Trials in Elderly Melanoma Patients (with a focus on immunotherapy)

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Royal Marsden Hospital / Institute of Cancer Research
London

Where we were
Immunotherapy Trials: past and present
Relevance for real world practice

Where we are

<table>
<thead>
<tr>
<th>Normal LDH</th>
<th>Abnormal LDH</th>
</tr>
</thead>
<tbody>
<tr>
<td>n 2-year survival</td>
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</tr>
<tr>
<td>Bedikan JCO 2006</td>
<td>508 18%</td>
</tr>
<tr>
<td>Keilholz JCO 2005</td>
<td>115 22%</td>
</tr>
<tr>
<td>Keilholz* JCO 2000</td>
<td>268 (24-36%)</td>
</tr>
</tbody>
</table>

*case records and trial patients
[] patients with normal LDH but categorised < or > median value within normal limits

Paradigm Shift: Effective Targeted Therapy

48% confirmed response rate (2 complete responses)

Chapman NEJM 2011

5% confirmed response rate (0 complete responses)

Chapman NEJM 2011

Relevance for Real World Practice?

- Critical questions for clinicians and patients (and payers!!)
- Safety study of vemurafenib largest ever drug study in melanoma (3000+ enrolled to date)
- ‘Real world’ population (PS 2, brain mets, more elderly patients (age range 21 to 88))
- Preliminary analysis: safety consistent with clinical trial experience

Larkin ASCO 2012
(Some) Challenges for Targeted Therapy

1) Resistance
2) Chronic side effects (compare cytotoxics)
3) Optimal scheduling
4) Adjuvant setting
5) Cost and access to treatment

Resistance: disease biology

- The paradigm for targeted therapy is to predict resistance mechanism from the outset or sample tissue at progression, analyse and treat rationally (as opposed to best guess)
- In melanoma at least, this may not be easy
- For example, in patients at RMH treated with vemurafenib, 16/42 (38%) of patients were too ill after progression on vemurafenib to receive 2\textsuperscript{nd} line therapy


Resistance: possible solutions

- Knowledge of possible resistance mechanism from the start (e.g. presence of rare subclones detected pretreatment)
- Sensitive non-invasive methods to detect and characterise resistance early
- Combining targeted drugs is touted as a solution but I think this will just delay the emergence of resistance and not solve the problem
- Immunotherapy

Su JCO 2012

Immunotherapy
Trials: past and present

ASCO 2011: Plenary Session

Abstract #LBA4
Twelve versus 36 months of adjuvant imatinib (IM) as treatment of operable GIST with a high risk of recurrence: Final results of a randomized trial (SSGXVIII/AIO)
Abstract #1
Comparison of high-dose methotrexate with a combination of methotrexate, etoposide, and cisplatin in elderly adults with high-risk acute lymphoblastic leukemia (MTX vs. ME): A report from the Medical Oncology Group Study (AALL0232)

Abstract #LBA5
Phase III randomized study of ipilimumab (IPI) plus dacarbazine (DTIC) in patients with unresectable stage III or IV melanoma

Ipilimumab
Melanoma previously untreated
Robert NEJM 2011

Primary endpoint: OS

Ipilimumab (10 mg/kg) + DTIC (850 mg/m²)

No prior Rx

DTIC (850 mg/m²) + placebo

Weeks 1, 4, 7, 10 then DTIC alone q21 to week 22 then SD or PR every 12 weeks as maintenance therapy
**Ipilimumab**  
Melanoma previously untreated  
Robert NEJM 2011, Wolchok ASCO 2011

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<td><strong>Response, %</strong></td>
<td>15.2</td>
<td>10.3</td>
</tr>
<tr>
<td><strong>Duration, median mos</strong></td>
<td>19.3</td>
<td>8.1</td>
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<tr>
<td><strong>PFS, median mos</strong></td>
<td>2.8</td>
<td>2.6</td>
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<td><strong>OS, median mos</strong></td>
<td>11.2*</td>
<td>9.1*</td>
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<tr>
<td><strong>1 yr survival</strong></td>
<td>47.3</td>
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*HR= 0.72; p= 0.0009

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**Ipilimumab**  
Melanoma previously treated  
Hodi NEJM 2010

- **Pre-treated**  
- **Primary endpoint:** OS  
- **Secondary endpoints:** ORR, duration, PFS

<table>
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<tr>
<th>Treatment</th>
<th>Ipil + gp100</th>
<th>Ipil + placebo</th>
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<tr>
<td></td>
<td>n=403</td>
<td>n=137</td>
<td>n=136</td>
</tr>
<tr>
<td>1 yr survival</td>
<td>44%</td>
<td>46%</td>
<td>25%</td>
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<td>22%</td>
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**Ipilimumab**  
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- **Overall survival**

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<th>Subgroup</th>
<th>No. of patients</th>
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<th>gp100 (3 mg/kg)</th>
<th>Hazard Ratio (95% CI)</th>
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<td>133</td>
<td>513</td>
<td>496</td>
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<tr>
<td>No</td>
<td>41</td>
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<td>142</td>
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<td>q 3 weeks x 4 doses</td>
<td></td>
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Immunotherapy vs Signal Inhibition (or, ipi vs vem)

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<th>Vemurafenib</th>
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<tr>
<td>Given how?</td>
<td>Brief course intravenous</td>
<td>Continuous daily oral</td>
</tr>
<tr>
<td>Side effects?</td>
<td>Temporary</td>
<td>Chronic</td>
</tr>
<tr>
<td>Severity?</td>
<td>Can rarely be severe</td>
<td>Mild to moderate</td>
</tr>
<tr>
<td>Prolonged disease control?</td>
<td>Possible</td>
<td>Unknown</td>
</tr>
<tr>
<td>Tumour shrinkage</td>
<td>Slow</td>
<td>Rapid</td>
</tr>
<tr>
<td>Who benefits?</td>
<td>~15% across the board</td>
<td>Almost all with BRAF mutation</td>
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ASCO 2011

Anti PD-1 antibody in cancer
Topalian NEJM 2012

Phase 1
1-10mg/kg
296pts
All prior Rx
(47% >3 prior Rx)

NSCLC 122pts
Melanoma 104pts
RCC 34pts
CRC 19pts
CRPC 17pts

Melanoma
- all prior Rx
  immune 64%
  BRAFi 8%
- at 3mg/kg ORR=41%
- 18pts FU >1year
  13 continuing response

Anti PD-1 antibody in cancer
Topalian NEJM 2012

ASCO 2012
Selected current/future trials

Cutaneous - Advanced
Ipilimumab 3mg/kg vs 10mg/kg (closed)
Ipilimumab + vemurafenib (Phase 1)
(PDL-1 and PD-1 registration studies)

Cutaneous - Adjuvant
Ipilimumab (10mg/m²) vs observation (closed)
Ipilimumab (10mg/m²) vs HDI

Relevance for Real World Practice?
GET IN EARLY WITH
ANTI-CTLA4 OR ANTI-PD-1 / PDL-1

• treatment takes 3 months to work
• don’t wait for patient to be poor prognosis
• ie no time for therapy to take effect
• don’t wait for symptomatic CNS disease
• use targeted agents as ‘rescue palliative therapy’

THERAPEUTIC OPTIONS AND OUTCOMES
GOVERN FOLLOW UP

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Change in the management of melanoma

Screen for 2’s in high risk patients (Stage 3)

CT TAP/MRI
Month 3 then 6-monthly for 3 years

Ipilimumab at first diagnosis of systemic 2’s

BRAFmut
BRAFI +/- MEKi

Where we are
Conclusions

- Ipilimumab first RCT evidence that immunotherapy works!
- Vemurafenib not curative, ipilimumab curative but small
- Immunotherapy ? solution to resistance to targeted therapy
- Safety and efficacy appear no different in the elderly
- High clinical trial recruitment vital for further progress
- Best yet to come targeting PD-1/PDL-1?