Treatment of multiple myeloma with high-risk cytogenetics: a consensus of the International Myeloma Working Group

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The International Myeloma Working Group consensus updates the definition for high-risk (HR) multiple myeloma based on cytogenetics Several cytogenetic abnormalities such as t(4;14), del(17/17p), t(14;16), t(14;20), nonhyperdiploidy, and gain(1q) were identified that confer poor prognosis. The prognosis of patients showing these abnormalities may vary with the choice of therapy. Treatment strategies have shown promise for HR cytogenetic diseases, such as proteasome inhibition in combination with lenalidomide/ pomalidomide, double autologous stem cell transplant plus bortezomib, or combination of immunotherapy with lenalidomide or pomalidomide. Careful analysis of cytogenetic subgroups in trials comparing different treatments remains an important goal. Cross-trial comparisons may provide insight into the effect of new drugs in patients with cytogenetic abnormalities. However, to achieve this, consensus on definitions of analytical techniques, proportion of abnormal cells, and treatment regimens is needed. Based on data available today, bortezomib and carfilzomib treatment appear to improve complete response, progression-free survival, and overall survival in t(4;14) and del(17/17p), whereas lenalidomide may be associated with improved progression-free survival in t(4;14) and del(17/17p). Patients with multiple adverse cytogenetic abnormalities do not benefit from these agents. FISH data are implemented in the revised International Staging System for risk stratification. (Blood. 2016;127(24):2955-2962)

Introduction

Multiple myeloma (MM) is a proliferation of monoclonal plasma cells that produce a monoclonal protein.1 Indications for treatment are based on end-organ damage (hypercalcemia, renal impairment, anemia, bone lesions) and markers of active disease (ie, an involved:uninvolved serum-free light-chain ratio ≥100, bone marrow plasma cells ≥60%, or >1 lesion found on magnetic resonance imaging).2 Response to treatment and survival of newly diagnosed MM (NDMM) is heterogeneous, with median overall survival (OS) ranging from 2 to >10 years. MM is characterized by chromosomal instability, and cytogenetic abnormalities (CA) have an impact on prognosis.1,3 This perspective will define high-risk (HR) CA and provide recommendations for treatment of HR NDMM patients.

Methods

We will describe techniques for identification of CA followed by a discussion of prognostic impact and treatments. This perspective was developed by an international expert panel based on evidence of published studies through November 15, 2015. The statement was drafted and circulated among all panel members, followed by rounds of revision.

Diagnostic techniques for CA

Conventional karyotyping. Karyotyping reveals CA in 20% to 30% of patients, those being mainly numerical abnormalities. Several translocations including t(4;14) are not detected. The normal karyotype in patients with a low proliferation index corresponds to the kinetics of normal bone marrow cells. Abnormal karyotype had an unfavorable impact in the Total Therapy programs.5 Because more sensitive techniques reveal CA in nearly all MM, karyotyping is not a routine test.

Fluorescence in situ hybridization. Fluorescence in situ hybridization (FISH) is performed in interphase cells, thereby overcoming the problem of karyotyping. Purification of CD138-expressing plasma cells or dual staining for cytoplasmic immunoglobulin (Ig) and FISH is required for FISH. Currently, FISH is the standard technique for analysis of CA. Samples are usually screened for CA, which occur in >1% of patients. FISH is a practical cytogenetic tool to detect genomic aberration in situ and to...
enumerate the percentage of cells harboring such abnormalities. It does not detect single-nucleotide variants. For example, TP53 on chromosome 17p is deleted in 7% of myeloma, yet mutated at a much higher frequency in myeloma based on exome sequencing. Knowing these restrictions, FISH testing may include gain (1q), del (1p), t (4;14) (p16q32), t (14;16q32;q23), del (17p13), and a marker for aneuploidy (Table 1). For routine diagnosis, testing of t (4;14) and del (17p13) suffices.

**Singlenucleotide polymorphism-based mapping arrays.** High-resolution genome-wide analysis (GWAS) of single-nucleotide polymorphisms (SNP) detects regions with loss of heterozygosity and numerical abnormalities. SNP mapping arrays identify copy number variations (CNV). Translocations are not usually detected and will require additional FISH.

**Comparative genomic hybridization.** Array-based comparative genomics hybridization is a tool for genome-wide classification of CNVs, which primarily detects numerical abnormalities.

**Gene expression profiling.** Gene expression profiling (GEP) is a technique to identify expression of genes and pathways. Based on RNA expression using microarrays, subgroups of patients are identified with a unique GEP phenotype that partly corresponds to the TC classification. GEP from patients in clinical trials can be used to identify HR profiles with significant prognostic significance.

**Consensus statement.** FISH is the standard approach for identification of primary genetic events and secondary numerical events. SNP-based mapping arrays and CGH are more sensitive techniques to detect small numerical aberrations, and therefore these can be used in clinical trials. GEP profiling is useful for prognostication and may require bioinformatics support.

**High-risk CA**

**IgH translocations.** In MM, primary events are chromosome translocations involving the immunoglobulin heavy chain (IgH) locus and hyperdiploidy, with multiple copies of odd-numbered chromosomes (Table 1).9 IgH translocations are observed in 40% of cases. Frequently involved partner chromosomes/loci are 4p16 (FGFR3/MMSET) (12%-15%), 11q13 (CCND1) (15%-20%), 16q23 (MAF) (3%), 6p21 (CCND3) (<5%), and 20q11 (MAFB) (1%).10 Translocation t (4;14) leads to deregulation of fibroblast growth factor receptor 3 (FGFR3) and multiple myeloma SET domain (MMSET).11,12 Because FGFR3 is not expressed in one third of patients with t (4;14), the target gene is most likely MMSET.13 t (4;14) is associated with impaired progression-free survival/overall survival (PFS/OS).14 Importantly, bortezomib seems to improve the negative prognostic impact of t (4;14).15,16 Prolonged survival was reported in t (4;14) treated with high-dose therapy (HDT) and tandem autologous stem cell transplant (ASCT).19,20 SNP arrays showed the heterogeneous adverse impact of t (4;14) related to concomitant CA.21 Translocation t (14;16) results in deregulation of the c-MAF proto- oncogene and predicts poor outcome.11,12,15,18 An Intergroupe Francophone de Mylome (IFM) analysis showed no adverse impact of t (14;16), possibly because 60% of patients received a double ASCT.23 Translocation t (14;20) results in deregulation of the MAFB oncogene and confers a poor prognosis.12

Table 1. Primary and secondary genetic events that can be identified by FISH

<table>
<thead>
<tr>
<th>Primary genetic events</th>
<th>Secondary genetic events</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgH translocation</td>
<td>Deletion</td>
</tr>
<tr>
<td>t (4;14)</td>
<td>1p</td>
</tr>
<tr>
<td>t (6;14)</td>
<td>6q</td>
</tr>
<tr>
<td>t (11;14)</td>
<td>8p</td>
</tr>
<tr>
<td>t (14;16)</td>
<td>13</td>
</tr>
<tr>
<td>t (14;20)</td>
<td>11q</td>
</tr>
<tr>
<td></td>
<td>t (14;20) (p16q32) and t (14;16q32; q23), del (17p13) and a marker for aneuploidy (Table 1). For routine diagnosis, testing of t (4;14) and del (17p13) suffices.</td>
</tr>
</tbody>
</table>

**Translocation t (11;14) results in upregulation of cyclinD1 and was identified as favorable in some studies, whereas it had no impact in others.14-24 This translocation is associated with CD20 expression and a lymphoplasmocytic morphology.** In general t (6;14), t (11;14), gain (5q), and hyperdiploidy do not confer poor prognosis. **Genomic imbalance.** Hyperdiploidy, which occurs in ~50% of NDMM, is associated with improved PFS/OS.15 In the MRC IX trial, coexisting hyperdiploidy did not abrogate the poor prognosis of adverse CA.20 In contrast, in a retrospective analysis, PFS of patients with t (4;14) was negatively affected by del (1p32), del (22q), and >30 structural CA, whereas del (6q) worsened PFS and del (1p32) worsened OS, and >8 numerical changes improved OS in del (17p).21 Modern techniques (GWAS) identify additional CNV above karyotypic hyperdiploidy.22 Del (1q3) predicts impaired PFS/OS when detected by karyotyping.28 The adverse impact of del (1q3) by FISH is associated with del (17p) and t (4;14), del (19q) as single CA does not confer poor survival.12,29 Del (17p) or del (17) has a negative impact on PFS/OS. Deletion of TP53 induces clonal immortalization and survival of tumor cells.30 Patients with ≥3 copies of 1q have a worse treatment outcome, reflecting a dosage effect of genes such as CKB1.12,29,31 Gain (1q) frequently coincides with del (1p32), which confers poor prognosis.21,29,31 Hyperdiploidy is regarded as a poor prognostic CA. It is currently unclear which minimum percentage of cells carrying del (17p) is required for an adverse prognosis or whether this varies with the choice of therapy and stage of disease. Minimal percentages of 20% and 60% have been recommended for del (17p).12,21 An international effort will address this issue in a meta-analysis.

The prognostic impact of CA may vary from diagnosis to (refractory) disease because of the selection of subclonal disease.35 In solitary plasmacytoma or extramedullary disease, del (17p) may occur more frequently.36,37 **Multiple adverse CA.** Among patients with an adverse IgH translocation 62% have gain (1q) compared with 32.4% in controls.12 The frequency of del (17p) is similar in patients without adverse IgH translocations. Among patients with an IgH translocation and/or gain (1q) or del (17p), 20% shared ≥2 CA. When CA occurred in isolation, each lesion had a similar impact on OS. The triple combination of an adverse IgH translocation, gain (1q), and del (17p) was associated with a median OS of 9.1 months.12 Prognostic impact of cosegregation of multiple adverse CA on OS. The IFM showed that in 110 patients displaying either t (4;14) or del (17p), 25 had both abnormalities. In patients with t (4;14), PFS was worse with concomitant del (1p32), del (22q), and/or >30 structural changes, whereas del (13q14), del (1p32), and higher number of CA shortened OS. In patients with del (17p), del (6q) reduced PFS, whereas gain (1q) and del (14) had a protective effect. Del (1p32) shortened OS, whereas >8 numerical changes improved OS.21 Good combined with adverse CA. Gain of 5q (31) improved outcome with hyperdiploidy MM.38 Among patients with hyperdiploidy, trisomies 3 and 5 confer a favorable prognosis.21
In the Myeloma IX study, 58% of patients had hyperdiploidy.\textsuperscript{39} Of these, 61% had ≥1 adverse lesion (t(4;14), t(14;16), t(14;20), gain1q, or del(17p)). OS and PFS were worse in patients with hyperdiploidy plus an adverse lesion, compared with hyperdiploidy alone (median PFS, 23 vs 15.4 months; median OS, 60.9 vs 35.7 months). Alternatively, presence of hyperdiploidy did not change the outcome in patients with an adverse lesion.

Presence of trisomies in patients with t(4;14), t(14;16), t(14;20), or TP53 deletion in MM reduced their adverse impact.\textsuperscript{40}

### Cytogenetic risk classifications

The definition of HR disease is subject to diagnostic and treatment options. With median PFS and OS of transplant-eligible (TE) patients approaching 4 and 10 years, HR disease based on objective criteria. IMWG proposed a model of HR MM defined as at least one of the following: del17p, t(4;14), or t(14;16) determined by FISH.\textsuperscript{15} The Mayo Clinic classification added hypodiploidy and t(14;20) to the definition of HR MM (Table 2).\textsuperscript{44} Later classifications attempted to separate MM into several risk groups. In MRC IX, 3 groups were identified (ie, favorable risk [FR: no adverse IgH translocation, del (17p), or gain(1q)], intermediate risk [IR: 1 adverse CA]), and HR (>1 adverse CA). Median PFS/OS of patients with FR, IR, or HR was 23.5, 17.8, and 11.7 months and 60.6, 41.9, and 21.7 months, respectively.\textsuperscript{12} Ultra-HR was defined as ≥3 CA (2%; median OS, 9 months). These classifications may change with treatment modalities. An example is t(4;14), which may be IR rather than HR when novel agents are given.\textsuperscript{15,45,46} IMWG stated that HR MM should include t(4;14), t(14;16), or del(17p).

### Risk classifications based on FISH

IMWG proposed a model of HR MM defined as at least one of the following: del17p, t(4;14), or t(14;16) determined by FISH.\textsuperscript{15} The Mayo Clinic classification added hypodiploidy and t(14;20) to the definition of HR MM (Table 2).\textsuperscript{44} Later classifications attempted to separate MM into several risk groups. In MRC IX, 3 groups were identified (ie, favorable risk [FR: no adverse IgH translocation, del (17p), or gain(1q)], intermediate risk [IR: 1 adverse CA]), and HR (>1 adverse CA). Median PFS/OS of patients with FR, IR, or HR was 23.5, 17.8, and 11.7 months and 60.6, 41.9, and 21.7 months, respectively.\textsuperscript{12} Ultra-HR was defined as ≥3 CA (2%; median OS, 9 months). These classifications may change with treatment modalities. An example is t(4;14), which may be IR rather than HR when novel agents are given.\textsuperscript{15,45,46} IMWG stated that HR MM should include t(4;14), t(14;16), or del(17p).

### Risk classifications based on FISH and ISS

The combination of International Staging System (ISS) with HR CA reflects tumor mass, patient condition, and genetics. IMWG showed that t(4;14) and/or del(17p) separates FR, IR, and HR from Ultra-HR.

### Table 2. Summary of cytogenetic risk features

<table>
<thead>
<tr>
<th>Cytogenetic abnormality</th>
<th>High-risk</th>
<th>Standard-risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FISH: t(4;14), t(14;16, t(14;20, del(17/17p), gain(1q))</td>
<td>All others including: FISH: t(11;14), t(6;14)</td>
</tr>
<tr>
<td>Nonhyperdiploid karyotype</td>
<td>Karyotype del(13)</td>
<td>GEP: high-risk signature</td>
</tr>
</tbody>
</table>

### Table 3. Survival of MM patients with high-risk FISH compared with those without high-risk FISH

<table>
<thead>
<tr>
<th>FISH</th>
<th>Np/Na</th>
<th>End point</th>
<th>Therapy</th>
<th>Present</th>
<th>Absent</th>
<th>Comment</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>t(4;14)</td>
<td>100/161</td>
<td>3-y OS</td>
<td>VBMCP</td>
<td>24%</td>
<td>64%</td>
<td>E9486</td>
<td>25</td>
</tr>
<tr>
<td>3-y OS</td>
<td>VAD + ASCT × 2</td>
<td>55%</td>
<td>40%</td>
<td>72%</td>
<td>IFM-99</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td>3-y OS</td>
<td>VABMCP</td>
<td>32%</td>
<td>68%</td>
<td>E9486</td>
<td>13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>del17p</td>
<td>37/308</td>
<td>3-y OS</td>
<td>VAD + ASCT × 1/2</td>
<td>50%</td>
<td>78%</td>
<td>E9486</td>
<td>13</td>
</tr>
<tr>
<td>3-y OS</td>
<td>VAD + ASCT × 1</td>
<td>49%</td>
<td>82%</td>
<td>IFM-2005</td>
<td>68</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-y OS</td>
<td>CVAD + ASCT × 1</td>
<td>58%</td>
<td>81%</td>
<td>MRC IX intensive</td>
<td>62</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unfavorable</td>
<td>59/125</td>
<td>3-y OS</td>
<td>MP</td>
<td>26%</td>
<td>48%</td>
<td>MRC IX non-intensive</td>
<td>61</td>
</tr>
<tr>
<td>98/129</td>
<td>3-y OS</td>
<td>Placebo maintenance</td>
<td>69%</td>
<td>72%</td>
<td>MRC IX maintenance</td>
<td>61</td>
<td></td>
</tr>
<tr>
<td>18/111</td>
<td>3-y OS</td>
<td>VBMCP/VBAD +Bz × 2 + ASCT × 1</td>
<td>48%</td>
<td>84%</td>
<td>GEM2005 &lt; 65</td>
<td>63</td>
<td></td>
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<tr>
<td>Thalidomide</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>t(4;14)</td>
<td>57/181</td>
<td>3-y PFS</td>
<td>TD + ASCT × 2 + TD</td>
<td>20%</td>
<td>48%</td>
<td>GIMEMA</td>
<td>102</td>
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<tr>
<td>26/156</td>
<td>3-y OS</td>
<td>VAD + ASCT × 1 + Thal maintenance</td>
<td>44%</td>
<td>79%</td>
<td>HOVON65/GMMG-HD4</td>
<td>29</td>
<td></td>
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<tr>
<td>del17p</td>
<td>21/161</td>
<td>3-y OS</td>
<td>VAD + ASCT × 1 + Thal maintenance</td>
<td>17%</td>
<td>79%</td>
<td>HOVON65/GMMG-HD4</td>
<td>29</td>
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<tr>
<td>Unfavorable</td>
<td>43/302</td>
<td>5-y OS</td>
<td>Thal induction, consolidation, maintenance</td>
<td>56%</td>
<td>72%</td>
<td>Total Therapy 2</td>
<td>18</td>
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<tr>
<td>152/167</td>
<td>3-y OS</td>
<td>CTD + ASCT × 1</td>
<td>59%</td>
<td>82%</td>
<td>MRC IX intensive</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>96/129</td>
<td>3-y OS</td>
<td>CTDa</td>
<td>58%</td>
<td>78%</td>
<td>MRX IX non-intensive</td>
<td>61</td>
<td></td>
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<tr>
<td>99/126</td>
<td>3-y OS</td>
<td>Thalidomide maintenance</td>
<td>45%</td>
<td>76%</td>
<td>MRX IX maintenance</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>17/110</td>
<td>3-y OS</td>
<td>TD + ASCT × 1</td>
<td>56%</td>
<td>86%</td>
<td>GEM2005 &lt; 65</td>
<td>63</td>
<td></td>
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<tr>
<td>Lenalidomide</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t(4;14)</td>
<td>28/102</td>
<td>Median OS</td>
<td>RD in RRMM</td>
<td>18 m</td>
<td>23 m</td>
<td>MM-016</td>
<td>103</td>
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<tr>
<td>26/158</td>
<td>Median OS</td>
<td>RD in RRMM</td>
<td>9 m</td>
<td>15 m</td>
<td>IFM</td>
<td>83</td>
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<tr>
<td>3-y OS</td>
<td>Median PFS</td>
<td>Lenalidomide maintenance</td>
<td>27 m</td>
<td>42 m</td>
<td>IMF-2005</td>
<td>68</td>
<td></td>
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<tr>
<td>6.6%</td>
<td>Median PFS</td>
<td>Lenalidomide maintenance</td>
<td>29 m</td>
<td>42 m</td>
<td>IMF-2005</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td>Unfavorable</td>
<td>1684</td>
<td>3-y OS</td>
<td>RD</td>
<td>77%</td>
<td>86%</td>
<td>Mayo Clinic</td>
<td>76</td>
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<tr>
<td>21/105</td>
<td>2-y OS</td>
<td>RD</td>
<td>76%</td>
<td>91%</td>
<td>E4A03</td>
<td>104</td>
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<tr>
<td>Bortezomib</td>
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<td></td>
<td></td>
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<td></td>
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<tr>
<td>t(4;14)</td>
<td>106/401</td>
<td>4-y OS</td>
<td>VD + ASCT × 1</td>
<td>63%</td>
<td>85%</td>
<td>IFM-2005</td>
<td>68</td>
</tr>
<tr>
<td>53/183</td>
<td>3-y PFS</td>
<td>VTD + ASCT × 2 + BzTD</td>
<td>65%</td>
<td>61%</td>
<td>GIMEMA</td>
<td>102</td>
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<tr>
<td>24/148</td>
<td>3-y OS</td>
<td>VAD + ASCT × 1 + Bz</td>
<td>66%</td>
<td>82%</td>
<td>HOVON65/GMMG-HD4</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>del17p</td>
<td>54/453</td>
<td>4-y OS</td>
<td>VD + ASCT × 1</td>
<td>50%</td>
<td>79%</td>
<td>IMF-2005</td>
<td>68</td>
</tr>
<tr>
<td>16/158</td>
<td>3-y OS</td>
<td>VAD + ASCT × 1 + Bz</td>
<td>69%</td>
<td>82%</td>
<td>HOVON65/GMMG-HD4</td>
<td>29</td>
<td></td>
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<tr>
<td>Unfavorable</td>
<td>18/112</td>
<td>3-y OS</td>
<td>VTD + ASCT × 1</td>
<td>60%</td>
<td>86%</td>
<td>GEM2005 &lt; 65</td>
<td>63</td>
</tr>
<tr>
<td>44/188</td>
<td>3-y OS</td>
<td>VMP/BzTP, BzT/BzP</td>
<td>55%</td>
<td>73%</td>
<td>GEM2005 &lt; 65</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>28/140</td>
<td>3-y OS</td>
<td>VMP</td>
<td>56%</td>
<td>71%</td>
<td>VISTA</td>
<td>72</td>
<td></td>
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</tbody>
</table>

Adapted from Bergsagel et al.\textsuperscript{58}
2 groups with different event-free survival (EFS) and OS within each ISS stage. Combining t(4;14) and del(17p) with ISS stage improved prognostic staging. Neben et al combined ISS with t(4;14) or del(17p). Median PFS after ASCT was 2.7, 2.0, and 1.2 years for the FR group (ISS I, no HR CA), FR (ISS I and HR CA or ISS II/III without HR CA), and HR (ISS II/III and HR CA). Five-year OS were 72%, 62%, and 41%, respectively. Identical results were obtained in the HOVON-65/GMMG-HD4 trial.

The MRC IX study combined ISS and the presence of 0, 1, or >1 adverse CA. Median OS in the ultra-HR group, defined by ISS II or III plus >1 adverse CA, were 9.9 and 19.4 months, compared with OS 67.8 months in the favorable group.

Risk classifications based on FISH, ISS, and lactodehydrogenase. A meta-analysis of randomized trials in NDMM confirmed that combining ISS, serum lactodehydrogenase (LDH), and FISH identifies 4 risk groups including a very HR population (5%-8%). Patients with ISS stage III, elevated LDH, and t(4;14) or del(17p) have a 2-year OS of only 54.6%. More recently, the revised ISS was defined, incorporating HR FISH (t(4;14), t(14;16), and del(17p) with ISS and LDH.

Gene expression profiling. The prognostic impact of GEP by microarray was examined in several studies. The UAMS identified a 70-gene subset as an independent prognostic factor. Presence of a HR signature (13.1%) resulted in a very HR population (5%-8%). Patients with ISS stage III, elevated LDH, and t(4;14) or del(17p) have a 2-year OS of only 54.6%. More recently, the revised ISS was defined, incorporating HR FISH (t(4;14), t(14;16), and del(17p) with ISS and LDH.

mSMART. The Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) criteria use a combination of FISH, plasma cell labeling index, and GEP as tools to identify 3 risk categories (standard risk [SR], IR, HR) for prognostication of patients with NDMM. Patients can be stratified for different therapeutic approaches. However, risk-adapted therapy has not been validated in prospective studies.

Table 4. Survival of high-risk genetic subgroups in randomized, controlled clinical trials of newly diagnosed MM: effect of treatment modalities and novel drugs

<table>
<thead>
<tr>
<th>FISH</th>
<th>N1/N2</th>
<th>End point</th>
<th>Arm 1</th>
<th>Arm 2</th>
<th>Arm 1 (%)</th>
<th>Arm 2 (%)</th>
<th>Comment</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>t(4;14)</td>
<td>26/24</td>
<td>3-y OS</td>
<td>PAD/ASCT/tahmidomide*</td>
<td>VAD/ASCT/bortezomib*</td>
<td>44</td>
<td>66</td>
<td>HOVON65/GMMG-HD4</td>
<td>15</td>
</tr>
<tr>
<td>98/106</td>
<td>4-y OS</td>
<td>VAD</td>
<td>VD</td>
<td>32</td>
<td>63*</td>
<td>IFM-2005</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td>21/23</td>
<td>2-y OS</td>
<td>Thalidomide*</td>
<td>Placebo*</td>
<td>67</td>
<td>87</td>
<td>TT2</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>21/29</td>
<td>2-y OS</td>
<td>Thalidomide-TT2</td>
<td>Bortezomib TT3</td>
<td>67</td>
<td>97*</td>
<td>TT2 vs TT3</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>Del(17p)</td>
<td>21/16</td>
<td>3-y OS</td>
<td>VAD/ASCT/tahmidomide</td>
<td>PAD/ASCT/bortezomib*</td>
<td>17</td>
<td>69*</td>
<td>HOVON65/GMMG-HD4</td>
<td>15</td>
</tr>
<tr>
<td>119/54</td>
<td>4-y OS</td>
<td>VAD</td>
<td>V D</td>
<td>36</td>
<td>50</td>
<td>IFM-2005</td>
<td>68</td>
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<tr>
<td>Nonhyperdiploid</td>
<td>92</td>
<td>3-y OS</td>
<td>VTD</td>
<td>VMP</td>
<td>53</td>
<td>72&quot;</td>
<td>PETHEMA</td>
<td>63</td>
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<tr>
<td>Unfavorable FISH</td>
<td>152/141</td>
<td>3-y OS</td>
<td>CTD</td>
<td>VAD-cyclophosphamide</td>
<td>58</td>
<td>56</td>
<td>MRC IX intensive</td>
<td>62</td>
</tr>
<tr>
<td>96/90</td>
<td>3-y OS</td>
<td>CTD</td>
<td>Placebo MP</td>
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<td>26</td>
<td>MRC IX nonintensive</td>
<td>61</td>
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<tr>
<td>99/98</td>
<td>3-y OS</td>
<td>Thalidomide</td>
<td>Placebo</td>
<td>45</td>
<td>69*</td>
<td>MRC IX maintenance</td>
<td>39</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Bergsagel et al. *Significant better survival outcome.

GEP is emerging as a prognostic tool for risk stratification. New approaches to predict survival include analysis of microRNAs, custom capture mutation analysis, and evaluation of methylation and splicing patterns.

Here we address the treatment choices for patients with HR NDMM based on cytogenetic profile. Recently, 2 reviews addressed the issue of general treatment strategies for HR myeloma. This review covers treatment options for t(4;14) and/or del(17/17p).

Thalidomide. Thalidomide does not overcome adverse impact of HR CA. In the UAMS trial for RRMM, del(13q) by karyotyping had a shorter survival with thalidomide. Three trials studying thalidomide during induction in NDMM (MRC IX: CTD vs CTDa; HOVON50/GMMG-HD2: VAD vs TAD; GEM2005:TD) observed shorter OS in HR CA.61,64 Thalidomide maintenance did not improve survival in HR CA in 3 trials, MRC IX (3-year OS 45% vs 69%), HOVON50 (3-year OS 17% vs 69%) trials and Total Therapy 2 (TT2) (5-year OS 56% vs 72%),15,18,25,61,62,65 In MRC IX, 3-year OS was worse in patients with HR-CA (45%).66 In HOVON50/GMMG-HD2, first PFS was better with thalidomide treatment, but second PFS was significantly shorter, resulting in a reduced OS. In TT2, presence of CA was associated with inferior survival, and a benefit with thalidomide was only observed in a subgroup of patients after 10 years.67

Consensus statement. Thalidomide does not abrogate the adverse effect of t(4;14), t(14;16), t(14;20), and del(17) or del(17p) and gain(1q) CA in TE patients. Conclusive data for elderly or frail patients are not available.

Bortezomib. Several randomized trials have evaluated bortezomib for induction, consolidation, or maintenance treatment in cytogenetic subgroups. In IFM-2005-01, bortezomib/dexamethasone showed a superior response and OS compared with vincristin/doxorubicin/dexamethasone. This combination resulted in a better EFS and OS for patients with t(4;14), but did not improve outcome in del(17p) (4-year OS 50% vs 79%).68 In HOVON65/GMMG-HD4, bortezomib-based induction and maintenance showed an improved outcome for patients with del(17p) (median PFS 26 vs 12 months; 3-year OS 69% vs 17%). At long-term follow-up, this advantage is still present. However, OS remains inferior to patients without del(17p) (3-year OS 85%). In patients with t(4;14), PFS was not better with bortezomib (25 vs 22 months), whereas OS was improved (3-year OS 69% vs 44%) compared with 85% in patients without t(4;14). In the GEM 2005 trial, bortezomib/thalidomide/dexamethasone (VTD) followed by ASCT and maintenance did not improve OS in HR CA (3-year OS 60% vs 88%). The GIMEMA group compared VTD with thalidomide/dexamethasone (TD) for induction and consolidation with double ASCT. In the subgroup of 25% with t(4;14), OS was 69% vs 37% in favor of VTD compared with 74% vs 63% without t(4;14) and/or del(17p). A meta-analysis of 4 randomized trials showed that the odds of posttransplantation complete response (CR) + near CR in bortezomib-treated patients were similar for HR (del(17p) + t(4;14)) and SR cytogenetics (2.44 vs 1.67, n.s.). These trials (1874 patients) showed that bortezomib plus ASCT was superior (PFS 41 vs 33 months) (P < 0.0001). In patients with HR FISH, this was 32 vs 22 months (P < 0.001). PFS benefit was observed in patients with t(4;14) but lacking del(17p) (36 vs 24 months, P = 0.01) and in del(17p) lacking t(4;14) (27 vs 19 months, P = 0.04), but not in patients carrying both CA.67 In TT3, OS was significantly shorter in patients with a HR profile (2-year OS 56% vs 88%) compared with SR GEP profile, with the
exception of low TP53 expression.\textsuperscript{70} Addition of bortezomib improved OS compared with TT2 in LR MM.\textsuperscript{70,71}

Data in NTE patients are scarce. The VISTA trial combined melphalan/ prednisone (MP) with MP + bortezomib (VMP). In patients treated with VMP, HR-CA did not influence outcome when compared with SR (OS 56% vs 71%).\textsuperscript{72} In a Pethema trial comparing VMP with bortezomib/thalidomide/prednisone (VPT) followed by maintenance with bortezomib/thalidomide vs bortezomib/ prednisone, HR patients had shorter PFS than SR patients from the first (24 vs 33 months) and second randomization (17 vs 27 months) and shorter survival (3-year OS: 55% vs 77%).\textsuperscript{73} The GIMEMA group compared VMP with VMP/ thalidomide. In this bortezomib-dense treatment, HR vs SR patients had similar PFS.\textsuperscript{74} The IFM group observed that across bortezomib regimens, no benefit was achieved in HR-CA NTE patients.\textsuperscript{75}

Consensus statement. Bortezomib partly overcomes the adverse effect of t(4;14) and possibly del(17p) on CR, PFS, and OS. There is no effect in t(4;14) combined with del(17p) in TE patients. In non-TE patients, VMP may partly restore PFS in HR cytogenetics.

Lenalidomide and pomalidomide. Experience with lenalidomide in first-line therapy for HR-CA patients is limited. In HR-CA, PFS with lenalidomide was inferior compared with SR patients (18 vs 26 months).\textsuperscript{76} In the GIMEMA trial comparing high-dose melphalan with MP, there was a trend for better PFS with lenalidomide maintenance in SR compared with HR-CA (HR 0.38 [0.24-0.62] vs 0.73 [0.37-1.42]). However, there was no effect on OS.\textsuperscript{77} In the IFM 2005-02 trial, lenalidomide maintenance did not overcome the poor prognosis of t(4;14) (27 vs 24 months) and only partly of del(17p) (29 vs 14 months for 42 months in all patients).\textsuperscript{78} Convincing data for continuous lenalidomide in CA groups are lacking.\textsuperscript{79,80} Subgroup analysis of the FIRST trial in NDMM did not demonstrate a benefit of continuous lenalidomide in HR-CA.\textsuperscript{81}

In relapse MM, carfilzomib combined with lenalidomide and dexamethasone (K-RD) was effective across HR and SR patients (23 vs 29 months, P = NS), whereas RD showed less activity (13 vs 19 months, P = .004).\textsuperscript{82} Data of IFM did not show a benefit of RD in relapse/refractory multiple myeloma (RRMM) with del(13q) or t(4;14).\textsuperscript{83} In the Eloquent 2 trial for RRMM, elotuzumab with RD (E-RD) improved outcome over RD in del(17p).\textsuperscript{84} Recent data of the effect of pomalidomide with dexamethasone in patients with RRMM show that this combination does not abrogate overall adverse outcome in HR-CA, whereas OS may improve in del(17p).\textsuperscript{85} In phase 2 trials, a response benefit of pomalidomide with dexamethasone was shown in patients with del(17p).\textsuperscript{86}

Consensus statement. Lenalidomide partly improves the adverse effect of t(4;14) and del(17p) on PFS, but not OS, in TE patients. In non-TE patients, there are no data suggesting that the drug may improve outcome with HR cytogenetics. Pomalidomide with dexamethasone showed promising results in RRMM with del(17p).

Combined proteasome inhibition and lenalidomide. Bortezomib combined with RD (VRD) in a phase 1/2 trial in 66 patients with NDMM showed 18-month PFS of 100% in 13 patients with del(17p) and/or t(4;14).\textsuperscript{87} The EVOLUTION trial examined several schedules including VRD in NDMM. One-year PFS was similar in HR-CA (17% of all patients) and SR patients.\textsuperscript{88} VRD in TE patients with NDMM had similar 3-year PFS (86%) in patients with >60% del(17p) or t(4;14) or del(13q) compared with all patients.\textsuperscript{89} Carfilzomib monotherapy did not improve PFS/OS in t(4;14) or del(17p) in RRMM.\textsuperscript{90} Carfilzomib combined with pomalidomide/dexamethasone had equivalent PFS and OS in HR vs SR RRMM.\textsuperscript{91} In the Aspire trial, in RRMM, KRD was superior to RD for PFS across cytogenetic risk groups, suggesting that this combination (partly) abrogates the negative impact of t(4;14) and del(17p).\textsuperscript{92} Similarly, in Tourmaline-MM1, ixazomib combined with RD showed identical PFS in patients with del(17p) or t(4;14) or no CA (20 vs 18 vs 20 m).\textsuperscript{93} More recently, carfilzomib combined with lenalidomide (KRD) or thalidomide (KTd) and dexamethasone in NDMM showed similar CR rate (>60%) and PFS between HR and SR patients.\textsuperscript{93,94}

Recently, favorable responses were observed with monoclonal antibodies against CD38 (daratumumab) or SLAMF7 (elotuzumab) combined with RD in MM across cytogenetic subgroups.\textsuperscript{95}

Consensus statement. Combining a proteasome inhibitor with lenalidomide and dexamethasone greatly reduces the adverse effect of t(4;14) and del(17p) on PFS in NDMM. Carfilzomib with lenalidomide and dexamethasone seems effective in patients with HR cytogenetics. However, with exception of Aspirole and Tourmaline, most data were obtained in nonrandomized studies and long-term follow-up has not been reported. The group advises treating NDMM patients with HR cytogenetics with the combination of a proteasome inhibitor with lenalidomide or pomalidomide and dexamethasone.

High-dose therapy and ASCT. In TE patients with NDMM, the hallmark of first-line treatment is high-dose therapy and ASCT combined with novel agents. This strategy has significantly improved PFS and OS. Therefore, it is difficult to address the role of HDT/ASCT for HR-CA. Few studies have investigated the effect of a second ASCT. In TT3, the addition of bortezomib to double ASCT improved outcome in patients with t(4;14), indicating that the effect of HDT/ASCT varies with induction and consolidation/maintenance.\textsuperscript{96} Similarly, addition of RVD for consolidation and maintenance after ASCT may improve PFS in HR MM.\textsuperscript{96,97} A meta-analysis of 4 European trials showed that double ASCT combined with bortezomib-based treatment partially abrogates poor PFS in patients carrying both t(4;14) and del(17p).\textsuperscript{98}

Consensus statement. HDT with ASCT is standard therapy for TE patients with NDMM. It contributes to improved outcome across prognostic groups. Double HDT/ASCT combined with bortezomib may improve PFS in patients with t(4;14) or del(17p), and in those with both abnormalities. Although results from stratified randomized trials are not yet available, HDT plus double ASCT is recommended for patients with HR cytogenetics. The results from clinical trials with bortezomib and thalidomide combinations with/without HDT + ASCT in HR cytogenetics are summarized in Tables 3 and 4.

Allogeneic stem cell transplantation. Allogeneic SCT has been proposed as a treatment of HR younger patients. Data on CA are scarce and partly based on classic karyotyping. In a trial of 73 NDMM patients, tandem auto-allo-transplantation yielded similar 5-year PFS (24% vs 36%) and OS (50% vs 54%) in patients without t(4;14) or del(17p).\textsuperscript{99} The EBMT-NMAM2000 study showed better OS in patients treated with ASCT/RIC-allo or ASCT alone: 49% vs 36% at 96 months, respectively (P = .030). Unfortunately, convincing FISH data are lacking.\textsuperscript{99} A retrospective analysis in 143 patients indicated that patients with del(13q) or t(4;14) or del(17p) or t(11;14) had similar 3-year PFS and OS as patients without abnormality.\textsuperscript{100} A study of allo-SCT in 101 relapsed MM showed worse 4-year PFS (28 vs 43%) and OS (30 vs 49%) in 16 patients with del(17p), whereas in 16 patients with t(4;14) no impact was observed.\textsuperscript{101}

Consensus statement. Allogeneic SCT or tandem auto-allo-SCT may improve PFS in patients with t(4;14) or del(17p). Results are better in an early stage of the disease. The novel treatments may challenge the role of allo-SCT and its use should be restricted to clinical trials.

Concluding remarks and future perspectives

Risk stratification in MM is important to predict survival and to define a treatment strategy. Cytogenetic abnormalities by FISH currently are clinically relevant prognostic factors in MM. The IMWG consensus panel on FISH advises to test for the presence of del(17p), t(4;14), and possibly t(14;16). An extended panel, which may be incorporated in clinical trials, includes t(11;14), t(14;20), gain(1q), del(1p), del(13q), and ploidy status. Bortezomib and lenalidomide may partially abrogate the adverse effect of del(17p). Bortezomib combined with iMIDS may improve outcome in t(4;14). Double HDT/ASCT plus bortezomib may improve outcome in patients with both adverse CA. Application of these risk factors may be a first step toward precision medicine in patients with MM.

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