New guidelines for MGUS

Update on MRC Myeloma Trials

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UK Nordic Guidelines on MGUS
Monoclonal Gammopathy of Undetermined Significance

UK Myeloma Forum (UKMF)
Robert Beetham, Judith Behrens, Jenny Bird, Mark Drayson, Shirley D’Sa, Richard Soutar

Nordic Myeloma Study Group (NMSG)
Jan Westin, Ingemar Turesson, Anders Waage, Nina Gulbrandsen, Henrik Gregerson

Myeloma UK (patient advocate group)
Mr Eric Low
### Levels of evidence

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia</td>
<td>Evidence obtained from meta-analysis of randomised controlled trials</td>
</tr>
<tr>
<td>Ib</td>
<td>Evidence obtained from at least one randomised controlled trial</td>
</tr>
<tr>
<td>Ila</td>
<td>Evidence obtained from at least one well-designed, non-randomised study, including phase II trials and case-control studies</td>
</tr>
<tr>
<td>Iib</td>
<td>Evidence obtained from at least one other type of well-designed, quasi-experimental study, i.e. studies without planned intervention, including observational studies</td>
</tr>
<tr>
<td>II</td>
<td>Evidence obtained from well-designed, non-experimental descriptive studies</td>
</tr>
<tr>
<td>III</td>
<td>Evidence obtained from meta-analysis or randomised controlled trials or phase II studies which is published only in abstract form</td>
</tr>
<tr>
<td>IV</td>
<td>Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities</td>
</tr>
</tbody>
</table>

**MGUS does not require therapy**

**Evidence based on observational studies**

**Epidemiology**

**Prognosis**

**Establishing diagnosis**

**Monitoring**
An **M-protein** (or paraprotein) is monoclonal immunoglobulin secreted by an abnormally expanded clone of plasma cells in an amount that can be visualised by immunofixation of serum and/or urine.

M-proteins can be whole (heavy and light chain) or just free light chain immunoglobulin.
Types of plasma cells

Spleen and lymph nodes / secrete IgM
Waldenstroms macroglobulinaemia

2) Bone marrow / secrete IgG, IgA
Multiple myeloma

Mucosal plasma cells secrete IgA
Malignancy is rare
Neoplastic expansions of plasma cells may cause damage:
By what their M-protein does
By other secretions or actions of the neoplastic clone

Diseases caused by M-protein aggregation
- Light chain-cast nephropathy
- AL amyloidosis
- Light chain-deposition disease
- Crystal-storing histiocytosis: adult Fanconi syndrome
- Cryoglobulinemia type I

Diseases caused by M-protein antibody activity
- Mixed cryoglobulinemia type II
- Monoclonal cold agglutinins
- Polyneuropathies
Plasma cell dyscrasias (neoplastic clonal plasma cell expansions) include:

MGUS

AL amyloidosis

Solitary plasmacytoma (skeletal or extra-medullary)

Multiple myeloma

Waldenstrom's macroglobulinaemia other
B cell lymphoma / lymphoproliferative disorder
Definition of MGUS
Monoclonal gammopathy of uncertain significance

M-protein in serum <30g/l
Bone marrow plasma cells <10% and low level infiltration in trephine biopsy
No evidence of other B-cell proliferative disorder
No related organ or tissue impairment

Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders
International Myeloma Working Group  B. J Haem 2003, 121 749-757
Myeloma related organ or tissue impairment (ROTI)

C  calcium >0.25mmol/l above normal / >2.75mmol/l

R  renal impairment attributable to myeloma

A  anaemia 2g/dl below normal or <10g/dl

B  bone lesions lytic or osteoporosis with compression fracture

O  other symptomatic hyperviscosity, amyloidosis, recurrent bacterial infection
Epidemiology of MGUS


Normal Minnesota population 21,463 people >50yrs

694 MGUS (2.3%)  
Age 50s 1 - 2%

Male 3.7%  
60s 2 - 4%

Female 2.9%  
70s 4 - 5%

Black x2 whites

69% IgG, 17% IgM, 11% IgA and 3% biclonal

<10g/l 63.5% 30% have immunoparesis
10 - 1.49g/l 16.6% 20% have urinary flc
15 – 19.9 15.4%
20+ g/l 4.5%
Epidemiology of M-proteins
Prevalence >65 yrs age

MGUS  5%
Myeloma  0.1%
Other  <0.1%
# New M-proteins in a Hospital Laboratory

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Mayo (1510)</th>
<th>Malmo (930)</th>
<th>St Helier (200)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MGUS</td>
<td>51%</td>
<td>72%</td>
<td>74%</td>
</tr>
<tr>
<td>Myeloma</td>
<td>24%</td>
<td>19%</td>
<td>16%</td>
</tr>
<tr>
<td>WM</td>
<td>3%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>AL</td>
<td>11%</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Other</td>
<td>11%</td>
<td>6%</td>
<td>7%</td>
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</tbody>
</table>
Prognosis of MGUS

1384 MGUS patients 11,009 years follow up 1960 – 1994

115 progressed –

<table>
<thead>
<tr>
<th>Disease specific RR</th>
<th>75</th>
<th>Myeloma</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>8.5</td>
<td></td>
</tr>
</tbody>
</table>

Overall risk of progression 1% per year
The risk remains even after 25 years

A long-term study of prognosis in monoclonal gammopathy of undetermined significance.
1324 Danish patients with MGUS
Danish death registry North Jutland 1978 - 1993
7785 patient years follow up

868 deaths -409.6 expected

107 cases malignant transformation (6 expected)

76% of that increased risk was not attributable to malignant transformation and occurred in first 4 years

2001 British Journal of Haematology 112: 353±357
Prognostic indicators for malignant transformation of MGUS

IgA and IgM have a higher risk of progression

Paraprotein level  20 year risk of progression to disease:

- 5g/l  14%
- 10g/l  16%
- 15g/l  25%
- 20g/l  41%
- 25g/l  49%

Bone marrow plasmacytosis >5%
% aberrant plasma cells >95%
Bone marrow angiogenesis
Plasma cells in the blood
Abnormal serum free light chain ratio

1148 Mayo patients with MGUS – 87 progressed in a median follow up of 15 years

379 (33%) had an abnormal ratio and their relative risk of progression was higher than those with normal ratios

Multivariate Analysis of Prognostic Factors

<table>
<thead>
<tr>
<th>Prognostic factor</th>
<th>Hazard ratio (95% confidence interval)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal FLC ratio</td>
<td>2.6 (1.7 - 4.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum M protein size</td>
<td>2.4 (1.7 - 3.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IgA, IgM,</td>
<td>2.6 (1.7 - 4.0)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
**Risk stratification model incorporating all 3 predictive factors**  
(Serum M protein <15g/l), IgG subtype, normal FLC ratio (0.26-1.65)

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>No. of patients</th>
<th>Relative risk (95% CI)</th>
<th>Absolute risk of progression at 20 years</th>
<th>accounting for death as competing risk at 20 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-risk</td>
<td>449</td>
<td>1</td>
<td>5%</td>
<td>2%</td>
</tr>
<tr>
<td>Low-Intermediate-risk</td>
<td>420</td>
<td>5.4</td>
<td>21%</td>
<td>10%</td>
</tr>
<tr>
<td>(Any 1 factor abnormal)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-Intermediate-risk</td>
<td>226</td>
<td>10.1</td>
<td>37%</td>
<td>18%</td>
</tr>
<tr>
<td>Any 2 factors abnormal)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-risk</td>
<td>53</td>
<td>20.8</td>
<td>58%</td>
<td>27%</td>
</tr>
<tr>
<td>(All 3 factors abnormal)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
IgG PP < 15g/l
IgA PP < 10g/l
Asymptomatic
No other abnormal results
BJP pos or neg
Uninvolved Igs low or normal

Symptomatic / physical signs suggestive of underlying treatable B lineage disorder
Unexplained abnormal investigation results (blood or X-ray)
  IgG PP > 15g/l
  IgA PP > 10g/l
  FLC >0.5 g/l urine 500mg/l serum
  Any IgD or IgE paraprotein

Distant follow up:
Supply GP & patient with info leaflet
Repeat blood tests 3 monthly initially
Review if abnormality or symptoms arise

Out Patient assessment
Key developments in treatment of myeloma

Gased by John Singer Sargent

MELPHALAN
<table>
<thead>
<tr>
<th>Year Range</th>
<th>Study Description</th>
<th>N</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1958</td>
<td>melphalan</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1964 - 68</td>
<td>cyclophosphamide versus melphalan 276</td>
<td>nd</td>
<td></td>
</tr>
<tr>
<td>1968 - 75</td>
<td>intermittent melphalan +/- P or cyclo 372</td>
<td>nd</td>
<td></td>
</tr>
<tr>
<td>1975- 78</td>
<td>MP vs 3wkly cylco + maintenance 353</td>
<td>nd</td>
<td></td>
</tr>
<tr>
<td>1980 – 82</td>
<td>MP vs MVP + maintenance 532</td>
<td>nd</td>
<td></td>
</tr>
<tr>
<td>1982 – 86</td>
<td>M7 vs ABCM 691</td>
<td>sd</td>
<td></td>
</tr>
<tr>
<td>1986 – 91</td>
<td>ABCM vs ABCMP 1011</td>
<td>nd</td>
<td></td>
</tr>
<tr>
<td>1993 – 02</td>
<td>ABCM vs Cweekly 468</td>
<td>nd</td>
<td></td>
</tr>
<tr>
<td>1993 – 00</td>
<td>ABCM vs Intensive 405</td>
<td>sd</td>
<td></td>
</tr>
<tr>
<td>2002 -</td>
<td>MP vs CTDa / CVAD vs CTD 1871</td>
<td>ip</td>
<td></td>
</tr>
</tbody>
</table>
Overall survival with conventional chemotherapy

In patients randomised to receive ABCM based therapy in MRC V\textsuperscript{th} and VI\textsuperscript{th} myeloma trials

428 patients were aged $\geq 65$
571 patients were aged $<65$

651 patients reached plateau
348 patients did not reach plateau

Median survival (95% CI) in months

<table>
<thead>
<tr>
<th></th>
<th>&lt;65 years</th>
<th>$\geq 65$ years</th>
</tr>
</thead>
<tbody>
<tr>
<td>No plateau</td>
<td>7.9 (6.2-9.0)</td>
<td>3.8 (2.6-4.9)</td>
</tr>
<tr>
<td>Plateau</td>
<td>51.4 (47.2-55.8)</td>
<td>45.0 (41.4-49.1)</td>
</tr>
</tbody>
</table>
Fewer patients aged ≥65 years achieved plateau (60.5% versus 68.7% for younger patients Chi² 7.1 p=0.007)
Achievement of plateau phase and survival from entry stratified by response

**M-protein Response**

Percentage patients reaching plateau

75%  Median  25% survival

Survival in months

Achievement of plateau phase and survival from entry stratified by response
Overall survival by response for 999 ABCM patients

\[ \chi^2 = 1.15, \ P = 0.56 \]
<table>
<thead>
<tr>
<th>Response</th>
<th>percent of all patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete</td>
<td>9</td>
</tr>
<tr>
<td>Partial</td>
<td>55</td>
</tr>
<tr>
<td>Stable</td>
<td>13</td>
</tr>
<tr>
<td>Non-secretor</td>
<td>2</td>
</tr>
<tr>
<td>Progression ab initio</td>
<td>2</td>
</tr>
<tr>
<td>Trial deviation</td>
<td>5</td>
</tr>
<tr>
<td>No data</td>
<td>2</td>
</tr>
<tr>
<td>Death &lt;90 days</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>100</td>
</tr>
<tr>
<td>Response</td>
<td>percent of all patients</td>
</tr>
<tr>
<td>--------------------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>Complete</td>
<td>9</td>
</tr>
<tr>
<td>Partial</td>
<td>55</td>
</tr>
<tr>
<td>Stable</td>
<td>13</td>
</tr>
<tr>
<td>Non-secretor</td>
<td>2</td>
</tr>
<tr>
<td>Progression <em>ab initio</em></td>
<td>2</td>
</tr>
<tr>
<td>Trial deviation</td>
<td>5</td>
</tr>
<tr>
<td>No data</td>
<td>2</td>
</tr>
<tr>
<td><strong>Death &lt;90 days</strong></td>
<td><strong>12</strong></td>
</tr>
</tbody>
</table>

Can we reduce the proportion of patients who do not survive long enough to reap the benefits of anti-tumour therapy?
Deaths within 60 days of entry to MRC myeloma IVth – VIIIth trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Total</th>
<th>Age (yrs)</th>
<th>Trial dates</th>
<th>Induction Treatment</th>
<th>No pts</th>
<th>Total early death</th>
<th>early Deaths % all pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV&lt;sup&gt;th&lt;/sup&gt;</td>
<td>532</td>
<td>&lt;80</td>
<td>1980-1982</td>
<td>MP, MPV</td>
<td>264</td>
<td>37</td>
<td>12</td>
</tr>
<tr>
<td>V&lt;sup&gt;th&lt;/sup&gt;</td>
<td>691</td>
<td>&lt;75</td>
<td>1982-1986</td>
<td>C-weekly-plts</td>
<td>61</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>V&lt;sup&gt;th&lt;/sup&gt;</td>
<td>712</td>
<td>&lt;75</td>
<td>1986-1991</td>
<td>HDM (M140)</td>
<td>15</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>VI&lt;sup&gt;th&lt;/sup&gt;</td>
<td>405</td>
<td>&lt;66</td>
<td>1993-2000</td>
<td>ABCM</td>
<td>202</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>VII&lt;sup&gt;th&lt;/sup&gt;</td>
<td>468</td>
<td>&gt;65 or &lt;65 if HDT contraindicated</td>
<td>1993-2002</td>
<td>ABCM to plateau, ABCM X3 then C-weekly NR</td>
<td>125</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>Total</td>
<td>3107</td>
<td></td>
<td></td>
<td></td>
<td>3107</td>
<td>299</td>
<td>10</td>
</tr>
</tbody>
</table>
Main modes of early deaths

Number of patients

- Pneumonia
- Other infection
- Renal failure
- Vascular
- Sudden death
- Cardiac failure
- Bleed
- Pulmonary Embolus
- Skeletal event
- Treatment withdrawn
- Other
- No Information

Contributing Cause
Mode of death
Main modes of early deaths

Infection
8% neuts <2.0 x 10^9/l
15% neuts 2 - 3 x 10^9/l
1/3 developed at home with delay to hospital in ½
Iv IgG replacement trial nd ?antibiotic prophylaxis
Main modes of early deaths

Renal failure
½ FLC, ¾ hyper Ca
¼ presented with Cr <200
NSAIDs, post chemo dehydration
MERIT trial
## Predicting early deaths

<table>
<thead>
<tr>
<th>Factor</th>
<th>Grouping</th>
<th>Patients surviving &gt;60 days (n=2809)</th>
<th>Early death pts (n=299)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&lt;65</td>
<td>1650 (59)</td>
<td>118 (7.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>≥65</td>
<td>1157 (41)</td>
<td>176 (15.2)</td>
<td></td>
</tr>
<tr>
<td>Performance</td>
<td>Asymptomatic</td>
<td>267 (12)</td>
<td>10 (3.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>status</td>
<td>Minimal symptoms</td>
<td>856 (38)</td>
<td>52 (6.1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Restricted activity / bedridden</td>
<td>1099 (50)</td>
<td>204 (18.6)</td>
<td></td>
</tr>
<tr>
<td>Sβ2M</td>
<td>≤4</td>
<td>637 (28)</td>
<td>29 (4.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>4-8</td>
<td>947 (41)</td>
<td>64 (6.8)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;8</td>
<td>713 (31)</td>
<td>171 (24.0)</td>
<td></td>
</tr>
</tbody>
</table>

Best model sensitivity 67%

J Clin Oncol 2005
MRC 1980 – 1997 so minimum of 7.5 yrs follow up

Melphalan - 845 pts  ABCM - 1622 pts
1372 (54%) achieved stable plateau phase

Overall median survival 3.9 yrs

Median survival from relapse 1.2yrs

Duration of plateau  <1yr  423  (37%)
                 1 – 3yrs  567  (49%)
                      >3yrs  161  (14%)

(no progression or non-myeloma death 221)
Survival following relapse for patients with plateau durations of: < 1 year, 1-3 Years and > 3 Years

\[ \chi^2 = 44.73, \ p < 0.0001 \]
Plateau duration, time to plateau and survival following relapse for:

cases - 225 patients survived >7.5yrs
controls – 225 shortest lived patients
Non-randomised second line treatment

For 612 patients (45% of total) second line treatment was known
Same versus different second line treatment

No at risk:

<table>
<thead>
<tr>
<th></th>
<th>Same</th>
<th>Different</th>
</tr>
</thead>
<tbody>
<tr>
<td>at risk:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Same</td>
<td>232</td>
<td>370</td>
</tr>
<tr>
<td>Different</td>
<td>168</td>
<td>227</td>
</tr>
<tr>
<td></td>
<td>102</td>
<td>131</td>
</tr>
<tr>
<td></td>
<td>67</td>
<td>80</td>
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<td>5</td>
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<tr>
<td></td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

Stratified for beta-2 microglobulin $\chi^2 = 7.85$ $p = 0.005$
Stratified for duration of plateau $\chi^2 = 4.45$ $p = 0.04$
The clodronate trial showed:
Reduced morbidity from skeletal disease
Patients (155) without overt skeletal disease at presentation appeared to benefit more than patients with fractures at presentation
No overall survival benefit

Overall survival by treatment

Overall survival by treatment for those patients presenting with no fractures

χ²=0.94, P=0.33

χ²=8.24, P=0.004
Interferon alpha

In a large meta-analysis there was a significant benefit for the use of interferon.
The magnitude of this effect is small.
It is difficult to justify the use of interferon based on this data.
Immunoglobulin
2 identical heavy chains  (Gene chromosome 14)
2 identical light chains (Gene chromosome 2)
Either Kappa (Gene chromosome 22)
Or Lambda

Normal plasma cell secretion of whole immunoglobulin and free light chains

Kappa Plasma cells
Lambda Plasma cells
### Serum Free Light Chains – Normal Ranges (mg/L)

<table>
<thead>
<tr>
<th></th>
<th>mean</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>κ</td>
<td>8.36</td>
<td>3.3 - 19.4</td>
</tr>
<tr>
<td>λ</td>
<td>13.43</td>
<td>5.71 - 26.3</td>
</tr>
<tr>
<td>κ/λ ratio</td>
<td>0.63</td>
<td>0.26 - 1.65</td>
</tr>
</tbody>
</table>

The serum flc ratio becomes abnormal at much lower levels of malignant flc secretion than are required to overcome renal tubular reabsorption.
Serum flc ratio more sensitive than Bence Jones protein in urine

Non-secretory myeloma (no M-protein detectable in serum or urine by immunofixation)

64 of 2323 patients from MRC Trials 1983 – 1999 had Non-secretory myeloma (3.6%). 28 cases studied. Blood 2001 97, 9: 2900 – 2902
Serum free light chain concentrations (mg/L)

Normal range
12 elevated free $\kappa$ and increased $\kappa/\lambda$ ratio
7 elevated free $\lambda$ with reduced $\kappa/\lambda$ ratio
4 suppression of either $\kappa/\lambda$ or both flc
5 $\kappa/\lambda$ normal or borderline and normal $\kappa/\lambda$ ratio
Changes in serum flc concentrations and clinical status in patients with nonsecretory myeloma.
Free light chain only myeloma
(No whole M-protein in serum. FLC in urine)

MRC trials 1983 – 1999 (13% of all patients)

Kappa FLC only – 122 patients
Lambda FLC only – 103 patients

In all 225 cases serum flc measurements identified the abnormal production of flc.

LANCET 2003 361 489 - 490
Advantages of measuring flc in serum
Malignant flc production must exceed renal threshold for reabsorption before flc become detectable in urine

At time of diagnosis of these 225 patients:
  >60% significant renal morbidity
  >60% significant skeletal morbidity

Could wider use of serum flc assays enable earlier diagnosis
Patient with FLC in urine but urine not sent to the laboratory

False impression of complete remission
Using urine flc assays 26 patients (32%) achieved CR
Using serum flc assays 9 patients (11%) achieved CR
Earlier diagnosis of relapse
Myeloma, free light chains and renal failure

Co-incident pre-existing renal disease
hypercalcaemia
infection / dehydration

Causal histology

Urinary flc/24 hours Percentage patients with renal failure

None 2%
<8 grams 9%
8 – 24 grams 29%
> 24 grams 49% (2362 patients)
SERUM FREE LIGHT CHAIN LEVELS AT ENTRY TO TRIAL

29 patients
monoclonal kappa
(polyclonal lambda)
(mk / pl) flc

32 patients
monoclonal lambda
(polyclonal kappa)
(ml / pk) flc

Normal range

MERIT
MFLC values at entry by dialysis status at 100 days

YES (16)  
NO (34)

Alive and dialysis independent

Lowest level of MFLC measured over first 2 weeks by dialysis status at 100 days

YES (16)  NO (34)

Alive and dialysis independent
Malignant plasma cells
FLC production

Serum free light chains
Grams / l

dexamethasone

Renal excretion
Grams / litre

Plasma exchange 7 x 3 litres
For half of these patients
17 – 587 grams removed

Renal failure
Key developments

Non-intensive therapy
Med survival 2 – 3 years
Melphalan
Cyclophosphamide
Combination eg. ABCM
Key developments

**Intensive therapy**
- Med survival 4 - 5 years
- Induction (stem cell sparing)
- High dose melphalan

**Non-intensive therapy**
- Med survival 2 – 3 years
- Melphalan
- Cyclophosphamide
- Combination eg. ABCM
## MRC myeloma 7 response rates

<table>
<thead>
<tr>
<th>Response Type</th>
<th>Standard</th>
<th>Intensive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>8.5%</td>
<td>44.5%</td>
</tr>
<tr>
<td>Partial response</td>
<td>40.5%</td>
<td>42.3%</td>
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<tr>
<td>Minimal response</td>
<td>17.5%</td>
<td>3.5%</td>
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<tr>
<td>No change</td>
<td>15%</td>
<td>2%</td>
</tr>
</tbody>
</table>

N Eng J Med 2003
MRC VII; Progression-free Survival

![Graph showing progression-free survival rates for Intensive and Standard treatments]

- Proportion surviving
- Survival in months
- Number at Risk

<table>
<thead>
<tr>
<th></th>
<th>Int</th>
<th>Stand</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>199</td>
<td>196</td>
</tr>
<tr>
<td>90</td>
<td>157</td>
<td>142</td>
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<tr>
<td>80</td>
<td>124</td>
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<td>70</td>
<td>87</td>
<td>47</td>
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<tr>
<td>60</td>
<td>65</td>
<td>25</td>
</tr>
<tr>
<td>50</td>
<td>38</td>
<td>16</td>
</tr>
<tr>
<td>40</td>
<td>55</td>
<td>9</td>
</tr>
<tr>
<td>30</td>
<td>27</td>
<td>5</td>
</tr>
<tr>
<td>20</td>
<td>11</td>
<td>3</td>
</tr>
<tr>
<td>10</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

- P-value for Wilcoxon test = <0.01
- P-value for Logrank test = <0.01
Overall Survival - ITT

Number at Risk
- Int: 201, 170, 148, 119
- Stand: 200, 167, 129, 100

Survival in months
- Int: 79, 58, 38, 21, 8, 1, 0
- Stand: 70, 47, 30, 16, 8, 1, 0

Proportion surviving
Overall Survival: $\beta_2m > 8\text{mg/l}$

- 27 trials with 6633 patients
- Excluded MRC Myeloma V

**Graph Details:**
- Proportion surviving
- Intensive
- Standard
- P-value for Wilcoxon test = .0010
- P-value for Logrank test = .0013

**Number at Risk vs Survival in Months:**

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>10</th>
<th>20</th>
<th>30</th>
<th>40</th>
<th>50</th>
<th>60</th>
<th>70</th>
<th>80</th>
<th>90</th>
<th>100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Int</td>
<td>52</td>
<td>43</td>
<td>35</td>
<td>29</td>
<td>18</td>
<td>13</td>
<td>8</td>
<td>4</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Stand</td>
<td>43</td>
<td>27</td>
<td>13</td>
<td>9</td>
<td>8</td>
<td>4</td>
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<td>3</td>
<td>1</td>
<td>0</td>
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Med survival 2 – 3 years
Melphalan
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Combination eg. ABCM
Intensive therapy

Med survival 4 - 5 years
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Non-intensive therapy

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Melphalan
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Combination eg. ABCM

New therapies
Thalidomide
Proteasome inhibitors

Key developments
Myeloma IX Intensive pathway

Bisphosphonate:
- Clodronate
- Zoledronate

Chemotherapy:
- C-VAD: 4-6 courses
- C-TD: 4-6 courses

Randomise

Maintenance:
- Thalidomide
- No Thalidomide

HDM200 + PBSCT (autograft)
Myeloma IX Recruitment - Initial Randomisation
(Intensive pathway)

Thalidomide randomisation = 405 patients
Myeloma IX Non-Intensive pathway

Randomise

Bisphosphonate: Clodronate VS Zoledronate

Chemotherapy: MP VS CTDa

Maintenance: Thalidomide VS No Thalidomide
Thalidomide randomisation = 265 patients
Intensive Arm: Response rates post induction

ORR=87.1%  P=0.016  ORR=74.8%

CTD
n=124

PR 48.4
VPR 19.4
CR 19.4

CVAD
n=127

PR 48.0
VPR 17.3
CR 9.4

P=0.031
Intensive Arm: Response rates post High Dose Melphalan

**ORR=87.8%**

P=0.843

**ORR=86.5%**

CTD  
\[ n=115 \]

CR 51.3

PR 20.9

VPR 15.7

CVAD  
\[ n=111 \]

CR 39.6

PR 33.3

VPR 13.5

P=0.084
Non-Intensive Arm: Response rates post induction

CTDa
n=120

PR 35.0
VPR 25.0
CR 22.5

ORR=82.5%
P<0.001

MP
n=113

PR 38.9
VPR 3.5
CR 6.2

ORR=48.7%
P<0.001
Myeloma IX Laboratory studies

Prospective study of utility of serum flc
Non-secretory / Crypto-secretory (50 patients)
Light chain only (300 patients)
Early indicator of response and relapse

Minimal Residual Disease
Flowcytometry and sflc

Prognostic markers
Sol CD40, CD80, CD138

Cytogenetics and FISH studies

Inherited SNPs and copy number variation
Selected myeloma cells Affymetrix U135 Plus 2.0 expression arrays

Myeloma XI (results for IX, running costs, drug costs)

ACKNOWLEDGEMENTS