Four decades of myeloma

Ken Romeril
Wellington Blood and Cancer Centre
The first recorded case
Sarah Newbury - 1844
Sarah’s Treatment at Barts in 1844

- Hospitalised with multiple fracture of clavicles and right humerus and radius
- Given wine and arrowroot, a mutton chop and a pint of porter daily
- Also treated with a rhubarb pill, an infusion of orange peel and an opiate
- Died suddenly and autopsy revealed that the sternum was replaced by a red substance similar to that seen in Mr McBean (a grocer treated by Dr Bence-Jones)
Move forward to 1974

- Dr Milan Brych ran Auckland Cancer Ward
- We treated myeloma with Melphalan and Pred
- Average survival about 2 years
- Patients with myeloma and renal failure were not treated (at least not in ChCh)
1983 – McElwain and Powles (Marsden) pioneered approach using HDM 140 mg/m²

1987- Treated 6 patients at Wellington but HDM given with no stem cell rescue and some patients did not recover their marrows. This approach abandoned until next decade because of excessive toxicity and advent of new technology.
Move forward to 1994
Success at last!

- Autologous transplantation for myeloma commenced at Wellington Hospital mainly because of new Kobe cell separator and the discovery of the mobilisation of peripheral blood stem cells using growth factors.

- Still using melphalan and cyclophosphamide plus prednisone but VAD induction to preserve stem cells.
“If its alright with you Mr. VAD ... I like a second opinion.”
CIRCOS PLOT GENOME

Nature Reviews | Cancer
Wellington Myeloma Incidence
Depths of remission in MM

Tumour cells

Clinical CR

Long-term remission

Molecular CR

 Cure

1 2 3 4 5 years

10^{-1} 10^{-2} 10^{-3} 10^{-4} 10^{-5} 10^{-6} 10^{-7}

autologous SCT
allogeneic ACT
H Ludwig, JS Miiguel, MA Dimopoulos, A Palumbo, R Garcia Zanz, R Powles, S Lentzsch, W Ming Chen, J Hou, K Romeril et al

“cytogenetic testing is desirable but not mandatory”

LEUKAEMIA 2014 28, 981-992
mSMART: Classification of Active MM

High-Risk (25%)

- FISH
  - Del 17p
  - t(4;14)*
  - t(14;16)
- Cytogenetic Deletion 13
- Cytogenetic Hypodiploidy
- PCLI ≥3%

Standard-Risk (75%)*

- All others including:
  - Hyperdiploid
  - t(11;14)
  - t(6;14)

*Patients with t(4;14), β2M<4 mg/l and Hb≥10g/dl may have intermediate risk disease
A High-Risk Genetic signature is predictive for poor outcome in auto-transplant eligible multiple myeloma patients even with use of novel agents. A single institution study.

Looked at 140 patients on basis of cytogenetics and FISH and analysed their OS

K. Romeril, H Buyck, R Parfitt, C Wood, A d’Souza and R Weinkove
**t(4;14) - 15% of myeloma**

<table>
<thead>
<tr>
<th>Gene</th>
<th>CCND3</th>
<th>CCND2</th>
<th>MAF</th>
<th>MMSET</th>
<th>FGFR3</th>
<th>CCND1</th>
<th>ITGB7</th>
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<tr>
<td>Heatmap of gene expression levels...</td>
<td>Heatmap of protein expression levels...</td>
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Bortezomib mechanisms of action

http://www2.cch.org.tw/tumor/images/drug/durg23.png
Bortezomib plus dexamethasone induction improves outcome of patients with t(4;14) myeloma

Avet-Loiseau et al
How can we achieve cure in Myeloma?

To eradicate the tumor clone: *to achieve and maintain the best possible response*

- A small number of residual tumor cells may persist under control of the immune system for a long time.
- Some long-term survivors do not achieve complete remission (CR) and revert to myeloma-like profile. Not to confuse this with suboptimal response (PR or VGPR).
- Avoid over-treatment.
The Red Baron?
Motto: Hit Him With Everything

http://www.nbbd.com/festivals/warbird/2006/RedBaronDemoTeam.jpg
Current Wellington approach

Transplant eligible
- Induce with 4 cycles of CyBorDex
- Auto-transplant
- Consider consolidation with 4-5 cycles of VTD consolidation

Transplant ineligible > 65 years
- Induction with 9 cycles of either CyBorDex or 9 cycles of VMP as in modified Vista protocol
- Relapsed patients get similar (if Velcade naïve)
- Consider clinical trial novel agents
Study outline

- All new MM auto eligible patients treated in a standard approach with 4 CyBorD cycles
- Diagnostic marrow with FISH and flow studies using 8 colour flow.CD38,138,56,20,19 L.C.
- Stem cell mobilisation with Cyclo – Peg and stored
- A HDM of 200 mg/m2 was performed
- Day 100 marrow for MRD analysis and all patients offered 5 cycles VTD consolidation
Response post 4 cycles

<table>
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<tr>
<th>RESPONSE</th>
<th>PERCENTAGE</th>
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<tr>
<td>CR/nCR</td>
<td>46%</td>
</tr>
<tr>
<td>&gt;VGPR</td>
<td>23%</td>
</tr>
<tr>
<td>PR</td>
<td>23%</td>
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<tr>
<td>SD progressive</td>
<td>6%</td>
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Progression Free Survival
AutoSCT vs. No AutoSCT

Overall Survival
Auto SCT vs. No Auto SCT

Percent survival

Progession Free Survival (months)

Overall Survival (months)

Auto
No Auto
p = 0.05

p = 0.02

45 Auto cases
PFS according to genetic risk

Progression Free Survival
High Risk vs Standard risk

Percent survival

Progression Free Survival (months)

- highRisk
- StandardRisk

p = 0.01
Estimated OS at 36m = 81%
TRIPLE HIT or ULTRA HR

- These are co-segregated adverse FISH lesions
- Include an IgH such as t(4;14) or t(14:16) case
- Also a P53 deletion
- Also a 1Q gain and a 1P deletion
- Confers median survival of 9 months.
- Found 3 cases in our series of 200 auto-transplant cases
CyBOrD induction yields very good CR rates

Allows adequate stem cell harvests

Extra post auto therapy with either VTD consolidation or 5 more cycles of CyBorD will confer excellent OS figures

Once weekly bortezomib schedule has low neuropathy rates and low thrombosis risk

Can overcome some high risk genetics but not double and triple hits and some t (14;16) cases
Monoclonal antibodies

Now several agents that target various CD sites

Daratumamab targets CD38, transmembrane glycoprotein

Has been used in the CASTOR and POLLUX studies in the relapsed / refractory setting

Also Elotuzamab which targets SLAMF7, universal site

ELOQUENT-2 study shows benefit of a MAB + chemo.
Other approaches

- Use of oral PI 's such as in TOURMALINE study
- Check point inhibitors such as Pembrolizamab
- Panbinostat
- CAR-T cell therapy was very promising in a recent paper
Acknowledgements

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