Sex Differences in Multiple Myeloma Biology and Clinical Outcomes: Results from 3894 Patients in the Myeloma XI Trial

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Background

• Multiple myeloma (MM) is more common in men than women but the mechanism(s) driving this are not understood.
• In our previous study (Myeloma IX) we found sex disparities in the cytogenetic lesions present in myeloma cells at the time of diagnosis and that female sex was associated with reduced overall survival in the context of treatment with traditional chemotherapy (CVAMP/MP) or thalidomide combinations.
• Here, we evaluate sex differences in almost 4000 patients recruited to the recent UK NCRI Myeloma XI trial, in which treatment exposure to lenalidomide predominated.

Methods

• Myeloma XI recruited 3894 newly diagnosed patients of all ages, with pathways for transplant eligible (TE) and ineligible (TNE) patients.
• Patients received immunomodulatory based induction and maintenance therapies:
  - Induction: CTD, cyclophosphamide, thalidomide, dexamethasone; CRD, cyclophosphamide, lenalidomide, dexamethasone.
  - *Patients with a suboptimal response to induction (<VGPR) were eligible for intensification. Patients with PR/MR were randomised to CVD (cyclophosphamide, bortezomib and dexamethasone) or no further therapy prior to ASCT. Patients with SD/PD all received CVD.

• Patient characteristics were compared using the Fisher’s Exact test for categorical variables and the Wilcoxon-Mann-Whitney test for continuous variables. Progression-free (PFS) and overall survival (OS) were compared using the log-rank test.

• Baseline characteristics were compared using the Fisher’s Exact test for categorical variables and the Wilcoxon-Mann-Whitney test for continuous variables. Progression-free (PFS) and overall survival (OS) were compared using the log-rank test.
• Adverse molecular risk lesions were defined as t(4;14), t(14;16), t(14;20), del(17p), and gain(1q). Standard risk (SR) was defined as the cytogenetic lesion(s) present in myeloma cells at the time of diagnosis and that female sex was associated with reduced overall survival in the context of treatment with traditional chemotherapy (CVAMP/MP) or thalidomide combinations.

Patient characteristics

• Of those recruited 2268 (58%) were male and 1626 (42%) were female, in keeping with the known sex disparity in MM.
• There was no difference in the median age, WHO performance status, ethnicity and most laboratory values of the two groups.

Patient molecular features

• Females more likely to have the molecular risk lesions t(14;16) and del(17p) and had proportionately more HiR and UHiR disease.

Progression-free and overall survival

• There was no difference in PFS or OS between sexes when analysed within different induction regimens (thalidomide or lenalidomide based, not shown). There was no difference in outcome between sexes with and without maintenance therapy.
• There was no difference in PFS (not shown) or OS when we compared males and females within each molecular risk category.

Conclusions

• Molecular lesions that have been associated with outcome remained prognostic in both sexes for both PFS (not shown) and OS.
• There was no significant difference in PFS (not shown) or OS when we compared males and females with each molecular risk lesion.
• In the Myeloma XI trial the female cohort had a higher proportion of the adverse molecular risk lesions (del(17p) and t(14;16)) and were more likely to have UHiR disease.
• Despite this, there was no difference in PFS or OS, either overall or within each of the induction or maintenance randomisation treatment options.
• Molecular risk stratifiers remained prognostic within both the male and female cohorts. There was a trend toward improved outcomes for females with t(14;16) and UHiR disease but this did not reach statistical significance.
• Overall our data suggest that in women the treatment delivered may have been able to overcome some of the adverse effects of the risk lesions present.

Affiliations and contacts


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Conflicts

All authors have no conflicts of interest. For full details of other authors please see abstract book.

PFS and OS by cytogenetic risk

<table>
<thead>
<tr>
<th>Cytogenetic lesion</th>
<th>Males (total n = 2268)</th>
<th>Females (total n = 1626)</th>
<th>p - value</th>
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<tbody>
<tr>
<td>(4;14)</td>
<td>105 (11%)</td>
<td>78 (12%)</td>
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<td>(14;16)</td>
<td>17 (1.8%)</td>
<td>27 (4.2%)</td>
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<td>(14;20)</td>
<td>9 (0.9%)</td>
<td>7 (1.1%)</td>
<td>0.774</td>
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<td>del(17p)</td>
<td>71 (7.4%)</td>
<td>69 (11%)</td>
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<td>gain(1q)</td>
<td>312 (32%)</td>
<td>226 (35%)</td>
<td>0.308</td>
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</table>

Risk status

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<tr>
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<th>Males (%</th>
<th>Females (%</th>
<th>p - value</th>
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<tr>
<td>SR</td>
<td>551 (57%)</td>
<td>333 (51%)</td>
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<tr>
<td>HR</td>
<td>317 (33%)</td>
<td>229 (35%)</td>
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<tr>
<td>UHiR</td>
<td>44 (4.9%)</td>
<td>86 (13%)</td>
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Observation OS t(14;16) OS t(14;20) OS del(17p) OS