Paper del trasplantament de progenitors hematopoètics en el tractament del limfoma de Hodgkin l’era dels nous fàrmacs

Diada Internacional de la Societat Catalana de Hematologia i Hemotèrapia
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Carmen Martínez
Hematòleg Consultor
Unitat Trasplantament Hematopoètic
Servei d’Hematologia, ICMHO
Hospital Clínic, Barcelona
Current paradigm of HL treatment

First-line therapy

- ABVD
- BEACOPP
- Stanford V
- + Radiotherapy

- Cure rate 80%
- Chemosensitive Relapse
- Primary refractory
- Early relapse

Salvage therapy + ASCT

Progressive disease or relapse

Conventional QT+RT
Allogeneic SCT
New drugs ± Allo
Palliative care
EBMT classification of transplant procedures for adults with HL—2015

<table>
<thead>
<tr>
<th>Disease risk</th>
<th>Sibling donor</th>
<th>Well-matched URD</th>
<th>Alternative donor</th>
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<tr>
<td>First remission</td>
<td>GNR/III</td>
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<td>Chemosensitive relapse, prev auto no</td>
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<tr>
<td>Chemosensitive, prev auto yes</td>
<td>S/II</td>
<td>S/II</td>
<td>CO/III</td>
<td>CO/III</td>
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GNR = generally not recommended; D = developmental, further trials are needed; S = standard of care generally indicated in suitable patients; CO = clinical option, can be carried after careful assessment of risks and benefits.
### EBMT classification of transplant procedures for adults with HL—2015

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ASCT is the standard therapy for chemosensitive HL relapsing after 1st Line Chemotherapy

BNLI Trial

Mini-BEAM + ABMT vs Mini-BEAM

<table>
<thead>
<tr>
<th></th>
<th>N. of patients</th>
<th>TRM</th>
<th>EFS (3 yrs)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mini-BEAM</td>
<td>20</td>
<td>9</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Mini-BEAM + ABMT</td>
<td>20</td>
<td>5</td>
<td>53</td>
<td>0.025</td>
</tr>
</tbody>
</table>

Linch et al, Lancet 1992
ASCT is the standard therapy for HL Relapsing after 1st Line CT

HDR1 Trial (GHSG/EBMT)

Dexa-BEAM + ASCT vs Dexa-BEAM

N = 161 Early, late and multiple relapse

- 2 x Dexa-BEAM
  - CR or PR
  - 2 x Dexa-BEAM

- 2 x Dexa-BEAM
  - CR or PR
  - BEAM + PBSCT

Schmitz et al, Lancet 2002
Aggressive conventional chemotherapy compared with high-dose chemotherapy with autologous haemopoietic stem-cell transplantation for relapsed chemosensitive Hodgkin’s disease: a randomised trial  

Schmitz et al, Lancet 2002

N=161

Freedom from treatment failure (%)

BEAM-HSCT
Dexa-BEAM

Months after randomisation

p=0.0187
Age is not a limitation for autologous SCT

Carmen Martínez et al, GELTAMO, Submitted 2016
...but commorbidities should be taken into account!

Hematopoietic Cell Transplant Comorbidity Index (HCT-CI)

Charlson Comorbidity Index (CCI)

Carmen Martínez et al, GELTAMO, Submitted 2016
Not all Relapsing Patients do so Well after an Autologous Stem Cell Transplantation

Predictors of poor response:
- Primary refractory disease
- Early (<12 months) relapse
- Advanced stage at relapse
- Extranodal involvement
- Bulky disease
- B-symptoms
Is further improvement in the ASCT setting possible?

- PET-CT: standard imaging test in lymphoma management
  - Inclusion of PET/CT evaluation in the ASCT
  - Risk adapted-therapeutic programs
- Use new drugs
  - Increase response rate prior to ASCT
  - Maintenance therapy after ASCT
Impact of PET-negativity before transplant on ASCT outcome

Gentzler et al, BJH 2014

Akhtars et al, BMT 2013
Ofatumumab-ESHAP GELTAMO trial
Impact of PET on ASCT outcome

C. Martínez et al, GELTAMO, Br J Haematol 2016
PET-adapted sequential salvage therapy with brentuximab vedotin followed by augmented ifosamide, carboplatin, and etoposide for patients with relapsed and refractory Hodgkin’s lymphoma: a non-randomised, open-label, single-centre, phase 2 study

BV 1.2mg/kg days 1, 8 and 15 (two 28d cycles)

PET

ICE x 2

ASCT

N=46 ‡ 76% PET-ve

Treated according to treating physician

Moskowitz, Lancet Oncol 2015
Brentuximab Vedotin + Bendamustine: An Effective First Salvage Therapy in R/R HL prior to ASCT

**Design**
- Phase I/II treatment combination study
- 55 patients
- 1.8 mg/kg brentuximab vedotin D1; 90 mg/m² bendamustine D1–2, every 3 weeks, at least 2 cycles, up to 6 cycles in an outpatient setting

**Efficacy**
- **ORR: 93%**
- **CR: 74%**
- Peripheral blood stem cells collection adequate

**Safety**
- Premedication was required for combination therapy
- The most common AEs were infusion-related reactions (56%): pyrexia (26%), chills (20%), dyspnoea and nausea (15% each), flushing (13%)

La Casce et al. ASH 2014
Phase I-II trial of Brentuximab Vedotin in Pre-transplant Induction and Consolidation for Relapsed or Refractory HL.

GELTAMO

Brentuximab Vedotin*: 1.8 mg/Kg, 1st day ESHAP and day +21 after 3rd ESHAP (c/21 – 28d)

PBSC

ESHAP

ASCT / BEAM

± Radiotherapy (if Bulky)

BV post-ASCT (3 doses)
Phase I + Phase II

- N=36
  - Primary refractory 21 (58%)
  - Relapse 15 (5 early)
- Stem cell collection: 24 patients (no failures)
- Evaluable for response n=24
  - ORR 96%
  - CR 83%

García-Sanz,….Martínez C. ASH 2015
A Randomized, Double-Blind Placebo-Controlled Phase 3 Trial of SGN-35 vs Placebo in High-Risk HL Patients Undergoing and ASCT (AETHERA Trial)

Inclusion criteria:
- >18 years
- Primary refractory HL
- HL relapse:
  - CR < 12 months
  - Extranodal

SGN-35 (brentuximab vedotin) 1.8mg/kg/3w, 16 cycles post-transplant vs. placebo

Median PFS 43 vs. 24 months

Moskowitz C, Lancet, March 2015
Overall survival from relapse after an ASCT. The experience of the LWP EBMT/GITMO

- N=462
- Salvage therapy after ASCT failure
  - 64% CT/RT
  - 29% AlloSCT
  - 8% 2nd ASCT

- Median follow-up of survivors 50 months (75% of cases > 34 months)

39.5% (95% CI: 35-44) at 3 years
29.7% (95% CI: 25-34) at 5 years

C. Martínez et al. Ann Oncol 2013
**EBMT classification of transplant procedures for adults with HL—2015**

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Sureda et al, BMT 2015
EBMT Registry: SCT for HL 1992-2012

HL: Type of SCT By Year

Number of SCT

AutoSCT

AlloSCT
RIC vs MAC in allo-SCT: 1990-2009

RIC or conventional conditioning by year

The European Group for Blood and Marrow Transplantation
HLA identical sibling vs MUD: 1990-2009

HLA identical sibling vs MUD by year

The European Group for Blood and Marrow Transplantation
AlloSCT using conventional conditioning regimens is associated a high NRM

Restrospective study form IBMTR, Gajewski JL, JCO 1996

- n= 100
- Sibling donor
- Prior to alloSCT
  - 89 pts with active HL
  - 50 pts KS < 90%
  - 27 active infection
- Results:
  - SG 21% 3 y
  - SLE 15% 3 y
  - Relapse 65%
We Have Been Able to Reduce NRM with RIC Protocols

Estimate of the NRM and PFS based on a COX model, adjusted by all covariates with impact on the outcomes. RR and p values from multivariate Cox model.

Sureda et al, JCO 2008
Myeloablative Versus Reduced Intensity AlloSCT in recent years
A Retrospective Analysis of LWP-EBMT

Genadieva-Stavrik et al, accepted
RIC vs. MAC: Event Free Survival

P = 0.09

Genadieva-Stavrik et al, accepted
AlloRIC offers better results than non-transplant strategies. The GITMO experience.

Overall survival from autograft

Sarina et al. *Blood* 2010;115:3671-7
Comparison of alloRIC vs. chemo/radiotherapy strategies after autoSCT failure: the experience of the LWP-EBMT

Probability of OS vs. Months after ASCT failure

N = 462

- alloRIC: 48%
- Chemo/Radiotherapy: 32%

p = 0.08
Haploidentical SCT with busulfan-based RIC and post-transplant cyclophosphamide as GVHD prophylaxis in relapsed/refractory HL: Spanish experience

Relapse at 2 years 24% (95%CI: 14-41)

NRM at 1 year 21% (95%CI: 12-38)
Haplo vs. conventional donors in R/R HL
LWP-EBMT retrospective study

Months after allo-SCT

- Haploidentical, 46%
- Unrelated Donor 44%
- HLA id sibling, 38%

N=709

C. Martínez, EBMT 2016
Relapse rate remains a major issue after alloSCT

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Relapse Rate</th>
<th>Impact of disease status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alvarez et al, 2006</td>
<td>47% (3 yrs)</td>
<td>2.5 (1.2 – 5.6), p = 0.01</td>
</tr>
<tr>
<td>Anderlini et al, 2008</td>
<td>55% (2 yrs)</td>
<td>2.9 (0.9 – 8.8), p = 0.05</td>
</tr>
<tr>
<td>Sureda et al, 2008</td>
<td>58% (5 yrs)</td>
<td>1.51 (0.95 – 2.39), p = 0.08</td>
</tr>
<tr>
<td>Robinson et al, 2009</td>
<td>59% (5 yrs)</td>
<td>2.1 (1.5 – 2.9), p &lt; 0.001</td>
</tr>
<tr>
<td>Claviez et al, 2009</td>
<td>44% (5 yrs)</td>
<td>2.1 (1.0 – 4.4), p = 0.04</td>
</tr>
<tr>
<td>Devetten et al, 2009</td>
<td>47% (2 yrs)</td>
<td>----</td>
</tr>
<tr>
<td>Sureda et al, 2012</td>
<td>59% (3 yrs)</td>
<td>2 (1.6 – 3), p = 0.01</td>
</tr>
</tbody>
</table>

~ 40-60%
Disease status is the most important predictive factor for relapse

Sureda et al. Haematologica 2012
Impact of PET-negativity before transplant on AlloSCT outcome

N= 27

Ortiz V, Diada Internacional Societat Catalana Hematologia, 2016
Patients with R/R HL who received reduced intensity allo-SCT post brentuximab vedotin

Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N=19*</th>
</tr>
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<tbody>
<tr>
<td>Median age, years (range)</td>
<td>31 (23–55)</td>
</tr>
<tr>
<td>Prior chemotherapy regimens, median (range)</td>
<td>5 (3–8)</td>
</tr>
<tr>
<td>Prior ASCT, n</td>
<td>18/19</td>
</tr>
<tr>
<td>Prior XRT, n</td>
<td>10/19</td>
</tr>
<tr>
<td>Best response to brentuximab vedotin, %</td>
<td>CR: 42%; PR: 42%; SD: 11%; PD: 5%</td>
</tr>
<tr>
<td>Number cycles of brentuximab vedotin, median (range)</td>
<td>8 (2-16)</td>
</tr>
<tr>
<td>Disease status at time of allo-SCT</td>
<td>CR : 37%; PR: 37%; SD: 11%; PD: 16%</td>
</tr>
</tbody>
</table>

* Treated at City of Hope or Seattle Cancer Care Alliance/Fred Hutchinson Cancer Center

Chen R et al. Oral presentation at ICML 2013, Lugano, Switzerland
Brentuximab pre-allo:
post-transplant clinical outcomes

- The addition of BV did not adversely affect engraftment, GVHD or OS

<table>
<thead>
<tr>
<th>Metric</th>
<th>Value</th>
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<tbody>
<tr>
<td>Median follow-up, months</td>
<td>25.6</td>
</tr>
<tr>
<td>2 - year OS, %</td>
<td>79.3 (CI: 56.0, 91.1)</td>
</tr>
<tr>
<td>2 - year PFS, %</td>
<td>59.3 (CI: 43.9, 71.7)</td>
</tr>
<tr>
<td>2 – year PFS in CR patients, %</td>
<td>71.4 (CI: 40.3, 88.3)</td>
</tr>
<tr>
<td>2 - year PFS in non-CR patients, %</td>
<td>54.6 (CI: 37.5, 68.9)</td>
</tr>
</tbody>
</table>

Chen R et al. Oral presentation at ICML 2013, Lugano, Switzerland
PD-1 inhibitors

Nivolumab
Pembrolizumab

ORR 53%-87%
Safety and Efficacy of Allogeneic HSCT after Treatment with Programmed Cell Death 1 (PD-1) Inhibitors
Merryman et al ASH 2015

- Retrospective analysis of alloSCT outcome after PD-1 inh (nivolumab or pembrolizumab)

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<th>Characteristics</th>
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<tr>
<td>Number of treatment lines prior to antiPD-1</td>
<td>4 (2-8)</td>
</tr>
<tr>
<td>Prior ASCT</td>
<td>79%</td>
</tr>
<tr>
<td>Cycles of antiPD-1</td>
<td>8 (3-20)</td>
</tr>
<tr>
<td>Salvage therapy between antiPD-1 and alloSCT</td>
<td>74%</td>
</tr>
<tr>
<td>Time between last dose of antiPD-1 and alloSCT</td>
<td>130 days (7-260)</td>
</tr>
<tr>
<td>Disease status at transplant: CR / Refractory</td>
<td>63% / 16%</td>
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<tr>
<td>RIC regimen</td>
<td>100%</td>
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Safety and Efficacy of Allogeneic HSCT after Treatment with Programmed Cell Death 1 (PD-1) Inhibitors
Merryman et al ASH 2015

- **Toxicity**
  - 3 cases of VOD (16%) † one fatal
  - 180-day CI of acute GVHD I-II 32%, III-IV 11%
  - 1 year CI of chronic GVHD 30%
  - 4 treatment-related death: 1 VOD, 3 severe acute GVHD within 14 days of transplant
  - 6 patients: febrile syndrome with elevated transaminases (n=3), rash (n=4), and arthralgias (n=1) shortly after transplant

- **Efficacy**
  - Relapse 3 patients
  - Median follow-up 10 (3-23) months † 1y OS 78%, PFS 67%
  - 1 year CI of relapse 11%
  - 1 year CI of NRM 22%
Conclusions

• The introduction of PET in the evaluation of disease status before ASCT and of new drugs is “already changing” the landscape of relapsed / refractory HL

• Results of ASCT will improve with:
  • Better selection of ASCT candidates
  • Better disease response before ASCT
  • Maintenance tx after ASCT in high risk patients

• With respect to allo-SCT:
  • More information is needed
  • BV can improve the results of allo-SCT if used as a “bridge to”
  • Caution should be taken with the use of check point inhibitors
  • Outcome of haplo-SCT do not seem to differ from “standard sources”