The Role of 1q21 Gain on the Prognosis of Multiple Myeloma

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Abstract: Multiple myeloma (MM) is a clonal expansion of malignant plasma cells, and comprises approximately 10% of hematologic malignancies. Although various therapeutic agents and strategies, such as immunomodulatory agents, proteasome inhibitors, monoclonal antibodies and hematopoietic stem cell transplantation (HSCT) have been evaluated, MM remains largely incurable. It is therefore important to further explore the risk factors for disease progression, and to design trials aimed at improving the patient outcomes. Previous studies have considered the presence of a gain in 1q21 as a risk factor for a poorer overall survival. Gain of 1q21 is one of the most common chromosomal aberrations in MM, being detected by FISH in 36% to 47% of newly-diagnosed patients, as well as 52% and 62% patients with relapsed MM. Although a series of reports identified 1q21 gain in MM as a significant and independent poor prognostic factor, other studies failed to demonstrate any prognostic value. Thus, the prognostic value of 1q21 gain in MM remains controversial. We reviewed the current knowledge about 1q21 gain and its value for the clinical management of MM.

Key words: Multiple myeloma; 1q21 gain; Poor prognosis; Drug resistance

Introduction

Multiple myeloma (MM), a malignancy derived from B-cells, initially resides in the bone marrow, but may become disseminated to various locations via the bloodstream. The National Comprehensive Cancer Network (NCCN) guidelines indicate that the preferred treatment regimens for MM are bortezomib/lenalidomide/dexamethasone (VRD), daratumumab/lenalidomide/dexamethasone (DRD) or bortezomib/cyclophosphamide/dexamethasone (VCD). Although these treatments are associated with higher response rates and increased survival, almost all MM patients will eventually relapse or experience disease progression.

High-risk MM patients comprise 15% to 25% of the overall cases, these patients may initially respond to treatment, but their response is weaker and less durable, and they have a median survival of less than 3 years (approximately 2 years shorter than the overall median survival of MM patients) [1-4]. The prognostic factors for MM, including the β2-microglobulin, lactate dehydrogenase, and hemoglobin concentrations, and the International Scoring System (ISS) or Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) system scores, are useful for predicting patient outcomes and directing treatment, but are insufficient to describe the full extent of the patient’s prognosis. It remains a challenge to identify which patients are likely to have a poorer prognosis, but significant progress has been made in testing methods. The most common method is fluorescence in situ hybridization (FISH), which can be used to detect cytogenetic abnormalities in high-risk genetic markers. There is increasing evidence that 1q21 is a useful marker for the disease, with increasing expression during the progression from monoclonal gammopathy of undetermined significance (MGUS) to smoldering myeloma (SMM), newly-diagnosed and relapsed MM [5], implying that a gain of 1q21 is a negative prognostic factor. In this review, we describe the causes and consequences of 1q21 gain in MM, and suggest ways that monitoring 1q21 may guide the development of new targeted therapies.

Important Prognostic Regions in the 1q21 Region

A gain of the 1q21 region is found in about 40% of MM cases, most of which are associated with secondary aberrations involving 1q12 jump translocations [6-8]. Genes of prognostic importance located on 1q21 include CKS1B, ANP32E, PSMD4, BCL-9, MUC1, MCL1, PDZK1, JIL6R, UBAP2L and UBE2Q1 [9-15]. We discuss these genes and their possible relationship with the severity of MM below.

CKS1B in 1q21

CKS1B

Overexpression of CKS1B (CDC28 protein kinase regulatory subunit 1B), which maps within a minimally-amplified region of chromosome 1q21, plays an important role in cell cycle progression and is associated with a poor prognosis in MM [16-18]. Overexpression of CKS1B...
promotes myeloma cell growth and drug resistance through SKP2 and via both p27Kip1-independent and -dependent pathways. **CKS1B** binds to and activates cyclin-dependent kinases and also interacts with SKP2 to regulate the ubiquitination and proteasomal degradation of the cyclin-dependent kinase (CDK) inhibitor p27Kip1 [16-18]. This leads to dysregulation of both the G1 and S phases of the cell cycle, which play an important role in tumorigenesis and tumor progression [16-18]. **CKS1B** amplification also stimulates STAT3 and MEK/ERK/BCL2 downstream signaling pathways, independent of p27Kip1 and SKP2. Shi L et al. [19] concluded that specifically targeting STAT3 and MEK/ERK/BCL2 resulted in significant MM cell death and tumor growth inhibition. Therefore, these molecules provide targets for the development of new therapeutic approaches for **CKS1B** over-expressing myeloma.

Bock F et al. [20] analyzed the outcomes of MM with **CKS1B** amplification after autologous hematopoietic stem cell transplantation (ASCT), and observed that the median PFS was 15.0 months in the group with **CKS1B** amplification and 33.0 months in the group without (P = 0.002). The 2-year overall survival (OS) rates of these groups were 62% and 91%, respectively (P = 0.02). **CKS1B** amplification also predicted an adverse outcome for patients with relapsed/refractory MM. The patients with **CKS1B** overexpression had a significantly shorter PFS (1.9 VS 5.6 months; P < 0.0001) and OS (4.9 VS 22.4 months; P = 0.012) compared with those without **CKS1B** overexpression [21]. However, a different study showed that, compared with TP53 deletion alone, MM patients with additional **CKS1B** amplification did not show a significantly poorer prognosis [22].

**ANP32E**

**ANP32E**, a member of the acidic leucine-rich nuclear phosphoprotein 32 family, is located on 1q21.2 and is ubiquitously expressed in the lymph nodes, bone marrow and other tissues. **ANP32E** is a histone acetyltransferase inhibitor (INHAT) that is overexpressed in cells with 1q21 gains, potentially resulting in increased histone methylation, which is associated with altered transcriptional regulation and chromatin modification [23]. Gain of the region was associated with a poorer OS [24], but mechanism remains unclear.

**BCL9**

**B-cell/lymphoma-9 (BCL9)**, a transcriptional coactivator of the Wnt–β-catenin pathway, is located on chromosome 1q21. However, 1q21 gain and **BCL9** mRNA expression have a low correlation, suggesting that additional mechanisms also drive **BCL9** expression. The expression of **BCL9** in normal plasma cell is negligible, but it is highly expressed in approximately 60% of MMs [25]. **BCL9** promotes the proliferation of bone marrow endothelial cells (BMECs), thereby promoting the migration and proliferation of MM cells, targeting the **BCL9**/β-catenin complex provides a potential therapeutic target for inhibiting canonical Wnt signaling in MM cells [26].

**MCL1**

**MCL1**, a member of the Bcl-2 family of antiapoptotic proteins, is located on chromosome 1q21.2. **MCL1** is widely expressed in normal tissues, such as germinal center cells, neuroendocrine cells, and so on. It is essential for maintaining many physiological functions including nerve development, lymphocyte development, macrophage regulation and neutrophil apoptosis [27,28]. **MCL1** is a critical prognostic indicator in MM. Mylin AK et al. [29] showed that positive **MCL1** mRNA expression was more frequently detected in MM compared to MGUS (P = 0.0008). Of note, the **MCL1** mRNA expression is associated with the Durie-Salmon (DS) stage (64% I, 58% II, 80% III; P = 0.05) [29]. Similarly, Wuilleme-Toumi S et al. [30] showed that the level of **MCL1** expression is related to disease severity, where 52% of newly-diagnosed MM patients and 81% of relapsed MM patients had higher expression of the Mcl-1 protein. Compared with the low protein expression group, the event-free survival of patients with high expression of the Mcl-1 protein was significantly shorter (P = 0.002) [30]. **MCL1**, which has been shown to be related with relapse and shorter survival, represents another potential therapeutic target in MM.

**MUC1**

The **MUC1** region is rearranged in 6% of tumors with 1q21 cytogenetic aberration [31]. **MUC1**, as an oncogenic target associated with treatment-refractory MM, is comprised of an N-terminus that is shed and a transmembrane C-terminus, which may be used as a target for immunotherapy [31]. A MUC1-C inhibitor, GO-203, reduced the production of nicotinamide adenine dinucleotide phosphate (NADPH) and glutathione (GSH), down-regulated p53-inducible regulator of glycolysis and apoptosis (TIGAR) expression, and contributed to ROS-mediated late apoptosis/necrosis of multiple myeloma cells [32]. Heightened levels of MUC1 expression are associated with increased resistance to lenalidomide (LEN) and bortezomib (BZT). Targeting MUC1-C attenuates LEN and BZT resistance in MM cells, a study has demonstrated the GO-203/LEN combination suppressed the expression of WNT target genes, MYC and CD44, and induced MM cell death[33]. In addition, the combination with GO-203 and BTZ synergistically downregulated TIGAR and GSH [33].

**IL6R and ADAR1**

**IL6R** ([IL6 receptor]) and **ADAR1** (RNA editing enzyme) are critical genes located in close proximity on 1q21. High
**IL6R** confers hypersensitivity to IL6, which activates the JAK (Janus kinase)/STAT3 (signal transducer and activator of transcription 3) pathway and exerts oncogenicity through its binding to the **IL6R** transmembrane receptor [34]. IL6/STAT3 signaling stimulates the PI3K/Akt and MEK/ MAPK pathways, and consequently the expression of anti-apoptotic proteins like Mcl-1, Bcl-XL and c-Myc, which promote MM cell survival [35,36]. With reference to **ADAR1**, the P150 isoform is more highly expressed in IL6-dependent-cells, whereas expression of the P110 isoform is not significantly affected [34]. **ADAR1** forms a constitutive feed-forward loop with STAT3, so the concomitant gain of **IL6R** and **ADAR1** confers a hyper-activation of the STAT3 pathway, resulting in a worse disease outcome in patients with 1q21(amp) MM [34].

In a clinical study, Kim SY et al. [37] found that in MM patients treated with autologous stem cell transplantation (ASCT), the 5-year OS rate of those with ≥ 3.1 copy numbers of IL-6R had a significantly shorter 5-year OS rate than those with < 2.1 copies (44.4% vs 78.0%, P = 0.024). Therefore an increase in IL-6R copy numbers appears to be an independent prognostic factor.

**A 1q21 Gain is Associated with an Adverse Prognosis in Multiple Myeloma Patients**

A gain of 1q21 is included in the mSMART 3.0, Revised International Staging System (R-ISS) and International Myeloma Working Group (IMWG) risk staging systems as an adverse risk factor. The latest mSMART 3.0 system refers to gain(1q) as a high risk factor, particularly when part of a “double-hit” (e.g. bi-allelic inactivation of TP53 or ISS stage III with amplification of CKS1B). Despite the promise of new therapeutic approaches, such double-hit myeloma patients had an extremely poor outcome, with 18-month estimates of the progression-free survival (PFS) and OS of only 39% and 48%, respectively, which were similar to the IMWG high-risk group values (35% and 37%, respectively) [38]. In addition, The Myeloma Genome Project (MGP) has established a large molecular database to examine the clinical prognosis of newly diagnosed multiple myeloma (NDMM), and emphasized the importance of 1q21. In fact, 1q21 gains (defined as ≥ 3 copies) were detected in 30% to 43% of newly-diagnosed patients, and 1q21 amplification (defined as ≥ 4 copies) was present in about 10% of newly-diagnosed cases. Moreover, the Mayo Clinic and most clinical trials have used 1q gain as a risk marker. Boyd KD et al. [39] showed that +1q21 was found to have a negative impact on the median OS compared with patients without any gain (41.9 months vs 60.6 months, P = 0.017). Shah V et al. [40] performed a large meta-analysis of 1905 patients from multi-central trials (Myeloma IX and Myeloma Xi trial) and reported that gain (1q21) was a risk factor for a poorer overall survival (OS) (HR = 1.68, P = 2.18 × 10⁻⁴). Walker BA et al. [24] studied 531 samples in the intensive arm of the trial using a FISH probe specific for CKS1B, and also confirmed that CKS1B overexpression due to 1q21 gain was associated with a poorer prognosis. Numerous studies have similarly found that 1q21 gain exerts an adverse effect on the prognosis of multiple myeloma patients [Table 1].

However, the prognostic value of 1q21 gains in MM remains controversial. Its role as an independent risk factor needs to be further elucidated. Although most clinical trials have indicated that 1q21 was an independent poor prognostic factor [42-45]; other studies have failed to confirm this finding [46,47]. One possible explanation could be the treatment strategies used for the patients in the different studies; another could be the fact that 1q21

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**Table 1 1q21 gain exerts adverse prognosis in myeloma in different centers.**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patients</th>
<th>PFS</th>
<th>OS</th>
</tr>
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<tbody>
<tr>
<td>Yu et al.[12]</td>
<td>86</td>
<td>Gain VS Normal: 14 vs 21m; P = 0.088; HR 2.344; 95% CI:0.882-6.233</td>
<td>Gain VS Normal: 31.63 vs 31m; P = 0.349; HR 1.613; 95% CI:0.593-4.386</td>
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<td>Amp VS Normal: 5.72 vs 21m; P &lt; 0.001; HR 11.344; 95% CI:3.037-42.348</td>
<td>Amp VS Normal: 14.6 vs 31m; P = 0.012; HR 6.209; 95% CI: 1.504-25.635</td>
</tr>
<tr>
<td>Walker et al.[20]</td>
<td>531</td>
<td>NA</td>
<td>Gain VS Normal: Median OS:52.1 vs 70m; P &lt; 0.001</td>
</tr>
<tr>
<td>Boyd et al.[35]</td>
<td>1960</td>
<td>Amp/Gain VS Normal: Median PFS: 13.8 vs 22.1m; P &lt; 0.001; HR 1.46; 95% CI:1.21-1.76</td>
<td>Amp/Gain VS Normal: Median OS: 31 vs 54.8m; P &lt; 0.001; HR1.53; 95% CI:1.20-1.94</td>
</tr>
<tr>
<td>Shah et al.[36]</td>
<td>1905</td>
<td>Gain VS Normal: Median PFS: 21.8 vs 30.1 m; P = 3.53*10⁻⁵; HR 1.56</td>
<td>Gain VS Normal: 2year-OS: 77.5 vs 83.5%; P = 3.30*10⁻⁶; HR1.67</td>
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<td></td>
<td>Amp VS Normal: Median PFS: 19.4 vs 30.1m; P = 0.01; HR 1.44</td>
<td>Amp VS Normal: 2year-OS: 63.8 vs 83.5%; P = 2.32*10⁻⁶; HR 2.28</td>
</tr>
<tr>
<td>Schmidt et al.[37]</td>
<td>201</td>
<td>Gain/Amp VS Normal: Median PFS: 41.9 vs 65.1m; P = 0.002, HR 1.9</td>
<td>Gain/Amp VS Normal: 5year-OS: 66.9 vs 88.5%; P = 0.003, HR 2.69</td>
</tr>
<tr>
<td>An et al.[38]</td>
<td>290</td>
<td>Gain/Amp VS Normal: P &lt; 0.001, HR 3.831; 95% CI:1.89-8.292</td>
<td>Gain/Amp VS Normal: P = 0.002, HR 3.245; 95% CI: 1.555-6.773</td>
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</table>
gain is frequently accompanied by numerous high-risk genetic aberrations, which might also affect the survival. For example, + (1q21) is strongly associated with adverse immunoglobulin heavy chain gene (IGH) translocation [t(4;14), t(14;16) and t(14;20)], which is an adverse prognostic factor for MM [39], with 72% of IGH cases also carrying +1q. Moreover, a gain of chromosome 1q21 frequently coexists with 1p21 deletions, which is an independent poor prognostic factor [47]. The co-segregation of these lesions impacts the overall prognosis, with the accumulation of additional genetic abnormalities further reducing the PFS and OS [48].

**The Effect of 1q21 Copy Number Variation on the Prognosis**

The impact of copy number variations of 1q21 on survival has been reported in a few studies, but with contradictory results (Table 2). Some research showed that increased copy numbers of 1q21 are linked to an adverse outcome. For example, Neben K et al. [49] showed that, compared with a normal copy number of 1q21 (2 copies), there was a shorter median PFS time of 17.6 months and 3-year OS rate of 52% for patients with > 3 copies of +1q21, although having exactly 3 copies had only a marginal effect on the outcome. In agreement with this finding, Fonseca R et al. [46] studied a cohort of 159 primary myeloma patients, and clarifying that the extent of 1q21 amplification (number of copies) was directly correlated with the prognosis and progression of the disease. Hanamura I et al. [5] reported that patients with 3 copies and at least 4 copies of 1q21 had similar 5-year event-free survival (EFS) and OS rates, which were inferior to those of patients with 2 copies of 1q21. However, the post-relapse survival of patients with at least 4 copies of 1q21 were inferior to those with 3 copies of 1q21, consistent with the findings reported by Fonseca R et al. Compared with the patients with 3 copies of 1q21, those with at least 4 copies of 1q21 at the time of both diagnosis and relapse tended to have a higher percentage of myeloma cells with Ampl1q21 and significantly inferior clinical outcomes. However, in a different study, An G et al. [42] divided the gains of 1q21 into three categories based on copy numbers. Patients with three, four, or at least five copies of 1q21 had similar median PFS and OS rates. No statistically significant differences were found in terms of the frequency and percentage of plasma cells with different numbers of copies of 1q21 between relapsed and newly-diagnosed MMs.

Collectively, although confirmation is needed, it appears that three copies of 1q21 might be an optimal cutoff to determine the prognosis. However, whether additional copies of 1q21 gain worsen the outcome remains controversial.

**Drug Resistance in Myeloma Patients with 1q21**

Although bortezomib, thalidomide, and ASCT have improved the survival outcomes, they have not been able to cure MM. Most MM patients with amp (1q21) will relapse after treatment with these agents, and have a poor prognosis even when they receive the recommended treatment regimens. A major cause of bortezomide or thalidomide resistance is the existence of drug-resistant subclones. Based on gene expression profiling (GEP), Zhan W et al. [50] identified several genes located at chromosome 1q, including NEK2, FAM72A, Nuf2, and CDC20, that appear to play important roles in resistance to bortezomib. Moreover, genes involved in the unfolded protein response (UPR) are significantly modulated in patients with 1q21 gains. These modulations can include the upregulation of chaperone gene CLN3, UBA2, UBE2Q1, PSMD4 (involved in proteasomal degradation) and CASP4, which is involved in initiating apoptosis, all of which are associated with bortezomib resistance in patients [51]. Additionally, a PSMD4 fragment, antisecretory factor 1, inhibits the secretory properties of plasma cells (PCs) at the transcriptional level, reducing the load of the endoplasmic reticulum and proteasome, thereby regulating the differentiation and death of PCs and reducing the sensitivity to bortezomib [12]. The sensitivity of MM tumors to proteasome inhibitors is mainly dependent on the level of immunoglobulin, Activation of the UPR is very important for the survival of plasma cells, and a decrease in the UPR inhibits the synthesis of immunoglobulin, which thereby decreases the sensitivity to bortezomib [52]. ARNT/HIF-1β, another 1q21 gene, is also associated with bortezomib resistance [53]. HIF-1β expression can be induced by hypoxia via a NF-κB-dependent process, which will reduce the bortezomib sensitivity of the malignant cells [53]. Additionally, CKS1B expression is considered a marker

### Table 2 The effects of 1q21 copy number variation on the patient prognosis.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patients</th>
<th>PFS/EFS</th>
<th>OS</th>
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<tbody>
<tr>
<td>Hanamura et al.[1]</td>
<td>478</td>
<td>3 copies vs ≤ 2 copies: 5y-EFS: 40 vs 62%; <em>P</em> &lt; 0.0001</td>
<td>3 copies vs ≤ 2 copies: 5year-OS: 53 vs 78%; <em>P</em> &lt; 0.0001</td>
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<td></td>
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<td>3 copies vs ≥ 4 copies: 5y-EFS: 40 vs 38%; <em>P</em> = 0.3440</td>
<td>3 copies vs ≥ 4 copies: 5year-OS: 53 vs 50%; <em>P</em> = 0.4533</td>
</tr>
<tr>
<td>An et al.[38]</td>
<td>290</td>
<td>3 copies vs ≥ 4 copies: 14 vs 10m; <em>P</em> = 0.737</td>
<td>3 copies vs ≥ 4 copies: 24 vs 30m; <em>P</em> = 0.382</td>
</tr>
<tr>
<td>Neben et al.[45]</td>
<td>344</td>
<td>2 copies vs 3 copies; <em>P</em> = 0.001</td>
<td>2 copies vs 3 copies; <em>P</em> = 0.032</td>
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<tr>
<td></td>
<td></td>
<td>2 copies vs &gt; 3 copies; <em>P</em> = 0.0062</td>
<td>2 copies vs &gt; 3 copies; <em>P</em> = 0.0009</td>
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</tbody>
</table>
of drug-resistant [19]. Most studies have demonstrated that thalidomide-based regimens are also unable to overcome the poor prognosis of patients with 1q21 gains [43,54,55].

Conclusion
In summary, the prognostic value of 1q21 gain/amplification in MM patients is still controversial. However, there is compelling evidence that 1q21 gains may be associated with several adverse prognostic markers. Existing chemotherapy drugs, including those recommended in various treatment guidelines, cannot completely overcome the influence of 1q21, but may be able to improve the prognosis. Much effort has been devoted to researching drug response and resistance mechanisms and to identifying target genes which are located at 1q21. Many of these genes, such as MCL-1, CKS1B, IL6R, and MUC1, have effects on MM growth and progression. Moreover, while it is currently unclear whether additional copies of 1q21 gain worsen the outcome, evidence indicates that having three copies of 1q21 is sufficient to confer an adverse prognosis. Large prospective studies are required to further investigate the clinical significance of 1q21 chromosomal abnormalities, and to identify ways that these abnormalities can be targeted to improve the prognosis of patients.

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Conflicts of interest
The authors have no relevant conflicts of interest.

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