Autologe Transplantation in ungewöhnlicher Indikation

SARKOME
Principles

HD: Application of high doses of cytotoxic agents that may ablate patient’s marrow

TBI/TLI: Total Body Irradiation/dose/volume radiotherapy ablates patient’s marrow

Followed by retransfusion of autologous hematopoietic stem cells to reconstitute

Aim: Application of one or more chemotherapeutic agents in high dose
Today

- Ewing sarcoma
  - Disease
  - Selected overview on the literature
  - Discussion relapsed disease, localized disease, metastatic disease
- Rhabdomyosarcoma
  - Disease
  - Selected overview on the literature
  - Discussion
- Non-RMS Soft tissue sarcoma
  - Diseases
  - Selected overview on the literature
  - Discussion
- Osteosarcoma
  - Disease
  - Selected overview on the literature
  - Discussion
- CONCLUSION
Ewing Sarkom

Weichteil 15%

Knochen 85%

Kopf und Hals 4.0%
Clavicula 1.0%
Humerus 4.5%
Thoraxwand 23%
Ulna/Radius 2.0%
Becken 23.0%
Hand 0.5%
Femur 11%
Fibula/Tibia 15%
Fuß 1.0%

Alters und Geschlechtsverteilung
Metastases

Response

Site

Size

Age


British Journal of Cancer (2001) 85(11), 1646–1654
<table>
<thead>
<tr>
<th>study</th>
<th>patients (pts)</th>
<th>status at transplant</th>
<th>regimen</th>
<th>control (c) pts</th>
<th>survival</th>
<th>author</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retrosp. 84-92</td>
<td>79 MET</td>
<td>49% CR 44% PR 5% PD</td>
<td>+TBI MEC, ME, M, E, CYC VIC-ME</td>
<td>289 cMET</td>
<td>5y EFS MET/cMET 19%/27% p=0.9</td>
<td>Fröhlich et al. 1999</td>
</tr>
<tr>
<td></td>
<td>52 REL</td>
<td>42% CR 38% PR 17% N.A.</td>
<td>Double ME, CyTbC Cy/Tp-BuM CyTp-ME CyTp-ME-ME</td>
<td></td>
<td></td>
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<tr>
<td>Retrosp. 92-00</td>
<td>54 MET/REL</td>
<td>N.A.</td>
<td>+WB-RT ME</td>
<td>N.A.</td>
<td>5y EFS 22% 29%</td>
<td>Burdach et al. 2003</td>
</tr>
<tr>
<td>Retrosp. 00-11</td>
<td>73 REL</td>
<td>CR PR 1% PD</td>
<td>15 BuMel 38 TreoMEL 20 other</td>
<td>128 cREL</td>
<td>5y EFS 20%/24% REL 6% cREL</td>
<td>Rasper et al. 2014</td>
</tr>
</tbody>
</table>
Value of autologous SCT in patients with relapsed EwS

Further analysis necessary:
Non-HDtx CR/PR patients after 4-6 cycles of relapse chemotherapy

vs

CR/PR Bu-Mel and Treo-Mel-HDtx-patients

p<0.0001
A solid prospective randomised study would be required to assess the benefit from HD in patients with relapsed disease.
## Ewing Sarcoma- prospective studies

<table>
<thead>
<tr>
<th>study</th>
<th>patients (pts)</th>
<th>status at transplant</th>
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<th>control (c) pts</th>
<th>survival</th>
<th>author</th>
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</thead>
<tbody>
<tr>
<td>Prosp. 99-08</td>
<td>103 MET</td>
<td>N.A.</td>
<td>BuMel</td>
<td>N.A.</td>
<td>5Y EFS 43%</td>
<td>Luksch et al. 2012</td>
</tr>
<tr>
<td>Prosp. 02-09</td>
<td>18 MET</td>
<td>CR vgPR</td>
<td>BuMel-BuMEL</td>
<td>N.A. (5 noHD/PD)</td>
<td>3Y EFS 11%</td>
<td>Loschi et al. 2015</td>
</tr>
<tr>
<td>Prosp. 91-99</td>
<td>75 MET</td>
<td>CR vgPR</td>
<td>BuMel</td>
<td>N.A.</td>
<td>5Y EFS 47% (52%) pMets</td>
<td>Oberlin et al. 2006</td>
</tr>
<tr>
<td>Prosp. 99-05</td>
<td>169 MET</td>
<td>CR vgPR SD/PD</td>
<td>136 BuMel 13 ME-ME 20 other</td>
<td>N.A. noHD PD 44 noHD other 68</td>
<td>3Y EFS/ Status prior HD 52% (in CR) 32% (in PR) 24% (in SD/PD)</td>
<td>Ladenstein et al. 2010</td>
</tr>
<tr>
<td>Prosp. 99-09</td>
<td>154 Loc. Poor resp</td>
<td>N.A.</td>
<td>BuMel</td>
<td>N.A. (28 noHD/PD)</td>
<td>5Y EFS 72% 33%</td>
<td>Ferrari et al. 2011</td>
</tr>
</tbody>
</table>
EURO-E.W.I.N.G. 99

Ewing sarcoma- randomized study

R 1
VIDE x 6

R 2
VIDE x 6

R 3
VIDE x 6

Randomisation

VAI
VAI
VAI
VAI
VAI
VAI
VAI

VAC x 7
VAI x 7
VAI x 7
Bu MelHDT
HDT
R2loc: HR localized disease; VAI vs BuMel HD

3327 patients assessed for eligibility

591 localised high risk patients

477 pts with documented eligibility criteria

216 pts included in the R2loc trial from 112 centres, 13 countries

2632 pts without localised high-risk disease

114 Loc-HR pts did not meet eligibility criteria

261 pts not included
  164 patient/clinician reasons
  97 for miscellaneous reasons

107 assigned to VAI rando

103 eligible for R2loc trial
  4 not eligible for R2loc trial

106 received assigned intervention
  1 received Bu-Mel

107 in the intention-to-treat analysis

109 assigned to BuMel rando

101 eligible for R2loc trial
  8 not eligible for R2loc trial

87 received assigned intervention
  17 did not receive any HDT
  5 received another HDT

109 in the intention-to-treat analysis
Benefit of BuMel in a subgroup

**Event Free Survival**

- BuMel, 3-y EFS = 67%
- VAI, 3-y EFS = 53%
- HR = 0.64 (95%CI, 0.43-0.94) p = 0.024

**Overall Survival**

- BuMel, 3-y OS = 78%
- VAI, 3-y OS = 70%
- HR = 0.60 (95%CI, 0.39-0.92) p = 0.019

ITT analysis, 103 events

ITT analysis, 88 deaths
No heterogeneity
3327 patients assessed for eligibility

592 pulmonary met. patients

480 pts with documented eligibility criteria

265 pts included in the R2pulm trial
from 144 centres, 14 countries

2735 pts other than pulmonary met. disease

112 pmets pts did not meet eligibility criteria

215 pts not included
128 because patient/clinical reasons
87 for miscellaneous reasons

132 assigned to VAI & WLI rando
131 eligible for R2pulm trial
1 not eligible for R2pulm trial

120 started assigned intervention
2 received BuMel
6 early stop of Tx due to progression
4 no information

132 in the intention-to-treat analysis

133 assigned to BuMel rando
130 eligible for R2pulm trial
3 not eligible for R2pulm trial

100 received assigned intervention
30 did not receive BuMel HD
1 received another HD
2 received BuMel + WLI

133 in the intention-to-treat analysis
No difference

Event Free Survival

ITT

BuMel, 3-y EFS = 55%

VAI+WLI, 3-y EFS = 51%

HR = 0.82 (95% CI, 0.58 – 1.15)  p = 0.24

Overall Survival

BuMel, 3-y OS = 68%

VAI+WLI, 3-y OS = 68%

HR = 0.96 (95% CI, 0.65 – 1.40)  p = 0.82
### Subgroup effect

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Hazard Ratio (95 CI)</th>
<th>P-value interaction</th>
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</thead>
<tbody>
<tr>
<td>Age &lt;12 years</td>
<td></td>
<td>0.08</td>
</tr>
<tr>
<td>Age 12-16 years</td>
<td></td>
<td></td>
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<tr>
<td>Age 18-25 years</td>
<td></td>
<td></td>
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<tr>
<td>Age &gt; 25 years</td>
<td></td>
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<tr>
<td>Recruiting group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EORTC</td>
<td></td>
<td>0.22</td>
</tr>
<tr>
<td>UK</td>
<td></td>
<td></td>
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<tr>
<td>France</td>
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<td>GPOH</td>
<td></td>
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<tr>
<td>COG</td>
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<td>Accrual period</td>
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<td>&lt; Nov 2003</td>
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<td>2003-2007</td>
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<td>&gt; March 2007</td>
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<tr>
<td>Primary tumour volume</td>
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<tr>
<td>&lt; 200 ml</td>
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<td>0.07</td>
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<tr>
<td>&gt; 200 ml</td>
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<tr>
<td>Primary tumour site</td>
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<tr>
<td>Limb</td>
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<td>0.48</td>
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<tr>
<td>Axis</td>
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<tr>
<td>Size of the largest nodule</td>
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<td></td>
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<tr>
<td>&lt;1 cm</td>
<td></td>
<td>0.09</td>
</tr>
<tr>
<td>&gt;1 cm</td>
<td></td>
<td></td>
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<tr>
<td>Pulmonary nodules</td>
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<tr>
<td>Unique</td>
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<td>0.90</td>
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<tr>
<td>Multiple</td>
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<tr>
<td>Histological response</td>
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<tr>
<td>&lt;10% cells</td>
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<tr>
<td>10-29 % cells</td>
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<td></td>
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<tr>
<td>&gt;30% cells</td>
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<tr>
<td>Overall</td>
<td></td>
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</tr>
</tbody>
</table>

BuMel better | VAI + WLI better
Discussion

HD in localized disease

Prospective Study; ISG/SSG group
Prospective, randomized; EE99 group

Benefit from BuMel- HD
in a subgroup of patients with poor histological response
Disseminated disease, stratification criteria

Fig 2. Outcome according to univariate parameters at diagnosis in the unselected patients with primary disseminated multifocal Ewing sarcomas. OS, overall survival; EFS, event-free survival; BM, bone marrow; pEFS, probability of event-free survival.
Dose intensity in patients with disseminated disease

INT- 0091
VAVA vs VACA/IE

AEWS0031
VDC/IE vs VDC/IE compressed

EE 99

A

B

Patients

Events

3- yrs pEFS ± SD

≤ 14 years

182

61

0.40 ± 0.05

< .001

> 14 years

182

145

0.19 ± 0.03

0.1

0.2

0.3

0.4

0.5

0.6

0.7

0.8

0.9

1.0

0

1

2

3

4

5

6

7

8

Time (years)

3- yrs pEFS ± SD

≤ 14 years

99

61

0.40 ± 0.05

< .001

> 14 years

99

61

0.19 ± 0.03
Prospective randomized clinical trial

Staging MRI, CT, PET + 99mTC

VIDE INDUcTION

1 2 3 4 5 6

HSCC

STAGING MRI, CT

STAGING MRI, CT

STAGING e(n)

STAGING Metastase(n)

OPERATION RANDOMISATION

VAC 1 2 3 4 5 6 7 8

TreoMei VAC 1 2 3 4 5 6 7 8

QoL QoL QoL
Discussion

HD in disseminated disease

Experimental, benefit not proven

Randomized clinical trial ongoing; results pending
Rhabdomyosarcoma

4 years, embryonales RMS: 85%

14 years, alveolar metastatic RMS <10%

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Sub-groups</th>
<th>Pathology</th>
<th>Post surgical stage (IRS group)</th>
<th>Site</th>
<th>Node stage</th>
<th>Size &amp; Age</th>
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<td>Low</td>
<td>A</td>
<td>Favourable</td>
<td>I</td>
<td>Any</td>
<td>N0</td>
<td>Favourable</td>
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<td>B</td>
<td>Favourable</td>
<td>I</td>
<td>Any</td>
<td>N0</td>
<td>Unfavourable</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>Favourable</td>
<td>II, III</td>
<td>Favourable</td>
<td>N0</td>
<td>Any</td>
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<tr>
<td></td>
<td>D</td>
<td>Favourable</td>
<td>II, III</td>
<td>Unfavourable</td>
<td>N0</td>
<td>Favourable</td>
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<td>Standard</td>
<td>E</td>
<td>Favourable</td>
<td>II, III</td>
<td>Unfavourable</td>
<td>N0</td>
<td>Unfavourable</td>
</tr>
<tr>
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<td>F</td>
<td>Favourable</td>
<td>II, III</td>
<td>Any</td>
<td>N1</td>
<td>Any</td>
</tr>
<tr>
<td></td>
<td>G</td>
<td>Unfavourable</td>
<td>I, II, III</td>
<td>Any</td>
<td>N0</td>
<td>Any</td>
</tr>
<tr>
<td>High</td>
<td>H</td>
<td>Unfavourable</td>
<td>II, III</td>
<td>Any</td>
<td>N1</td>
<td>Any</td>
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<tr>
<td>study</td>
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</tr>
<tr>
<td>Retros p 84-94</td>
<td>27 MET</td>
<td>100%CR</td>
<td>+WB-RT MEC +TLI Single MEC /BCNU</td>
<td>N.A.</td>
<td>2Y EFS 36%</td>
<td>Koscielniak et al. 1997</td>
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<td></td>
<td>9 REL</td>
<td>CR PR N.A.</td>
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<td>N.A.</td>
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<tr>
<td>Prosp.</td>
<td>70 MET</td>
<td>N.A.</td>
<td>consecutive courses of high dose TpMel CyTp Mel</td>
<td>N.A.</td>
<td>3Y OS 42%</td>
<td>Bisogno et al. 2006</td>
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<tr>
<td>Prosp not random</td>
<td>96 MET</td>
<td>N.A.</td>
<td>45 TpCY-ME</td>
<td>51 oTIE</td>
<td>5Y OS 27% pts 52% cpts</td>
<td>Klingebiel et al. 2008</td>
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<tr>
<td></td>
<td>RMS &amp; RMS-like</td>
<td>N.A.</td>
<td></td>
<td></td>
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<tr>
<td>89-02</td>
<td>112 MET</td>
<td>N.A:</td>
<td>N.A.</td>
<td>N.A.</td>
<td>5y OS 32%</td>
<td>Stiff et al. 2010</td>
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</tbody>
</table>

Rhabdomyosarcoma
NON-RMS

![Image of candies](image-url)
## Soft tissue sarcoma; Non-RMS

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients (pts)</th>
<th>Status at transplant</th>
<th>Regimen</th>
<th>Control (c) pts</th>
<th>Survival</th>
<th>Author</th>
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</thead>
<tbody>
<tr>
<td>Prosp. Rando. 84-94</td>
<td>38 various</td>
<td>N.A.</td>
<td>CaEl</td>
<td>45</td>
<td>3Y OS Pts 32% cpts 49%</td>
<td>Bui-Nguyen et al. 2012</td>
</tr>
<tr>
<td>Retrospl. 97-02</td>
<td>10 DSRCT</td>
<td>PR</td>
<td>various</td>
<td>N.A.</td>
<td>3Y OS 20%</td>
<td>Bertuzzi et al. 2003</td>
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<td>Retrospl. 99-08</td>
<td>14 DSRCT</td>
<td>PR</td>
<td>consecutive courses of high dose TpMel CyTp Mel</td>
<td>N.A.</td>
<td>3Y OS 48%</td>
<td>Bisognio et al. 2010</td>
</tr>
<tr>
<td>Retrospl. 99-07</td>
<td>36 DSRCT</td>
<td>REL/PR</td>
<td>various</td>
<td>N.A.</td>
<td>3Y OS 40%</td>
<td>Cook et al. 2012</td>
</tr>
<tr>
<td>Retrospl. 95-06</td>
<td>14 DSRCT</td>
<td>PR</td>
<td>various</td>
<td>N.A.</td>
<td>2Y OS 51%</td>
<td>Phillipe et al. 2012</td>
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<tr>
<td>Retrospl. 91-12</td>
<td>41 DSRCT</td>
<td>Various NON High dose</td>
<td>N.A.</td>
<td>2Y EFS 42%</td>
<td>2Y EFS 42%</td>
<td>Wong et al. 2013</td>
</tr>
</tbody>
</table>
High dose treatment in soft tissue sarcoma

Author`s conclusions

No benefit from high dose chemotherapy in RMS and NON-RMS soft tissue sarcoma in children and adolescents

No benefit from high dose chemotherapy in adult type soft tissue sarcoma

Most studies were done without any control arm

One prospective randomized study showed no benefit from high dose chemotherapy
Osteosarcoma

Adolescents and young adults

Elderly
OSTEOSARCOMA

Metastases

Response to induction chemotherapy

Resectablility

Age
<table>
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<tr>
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<td>Retros p 92-04</td>
<td>53 REL/Ref</td>
<td>N.A.</td>
<td>Tp</td>
<td>N.A.</td>
<td>5Y OS 52%</td>
<td>Marec-Berard et al. 2013</td>
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<tr>
<td>Prosp.</td>
<td>19 MET</td>
<td>N.A.</td>
<td>MECa</td>
<td>N.A.</td>
<td>3Y OS 42%</td>
<td>Hong et al. 2015</td>
</tr>
</tbody>
</table>
EURAMOS-1; Marina et al., 2014

Kempf-Bielack et al, 2006

Marec-Berard et al, 2014
Discussion

High dose chemotherapy is an experimental treatment
Many retrospective studies
Lack of clinical data
i.e. status prior transplant missing

Selection Bias
Reporting Bias
Various baseline characteristics
Heterogenous groups of patients

A high risk experimental treatment should be assessed in a controlled clinical trial setting