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

Pieter Sonneveld,1 Hervé Avet-Loiseau,2 Sagar Lonial,3 Saad Usmani,4 David Siegel,5 Kenneth C. Anderson,6 Wee-Joo Chng,7 Philippe Moreau,8 Michel Attal,9 Robert A. Kyle,10 Jo Caers,11 Jens Hillengass,12 Jesús San Miguel,13 Niels W. C. J. van de Donk,14 Hermann Einsele,15 Joan Bladé,16 Brian G. M. Durie,17 Hartmut Goldschmidt,18 María-Victoria Mateos,19 Antonio Palumbo,20 and Robert Orlowski21

1Department of Hematology, Erasmus MC Cancer Institute, Rotterdam, The Netherlands; 2Laboratory for Genomics in Myeloma, University Cancer Center of Toulouse, Toulouse, France; 3Winship Cancer Institute, Emory University Medical School, Atlanta, GA; 4Levine Cancer Institute/Carolina Hemato-Oncology, Charlotte, NC; 5John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, NJ; 6Jerome Lipper Multiple Myeloma Center, Dana-Farber Cancer Institute, Boston, MA; 7Division of Hematology, National University Cancer Center Institute, Singapore; 8Department of Hematology, University Hospital, Nantes, France; 9Department of Hematology, Purpur University Hospital, Toulouse, France; 10Department of Laboratory Medicine and Pathology, Mayo Clinic, Minneapolis, MN; 11Department of Hematology, Centre Hospitalier Universitaire de Liège, Liège, Belgium; 12Medical Clinic V, Section for Multiple Myeloma, University of Heidelberg, Heidelberg, Germany; 13Clinica Universidad de Navarra, Centro de Investigación Médica Aplicada, Pamplona, Spain; 14Department of Hematology, Free University Medical Center Amsterdam, Amsterdam, The Netherlands; 15Medical Clinic 2, Universitätsklinik Würzburg, Würzburg, Germany; 16University Hospital Clinic, Institut d’Investigacions Biomèdiques August Pi i Sunyer, Barcelona, Spain; 17International Myeloma Foundation, North Hollywood, CA; 18University Hospital Heidelberg and National Center for Tumor Diseases Heidelberg, Heidelberg, Germany; 19Department of Hematology, University Hospital of Salamanca, Salamanca, Spain; 20Myeloma Unit, University of Torino, Torino, Italy; and 21Division of Cancer Medicine, Department of Lymphoma/Myeloma, MD Anderson Cancer Center, Houston, TX

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 prognostic significance of 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.1,4 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 are 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.6 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)(p16;q32), t(14;16)(q23;q23),
del(17p13), and a marker for aneuploidy (Table 1). For routine diagnosis,
testing of t(4;14) and del(17p13) suffices.

Singe-nucleotide 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 genomic
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.7 GEP from
patients in clinical trials can be used to identify HR profiles with significant
prognostic significance.8

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%), 1q13 (CCND1) (15%-20%), 16q23
(NA1), 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 Prolonged survival was reported in
t(4;14) treated with high-dose therapy (HDT) and tandem autologous stem cell
transplant (ASCT).16-20 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.1,12,11,12 An Intergroupe Francophone de Myeloine
(IFM) analysis showed no adverse impact of t(14;16), possibly because 60% of
patients received a double ASCT.22 Translocation t(14;20) results in deregulation
of the MAFB oncogene and confers a poor prognosis.12

Translocation t(11;14) results in upregulation of cyclinD1 and was identified
as favorable in some studies, whereas it had no impact in others.14,24,25 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.11,25 In the MRC IX cohort, coexisting
hyperdiploidy did not abrogate the poor prognosis of adverse CA.26 In contrast,
in a retrospective analysis, PFS of patients with t(4;14) was negatively affected
by del(1p32), del22q, and >30 structural CA, whereas del(6q) worsened PFS
and del(1p32) worsened OS, and >8 numerical changes improved OS in del
(17p).27 Modern techniques (GWAS) identify additional CNV above karyotypic
hyperdiploidy.28

Del(13q) predicts impaired PFS/OS when detected by karyotyping.28 The
adverse impact of del(13q) by GEP is associated with del(17p) and t(4;14), del
(13q) as single CA does not confer poor survival.12,15,16,25,29 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 CKS1B.12,20,31 Gain(1q) frequently coincides with
del(1p32), which confers poor prognosis.12,13,25,29 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 gain1q 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 demonstrating the progressive 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
gain15 and del14 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 hyperdiploid MM.38 Among patients with hyperdiploidy, trisomies 3 and 5
confer a favorable prognosis.21

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><strong>Primary genetic events</strong></td>
<td><strong>Secondary genetic events</strong></td>
</tr>
<tr>
<td><strong>IgH translocation</strong></td>
<td><strong>Gene(s)</strong></td>
</tr>
<tr>
<td>t(4;14)</td>
<td>FGFR3/MMSET</td>
</tr>
<tr>
<td>t(4;14)</td>
<td>CCND3</td>
</tr>
<tr>
<td>t(11;14)</td>
<td>CCND1</td>
</tr>
<tr>
<td>t(14;16)</td>
<td>MAF</td>
</tr>
<tr>
<td>t(14;20)</td>
<td>MAFB</td>
</tr>
<tr>
<td>t(11;14)</td>
<td></td>
</tr>
<tr>
<td>t(14;16)</td>
<td></td>
</tr>
</tbody>
</table>

Hyperdiploidy | Gain

Trisomies of chromosomes 3, 5, 7, 9, 11, 15, 19, 21

NA | 50 | 1q | CKS1B, ANF32E | 40
In the Myeloma IX study, 58% of patients had hyperdiploidy. Of these, 61% had ≥1 adverse lesion (t(4;14), t(14;16), t(14;20), gain(1q), 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.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, conventional therapy is likely to have a survival benefit for patients with HR disease based on objective criteria.

### 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. The Mayo Clinic classification added hypodiploidy and t(14;20) to the definition of HR MM (Table 2). 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. 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. IMWG stated that HR MM should include t(4;14), t(14;16), or del(17p).11

### 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

---

### Table 2. Summary of cytogenetic risk features

<table>
<thead>
<tr>
<th>Cytogenetic abnormality</th>
<th>FISH: t(4;14), t(14;16), t(14;20), del(17/17p), gain(1q)</th>
<th>Nonhyperdiploid karyotype</th>
<th>Karyotype del(13)</th>
<th>GEP: high-risk signature</th>
</tr>
</thead>
</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>Conventional therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t(4;14)</td>
<td>42/290</td>
<td>3-y OS</td>
<td>VBMCP</td>
<td>24%</td>
<td>64%</td>
<td>E9486</td>
<td>13</td>
</tr>
<tr>
<td>100/616</td>
<td>3-y OS</td>
<td>VAD + ASCT × 2</td>
<td>55%</td>
<td>80%</td>
<td>IFM-99</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>98/414</td>
<td>3-y OS</td>
<td>VAD + ASCT × 1/2</td>
<td>40%</td>
<td>72%</td>
<td>IFM-2005</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td>del17p</td>
<td>37/308</td>
<td>3-y OS</td>
<td>VBMCP</td>
<td>32%</td>
<td>68%</td>
<td>E9486</td>
<td>13</td>
</tr>
<tr>
<td>58/474</td>
<td>3-y OS</td>
<td>VAD + ASCT × 2</td>
<td>50%</td>
<td>78%</td>
<td>IFM-99</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>119/393</td>
<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>
</tr>
<tr>
<td>Unfavorable FISH</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>141/166</td>
<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>
</tr>
<tr>
<td>90/125</td>
<td>3-y OS</td>
<td>Placebo maintenance</td>
<td>26%</td>
<td>48%</td>
<td>MRC IX non-intensive</td>
<td>61</td>
<td></td>
</tr>
<tr>
<td>98/129</td>
<td>3-y OS</td>
<td>VBMCP/VBAD +Bz × 2 + ASCT × 1</td>
<td>48%</td>
<td>84%</td>
<td>GEM2005</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>Thalidomide</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<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>GIMENA</td>
<td>102</td>
</tr>
<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>
</tr>
<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>
</tr>
<tr>
<td>Unfavorable FISH</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>
</tr>
<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>
</tr>
<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</td>
<td>65</td>
<td></td>
</tr>
<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>
</tr>
<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>
<td></td>
</tr>
<tr>
<td>152/355</td>
<td>Median PFS</td>
<td>Lenalidomide maintenance</td>
<td>27 m</td>
<td>42 m</td>
<td>IFM-2005</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td>del17p</td>
<td>12/118</td>
<td>Median OS</td>
<td>RD in RRMM</td>
<td>4 m</td>
<td>23 m</td>
<td>MM-016</td>
<td>103</td>
</tr>
<tr>
<td>6.6%</td>
<td>Median PFS</td>
<td>Lenalidomide maintenance</td>
<td>27 m</td>
<td>42 m</td>
<td>IFM-2005</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td>Unfavorable FISH</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>
</tr>
<tr>
<td>21/105</td>
<td>3-y OS</td>
<td>RD</td>
<td>76%</td>
<td>91%</td>
<td>E4A03</td>
<td>104</td>
<td></td>
</tr>
<tr>
<td>Bortezomib</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<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>GIMENA</td>
<td>102</td>
<td></td>
</tr>
<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>IFM-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>
</tr>
<tr>
<td>Unfavorable FISH</td>
<td>18/112</td>
<td>3-y OS</td>
<td>VTO + ASCT × 1</td>
<td>60%</td>
<td>88%</td>
<td>GEM2005</td>
<td>65</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</td>
<td>65</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>
</tr>
</tbody>
</table>

Adapted from Bergsagel et al.58
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/thalidomide*</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>V D</td>
<td></td>
<td>32</td>
<td>63*</td>
<td>IFM-2005</td>
<td>68</td>
</tr>
<tr>
<td>21/23</td>
<td>2-y OS</td>
<td>Thalidomide*</td>
<td>Placebo*</td>
<td></td>
<td>67</td>
<td>87</td>
<td>TT2</td>
<td>18</td>
</tr>
<tr>
<td>21/29</td>
<td>2-y OS</td>
<td>Thalidomide-TT</td>
<td>Bortezomib TT3</td>
<td></td>
<td>67</td>
<td>97*</td>
<td>TT2 vs TT3</td>
<td>70</td>
</tr>
<tr>
<td>Del(17p)</td>
<td>21/16</td>
<td>3-y OS</td>
<td>VAD/ASCT/thalidomide</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></td>
<td>36</td>
<td>50</td>
<td>IFM-2005</td>
<td>68</td>
</tr>
<tr>
<td>Nonhyperdiploid</td>
<td>92</td>
<td>3-y OS</td>
<td>VTD</td>
<td>VMP</td>
<td>53</td>
<td>72*</td>
<td>PETHEMA</td>
<td>63</td>
</tr>
<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></td>
<td>96/90</td>
<td>3-y OS</td>
<td>CTD</td>
<td>Placebo MP</td>
<td>34</td>
<td>26</td>
<td>MRC IX nonintensive</td>
<td>61</td>
</tr>
<tr>
<td>99/98</td>
<td>3-y OS</td>
<td>Thalidomide</td>
<td>Placebo</td>
<td></td>
<td>45</td>
<td>69*</td>
<td>MRC IX maintenance</td>
<td>39</td>
</tr>
</tbody>
</table>

Adapted from Bergsagel et al.58

*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.54,55 This review covers treatment options for t(4;14) and/or del(17p).56

**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.56 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%).15,18,25,51,62,65 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.24 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(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%).69 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).47 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%).66 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).57 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.).16 These trials (1874 patients) showed that bortezomib plus ASCT was superior (PFS 41 vs 33 months) (P < .0001). In patients with HR FISH, this was 32 vs 22 months (P < .0001). PFS benefit was observed in patients with t(4;14) but lackin del(17p) (36 vs 24 months, P = .01) and in del(17p) lacking t(4;14) (27 vs 19 months, P = .04), but not in patients carrying both CA.67 In TT2, 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.70 Addition of bortezomib improved OS compared with TT2 in LR MM.70,71

Data in NTE patients are scarce. The VISTA trial combined melphalan/prednisone (MP) with bortezomib (VMP). In patients treated with VMP, HR-CA did not influence outcome when compared with SR (OS 56% vs 71%).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%).73 The GIMEMA group compared VMP with VMP/thalidomide. In this bortezomib-dense treatment, HR vs SR patients had similar PFS.74 The IFM group observed that across bortezomib regimens, no benefit was achieved in HR-CA NTE patients.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).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.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 vs 42 months in all patients).78 Convincing data for continuous lenalidomide in CA groups are lacking.79,80 Subgroup analysis of the FIRST trial in NDMM did not demonstrate a benefit of continuous lenalidomide in HR-CA.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).82 Data of IFM did not show a benefit of RD in relapse/refractory multiple myeloma (RRMM) with del(13q) or t(4;14).83 In the Eloquent 2 trial for RRMM, elotuzumab with RD (E-RD) improved outcome over RD in del(17p).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).85 In phase 2 trials, a response benefit of pomalidomide with dexamethasone was shown in patients with del(17p).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).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.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.89 Carfilzomib monotherapy did not improve PFS/OS in t(4;14) or del(17p) in RRMM.89 Carfilzomib combined with pomalidomide/dexamethasone had equivalent PFS and OS in HR vs SR RRMM.87 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).80 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).81 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.90

Recently, favorable responses were observed with monoclonal antibodies against CD38 (daratumumab) or SLAMF7 (elotuzumab) combined with RD in RRMM across cytogenetic subgroups.85

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 Aspire 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 hallmarks 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.78 Similarly, addition of RVD for consolidation and maintenance after ASCT may improve PFS in HR MM.86,87 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).88

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 or without HDT + ASCT in HR cytogenetics are summarized in Tables 3 and 4.

Alogenetic stem cell transplantation. Alogenetic 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 autologous transplantation yielded similar 5-year PFS (24% vs 36%) and OS (50% vs 54%) in patients without t(4;14) or del(17p).89 The EBMT-NMMAM200 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.90 A retrospective analysis in 143 patients indicated that patients with del(13q) or t(4;14) or del(17p) or (11;14) had similar 3-year PFS and OS as patients without abnormality.91 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.92

Consensus statement. Alogenic SCT or tandem autolo-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(11;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.

Acknowledgments

The following members of the International Myeloma Working Group participated in this study: Kenneth C. Anderson, Dana-Farber Cancer Institute, Boston, MA; Michel Attal, Purpan Hospital, Toulouse, France; Hervé Avet-Loiseau, University of Toulouse,
Toulouse, France; Joao Bladé, University of Barcelona, Spain; Michele Cavo, University of Bologna, Bologna, Italy; Wee-Joo Chng, University of Singapore, Singapore; Dominik Dytfeld, Karol Marcinkowski University van de Donk, VU University Medical Center Amsterdam, Amsterdam, The Netherlands; Dominik Dytfeld, Karol Marcinkowski University of Medical Sciences, Poznan, Poland; Michael O’Dwyer, National University of Ireland, Ireland; Hermann Einsele, Universitätsklinik Würzburg, Würzburg, Germany; Laurent Garderet, Hopital Saint Toulouse, France; Joan Bladé, Hospital Clinic, IDIBAPS, University of Barcelona, Spain; Michele Cavo, University of Bologna, Bologna, Italy; Wee-Joo Chng, National University Health System, Singapore; Jo hand Ko, Seoul National University Hospital, Seoul, South Korea; Murielle Roussel, Wellington Hospital, Wellington, New Zealand; Murielle Roussel, University of Toulouse, Toulouse, France; Jesús San Miguel, Clinica Universitaria de Navarra, CIMA, Pamplona, Spain; Orhan Sezer, Memorial Sılsı Hastanesi, Istanbul, Turkey; Kazuyuki Shimizu, Tokai Central Hospital, Kakamigahara, Japan; David Siegel, Hackensack University Medical Center, Hackensack, NJ; Pieter Sonneveld, Erasmus MC, Rotterdam, The Netherlands; Evangelos Terpos, University of Athens School of Medicine, Athens, Greece; Saad Usmani, Levine Cancer Institute/Carolinas Healthcare System, Charlotte, NC; Sonja Zweegman, VU University Medical Center Amsterdam, Amsterdam, The Netherlands.

This study was supported by Amgen/Onyx, Celgene, Janssen, Karyopharm, and SkylineDx, and by honoraria from Amgen/Onyx, Celgene, Janssen, and Karyopharm.

Authorship

Contribution: P.S. wrote, revised, and approved the manuscript; and all authors revised and approved the manuscript.

Correspondence: Pieter Sonneveld, Department of Hematology, Rm Na822, Erasmus MC Cancer Institute, Erasmus MC, PO Box 2040, 3000 CA Rotterdam, The Netherlands; e-mail: p.sonneveld@erasmusmc.nl

References


33. Chang H, Qi X, Jiang A, Xu W, Young T, Reece D. 1p21 deletions are strongly associated with 1q21 gains and are an independent adverse prognostic factor for the outcome of high-dose chemotherapy in patients with multiple myeloma. Bone Marrow Transplant. 2010;45(1):117-121.


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