Classical Hodgkin Lymphoma - relapse

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Learning Objectives

• To understand the relevance of prognostic factors at relapse
• To understand the treatment pathway in R/R Hodgkin's
• To appreciate the (lack of) evidence base for what is done
• To understand how new agents are changing the treatment paradigm in relapsed disease
Summary

- Scale of the problem
- Prognostic factors
- Salvage therapy
- Autologous stem cell transplantation (ASCT)
- Brentuximab
- Nivolumab
- Allogeneic stem cell transplantation (AlloSCT)
- CAR T-cells
- Current clinical trials
- Barts Guidelines
- Case studies x 2
- Key messages
- Challenges
Scale of the problem

• Early stage: 10%
• Advanced stage: 10% won’t achieve CR; 20-30% will subsequently relapse

• Of these, ~50% will be cured with salvage therapy

• Primary refractory disease: Progression or non-response during induction treatment or within 90 days of completion

Kuruvilla 2011
Primary resistant/relapsed disease

• Small but challenging population
• Repeat biopsy recommended
  • In all relapse ? change in histology
  • Consider in those with residual FDG-avid lesions post therapy - confirm active disease
• Tissue type patient and siblings

Collins 2013
Prognostic factors

- Intensity of 1st line therapy (*Josting 2010*)
  - Relapse post BEACOPP more challenging than relapse post ABVD
- Time to relapse (*Josting 2000, Pfreundschuh 1994*)
  - 5y OS
    - Primary refractory: 26%
    - Early relapse (<12m): 46%
    - Late relapse (>12m): 71%
- Extranodal involvement prior to salvage (*Martin 2001*)
- Presence/absence of systemic symptoms prior to salvage (*Moskowitz 2001*)
- PS at time of salvage (*Ferme 1995*)
Prognostic factors

PET status post salvage: probably the most important predictor of outcome

- PET –ve post salvage – 3-5y PFS of > 70%
- PET +ve post salvage – 3-5y PFS 25-30%
- PET –ve post second line salvage – EFS >80%

Jabbour 2007, Moskowitz 2010, Moskowitz 2011
Salvage chemotherapy

- induce PET–ve CR
- minimize toxicity to stem cell compartment

**Aim of treatment in younger patients with no significant comorbidities: induce remission and proceed to ASCT**

Collins 2013
Salvage chemotherapy

- First-line salvage – all single arm phase II trials

Table I. Chemotherapy regimens in relapsed classical HL.

<table>
<thead>
<tr>
<th>Regimen</th>
<th>ORR (%)</th>
<th>CRR (%)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICE (ifosfamide, carboplatin, etoposide)</td>
<td>88</td>
<td>26</td>
<td>Moskowitz et al (2001)</td>
</tr>
<tr>
<td>IVE (ifosfamide, epirubicin, etoposide)</td>
<td>85</td>
<td>37</td>
<td>Proctor et al (2001)</td>
</tr>
<tr>
<td>MINE (mitoxantrone, ifosfamide, vinorelbine, etoposide)</td>
<td>75</td>
<td>34</td>
<td>Ferme et al (1995)</td>
</tr>
<tr>
<td>IVOx (ifosfamide, etoposide, oxaliplatin)</td>
<td>76</td>
<td>32</td>
<td>Sibon et al (2011)</td>
</tr>
<tr>
<td>IGEV (ifosfamide, gemcitabine, vinorelbine)</td>
<td>81</td>
<td>54</td>
<td>Santoro et al (2007)</td>
</tr>
<tr>
<td>GVD (gemcitabine, vinorelbine, liposomal doxorubicin)</td>
<td>70</td>
<td>19</td>
<td>Bartlett et al (2007)</td>
</tr>
<tr>
<td>Mini-BEAM (carmustine, etoposide, cytarabine, melphalan)</td>
<td>84</td>
<td>32</td>
<td>Colwill et al (1995)</td>
</tr>
<tr>
<td>DexaBEAM (dexamethasone, carmustine, etoposide, cytarabine, melphalan)</td>
<td>81</td>
<td>27</td>
<td>Schmitz et al (2002)</td>
</tr>
<tr>
<td>ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin)</td>
<td>73</td>
<td>41</td>
<td>Aparicio et al (1999)</td>
</tr>
<tr>
<td>ASHAP (doxorubicin, methylprednisolone, cytarabine, cisplatin)</td>
<td>70</td>
<td>34</td>
<td>Rodriguez et al (1999)</td>
</tr>
<tr>
<td>DHAP (dexamethasone, cytarabine, cisplatin)</td>
<td>89</td>
<td>21</td>
<td>Iosting et al (2002b)</td>
</tr>
<tr>
<td>DHAOx (dexamethasone, cytarabine, oxaliplatin)</td>
<td>74</td>
<td>43</td>
<td>Rigacci et al (2010)</td>
</tr>
<tr>
<td>Bendamustine (NB, more heavily pre-treated cohort)</td>
<td>53</td>
<td>33</td>
<td>Moskowitz et al (2013)</td>
</tr>
</tbody>
</table>

OS: 70-90%
CR: 20-55%

ORR, overall response rate; CRR, complete response rate.
Salvage – how do you choose?

• Use an established regimen which is familiar to treating centre.

• Tailor to individual patient needs
  – Avoid cisplatin in renal impairment
  – Avoid ifosfamide in patients at high risk of ifosfamide-induced encephalopathy (previous cisplatin / concomitant opioids or CYP2B6 inhibitors)

_Collins 2013_
Salvage – how much?

• No published evidence

• Consensus: 2 cycles of a multi-agent regimen then re-evaluation using CT-PET

• *Criteria to proceed to ASCT: PR by CT criteria*

*Collins 2013*
Salvage – what next?

PET –ve → stem cell harvest (?after #3 salvage) and ASCT

PET +ve → 2nd line salvage
Which second line salvage regimen?

- Choose another – GEM-P, mini-BEAM, ICE, DHAP....
- Bendamustine
- Brentuximab vedotin (BV)
- Combination Benda + BV (LaCasce Blood 2015)
  - Phase I/II single arm study
  - N=45
  - ORR 93%, CR 82%
  - Infusion reactions 56%
Brentuximab vedotin

First new drug to be approved in Hodgkins since 1977

Anti-CD30 monoclonal antibody conjugated to MMAE (= vinca alkaloid)
1.8mg/kg IV D1 every 21 days up to 16 cycles
SEs: peripheral neuropathy, bone marrow toxicity, lung toxicity (don’t give with gemcitabine/bleomycin or concurrently with mediastinal RT)
Efficacy of BV as bridge to ASCT

- *Eyre, BJH 2017*
  - UK-wide retrospective study
  - 99 SCT-naïve R/R
  - Non-toxic bridge to SCT in 34%
  - Deferred SCT (inadequate response to BV) in 27%
  - 39% never reached SCT with PFS of 3.0 months
The role of Brentuximab vedotin

- Recent evaluation by NICE informed by national audit
- Now approved for baseline commissioning:
  - R/R HL post-ASCT
  - R/R HL after at least 2 previous therapies when ASCT or multi-agent chemotherapy not an option (pre-SCT) (as of June 2018)
  - Re-use in patients being bridged to alloSCT or DLI
- Licensed for maintenance in HR patients following ASCT (AETHERA study) but not approved by NICE for this indication
Autologous stem cell transplantation

Conditioning regimen: BEAM most popular worldwide

2 randomised trials demonstrated significant benefit of ASCT over chemo alone (FFTF not OS)

• *Linch, Lancet 1993*
  • BNLI: 3y EFS 53% vs 10%

• *Schmitz, Lancet 2002*
  • GHSG: FFTF at 3y 55% vs 34%
If unfit for ASCT...

- No prospective studies
- Survival without ASCT (if in CR post salvage) \( (Longo \ 1992, \ Bonfante \ 1997) \)
  - Primary refractory: 0-8% survive >8y
  - Early relapse (<12m): 11% 20y OS
  - Late relapse (>12m): 22% 20y OS
- Combined modality therapy
- Single agent chemotherapy (vinblastine, lomustine, etoposide, gemcitabine)
- Multiagent oral regimens
  - PECC (Prednisolone, etoposide, CCNU (lomustine), chlorambucil)
  - ChlVPP (chlorambucil, vinblastine, procarbazine, prednisolone)
  - LD56 (Vinblastine, methotrexate, lomustine, chlorambucil, dexamethasone, bleomycin)
- Brentuximab vedotin following 2 previous therapies
- Consider clinical trial options
Other potential agents

• Everolimus
  – Oral inhibitor of MTOR
  – Large multicentre study (n=57) ORR 42%, 5 CRs, median PFS 9m
     (Johnston, Blood 2012 (abstract))
  – Well tolerated

• Lenalidomide
  – Immunomodulatory agent
  – 2 small phase II studies in HL
     • n=15, 2 PRs (Kuruvilla, Blood 2008)
     • n=36, ORR 19.4%, 13.9% had SD>6m (Fehniger Blood 2011)
Relapse >5 years post primary therapy

- Rare but does occur
- Data scarce
  - majority of reported cases did not undergo ASCT
- May not require ASCT but it is a reasonable option

Collins 2013
Relapse post ASCT

- Outcomes poor, especially if within 6-12 months
- Median OS 25-32 months
- Aim: to attain sufficient response to allow alloSCT

Collins 2013
Brentuximab vedotin

• **Pivotal phase II study** *(Younes 2012)*
  • In 102 CD30+ relapsed patients post SCT
    • Objective responses in 75%
    • CR in 34% (median duration of response 20.5 m in this group)
    • Median PFS 5.6m
    • Of note, patients who did not achieve CR at first re-staging were unlikely to achieve CR with further therapy
    • Only 8 proceeded to alloSCT

• **Chen, Blood 2012**
  • Retrospective cohort of patients (n=18) who proceeded to RIC alloSCT after BV
    • One yr PFS and OS 92% and 100%; TRM 0%
The role of Brentuximab vedotin

Re-evaluate following 3-4 cycles

- **CR**: early consolidation with alloSCT or continue up to 16 cycles
- **PR**: early alloSCT
- **SD**: consider risks vs benefits of continuation
- **PD**: discontinue

*Fedale 2015*
Checkpoint Inhibitors (CPI)

- Remove the T cell inhibition induced by tumour cells

- Anti-PD1 monoclonal antibodies:
  - Nivolumab
  - Pembrolizumab

- Anti-PD-L1 monoclonal antibodies:
  - Avelumab

- Genetically determined vulnerability in HL – consistent amplification of 9p seen. Locus for PD-L1 and PD-L2 genes
## Data on CPIs in R/R HL

<table>
<thead>
<tr>
<th>Antibody</th>
<th>ORR (%)</th>
<th>CR (%)</th>
<th>PFS</th>
<th>Follow-up</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>69 (63-75)</td>
<td>16 (NR)</td>
<td>mPFS 14.7m (11.3-18.5)</td>
<td>18m</td>
<td>Armand JCO 2018</td>
</tr>
<tr>
<td>N=243</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CheckMate 205</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>69 (62-75)</td>
<td>22 (17-29)</td>
<td>PFS@9m 63%</td>
<td>At 12m</td>
<td>Chen JCO 2017</td>
</tr>
<tr>
<td>N=210</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>KEYNOTE 087</td>
</tr>
</tbody>
</table>

Excellent single agent activity (lower CR rate) with favourable toxicity

EHA Education Session 2018
Side effects of CPI

**Nivolumab**
- Fatigue (25%)
- Infusion-related reactions (20%)
- Rash (16%)
- Pyrexia (14%
- Arthralgias (14%)
- Pruritus (10%)
- Diarrhoea (10%)
- Asymptomatic lipase elevation
- Neutropenia
- Pneumonitis in 2 patients that resolved with steroids

**Pembrolizumab**
- Pyrexia (11%)
- Hypothyroidism (10.5%)
- Diarrhoea (6.7%)
- Fatigue (6.7%)
- Headache (6.2%)
- Rash (6.2%)
- Nausea (5.7%)
- Grade 3/4: neutropenia, dyspnoea, diarrhoea
- 4.3% discontinued due to TR-AEs: myocarditis, myelitis, myositis, pneumonitis, CRS

No deaths attributable to treatment in either study
Role of CPIs

• Nivolumab:
  – 3mg/kg IV every 2w for up to 2y
  – NICE approved for R/R Hodgkins after treatment with ASCT and BV

• Pembrolizumab:
  – 200mg IV every 3w
  – FDA approved March 2018 for refractory HL or failed > 3 lines of therapy.
  – Under review by NICE. Expected publication date August 2018.
The future for new agents

- Lots of combination studies ongoing
- Durability of responses and toxicities need further investigation
- Is this really a better strategy than sequential use
  - BV + Nivolumab (E4412 study) *(Diefenbach 2017)*
    - 19 R/R patients
    - ORR 89%, CR 50%
    - 2 developed pneumonitis, fatal in 1
Allogeneic stem cell transplantation

- Reduced intensity conditioning
- Chemo-sensitivity at time of transplant most important prognostic indicator
- TRM has improved over time
  - <10% in <50y
  - 15% in 50-70y
- PFS 20-40% at 2-4 yrs; OS 35-60% 2y post
- Donor availability: no significant difference in PFS/OS between donor types (*EBMT Registry study, Martinez JCO 2017*)

Collins 2013
CPI and alloSCT

• Possibility of increased GvHD due to modulation of antigen-specific T cell responses

• Multicentre retrospective study (Merryman Blood 2017)
  – n=39 (79% with HL)
  – Median of 62d (range 7-260) between last dose CPI and allo
  – Grade 2-4 aGVHD in 44%; Grade 3-4 aGVHD in 23%
  – cGVHD in 41% by 1y
  – 1 year non-relapse mortality 11%

Remain vigilant
CAR T cells

- 2 studies published in HL
  - *Wang JCO 2017*:
    - n=18
    - Phase I
    - CD30 specific T cells
    - 39% PR rate with median PFS 6m
  - *Ramos JCI 2017*:
    - n=9
    - Phase I dose escalation
    - 2 CR, 3 transient stable disease

- Other trials underway:
  - NCT01316146,
  - NCT02690545,
  - NCT02917083

Microenvironment/tumour immunology clearly different to B NHLs
## Current clinical trials open in the UK

<table>
<thead>
<tr>
<th>Trial</th>
<th>Description</th>
<th>Phase</th>
<th>Sponsor</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ADCT-301:</strong></td>
<td>Monoclonal antibody with PBD warhead</td>
<td>I Escalation (first in human)</td>
<td>ADC Therapeutics SARL</td>
<td>Kings/Oxford &lt;br&gt; Preliminary results presented at ASH. Currently closed to recruitment due to case of GBS</td>
</tr>
<tr>
<td><strong>CheckMate 744:</strong></td>
<td>Nivolumab + BV after failure of first line therapy followed by BV + Benda in those with sub-optimal response</td>
<td>II</td>
<td>BMS</td>
<td>Numerous sites</td>
</tr>
<tr>
<td><strong>Keynote-204:</strong></td>
<td>Pembrolizumab vs BV</td>
<td>III</td>
<td>Merck</td>
<td>Worldwide &lt;br&gt; UCLH in UK</td>
</tr>
</tbody>
</table>

**On the horizon:** ANIMATE – phase II NCRI badged study: Nivolumab monotherapy in those fit for ASCT who fail to reach CMR after 1st/2nd line salvage

[https://clinicaltrials.gov](https://clinicaltrials.gov)
Barts Health
Treatment Guidelines

Relapsed/Refractory disease

Transplant ineligible

- ChIVPP
- or
- ChIVPP-vincristine

2nd Relapse

Brentuximab vedotin (NICE TA446)
For R/R disease after 2 previous therapies and cannot have an ASCT

Transplant eligible

IGEV x 2

PET -ve (Deauville 1-3)

IGEV x 1
SC harvest

LEAM/BEAM ASCT

2nd Relapse

Brentuximab (NICE TA426)
followed by AlloSCT if eligible

PET +ve (Deauville 4-5) but non-progressive

Progressive disease

(1) Further salvage e.g. Bendamustine [To be approved at Cancer DTC] / mini-Beam/ DHAP/ GEM-P/ ICE
(2) Chemo-sensitive patients: consolidate with RIC alloSCT or auto-allo tandem depending on response and availability of stem cells
(3) Brentuximab vedotin (NICE TA446)

3rd Relapse

Nivolumab (NICE TA426) or Brentuximab vedotin re-treat (NICE TA446)
Case Studies

x 2
DR, DoB: 16/1/1980

- 2013: Stage II NS HL with mediastinal bulk resulting in SVCO and thrombosis.
- ABVD x 6 to PD
- Oct 2013: IGEV x 2 to PD
- Nov 2013: Brentuximab to PR post #5 (D4)
- Mini-BEAM x 2 (D3)
- 13.5.14: Flu/Cy Sib alloSCT
- June 2014: PD
- 23.7.16: CSA stopped
- 7.10.14: 3 x DLI
- May 2015: RT to neck/axillae
- 2016: PD – LD56
- Died 8/10/16
Y.M. DoB 30/8/84

- Jan 2011 – Stage IIA Hodgkins lymphoma treated with ABVD x 4
- July 2011 – disease progression treated with IGEV x 4 (very good response post #3)
- Nov 2011 - further disease progression
- Dec 2011 – Local radiotherapy to mediastinum and supraclavicular fossa
- Feb 2012 – BEAM ASCT
- April 2012 – Flu/Cy RIC sibling alloSCT. Outcome at D100 – CMR
- Aug 2012 - ?mild gut GvHD (no biopsy performed) treated with short course of 1mg/kg prednisolone with rapid resolution of symptoms
- Oct 2012 – CSA discontinued
- Feb 2013 – PB chimerism 100% donor (CD3) / 99% donor (CD15)
- April 2013 – PET – CMR
- March 2014 – daughter Thea born
Key messages

- Cure is currently possible in 50% of R/R patients
- PET post salvage most important predictor of outcome
- No data to support one salvage regimen over another
- Aim to induce remission and proceed to ASCT
- Relapse post ASCT: new drugs – BV and nivolumab; aim for allo
- Non-transplant candidates: BV, single agents, multi-agent PO regimens
Challenges

• The lack of evidence!
  – How do we integrate the data out there to direct patient care?
• The need for validated biomarkers to aid clinical decision making
  – Can we predict who will get R/R disease?
  – (But if we could, would we treat them differently?)
• Improving our CR rate with salvage
• Better understanding of the role of BV/CPI
  – More may not necessarily be better....
Thank you for your attention

Any questions?