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Lenalidomide: Myelodysplastic syndromes with del(5q) and beyond

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ABSTRACT

Myelodysplastic syndrome (MDS) with deletion 5q (del(5q)) is a distinct clinical and pathological disease subset that is exquisitely sensitive to lenalidomide for the treatment of red blood cell transfusion-dependent anemia. Although lenalidomide has erythropoeitic promoting activity in MDS without del(5q) (non-del(5q) MDS), the frequency of response to treatment is lower and relates to biologically separate drug effects. In del(5q) MDS, lenalidomide suppresses the malignant clone to restore effective erythropoiesis by virtue of synthetic lethality, arising from cereblon-dependent degradation of haplodeficient proteins encoded within the commonly deleted region of the chromosome 5q deletion. In contrast, in non-del(5q) MDS, lenalidomide restores effective erythropoiesis via enhancement of erythropoietin (EPO) receptor-initiated transcriptional response arising from the assembly of signaling-competent receptor complexes within membrane lipid raft domains. Recently, large phase III clinical studies have explored the role of lenalidomide, alone and in combination with, erythropoiesis-stimulating agents showing additive improvement in erythroid responses. Herein, we will describe the mechanisms of lenalidomide action in MDS and pivotal clinical studies testing the benefit of lenalidomide in both del(5q) and non-del(5q) MDS. Furthermore, we discuss evidence-based strategies to incorporate lenalidomide into the treatment algorithm for patients with MDS.

1. Introduction

Myelodysplastic syndromes (MDS) represent a clinically and genetically diverse spectrum of hematopoietic stem cell malignancies. MDS share the morphological features of single-lineage or multilineage dysplasia, ineffective hematopoiesis manifested as cytopenias, and a risk for transformation into acute myeloid leukemia (AML). The International Prognostic Scoring System (IPSS) and the revised IPSS (IPSS-R) scoring system apply hematologic, pathologic, and cytogenetic findings to discriminate differences in disease behavior across morphologic disease categories [1,2]. Recent molecular characterization of MDS using next-generation sequencing (NGS) techniques have further identified an array of somatic gene mutations that can refine prognostic discrimination for overall survival, risk of transformation to AML, and treatment outcome [3–8]. In the largest cohort reported to date by the International Working Group for the Prognosis of MDS (IWG-PM), the *SF3B1* splicing gene mutation is the sole mutation associated with a favorable overall survival, while adverse outcomes occur with *TP53*, *CBL*, *EZH2*, *RUNX1*, *U2AF1*, and *ASXL1* that are independent of IPSS-R risk group [9]. As we further characterize the molecular biology of MDS, refinement of therapeutic decisions for both lower-risk and high-risk MDS are expected to follow. Nazha and colleagues developed a model incorporating molecular mutation data with the IPSS-R that enhances the predictive power of the current prognostic system in MDS [10]. Although our ability to refine prognosis has improved significantly, prospective data regarding the impact of early intervention is lacking.

Therapeutic decisions for MDS patients are guided by the assessment of risk based upon the IPSS with sub-classification into lower risk (ie, low and intermediate-1) and higher risk (ie, intermediate-2 and high) disease. Therapeutic choices remain limited for patients with MDS and include erythropoiesis-stimulating agents (ESAs), lenalidomide, hypomethylating agents (azacitidine and decitabine), and allogeneic hematopoietic cell transplant (allo-HSCT). Thus, sequencing of lines of therapy, as well as identification of subgroups of MDS with highest probability of benefit from specific therapeutics, is critical in order to maximize treatment outcomes.

Lenalidomide represents the first and only MDS therapeutic that targets a cytogenetically defined disease subset, specifically MDS with chromosome 5q deletion [11]. Since its original approval by the US Food and Drug Administration (FDA) in 2005, there have been further studies refining its utilization, as well as evaluating its use in combination with other therapies. In this review, we will discuss the advances of lenalidomide in MDS and attempt to outline the approach of treatment of this molecularly and cytogenetically heterogeneous disease.

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2. Pathobiology of del(5q) MDS

MDS with isolated del(5q) represents a distinct clinical and pathological entity recognized in the World Health Organization (WHO) classification [12]. The traditional definition of "5q- syndrome" consisted of a phenotype characterized by macrocytic anemia, erythroid hypoplasia, normal or elevated platelet count, hypolobulated megakaryocytes, and isolated del(5q), which was described by Van den Berghe and colleagues [13]. Whereas WHO defines this entity requiring presence of 1–2 cytopenias, dysplasia in 1–3 lineages, absence of Auer rods, $<1\%$ circulating peripheral blasts and $<5\%$ bone marrow blasts, and the presence of isolated del(5q), it does not specify megakaryocyte morphology, extent of trilineage dysplasia, or ring sideroblasts count. Furthermore, cytogenetics by conventional karyotype analysis must have either the presence of an isolated interstitial long arm deletion involving chromosome 5q or with one additional abnormality excluding monosomy 7 or del(7q). Chromosome 5q deletion is the most common cytogenetic abnormality in MDS [14]. Specifically, among 2,072 MDS patients with metaphase karyotyping analyzed by Haase et al for the IWG-PM, deletions involving chromosome 5q were found in 15% of the patients overall, and in 30% of the 1,080 patients harboring clonal cytogenetic abnormalities [14]. Furthermore, isolated del(5q) was found in 14% of the patients with clonal abnormalities, whereas del(5q) with one additional abnormality was found in 5% of patients. Among patients with a complex karyotype, chromosome 5q deletion was evident in 40% [14].

The pathobiology of del(5q) MDS is now well characterized. Critical to the syndrome is haploinsufficiency for one or more of the genes located in the commonly deleted region (CDR) of 5q, which was first described by Boultwood and colleagues [15]. They discovered two distinct CDRs, with the region encoded at 5q32 comprising 40 genes, 33 of which are expressed in $CD34^+$ cells at haplodeficient levels that account for the hematologic and biological features of the 5q- syndrome [15]. The more proximal 5q31 CDR, is distinct from the CDR located at 5q32, and was initially linked to advanced MDS, AML, or therapy-related MDS [15]. MDS with del(5q) has an indolent clinical course and is characterized phenotypically by hypoplastic anemia accompanied by dysplastic micro- or mononuclear megakaryocytes [16]. In a cohort of 76 patients with del(5q) MDS, median survival of patients with an isolated deletion was 146 months, whereas patients with an additional chromosomal abnormality had a significantly shorter overall survival of 45 months ($P = .0085$) [16]. Moreover, there was no difference noted in overall survival noted for different cytogenetic breakpoints among del(5q) MDS cases, including 5q31, owing largely to the inclusion of both CDRs in the interstitial segment of the majority of cases. Interestingly, overall survival in these lower-risk MDS patients with del(5q) was impacted by transfusion dependence status as demonstrated by Germing and colleagues [17]. Overall survival was 44 months for patients requiring transfusions compared to 97 months for patients who were transfusion-independent ($P < .0001$) [17]. Furthermore, transfusion dependence at diagnosis also translated in increased rate of transformation to AML (12.6%), indicating transfusion dependency at the time of diagnosis is a considerable risk for poor overall outcome in this population.

3. Lenalidomide: Mechanism of Action

3.1. Lenalidomide in del(5q) MDS

Preclinical studies demonstrated that lenalidomide selectively inhibits the growth of del(5q) progenitors in vitro, without significant effect on the growth of normal $CD34^+$ progenitors or cytogenetically normal progenitors from MDS del(5q) clones [18]. Two cell cycle–regulating dual-specificity phosphatases encoded within the proximal CDR region of 5q, *CDC25C* and *PP2A,* were initially implicated to play a pivotal role in the drug-specific, G2M cell cycle arrest [19,20]. PP2A dephosphorylates the regulatory sites on mouse double-minute 2 (MDM2) protein, thereby promoting p53 activation and accumulation in affected progenitors. Lenalidomide inhibits the dephosphorylation of CDC25C and indirectly suppresses the activity of the haplodeficient PP2A catalytic domain, resulting in hyperphosphorylation of MDM2 and p53 degradation in del(5q) erythroid progenitors to restore effective erythropoiesis [20]. This activity has been shown to be highly selective by virtue of haploinsufficiency for these genes, resulting in cell cycle arrest and cytotoxicity of del(5q) progenitors, while sparing non-del(5q) progenitors [20]. Furthermore, overexpression of *PP2A* and *CDC25A* stabilizes p53 in del(5q) progenitors, and indeed in those patients with acquired resistance to lenalidomide, PP2A was up regulated coincident with p53 in erythroid precursors [21]. A murine model of the human MDS del(5q) generated by allelic deletion of the syntenic genes in the distal CDR showed that *TP53* inactivation rescues the hematologic phenotype, indicating that the pathobiological features of del(5q) MDS are p53-dependent [22].

The discovery that lenalidomide and other thalidomide analogs exert many of their biological effects through direct interaction with cereblon provided further insight into the karyotype-selective actions of lenalidomide in del(5q) MDS. Lenalidomide binds to and modulates the specificity of cereblon (CRBN), the substrate adaptor of the $CRL4^{CRBN}$ E3 ubiquitin ligase, a cullin-ring ligase composed of damaged DNA-binding protein 1 (DDB1), cullin 4a (CUL4A), and regulator of cullins 1 (ROC1). In the presence of lenalidomide, protein substrates are selectively ubiquitinated to undergo proteosomal degradation. In del(5q) MDS, lenalidomide-bound cereblon selectively binds and degrades casein kinase 1A1 (CK1α), a member of the β-catenin–destruction complex. Heterozygous loss of the *CSNK1A1* gene encoded at 5q32 stabilizes β-catenin, contributing to self-renewal and dominance of the del(5q) clone [23]. In contrast, homozygous loss of *CSNK1A1*, as occurs with lenalidomide-induced degradation of the haplodeficient CK1α, leads to p53 induction and selective clonal arrest by virtue of synthetic lethality [24]. Fang and colleagues recently identified *GPR68,* which encodes a G-protein–coupled receptor implicated in calcium homeostasis, as a candidate gene involved in the cytotoxicity of lenalidomide in del(5q) MDS [25]. Lenalidomide induces GPR68 expression via IKAROS family zinc finger 1 (IKZF1) degradation, leading to influx of calcium, activation of the calcium-dependent protease calpain (CAPN1), and subsequent induction of apoptosis in MDS cells [25]. Decreased expression level of calpastatin (CAST), an endogenous CAPN1 inhibitor encoded by the *CAST* gene residing on chromosome 5q15, is haplodeficient in most del (5q) MDS clones, thereby promoting sensitivity to lenalidomide [25].

3.2. Mechanism of lenalidomide resistance in del(5q)MDS

Primary resistance of del(5q) MDS cl to lenalidomide has been linked to the presence of *TP53* mutations [26,27]. Among 107 lenalidomide-treated patients studied in a recent series, cytogenetic response to lenalidomide was only 12% in patients with mutant *TP53* compared to 73% in patients with wild-type [26,27]. Similarly, transfusion independence was achieved in 43% versus 73% of *TP53* mutant and wild-type patients ($P = .020$), respectively [26,27]. *TP53* mutations are detected in approximately 20% of patients with isolated del(5q) MDS NGS, whereas in the presence of chromosome 7 and/or 17 aberrations *TP53* mutations are demonstrable in 70%–100% [6,28]. Presence of the *TP53* mutation