Biological and Prognostic Significance of Chromosome 5q Deletions in Myeloid Malignancies

Aristoteles A.N. Giagounidis,[1] Ulrich Germing,[2] and Carlo Aul[1]

Abstract The presence of del(5q), either as the sole karyotypic abnormality or as part of a more complex karyotype, has distinct clinical implications for myelodysplastic syndromes (MDS) and acute myeloid leukemia. The 5q− syndrome, a subtype of low-risk MDS, is characterized by an isolated 5q deletion and <5% blasts in the bone marrow and can serve as a useful model for studying the role of 5q deletions in the pathogenesis and prognosis of myeloid malignancies. Recent clinical results with lenalidomide, an oral immunomodulatory drug, have shown durable erythroid responses, including transfusion independence and complete cytogenetic remissions in patients with del(5q) MDS with or without additional chromosomal abnormalities. These results indicate that lenalidomide can overcome the pathogenic effect of 5q deletion in MDS and restore bone marrow balance. The data provide important new insights into the pathobiology of 5q chromosomal deletions in myeloid malignancies.

Cytogenetic abnormalities are detected in the bone marrow of over 50% of patients diagnosed with primary myelodysplastic syndromes (MDS) or myeloid leukemias, and up to 80% of patients with secondary or therapy-related MDS (1, 2). These abnormalities can be characterized as being balanced or unbalanced (3, 4). Balanced cytogenetic abnormalities include reciprocal translocations, inversions, and insertions (3, 5, 6). Whereas balanced chromosomal abnormalities are prevalent in myeloid leukemias, such as acute myelogenous leukemia (AML) or chronic myelogenous leukemia, they are uncommon in MDS (3, 5). Conversely, unbalanced chromosomal abnormalities, which reflect a gain or loss of chromosomal material, also occur in myeloid leukemias, but are particularly common in MDS. In myeloid malignancies, the nature of chromosomal abnormalities has a profound effect on disease pathogenesis, prognosis, intensity of treatment, and response to treatment (3, 6–9).

Interstitial 5q deletions are the most frequent chromosomal abnormalities in MDS and are present in 10% to 15% of MDS patients as either the sole karyotypic abnormality or in combination with other chromosomal abnormalities (2, 10). The 5q− syndrome is a distinct subtype of MDS defined by the presence of an isolated interstitial deletion of chromosome 5q and <5% blasts in the bone marrow (11–13). Originally described >30 years ago by Van den Berghe et al. (14–16), the 5q− syndrome is characterized clinically by a marked female preponderance, refractory macrocytic anemia, normal or high platelet counts, hypolobulated megakaryocytes, and modest leukopenia (11, 14, 17). The prognosis is favorable in 5q− syndrome with relatively low risk of transformation to AML (11, 18). Although the limits of 5q deletions vary among patients with 5q− syndrome, the most frequent deletion is del(5)(q13q33) and, in nearly all cases studied, the critical region of deletion includes 5q31 (11, 17, 19).

Because 5q− syndrome has an interstitial 5q deletion as the sole karyotypic abnormality, the disease provides a unique opportunity for studying the effect of 5q deletion on bone marrow function and hematopoiesis as well as assessing the role of targeted therapies. This review discusses the biological significance of 5q deletion with respect to hematopoiesis and bone marrow function and the prognostic and clinical effect of 5q deletion in MDS and AML. Encouraging results from recent clinical trials assessing the use of the immunomodulatory drug (IMiD, a registered trademark of Celgene Corporation, Summit, NJ) lenalidomide in the treatment of patients with MDS and 5q deletion will also be discussed.

Biological Significance of 5q Deletion in Hematopoiesis and Bone Marrow Function

MDS are clonal hematopoietic stem cell disorders characterized clinically by ineffective hematopoiesis as a consequence of abnormalities in proliferation, differentiation, and apoptosis of hematopoietic precursors and their progeny. These disorders are typically more prevalent in the elderly with the median age at diagnosis between 60 and 80 years (3, 20–22). Overall, the clinical picture includes peripheral cytopenias in the setting of normocellular or hypercellular bone marrow and increased risk of transformation to AML. Hypocellular bone marrow is less common in MDS. A summary of the clinical and hematologic features that are specific to the 5q− syndrome subtype of MDS is shown in Fig. 1 (11, 13, 15, 22). Bone marrow features

Authors' Affiliations: [1]St. Johannes Hospital, Medizinische Klinik II, Duisburg, Germany and [2]Heinrich-Heine-Universität Düsseldorf, Klinik für Hämatologie, Onkologie und klinische Immunologie, Düsseldorf, Germany
Received 7/5/05; revised 10/5/05; accepted 10/13/05.
Grant support: German Bundesministerium für Bildung und Forschung, Competence Network "acute and chronic leukemias."
Requests for reprints: Aristoteles A.N. Giagounidis, St. Johannes Hospital, Medizinische Klinik II, An der Abtei 7-11, 47166 Duisburg, Germany. Phone: 49-203-546-2480; Fax: 49-203-546-2249; E-mail: gia@krebs-duisburg.de.

doi:10.1158/1078-0432.CCR-05-1437

associated with 5q− syndrome include hypolobulated megakaryocytes, erythroid hypoplasia, and <5% blasts.

Role of tumor suppressor genes in MDS pathogenesis. Chromosome 5q contains many genes that are involved in the regulation of hematopoiesis, including cytokines and their receptors, cell cycle regulators, transcription factors, and signaling mediators. The clustering of hematologic genes between 5q13 and 5q33 suggests a correlation between the genetic abnormality and the clinical features of 5q− syndrome and other del(5q) MDS subtypes (19, 23).

The prevalence of 5q deletions in patients with MDS raises the possibility of a tumor suppressor gene on the long arm of chromosome 5, the loss of which is the basic event leading to disease progression. Efforts to localize such a gene has resulted in the identification of critical, minimally deleted regions (24–26). In 5q− syndrome, the critical region of gene loss has been defined as a 1.5 Mb region at 5q31-q32 flanked by *D5S413* and the *GLRA1* gene (25, 26). Many genes have been mapped to this region, as evidenced by a review of the Online Mendelian Inheritance in Man database of the National Center for Biotechnology Information (http://www.ncbi.nlm.nih.gov/Omim/getmap.cgi?). Table 1 shows a selection of genes localized on the commonly deleted segment of chromosome 5 in the 5q− syndrome. This region is distinct from and distal to a 1.5 Mb region at 5q31.1 flanked by the genes *IL-9* and *EGR-1* and deleted in AML and other forms of MDS involving 5q deletions (24, 27). The specification of two separate genomic intervals on chromosome 5q implies that a different gene or group of genes contributes to the pathogenesis of these different myeloid disorders. These findings are consistent with categorizing 5q− syndrome as a distinct subtype of MDS with a different pathogenesis than other forms of MDS involving 5q deletions (28).

To date, no single tumor suppressor gene responsible for MDS on chromosome 5q has been identified. Although there are a number of interesting candidates (e.g., *MEGF1* and *G3BP*), none have yet been shown to be critical for disease progression (19, 28). Given the large size of the 5q deletions often occurring in MDS and the absence of a clear candidate gene, it is possible that one of several genes could result in MDS. An alternate possibility is a gene dosage effect caused by deletion of multiple genes contained in the 5q region, which are functionally related to hematopoiesis.

- **Clinical Presentation**
  - Older age
  - Female predominance (7:3 female to male ratio)
  - Diagnosis of refractive anemia
  - Low risk of leukemic progression
  - Good prognosis
- **Hematologic and Pathologic Presentation**
  - Macrocytic anemia
  - Modest leukopenia
  - Normal/high platelet counts
  - 5q deletion as the sole karyotypic abnormality
  - Bone marrow erythroid hypoplasia
  - Hypolobulated megakaryocytes in bone marrow
  - <5% bone marrow blast count

Fig. 1. Clinical and pathologic characteristics of 5q− syndrome.

Clonal basis of disease in 5q− syndrome. The frequency of 5q deletions, as well as other chromosomal abnormalities in MDS, indicates that these abnormalities are not random events but rather reflect the clonal evolution and multistep pathogenesis of MDS (21, 29). According to a multistep model, initiating or "primary" genetic lesions, which may be acquired or caused by spontaneous mutation, within a hematopoietic stem cell promote the acquisition of "secondary" genetic events, characterized by stepwise losses and/or gains of specific chromosomal regions (e.g., 5q−, −7, or +8; ref. 29). These secondary genetic alterations may affect cell cycle control, transcription, and/or tumor suppressor activity, providing the MDS clone with a growth advantage, resulting in expansion of the clone and potential for leukemic transformation.

To identify the cell of origin in 5q− syndrome, Nilsson et al. (30) purified pluripotent hematopoietic stem cells ($CD34^+CD38^-$) from MDS patients with a 5q deletion between bands 5q13 and 5q33. These included patients with 5q− syndrome. Virtually all (>90%) $CD34^+CD38^-$ cells belonged to the 5q− deleted clone, indicating that a lymphomyeloid hematopoietic stem cell is the primary target of 5q deletions in MDS and that 5q deletions represent an early event in MDS pathogenesis (30). Notably, although a pluripotent hematopoietic stem cell is the primary target of 5q deletions, mature lymphocytes do not seem to be involved in the 5q− clone, suggesting that the transformed pluripotent stem cell lacks the ability to differentiate toward lymphocytes (30).

Cellular distribution of 5q31 deletion within the bone marrow in 5q− syndrome. In bone marrow smears of patients with 5q− syndrome, the 5q31 deletion is found in all three principal hematopoietic lineages (erythroblasts, granulocyte precursors, and megakaryocytes; refs. 30, 31). This is consistent with transformation of a pluripotent stem cell, described above, retaining the ability to proceed along multiple differentiation pathways (30, 31). Bigoni et al. (31) found that despite the fact that all erythrocytes in bone marrow smears of patients with 5q− syndrome were consistently macrocytic, the 5q31 deletion was observed in only 35% to 50% of erythroblasts. The presence of the 5q31 deletion in only a portion of the erythroblasts indicates a mosaicism of cytogenetically altered and normal cells in the bone marrow. This mosaicism was found across all three lineages in 5q− syndrome and seems to be a general phenomenon in MDS (31).

Effect of 5q deletion on bone marrow dysfunction. Ineffective hematopoiesis in MDS is due primarily to excessive apoptosis of hematopoietic progenitors and their progeny in the bone marrow (7, 32). Increased rates of apoptosis in MDS may be triggered by intrinsic cellular mechanisms or by a cytokine/growth factor imbalance in the local environment. In 5q− syndrome and other forms of MDS with 5q deletion, the underlying genetic abnormality itself can give rise to aberrant cytokine production and inappropriate signaling due to deletion of one or more of the corresponding genes (7). Cytokine imbalance in the bone marrow can have broad effects

Table 1. Selected genes localized in chromosome 5 (q31-q33)

Gene	Description	Localization
IL-17β	Interleukin 17β	5q32-q34
CSNK1A1	Casein kinase 1, α1	5q32
FLJ41603	Codes for unknown protein	5q32
PPARGC1B	Selective coactivator of estrogen receptor α coactivator	5q32
PDE6A	6A α subunit of cyclic guanosine 3′,5′-monophosphate – specific phosphodiesterase	5q31.2-5q34
DTD	Solute carrier family 26 (sulfate transporter), member 2	5q31-q34
TIGD6	Codes for unknown protein	5q32
CSF1R	Colony stimulating factor 1 receptor	5q33-5q35
PDGFRβ	Platelet-derived growth factor β	5q31-q32
CDX1	Caudal type homeo box transcription factor 1	5q31-q33
SLC6A7	Neurotransmitter transporter, member 7	5q31-q32
CAMK2A	Calcium/calmodium dependent protein kinase II α-B subunit (CaM kinase)	5q32
ARSI	Arylsulfatase I	5q32
TCOF1	Treacher Collins-Franceschetti syndrome	5q32-q33.1
CD74	CD74 antigen	5q32
RPS14	Ribosomal protein S14	5q31-q33
NDSTI	Heparan sulfate *N*-deacetylase/*N*-sulfotransferase 1	5q33.1
SYNPO	Synaptopodin	5q33.1
MYOZ3	Myozenin 3	5q33.1
RBM22	RNA binding motif protein 22	5q33.1
DCTN4	Dynactin p62	5q31-q32
NID67	Putative small membrane protein NID67	5q33.1
IGRM	Immunity-related GTPase family, M	5q33.1
ZNF300	Zinc finger protein 300	5q33.1
GPX3	Glutathione peroxidase 3	5q23
NAF1 (TNIP1)	Nef-associated factor 1	5q32-q33.1
ANXA6	Annexin A6	5q32-q34
LOC442141	Similar to PDGFR-like	5q33.1
DKFZP434C171	Protein	5q33.1
GM2A	Ganglioside G-M_2 activator protein	5q31.3-q33-1
SLC36A3	Solute carrier family 36, member 3	5q33.1
SLC36A2	Solute carrier family 36, member 2	5q33.1
LOC 391840	Similar to thyroid hormone receptor-associated protein complex 240 kDa component	5q33.1
SLC36A1	Solute carrier family 36, member 1	5q33.1
MEGF1 (FAT2)	FAT tumor suppressor homologue 2	5q32-q33
SPARC	Secreted protein, acidic, cysteine rich (osteonectin)	5q31.3-q32
ATOX1	Antioxidant protein 1 homologue	5q32
LOC441112	Similar to ribosomal protein P1 isoform	5q33.1
G3BP	Ras-GTPase activating protein-binding protein	5q33.1

NOTE: Data were from National Center for Biotechnology Information gene data bank, accessed 5/08/05.

on hematopoiesis by impairing cellular development and function regardless of whether specific cells harbor the 5q deletion. Indeed, dysplastic features can be found in all three major lineages in patients with 5q deletions (18, 31).

However, bone marrow dysfunction in MDS patients with 5q deletions may be less pronounced than in other forms of MDS. Washington et al. (33), for example, found significantly lower rates of apoptosis in bone marrow cells isolated from patients with 5q− syndrome versus patients with other refractory anemias. They hypothesized that lower apoptosis in 5q− syndrome may explain the milder clinical course of the disease and distinguish 5q− syndrome from other MDS. Furthermore, Lopez-Holgado et al. (34) found a higher proportion of myeloid-committed progenitors in patients with 5q deletions compared with MDS patients with trisomy 8 or normal karyotype. Moreover, these myeloid-committed progenitors from patients with 5q deletions were less impaired as indicated by higher plating efficiencies in long-term bone marrow cultures compared with progenitors from patients with normal karyotype or monosomy 7. Together, these

observations suggest a lesser degree of functional impairment with respect to hematopoiesis in MDS patients with 5q deletions versus other chromosomal abnormalities.

Prognostic and Clinical Effect of 5q Deletion: Importance of Context

The most significant independent prognostic variables in MDS are the percentage of bone marrow blasts, the number of cytopenias, and cytogenetics. By weighting these variables according to their statistical power, an International Prognostic Scoring System separates MDS patients into four distinct risk categories regarding survival and potential for evolution to AML: low, intermediate-1, intermediate-2, and high risk (35).

5q− Syndrome: clinical features, prognosis, and treatment. By the International Prognostic Scoring System, patients with 5q− syndrome have a relatively good prognosis with low risk of transformation to AML and are assigned to the low-risk MDS category (35). These patients typically have an isolated 5q deletion between bands 5q31 and 5q33 and a medullary blast count <5% (11, 17, 22). Despite the low risk of transformation to AML in these patients, the dependence on RBC transfusions often has a negative effect on morbidity and mortality (18, 36). The presence of additional chromosomal abnormalities and/or high medullary blast percentage in patients with a 5q deletion can have a negative effect on disease progression and survival. In an analysis of 72 patients with del(5q) MDS, the median survival in patients with an isolated 5q deletion was 107 months, whereas the presence of one additional chromosomal abnormality reduced the median survival to 47 months (P = 0.06; Fig. 2A). An increased medullary blast count of >5% in patients with an isolated del(5q) also results in reduced median survival (24 months; Fig. 2B). Patients with complex karyotypes, including del(5q31), have a particularly ominous prognosis. Regardless of their medullary blast count, they succumb to their disease within 7 to 8 months (Fig. 2B; ref. 37).

All del(5q) MDS patients eventually become transfusion dependent. Studies investigating the potential of low-dose 1-β-D-arabinofuranosylcytosine in MDS patients with isolated 5q deletion or one additional chromosomal abnormality have shown good response rates (38, 39). The problem with this treatment option is that cytopenias occur frequently, which may be harmful to the patient. The differentiating agent, all-*trans*-retinoic acid, has also been investigated for treatment of MDS patients with 5q deletion, with only marginal effects in these patients (40). Until recently, supportive care, especially frequent RBC transfusions, has been the principal treatment for 5q− syndrome (41).

Stewart et al. (42) analyzed outcomes of hematopoietic stem cell transplants in patients with MDS and 5q deletion as the sole karyotypic abnormality versus 5q deletion in combination with other chromosomal abnormalities. Overall, patients with 5q deletions as the sole karyotypic abnormality had better outcomes as revealed by lower rate of relapse and increased prevalence of relapse-free survival. However, stem cell transplant did not improve the overall survival of patients with 5q− syndrome compared with outcomes observed in other patient series (13). Owing to the very good prognosis of patients with 5q− syndrome, allogeneic stem cell transplant is only appropriate for carefully selected patients (13).

5q Deletions in other MDS subtypes and AML. Unlike 5q− syndrome, the presence of 5q deletions in high-risk subtypes of MDS and AML is an unfavorable prognostic factor, associated with rapid disease progression and poor outcome and survival. In AML, 5q deletion is usually associated with a complex karyotype and is also associated with poorer outcomes following treatment (4, 6, 43). However, a small proportion of patients with a single del(5q) aberration, >1 normal metaphase in cytogenetic examination, and no antecedent

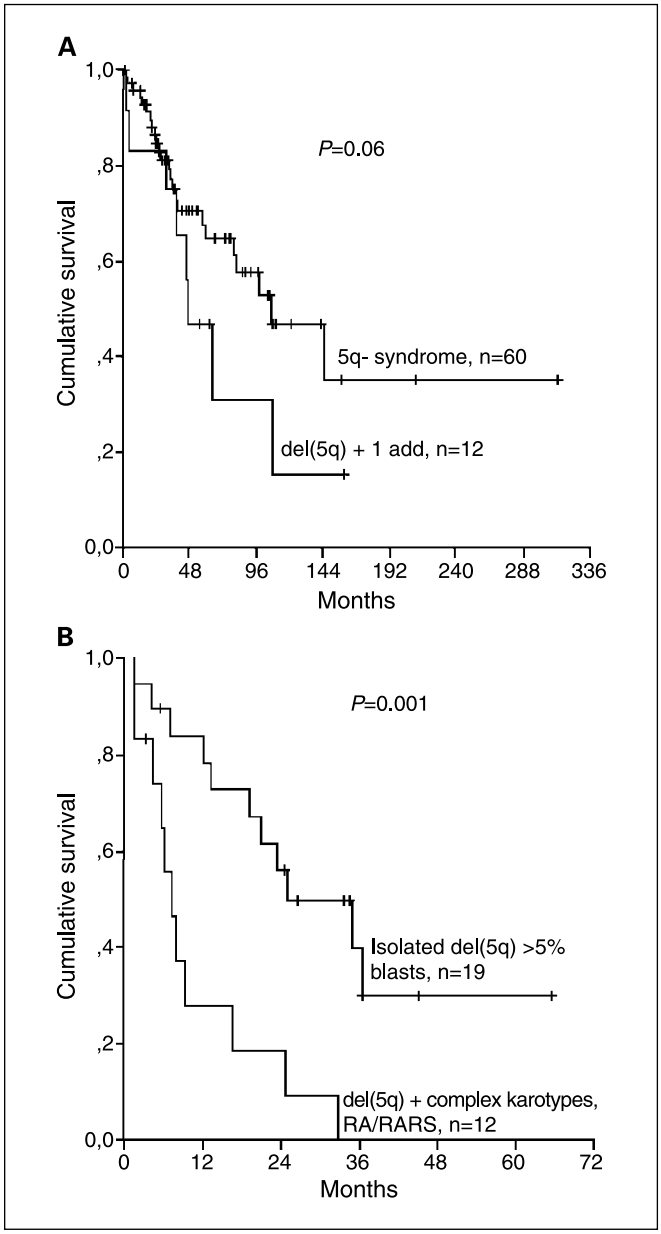

Fig. 2. Negative effect of additional chromosomal abnormalities or elevated blast count on overall survival of MDS patients with del(5q). *A,* the overall survival of patients with isolated 5q deletions and a blast count of <5% is adversely affected by one additional chromosomal abnormality, although this result did not reach statistical significance [P = 0.06, median survival 107 months for 5q− syndrome versus 47 months for del(5q) <5% blasts and one additional chromosomal abnormality]. *B,* the overall survival of 5q− patients with >5% blasts and an isolated del(5q) is reduced to 24 months and exceeds that of patients with del(5q) and complex karyotypic abnormalities <5% blasts by far (median survival 8 months, P = 0.001). RA, refractory anemia; RARS, refractory anemia with ringed sideroblasts.

hematologic disorder seem to have the same outcome as patients with a normal karyotype (44).

Targeting the 5q− clone. New treatment strategies in MDS are beginning to target the underlying genetic defect and molecular mechanisms that give rise to the disease. This approach has tremendous promise in the treatment of myeloid malignancies as shown by the successful use of the tyrosine kinase inhibitor imatinib in chronic myelogenous leukemia.

If the 5q− clone is targeted effectively, patients should experience hematologic improvement and cytogenetic remission. From a biological perspective, effectively targeting the 5q deletion involves restoring bone marrow balance and normalizing hematopoiesis. For patients with 5q deletions, a standardized approach to evaluating hematologic improvement is to assess erythroid response by measuring hemoglobin levels and/or dependence on RBC transfusions. The goal of therapy is to reduce or eliminate transfusion dependence.

5q− Cytogenetic remitting activity of lenalidomide. Lenalidomide is a more potent structural analogue of thalidomide that is nonteratogenic in animal models (45). Whereas these molecules are structurally similar, they exhibit distinct biological properties and have different safety profiles (45). Lenalidomide treatment seems to have remarkable erythroid and cytogenetic remitting activities in patients who have MDS with a 5q31.1 deletion (46). In a safety and efficacy study of 43 MDS patients, lenalidomide was highly effective in restoring RBC production in patients with MDS-related anemia. Twenty-four patients (56%) experienced an erythroid response, according to International Working Group response criteria, including major responses in 21 patients (46). Transfusion independence was achieved in 20 of 32 (63%) previously transfusion-dependent patients and a >2 g/dL increase in hemoglobin was achieved in 1 of 11 patients (9%) who had no transfusion requirements. As shown in Fig. 3, the erythroid response rate varied by cytogenetic pattern and was highest among patients with a chromosome 5q31.1 deletion (10 of 12; 83%) compared with patients who had normal karyotypes (13 of 23; 57%) or other chromosomal abnormalities (1 of 8; 12%), $P = 0.007$ (46).

Cytogenetic remissions in MDS patients with a 5q31.1 deletion were frequently achieved with lenalidomide treatment (Table 2; ref. 46). Ten of 12 (83%) patients with a 5q31.1 deletion experienced ≥50% reduction in abnormal metaphases, including 9 (75%) complete remissions. Of the nine patients with complete cytogenetic remission, eight had an isolated 5q31.1 deletion and one also had trisomy 21. The cytogenetic remissions corresponded with erythroid responses. Both the erythroid and cytogenetic responses achieved with lenalidomide treatment were durable (median, >48 weeks; range, 13+ to 101+ weeks; ref. 46).

Table 2. Cytogenetic response to lenalidomide

Chromosomal abnormality (*n*)	≥50% Decrease in abnormal cells in metaphase, *n* (%)	Complete cytogenetic response, *n* (%)
Del 5q31.1 (*n* = 12)	10 (83%)	9 (75%)
Isolated (*n* = 11)	9	8
With trisomy 21 (*n* = 1)	1	1
Del (20) (q11.2) (*n* = 2)	0	0
t(1;22)q(21p11.2) (*n* = 1)	1	1
Other* (*n* = 5)	0	0
Total (*n* = 20)	11 (55%)	10 (50%)

*Other = +19, t(3;3)(q21;q26.3), +8, −X, and complex karyotypes.

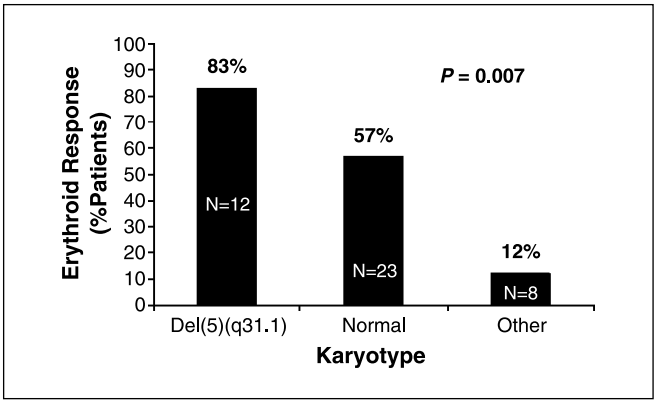

Fig. 3. Effect of karyotype on erythroid response rates to lenalidomide treatment. The cytogenetic profile significantly correlated with erythroid response to lenalidomide treatment ($P = 0.007$). Among the MDS patients studied, the patients with confirmed del(5)(q31.1) experienced the highest erythroid response rate (46).

Lenalidomide treatment was generally well tolerated. Myelosuppression was the most frequent grade 3 or 4 adverse event, but was manageable with dose reduction or interruption. The occurrence of myelosuppression did not correlate with erythroid or cytogenetic response (46).

Preliminary data from a larger multisite trial of lenalidomide in 148 patients conducted in over 30 clinical sites support these findings. Preliminary results indicate that 64% of patients have achieved transfusion independence (47). Cytogenetic response was achieved in 75% of patients, with complete cytogenetic response in >50% of cytogenetic responders. Notably, the highest response was reported in MDS patients who have an isolated 5q deletion. Overall, lenalidomide seems to rid these patients of the effects of the 5q deletion that defines the condition.

Restoring bone marrow function. The immunomodulatory activity of lenalidomide may correct the effects of 5q deletion in the bone marrow by rebalancing growth and differentiation signals within the microenvironment. The aberrant bone marrow morphology seen in 5q− syndrome was restored to normal in patients who were treated with lenalidomide (46). Restoration to normal histology included the size, number, and nuclear morphology of megakaryocytes.

How does lenalidomide work to eliminate the 5q− clone and restore effective erythropoiesis? Like the parent compound thalidomide, lenalidomide has both antiangiogenic and tumor necrosis factor-α inhibitory properties (45). The antiangiogenic activity of lenalidomide may play a role in inhibiting expansion of the 5q− clone by decreasing microvessel density in the bone marrow. Also, the tumor necrosis factor-α inhibitory properties of lenalidomide may play a role in reducing the rates of apoptosis of hematopoietic progenitors in the bone marrow (9, 22). Furthermore, a recent study showed that lenalidomide has preferential antiproliferative

activity on cell lines carrying a 5q deletion (48). This inhibition seemed to be due to G_0-G_1 arrest with a small apoptotic component. Furthermore, in one of the cell lines carrying a 5q deletion, lenalidomide interfered with growth regulatory signals by inhibiting Akt phosphorylation in response to CD19 or erythropoietin and increased expression of cell adhesion genes found at the 5q locus (48). These molecular events suggest that the 5q− hematopoietic precursors and their progeny are eliminated by lenalidomide treatment. Overall, lenalidomide seems to be a multifunctional immunomodulatory/antiangiogenic agent that can act on multiple molecular targets to inhibit expansion of the 5q− clone and apoptosis of hematopoietic progenitors in the bone marrow.

Conclusions

The remarkable clinical heterogeneity of myeloid malignancies, which has been a challenge for developing more effective treatments, is now being addressed at its genetic basis. Specific cytogenetic and molecular genetic abnormalities, such as 5q deletion, underlie the individuality of each MDS/AML case and, ideally, treatment should be individualized for each patient to optimize outcomes. The 5q cytogenetic remitting activity of lenalidomide provides an exciting opportunity to explore both the biology and the clinical effect of targeting the 5q chromosomal abnormality, which occurs frequently in patients with MDS and AML and effects prognosis.

References

1. Le Beau MM, Albain KS, Larson RA, et al. Clinical and cytogenetic correlations in 63 patients with therapy-related myelodysplastic syndromes and acute nonlymphocytic leukemia: further evidence for characteristic abnormalities of chromosomes no. 5 and 7. J Clin Oncol 1986;4:325–45.
2. Solé F, Espinet B, Sanz GF, et al. Incidence, characterization and prognostic significance of chromosomal abnormalities in 640 patients with primary myelodysplastic syndromes. Br J Haematol 2000;108:346–56.
3. Fenaux P. Myelodysplastic syndromes: from pathogenesis and prognosis to treatment. Semin Hematol 2004;41:6–12.
4. Haferlach T, Schnittger S, Kern W, Hiddemann W, Schoch C. Genetic classification of acute myeloid leukemia (AML). Ann Hematol 2004;83:S97–100.
5. Mauritzson N, Albin M, Rylander L, et al. Pooled analysis of clinical and cytogenetic features in treatment-related and *de novo* adult acute myeloid leukemia and myelodysplastic syndromes based on a consecutive series of 761 patients analyzed 1976-1993 and on 5098 unselected cases reported in the literature 1974-2001. Leukemia 2002;16:2366–78.
6. Mrózek K, Heerema NA, Bloomfield CD. Cytogenetics in acute leukemia. Blood Rev 2004;18:115–36.
7. Gallagher A, Darley RL, Padua R. The molecular basis of myelodysplastic syndromes. Haematologica 1997; 82:191–204.
8. Greenberg PL, Sanz GF, Sanz MA. Prognostic scoring systems for risk assessment in myelodysplastic syndromes. Forum (Genova) 1999;9:17–31.
9. Faderl S, Kantarjian HM. Novel therapies for myelodysplastic syndromes. Cancer 2004;101:226–41.
10. Heim S, Mitelman F. Chromosome abnormalities in the myelodysplastic syndromes. Clin Haematol 1986; 15:1003–21.
11. Boultwood J, Lewis S, Wainscoat JS. The 5q− syndrome. Blood 1994;84:3253–60.
12. Harris NL, Jaffe ES, Diebold J, et al. World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: report of the Clinical Advisory Committee meeting—Airlie House, Virginia, November 1997. J Clin Oncol 1999;17: 3835–49.
13. Giagounidis AAN, Germing U, Wainscoat JS, Boultwood J, Aul C. The 5q− syndrome. Hematology 2004;9:271–7.
14. Van den Berghe H, Cassiman J-J, David G, Fryns J-P, Michaux JL, Sokal G. Distinct haematological disorder with deletion of long arm of no. 5 chromosome. Nature 1974;251:437–8.
15. Sokal G, Michaux JL, Van den Berghe H, et al. A new hematologic syndrome with a distinct karyotype: the 5q− chromosome. Blood 1975;46:519–33.
16. Van den Burge H, Vermaelen K, Mecucci C, Barbieri D, Tricot G. The 5q− anomaly. Cancer Genet Cytogenet 1985;17:189–255.
17. Mathew P, Tefferi A, Dewald GW, et al. The 5q− syndrome: a single-institution study of 43 consecutive patients. Blood 1993;81:1040–5.
18. Giagounidis AAN, Germing U, Haase S, et al. Clinical, morphological, cytogenetic, and prognostic features of patients with myelodysplastic syndromes and del(5q) including band q31. Leukemia 2004;18:113–9.
19. Boultwood J, Fidler C, Strickson AJ, et al. Transcription mapping of the 5q− syndrome critical region: cloning of two novel genes and sequencing, expression, and mapping of a further six novel cDNAs. Genomics 2000;66:26–34.
20. Aul C, Germing U, Gattermann N, Minning H. Increasing incidence of myelodysplastic syndromes: real or fictitious? Leuk Res 1998;22:93–100.
21. Hofmann W-K, Lübbert M, Hoelzer D, Koeffler HP. Myelodysplastic syndromes. Hematol J 2004;5:1–8.
22. Lawrence LW. Refractory anemia and the myelodysplastic syndromes. Clin Lab Sci 2004;17:178–86.
23. Van den Berghe H, Michaux L. 5q−, twenty-five years later: a synopsis. Cancer Genet Cytogenet 1997;94:1–7.
24. Horrigan SK, Westbrook CA, Kim AH, Banerjee M, Stock W, Larson RA. Polymerase chain reaction-based diagnosis of del (5q) in acute myeloid leukemia and myelodysplastic syndrome identifies a minimal deletion interval. Blood 1996;88:2665–70.
25. Jaju RJ, Boultwood J, Oliver FJ, et al. Molecular cytogenetic delineation of the critical deleted region in the 5q− syndrome. Genes Chromosomes Cancer 1998;22:251–6.
26. Boultwood J, Fidler C, Strickson AJ, et al. Narrowing and genomic annotation of the commonly deleted region of the 5q− syndrome. Blood 2002;99:4638–41.
27. Zhao N, Stoffel A, Wang PW, et al. Molecular delineation of the smallest commonly deleted region of chromosome 5 in malignant myeloid diseases to 1-1.5 Mb and preparation of a PAC-based physical map. Proc Natl Acad Sci U S A 1997;94:6948–53.
28. Horrigan SK, Arbieva ZH, Xie HY, et al. Delineation of a minimal interval and identification of 9 candidates for a tumor suppressor gene in malignant myeloid disorders on 5q31. Blood 2000;95:2372–7.
29. Rosenfeld C, List A. A hypothesis for the pathogenesis of myelodysplastic syndromes: implications for new therapies. Leukemia 2000;14:2–8.
30. Nilsson L, Astrand-Grundström I, Arvidsson I, et al. Isolation and characterization of hematopoietic progenitor/stem cells in 5q-deleted myelodysplastic syndromes: evidence for involvement at the hematopoietic stem cell level. Blood 2000;96:2012–21.
31. Bigoni R, Cuneo A, Milani R, et al. Multilineage involvement in the 5q− syndrome: a fluorescent *in situ* hybridization study on bone marrow smears. Haematologica 2001;86:375–81.
32. Aul C, Bowen DT, Yoshida Y. Pathogenesis, etiology and epidemiology of myelodysplastic syndromes. Haematologica 1998;83:71–86.
33. Washington LT, Jilani I, Estey E, Albitar M. Less apoptosis in patients with 5q-syndrome than in patients with refractory anemia. Leuk Res 2002;26:899–902.
34. López-Holgado N, Arroyo JL, Pata C, et al. Analysis of hematopoietic progenitor cells in patients with myelodysplastic syndromes according to their cytogenetic abnormalities. Leuk Res 2004;28:1181–7.
35. Greenberg P, Cox C, LeBeau MM, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes [erratum appears in Blood 1998;91: 1100]. Blood 1997;89:2079–88.
36. Cheson BD, Bennett JM, Kantarjian H, et al. Report of an international working group to standardize response criteria for myelodysplastic syndromes. Blood 2000;96:3671–4.
37. Giagounidis AAN, Germing U, Strupp C, Hildebrandt B, Heinsch M, Aul C. Prognosis of patients with del(5q) MDS and complex karyotype and the possible role of lenalidomide in this patient subgroup. Ann Hematol 2005;84:569–71.
38. Juneja HS, Jodhani M, Gardner FH, Trevarthen D, Schottstedt M. Low-dose ARA-C consistently induces hematologic responses in the clinical 5q− syndrome. Am J Hematol 1994;46:338–42.
39. Giagounidis AAN, Haase S, Germing U, et al. Low-dose cytarabine in the treatment of patients with the 5q-syndrome. Onkologie 2002;25:66.
40. Giagounidis AAN, Haase S, Germing U, et al. Treatment of myelodysplastic syndrome with isolated del(5q) including bands q31-q33 with a combination of all-*trans*-retinoic acid and tocopherol-α: a phase II study. Ann Hematol 2005;84:389–94.
41. National Comprehensive Cancer Network (NCCN) Myelodysplastic panel members. NCCN practice guidelines: myelodysplastic syndromes v1. 2005. http://www.nccn.org/professionals/physician_gls/PDF/mds.pdf. Accessed August 12, 2005.
42. Stewart B, Verdugo M, Guthrie KA, Appelbaum F, Deeg HJ. Outcome following haematopoietic cell transplantation in patients with myelodysplasia and del (5q) karyotypes. Br J Haematol 2003;123:879–85.
43. Keating MJ, Cork A, Broach Y, et al. Toward a clinically relevant cytogenetic classification of acute myelogenous leukemia. Leuk Res 1987;11:119–33.
44. Estey EH, Pierce S, Keating MJ. Identification of a group of AML/MDS patients with a relatively favorable prognosis who have chromosome 5 and/or 7 abnormalities. Haematologica 2000;85:246–9.
45. Bartlett JB, Dredge K, Dalgleish AG. The evolution of thalidomide and its IMiD derivatives as anticancer agents. Nat Rev Cancer 2004;4:314–22.
46. List A, Kurtin S, Roe DJ, et al. Efficacy of lenalidomide in myelodysplastic syndromes. N Engl J Med 2005;352:549–57.
47. List AF, Dewald G, Bennett J, et al. Hematologic and cytogenetic (CTG) response to lenalidomide (CC-5013) in patients with transfusion-dependent (TD) myelodysplastic syndrome (MDS) and chromosome 5q31.1 deletion: results of the multicenter MDS-003 Study [abstract 5]. J Clin Oncol 2005;23:2S.
48. Gandhi AK, Naziruddin S, Verhelle D, Brady H, Schafer P, Stirling D. Anti-proliferative activity of CC-5013 in 5q− myelodysplastic syndrome (MDS) and acute lymphocytic leukemia (ALL) cell lines [abstract 6618]. J Clin Oncol 2004;22:587S.

Clinical Cancer Research

Biological and Prognostic Significance of Chromosome 5q Deletions in Myeloid Malignancies

Aristoteles A.N. Giagounidis, Ulrich Germing and Carlo Aul

Clin Cancer Res 2006;12:5-10.