Hodgkin Lymphoma Immunotherapy

David Joske

(with grateful thanks to Gavin Cull for use of his case and most slides)

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Hodgkin Lymphoma

First described by Thomas Hodgkin in 1832.
A B-cell lymphoma not expressing B-cell surface antigens.
Biological hallmark is large inflammatory response.
Four variants, little effect upon prognosis.
Incidence peaks: adolescents & young adults, then again in elderly.
Often presents with itch, large mediastinal mass.

Reed-Sternberg cells
17 year old male

- Classical Hodgkin lymphoma (nodular sclerosis subtype) diagnosed September 2014
- Multi-agent chemotherapy completed April 2015 (CMR; early relapse)
- Gemcitabine/rituximab 2 cycles
- BEAM + ASCT June 2015
- Relapsed disease August 2015
  - R-HiDICE with Brentuximab Vedotin (2 cycles)
  - IFRT (36 Gy)
- Progressive disease January 2016
17 year old male

• Referred to SCGH
• Commenced Nivolumab fortnightly 3mg/kg IVI
• Admitted shortly faster 1st infusion with chest pain and shortness of breath
17 year old male

- Admitted to ICU
- Pleural drainage
- Pericardial drainage
- Commenced ChlVPP
- Improved
  - Discharged home from ICU
- Nivolumab continued
  - 3-weekly infusion
Brentuximab Vedotin Mechanism of Action

Brentuximab vedotin (SGN-35) ADC
- monomethyl auristatin E (MMAE), potent antitubulin agent
- protease-cleavable linker
- anti-CD30 monoclonal antibody

1. ADC binds to CD30
2. ADC-CD30 complex traffics to lysosome
3. MMAE is released
4. MMAE disrupts microtubule network
5. G2/M cell cycle arrest
6. Apoptosis
Five-year survival and durability results of brentuximab vedotin in patients with relapsed or refractory Hodgkin lymphoma

BV 1.8mg/kg IV over 30 mins
Once every 3 weeks
Up to 16 cycles
Median cycles = 10
Figure 1 Summary of 5-year follow-up results

A

B

SCGH & PathWest
Clinical and Laboratory Haematology
CR Patients

- 34/102 (33%)
- Median duration of response not reached
- 5 years OS 64% and PFS 52%
- 13 CR patients remain in remission at study closure
  - 4 underwent a consolidative allo-SCT
  - 9 no further treatment (26% of all CR patients)
BV side-effects

- Peripheral neuropathy
  - Incidence 55%
  - Resolution or improvement in 88% after BV
- Nausea
- Fatigue
- Neutropenia
- Diarrhoea
Conclusion

• Among patients with relapsed/refractory Hodgkin lymphoma after ASCT, a substantial fraction of patients who obtained CR with single agent brentuximab vedotin have achieved long-term disease control and may potentially be cured.
Mechanisms of action of novel agents. A) The anti-CD30 antibody component of Brentuximab Vedotin (an anti-CD30 antibody-drug conjugate) binds to the CD30 receptor on HRS cells, which then mediates endocytosis of the complex. After internalisation, MMAE is released via proteolytic cleavage and, when bound to tubulin, disrupts the microtubular network, inducing growth arrest and apoptosis. B) The binding of the PD-1 receptor to PD-1 ligands on HRS cells induces and maintains immune effector cell tolerance, enabling tumour cells to escape immune surveillance. By inhibiting this receptor, T-cell anti-Hodgkin Lymphoma activity is restored.
Background

• PD-1 ligands are overexpressed in R-S cells of classical HL
• Amplification of 9p24.1 upregulates the genes for PD-1 ligands
• The 9p24.1 amplicon also activates JAK-STAT which further induces PD-1 ligand
• EBV infection also increases PD-1 ligand in EBV+ cHL
• Features suggest cHL may be vulnerable to PD-1 blockade
Checkmate 205: Nivolumab in Classical Hodgkin Lymphoma After Autologous Stem Cell Transplant and Brentuximab Vedotin, a Phase 2 Study

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Checkmate 205: Study Design, Cohort B

- Ongoing, multicenter, non-comparative, multi-cohort, international, phase 2 registrational study
- Cohort B: patients with progressive cHL after failure of autologous stem cell transplant (ASCT) followed by brentuximab vedotin

**Inclusion criteria**

- ASCT
- Brentuximab vedotin

- Failure to achieve ≥PR after the most recent treatment; or
- Relapse after CR, or PD after PR or SD

**Nivolumab 3 mg/kg (every 2 weeks)**
Treatment until disease progression or unacceptable toxicity

**Primary endpoint**
- ORR assessed by IRRC

**Secondary endpoints**
- IRRC-assessed CR and PR rate and DOR, duration of CR and PR
- Investigator-assessed ORR and DOR

Minimum follow-up: 6 months (median 8.9 months)

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 Patients may elect to discontinue nivolumab and proceed to hematopoietic SCT

 ORR was defined as the percentage of treated patients with a best overall response of CR or PR per the 2007 IWG criteria for malignant lymphoma; best response recorded between first dose and initial objectively documented progression

 IRRC = independent radiologic review committee; IWG = International Working Group
# Patient Characteristics and Disposition

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients (N = 80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), median (range)</td>
<td>37 (18–72)</td>
</tr>
<tr>
<td>Age &lt;65 years, n (%)</td>
<td>77 (96)</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>51 (64)</td>
</tr>
<tr>
<td>Previous lines of therapy,(^a) median (range)</td>
<td>4 (3–15)</td>
</tr>
<tr>
<td>(\geq5) lines of therapy, n (%)</td>
<td>39 (49)</td>
</tr>
<tr>
<td>Previous radiation therapy, n (%)</td>
<td>59 (74)</td>
</tr>
<tr>
<td>Previous ASCT treatments, n (%)</td>
<td>80 (100)</td>
</tr>
<tr>
<td>1</td>
<td>74 (93)</td>
</tr>
<tr>
<td>(\geq2)</td>
<td>6 (8)</td>
</tr>
</tbody>
</table>

\(^a\)Excluding high-dose preparative regimen prior to ASCT

- At database lock (DBL):
  - 51 patients (64%) remained on treatment
  - Median number of doses received at DBL was 17 (range 3–25)
- 29 patients (36%) discontinued; the main reasons for treatment discontinuation:
  - Disease progression (n = 13)
  - Stem cell transplantation (allogeneic SCT, n = 5; ASCT, n = 1)
### Objective Response Rate and Best Overall Responses to Therapy

<table>
<thead>
<tr>
<th></th>
<th>IRRC (N = 80)</th>
<th>Investigator (N = 80)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective response rate, n (%)</strong></td>
<td>53 (66)</td>
<td>58 (73)</td>
</tr>
<tr>
<td>95% CI</td>
<td>55–76</td>
<td>61–82</td>
</tr>
<tr>
<td><strong>Best overall response, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete remission</td>
<td>7 (9)</td>
<td>22 (28)</td>
</tr>
<tr>
<td>Partial remission</td>
<td>46 (58)</td>
<td>36 (45)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>18 (23)</td>
<td>18 (23)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>6 (8)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Unable to determine</td>
<td>3 (4)</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

*No post-baseline tumor assessment available before or on the day of subsequent therapy (if any) or assessment not available

*No radiographic assessment after the first dose

- Discordance in CR between IRRC and investigators was largely based on FDG-PET scan interpretation and was not considered to meaningfully impact clinical activity interpretation, as 13/19 investigator-assessed CR were assessed at least as PR by the IRRC
- IRRC ORR was 72% in patients (n = 43) with no prior response to their most recent brentuximab vedotin
Tumor Burden Change from Baseline (All Response-Evaluable Patients)

- All but 1 responder had a reduction of ≥50% from baseline in tumor burden
- This patient had a negative FDG-PET scan
Survival

- PFS rate at 6 months was 77% (95% CI 65–85)
- After a median follow-up of 8.9 months, with 24 events (23 progression, one death) median PFS was 10.0 months
- OS rate at 6 months was 99% (95% CI 91%–100%)

Per IRRC assessment
NA, not available
## Adverse Events

### Drug-Related AEs in ≥10% of Patients

<table>
<thead>
<tr>
<th>Patients with a drug-related event, n (%)</th>
<th>Any grade</th>
<th>Grade 3–4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>20 (25)</td>
<td>0</td>
</tr>
<tr>
<td>Infusion-related reaction</td>
<td>16 (20)</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>13 (16)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>11 (14)</td>
<td>0</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>11 (14)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>10 (13)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8 (10)</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>8 (10)</td>
<td>0</td>
</tr>
</tbody>
</table>

*AEs occurring within 30 days of last dose

- **All-cause AEs**: n=79 (99%)
- **Serious AEs**: n=20 (25%)

- **All-cause AEs leading to discontinuation**: n=3 (4%)
  - autoimmune hepatitis
  - ALT/AST increased
  - multi-organ failure due to EB virus–positive T-cell lymphoma

- **Death**: n=3 (4%)
  - disease progression
  - undetermined cause after lost follow-up
  - multi-organ failure due to EB virus–positive T-cell lymphoma

- The most frequently reported select adverse events (regardless of causality)
  - skin (41%)
  - gastrointestinal (26%)
  - hypersensitivity/infusion-related reaction (21%)
  - endocrine (18%)
  - hepatic (10%)
  - renal (5%)
  - pulmonary (1%)

*Same patient (CHL was pathologically confirmed during screening)*
Conclusions

• In this registrational study in patients with cHL who had failed ASCT followed by brentuximab vedotin, nivolumab demonstrated:
  – High IRRC ORR of 66.3%
  – Encouraging preliminary durability of response
    • Median duration of response at database lock: 7.8 months
    • Median PFS of 10.0 months, with ongoing responses (mostly partial responses [58%]) in 62% of patients at data cut-off
  – Acceptable safety profile with AEs mostly grade 1 or 2, consistent with those previously reported with solid tumors

• Nivolumab, an anti–PD-1 monoclonal antibody, is a potentially important new therapy to meet the unmet need in patients with cHL who have progressive disease and limited treatment options
Conclusions

• Brentuximab vedotin and nivolumab are novel immunotherapeutic agents
• Effective in chemo-resistant lymphoma
• In some circumstances may be curative; otherwise could be a so-called bridge to allogeneic BMT
• Financial implications to the health care system are considerable