compared to MP: Response Rate 40%, CR 3-4%

HD - Chemo (Mel200) with Stem Cell Support:
Unpublished Würzburg Results
Response Rate: > 95% (CR > 50%)
TRM: < 0,5%

Hematopoietic reconstitution

Days after HD-Therapy

- Mel 100-140 ohne SZ/CSF: 29 days
- Mel 100-140 + CSF: 21 days
- Mel 200 + PBSC + G-CSF: 10 days
Conventional vs High Dose Chemotherapy for younger patients with NOMM

**Standard dose CTX**
- VMCP/BVAP 18x

**High dose CTX**
- VMCP/BVAP 4-6x
- Cy 4
- TBI/Mel 140

**ORR**
- CR: 5% (22%)
- PR: 52% (59%)
- PD: 25% (12%)

**Graph**
- Overall survival (%)

Attal et al., NEJM, 1996
Side Effects of a Myeloablative Regimen

- Hair loss
- Nausea/vomiting
- Infection
- Secondary Neoplasms
- Inappetence
- Persistent organ dysfunction (heart, lung, liver)

Very rare
Infections

• Increased susceptibility to infection already at the time of diagnosis
• With induction therapy the susceptibility to infection increased by 100%
• During neutropenia after high-dose therapy $4 \times \uparrow$ risk of infection
• After discharge: increased susceptibility to infection for further 6-8 weeks
  → ACV/Cotrim
• After the end of treatment: Susceptibility to infection is largely dependent on the quality of response
GI-Toxicity

- Nausea / vomiting:
  - Food intake ↓: 50-80%!
  - Duration: 3 (median) days

- Constipation / diarrhea: 60%
  - Duration 3-4 days
  - Significantly more severe with TBI
Late effects of transplantation

secondary tumors
MDS, acute leukemias: very rare (<1%)
Exception: intensive pretreatment with Mel before Tx
Other secondary tumors in patients with myeloma regardless of the therapy
Long-term disease control only after HD-Therapy
Quality of Response determines PFS/OS after Auto-SCT

CR vs. nCR/VGPR/PR vs. SD/PD (n = 344)

- Landmark-study: plateau in OS and PFS after 11 years for patients with CR (35%)
- After 17 years 35% of the patients alive with CR and 11% of the patients with nCR+VGPR+PR

Martinez-Lopez J et al., Blood 2011
Intensification with Tandem Transplantation

- Comparison between Single and Tandem Transplantation
- In the era prior to the novel agents
- In the era of the novel agents
IFM 94: Single - vs Tandem-SCT

- EFS after 7 years
  - 10% vs 20% (p = 0.03)
- OS after 7 years
  - 21% vs 42% (p = 0.01)
- Tandem-SCT improves OS, esp. ln pts. <VGPR after 1st SCT
  - OS after 7 years – 11% vs 43% (p < 0.001)

(Post-hoc subgroup analysis)

Double vs single ASCT after bortezomib-based induction: OS data

- Pts with 2 adverse variables who received double ASCT had significantly longer OS compared to pts who received single ASCT
- OS benefit with double ASCT particularly relevant for pts who failed CR after bortezomib-based induction therapies and who had high-risk cytogenetics or ISS 3

Median OS 67 vs 31.5 months, P<0.001

Cavo et al. ASH 2013 (Abstract 767), oral presentation
US Trial
CTN/IBMTR-Study

Induction

PBSC

Mel 200

no consolidation

VRD4x

Mel 200

Len-Maintenance

Len-Maintenance

Len-Maintenance
DSMM XIV: Role of second ASCT in pts with at least VGPR after the first ASCT

Analysis of molecular response with immunophenotyping/PCR

EudraCT NUMMER: 2009-016616-21
Age Limit/Intensity of HD-Therapy in elderly Patients?

Background:
- HD-Melphalan controversially discussed for the elderly patient
  - More toxicity (?)
  - Lower efficacy (?)
  - Do novel combinations replace ASCT in the elderly patient?

DSMM II – MM 60-70 yrs

Results on:
- 549 Patients
- 5,3 yrs median follow-up
Age-adapted HD-Therapy for elderly MM patients

IFM Age 65-75 years
GIMEMA Age 51-70 years
DSMM II Age 60-70 years

A2
N = 218

N = 434

R

A1
N = 216

C + Dex
C + Dex
C + Dex
C + Dex

IEV
MEL 140
2 Mo

PBSCs

MEL 100
2 Mo

IFN

IEV
PBSCs

MEL 140
2 Mo

Ø

MEL 100

PBSCs

Ø
### DSMM II – Non-hematological Toxicity NCI-Grades 3/4

#### Age 60-64 vs. 65-70 years

<table>
<thead>
<tr>
<th></th>
<th>1. HD-Melphalan</th>
<th>2. HD-Melphalan</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Induction A1</td>
<td>No Induction A2</td>
</tr>
<tr>
<td><strong>Infection</strong></td>
<td>33 % vs. 35 %</td>
<td>45 % vs. 42 %</td>
</tr>
<tr>
<td><strong>Mucositis</strong></td>
<td>11 % vs. 10 %</td>
<td>18 % vs. 13 %</td>
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**Note:**
- HD-Melphalan refers to high-dose melphalan treatment.
- Induction A1 and A2 denote different induction regimens.
- Percentages compare side effects between age groups.
Progression-free survival (PFS)

Age 60-63 years  N = 138
Median PFS 19.4 months

Age 64-66 years  N = 125
Median PFS 20.5 months

Age 67-70 years  N = 157
Median PFS 22.4 months
Aggressive conventional chemotherapy compared with high-dose chemotherapy with HSCT for relapsed chemosensitive Hodgkin's disease

Schmitz N et al. Lancet 2002
Aggressive conventional chemotherapy compared with high-dose chemotherapy with HSCT for relapsed chemosensitive Hodgkin's disease

- High Dose Therapy followed by Auto-SCT standard of care for medically fit patients with relapsed HD

- 70% of these patients can be salvaged in first relapse

but: in early relapse only 40%
in refractory disease only 20-35%

} long term survival after ASCT

Schmitz N et al. Lancet 2002
Overall survival of 118 patients from date of relapse after auto SCT for relapsed or refractory Hodgkin lymphoma
Recent results with reduced-intensity allogeneic transplantation for Hodgkin lymphoma (HL)

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>Prior ASCT</th>
<th>Prior regimens (median)</th>
<th>TRM, % (time point)</th>
<th>PFS, % (time point)</th>
<th>OS, % (time point)</th>
</tr>
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<tbody>
<tr>
<td>Peggs</td>
<td>49</td>
<td>44</td>
<td>5</td>
<td>16 (2 y)</td>
<td>32 (4 y)</td>
<td>56 (4 y)</td>
</tr>
<tr>
<td>Sureda</td>
<td>89</td>
<td>55</td>
<td>85% ≥3</td>
<td>23 (1 y)</td>
<td>18 (3 y)</td>
<td>35 (3 y)</td>
</tr>
<tr>
<td>Alderlini</td>
<td>40</td>
<td>30</td>
<td>5</td>
<td>22 (18 m)</td>
<td>55 (18 m)</td>
<td>61 (18 m)</td>
</tr>
<tr>
<td>Armand</td>
<td>36</td>
<td>34</td>
<td>4</td>
<td>15 (3 y)</td>
<td>22 (3 y)</td>
<td>56 (3 y)</td>
</tr>
<tr>
<td>Alvarez</td>
<td>40</td>
<td>29</td>
<td>55% ≥3</td>
<td>25 (1 y)</td>
<td>32 (2 y)</td>
<td>48 (2 y)</td>
</tr>
</tbody>
</table>

Crump, M. Hematology 2008
Scheme of the allogeneic Stem Cell Transplantation

Chemotherapie ± Bestrahlung

Stammzellen

Ersatz des Immunsystems (Antigen-präsentierende Zellen / T-Zellen/B-Zellen)

Ersatz des Blutbildenden Systems

3-6 Wochen

12 Monate
Donor T Cells

Novel (Patient-specific)-Antigens = Target antigens of the Donor T cells
-> GvHD

But also: residual Tumor cells = Targets for the transfered donor-derived immune system
-> Transplantat-vs Tumor reaction

Self Tolerance → Alloimmune reaction
Graft-versus-Host Disease
Relapse Risk of Patients with AML
Graft-versus Myeloma Effect

Serum M (g/dL)

Days

Donor PB cells

a. GVHD

ctx MEL 100 MUD BMT

b. GVHD

CTX MEL 100 MUD BMT

c. GVHD

Outcome after Allo-SCT

Survival

TRM

G. Gahrton et al. 2001
Different Modalities of Allo-SCT

Non-myeloablative Conditioning

- **TBI**
  - 2 Gy
  - CSA/MMF

Classical Conditioning

- **TBI**
  - Cy
  - 12 Gy
  - 120mg/kg
  - CSA/MTX

- **Advantage:**
  - Organ Toxicity (TRM of 30% → < 15%)
  - upper age limit ↑ ( > 60 J )

- **Disadvantage:**
  - Tumor Reduction by Conditioning Therapy
Conditioning Therapy for Allo-SCT

Goals

1. Induce an intensive immunosupression of the recipient to allow engraftment of the hematopoetic and immune system of the donor and to prevent primary graft failure

2. Anti-leukemic activity – to eradicate as many malignant cells as possible

3. Inducing myeloablation to create „space“ for the transplanted donor-derived stem cells

But: preclinical models and clinical observation have shown that: The main anti-leukemic activity of allogeneic stem cell transplantation is induced by the graft-versus Tumor effect and that myeloablation is not Essential for a successful engraftment
Intensity of the Conditioning

1. Standard conditioning = Myeloablative Regimens
   High dose alkylating agents +/- TBI
   Irreversible eradication of the hematopoietic system of the recipient

2. Non-myeloablative regimens induce only minimal hematotoxicity and could be applied without a stem cell support
   -> autologous reconstitution
   But: sufficient to induce engraftment of the donor-derived hematopoietic system which replaces the recipient`s hematopoietic system

3. Reduced intensity regimens
   Does not fall in the category of 1. and 2.
   Intensity of chemotherapy and/or irradiation should be reduced by at least 30%
   when compared to a myeloablative regimen
   But due to a prolonged pancytopenia stem cell support is essential
MAC (Myeloablative Conditioning)

1. Definition of MA regimen: a combination of agents expected to produce profound pancytopenia and myeloablation within 1-3 weeks from administration; pancytopenia is long lasting, usually irreversible, and in most instances fatal, unless hematopoiesis is restored by hemopoietic stem cell infusion.

2. The combinations of Bu-Cy or Cy-TBI are considered to be an MA conditioning regimen. Further intensification: by addition of melphalan (MEL), thiotepa (THIO), etoposide (VP16), and dimethylbusulfan.

3. MA regimens usually produce rapid engraftment of donor cells, which may be followed in a proportion of patients, by graft-versus-host disease (GVHD).

1. Definition of NMA regimen: a regimen that will cause minimal cytopenia and does not require stem cell support.

2. Examples of NMA regimens include: Flu-Cy, TBI 2 Gy, TBI 1 Gy, total lymphoid radiation (TLI), and antithymocyte globulin (ATG). NMA typically cause minimal cytopenia, and little early toxicity, but are immunosuppressive to the extent that, when followed by granulocyte-colony stimulating factor (G-CSF) mobilized peripheral blood stem cells (PBSCs), they usually result in full engraftment of donor lymphohemopoietic SCs.

3. However, NMA also require a large number of donor T lymphocytes and donor CD34+ cells, to facilitate donor engraftment. It is therefore the combination of *immunoablation* and large numbers of donor cells that constitute the essence of NMA programs. These transplants are followed by low early toxicity, despite older patient age and greater number of patients with comorbidity. TRM is lower after NMA compared to MA regimens. Acute GVHD (aGVHD) after NMA is delayed, and may develop after day 100, at a time when chronic GVHD (cGVHD) is usually diagnosed after an MA regimen.

RIC (Reduced Intensity Conditioning)

1. A conditioning regimen that does not fulfill MA or NMA is defined as an *RIC regimen*.

2. An intermediate category of regimens that do not fit the definition for MA or NMA. *RIC regimens differ from NMA*: they cause cytopenia, which may be prolonged, and do require stem cell support.

3. *RIC regimens differ from MA conditioning*, because the dose of alkylating agents or TBI is reduced by at least 30%. Most often these regimens combine Flu with an alkylating agent, melphalan (Mel), Bu, thiotepa in reduced doses, or Flu with reduced-dose TBI. TRM is reduced after RIC regimens, as shown by several registry-based studies comparing RIC and MA regimens.

Intensity of the Conditioning and impact on duration of aplasia or need for stem cell support

# Myeloablative and Nonmyeloablative Regimens

<table>
<thead>
<tr>
<th>Myeloablative (MA)</th>
<th>Nonmyeloablative (NMA)</th>
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<tbody>
<tr>
<td>TBI ≥5 Gy single dose or ≥8 Gy fractionated</td>
<td>TBI ≤2 Gy± purine analog</td>
</tr>
<tr>
<td>Bu &gt;8 mg/kg orally or intravenous equivalent</td>
<td>Flu + Cy ± ATG</td>
</tr>
<tr>
<td></td>
<td>Flu +AraC + Ida</td>
</tr>
<tr>
<td></td>
<td>Cladribine + AraC</td>
</tr>
<tr>
<td></td>
<td>TNI + ATG</td>
</tr>
</tbody>
</table>

- **Reduced Conditioning**
  - Neither myeloablative nor non-myeloablative

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### GvT to Treat Relapse (Response to DLI)

<table>
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<tr>
<th>Condition</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>CML</td>
<td>Up to 80% molecular remissions</td>
</tr>
<tr>
<td>Hodgkin’s disease</td>
<td>79% responses</td>
</tr>
<tr>
<td>CLL</td>
<td>~ 50% responses</td>
</tr>
<tr>
<td>Myeloma</td>
<td>Responses in up to 50% [ \rightarrow \text{only patients in CR long-term disease control} ]</td>
</tr>
<tr>
<td>AML</td>
<td>Responses in 15-30% [ \text{Cure 20%} ]</td>
</tr>
<tr>
<td>High grade lymphoma</td>
<td>Remission 0-30%</td>
</tr>
<tr>
<td>ALL</td>
<td>Remission rate 0-20% [ \text{OS &lt;&lt; 15%} ]</td>
</tr>
</tbody>
</table>

Porter D, 2011
Why do we need RIC/NMA-Conditioning AlloSCT for MDS

- IPSS intermediate-2 or high risk
  - Age < 75 years

- IPSS intermediate-1
  - Individual decision with the patients

- IPSS low risk
  - Only in high selected patients
MDS:
PFS after Allo SCT

Deeg et al, Blood 2002;100:1201-1207
Allo-SCT for cMPS (non-CML)
Allo SCT for CMF

- Deeg et al. 2003: 56 Pat., MAC – Allo SCT
  Age: 43 years (10 – 66)
  3 yrs OS: 58%

- Anderson et al. 2001: 21 Pat.
  2 yrs OS: 61%

- Rondelli et al. 2005: 20 Pat., RIC-Allo-SCT (Flu-Bu – up to age 70 yrs)
  31 Mo. OS: 83%

→ Recommendation: Intermediate or High Risk Patients up to age 70-75 years
   allo-SCT but RIC or NMA, not MAC!
Comparison of MAC vs RIC Allo SCT
Conv. Allo-SCT vs. RIC-Allo-SCT for MM

Non-relapse Mortality

C. Crawley Blood et al. 2007
Conv. Allo-SCT vs. RIC-Allo-SCT for MM

Disease Progression

Time from transplant (months)

C. Crawley Blood et al. 2007
Conv. Allo-SCT vs. RIC-Allo-SCT for MM

C. Crawley Blood et al. 2007
MM-URD allo-SCT in AML: RIC vs. MAC: Conclusions

- There was no differences in RI after RIC vs. MAC regimens in both <50 and ≥50 year group after MM-URD allo-SCT

- Study shows no significant outcome difference between RIC and MAC regimens after MM-URD allo-SCT in patients younger than 50 years.

- Data support superiority of RIC regimen in patients ≥50 year receiving transplant from MM-URD

- Inherent limitations of a retrospective registry based study
Do we need intensified Conditioning Regimens? Yes – if there is little GvT

Allogeneic haematopoietic stem-cell transplantation for relapsed and refractory aggressive histology non-Hodgkin lymphoma*


1Division of Hematology, Leukemia/Bone Marrow Transplant Program of British Columbia, The Vancouver Hospital and Health Science Centre, 2Department of Medical Oncology, 3Department of Pathology and Laboratory Medicine, and 4Department of Radiation Oncology, British Columbia Cancer Agency and the University of British Columbia, Vancouver, BC, Canada

12 Gy  150 mg/kg Cyclo  CSA/short course MTX
EFS and OS for the entire group (n=44)

EFS 5 yrs 43%  OS  5 yrs 48%
Cumulative incidence of relapse

(Relapse Risk 44%)

(Relapse Risk 29%)

\( P\text{-value} = 0.2 \)
Cumulative incidence of relapse according to time to relapse after initial therapy

Relapse Risk 52%

Relapse Risk 7%

P-value = 0.02
Current Protocol of the DSHNL for Allo-SCT for high grade NHL

Agressive NHL, Age 18-65 years plus one of the following criteria:
1. Primary refractory disease
2. Relapse < 12 months after first line therapy plus 1 RF according to IPI
3. Relapse after HD and autologous SCT
4. Indication for HDT, no autologous Transplantat available

Salvage Therapie I:
ICE, R-ICE, DHAP, R-DHAP

Salvage Therapie II:
ICE, R-ICE, DHAP, R-DHAP

CR, PR, SD

Flu/Bu/Cy

Rituximab

No Rituximab

Off Study
Aggressive B-NHL - Relapse
Results of allo SCT – DSHNHL R3
Progression Free Survival, n=81

Glass et al.
Thanks for your attention!