Chapter 6
The 5q– Syndrome

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6.1 Introduction

In 1956, Tjio and Levan (1) reported in a seminal observation that the correct number of chromosomes in human somatic cells was 46, not 48, as previously thought. Since then, an increasing number of malignant hematological diseases have been directly attributed to abnormalities of the number or the structure of these 46 chromosomes. The first of those disorders, of course, was chronic myeloid leukemia showing a balanced translocation of chromosomal material between chromosomes 9 and 22, reported by Nowell and Hungerford in 1960 (2). In 1973, Rowley identified the translocation t(8;21) in acute myeloid leukemia (AML), a genetic abnormality that today defines this subgroup of AML (3). One year later, in 1974, van den Berghe and colleagues reported three patients with long-standing refractory anemia, macrocytic erythrocyte indices, mild leucopenia, and normal to elevated platelet counts who showed a consistent deletion of the long arm of No. 5 chromosome (4). This disease—now called 5q– syndrome (pronounce 5q "minus" syndrome)—is classified within the myelodysplastic syndromes (MDS) and shares a number of their characteristics. The MDS are a group of bone marrow disorders derived from an abnormal hematopoietic progenitor cell (5). Because of a proliferation advantage, these abnormal stem cells have the ability to clonally expand, leading to the substitution of a variable part of normal bone marrow by malignant hematopoiesis. On the other hand, MDS are characterized by inappropriate activation of growth arrest signals that lead to a high proportion of proliferating cells finally undergoing programmed cell death (6). This impairment in cellular homeostasis explains the paradox of a hypercellular bone marrow and peripheral cytopenias often encountered in MDS. The MDS with a del(5q) chromosomal abnormality are unique because of their defining genetic lesion, their clinical and prognostic features, and their response to immunomodulatory treatments (IMiDs®). Particularly the new treatment options with IMiDs® are exciting, because they seem to target the malignant cell population independent of high-risk morphological or genetic features. This chapter will not only cover the 5q– syndrome itself, but it will also review other forms of MDS with del(5q) chromosomal abnormality that are important to the understanding of this puzzling disease.

S.M. Ansell (ed.), *Rare Hematological Malignancies.*

6.2 Classification

Myelodysplastic syndromes are classified according to the French-American-British (FAB) or the newer World Health Organization (WHO) classifications (7, 8) (Tables 6.1 and 6.2). Although the WHO classification is becoming increasingly popular with hematologists, many current studies of new compounds in the field are still conceived on the basis of the FAB classification to ensure good comparability with previous investigations. Furthermore, the most widely used prognostic scoring index, the International Prognostic Scoring System (IPSS), is based on the FAB classification (Table 6.3). The FAB classification, of course, is a purely morphological system that categorizes the MDS in five different subtypes: Refractory anemia (RA), refractory anemia with ring sideroblasts (RARS), refractory anemia with excess blasts (RAEB), refractory anemia with excess blasts in transformation (RAEB-T), and chronic myelomonocytic leukemia (CMML). Accordingly, patients with a del(5q) chromosomal abnormality can be classified within the FAB system into any of those subgroups, depending on their bone marrow and peripheral blast count and the number of monocytic cells in the peripheral blood. Del(5q) abnormalities most often present as RA (67%) and rarely as RARS (14%), RAEB (17%), or RAEB-T (1%) (9). Exceptionally, del(5q) MDS might present as CMML (10). The FAB classification does not recognize the notion of 5q– syndrome and considerable confusion has arisen from this fact. Some physicians define the 5q– syndrome as a disease with the characteristics initially reported by van den Berghe (4) [i.e., macrocytic anemia, normal to elevated platelet counts, mild leucopenia, and an isolated deletion del(5q)]. Others use the term in a broader sense, including patients with additional chromosomal abnormalities and elevated blast counts. The WHO classification, instead, taking into account not only morphological but also cytogenetic and immunophenotypic findings of hematological diseases, defined a new entity within the MDS for del(5q) MDS. This classification narrows the notion of "myelodysplastic syndromes with chromosome 5 abnormality" to those patients who have an isolated deletion of del(5q) including bands q31 to q33 and displaying a blast count of <5% both in the bone marrow and the peripheral blood. Although this disease category is certainly helpful in recognizing the existence of a special subtype of MDS with del(5q) abnormality, the inclusion of patients

Table 6.1 The French-American-British classification of myelodysplastic syndromes (7)

	Blast percentage		
Subtype	Blood	Bone marrow	Additional features
Refractory anemia (RA)	<1%	<5%	
RA with ring sideroblasts (RARS)	<1%	<5%	>15% ring sideroblasts
RA with blast excess (RAEB)	<5%	5–20%	
RAEB in transformation (RAEB/T)	≥5%	21–30%	Optional Auer rods
Chronic myelomonocytic leukemia (CMML)	<5%	<20%	Peripheral monocytosis (>1000/μL)

Source. Ref. 7.

Table 6.2 Morphological classification of myelodysplastic syndromes (WHO classification) (8)

Subtype	Blast percentage		Additional features
	Blood	Bone marrow	
Refractory anemia (RA)	<1%	<5%	
RA with ring sideroblasts (RARS)	<1%	<5%	>15% ring sidero-blasts
Refractory cytopenia with multilineage dysplasia (RCMD)	<1%	<5%	Dysplasia >10% of bone marrow cells in ≥2 cell lineages
Refractory cytopenia with multilineage dysplasia and ring sideroblasts (RCMD-RS)	<1%	<5%	Dysplastic features in >10% of bone marrow cells in ≥ 2 cell lineages; >15% ring sideroblasts
Refractory anemia with blast excess (RAEB-I)	<5%	5–9%	
RAEB-II	5–19%	10–19%	Optional Auer rods
5q– Syndrome	<5%	<5%	
MDS, unclassified	<1%	<5%	Dysplasia exclusively in nonerythropoietic lineages

Table 6.3 International Prognostic Scoring System for evaluating prognosis in patients with myelodysplastic syndromes

Prognostic variable	Points				
	0	0.5	1	1.5	2.0
Bone marrow blasts (%)	<5	5–10	—	11–20	21–30
Number of cytopenias[a]	0–1	2–3	—	—	—
Cytogenetic category[b]	Good	Intermediate	Poor	—	—

Risk group	Score	Median survival (years)	25% AML transformation (years)[c]
Low	0	5.7	9.4
Intermediate-1	0.5–1	3.5	3.3
Intermediate-2	1.5–2.0	1.2	1.1
High	≥2.5	0.4	0.2

[a]Cytopenias defined as platelets < 100.000/μL; hemoglobin <10 g/dL; neutrophils <1800/μL.

[b]Good = normal karyotype, 5q–, 20q–, –Y; intermediate = other anomalies; poor = complex (≥3 abnormalities), chromosome 7 anomalies.

[c]Time interval for 25% of the patients to undergo evolution to acute myeloid leukemia.

with a peripheral blood blast count of up to 5% is inconsistent with the rest of the WHO MDS classification. Patients with <5% blasts in the peripheral blast count are considered to have RAEB-I, and it is unclear why patients with low (i.e., <1%) and higher (i.e., <5%) peripheral blast counts should be grouped together in this special subgroup, as there is ample evidence that patients with del(5q) having a higher blast count (i.e., RAEB) have a worse overall survival than those with a bone marrow blast count <5% and a peripheral blast count <1% (11).

It becomes clear from those considerations that the MDS classification for del(5q) disease needs further improvement. A suggestion for a practical classification is

given in Table 6.4. This suggestion is supported by several lines of evidence that are going to be discussed in detail in this chapter:

- Del(5q) is a recurrent chromosomal abnormality in MDS.
- Patients with an isolated del(5q) including bands q31 to q33 in conventional cytogenetic testing and a bone marrow blast count of <5% (and <1% in the peripheral blood) share common clinical, biological, and prognostic characteristics. The notion "5q– syndrome" should be restricted to this subgroup.
- The del(5q) chromosomal aberration occurs early in the development of the hematopoietic stem cell and further abnormalities are later events.
- Patients with additional chromosomal abnormalities have a worse prognosis than those with isolated del(5q).
- Del(5q) MDS patients with an elevated blast count have a worse outcome than those with a limited blast count.
- Del(5q) MDS cases can be effectively treated with IMiDs®, irrespective of additional chromosomal abnormalities or blast percentage.

Taking into account those basic characteristics, it becomes clear that patients sharing a del(5q) including bands q31 to q33 should be categorized as a subgroup of MDS, irrespective of their blast count or additional chromosomal abnormalities. Because of prognostic considerations in the *untreated* del(5q) patient cohort, those with an isolated del(5q) and a normal bone marrow and peripheral blast count should be considered as having the favorable 5q– syndrome. Patients with one additional abnormality but normal blast counts should be grouped into a separate category. Patients with two or more additional chromosomal aberrations (complex karyotype according to IPSS) have an ominous prognosis and should be included in a third group, irrespective of their blast counts, as this does not impact on their prognosis (12). Finally, patients with an increased bone marrow or peripheral blast count and isolated del(5q) or one additional abnormality should accordingly be grouped in another category (Table 6.4).

Table 6.4 A practical classification system for del(5q) MDS

Bone marrow blasts <5% or peripheral blasts <1%	Bone marrow blasts >5% or peripheral blasts >1%	Prognosis
Isolated del(5q) ("The 5q– syndrome")		Good
Del(5q) +1 abnormality		Intermediate
	Isolated del(5q) del(5q) + 1 abnormality	Bad
Del(5q) in association with a complex karyotype		Very bad

Note: A complex karyotype confers a very bad prognosis irrespective of the bone marrow blast count.

6.3 Clinical and Morphological Features

The median age of patients diagnosed with del(5q) MDS is around 70 years, however, patients as young as 30 years might occasionally be encountered (9). The male-to-female ratio has consistently been reported to be shifted to the female sex, with largest series reporting sex ratios between 1:1.6 and 1:5 (9, 13–15). In an analysis of 76 cases, the female preponderance was also found in patients with an increased medullary blast count (9). Both primary and secondary MDS have been identified bearing a del(5q) (9, 16). Usually, the disease is being diagnosed as refractory anemia according to FAB, but all other subtypes have been reported, exceptionally CMML (9, 10). The 5q– syndrome typically presents with macrocytic anemia, mild leukopenia, normal to elevated platelet counts, and erythroid hypoplasia in the bone marrow. Macrocytosis is not necessarily present in all cases; therefore, its presence or absence should not be used to define the "5q– syndrome," Also, a few cases might show erythroid hyperplasia in the bone marrow (9). Patients with a lower than normal platelet count in del(5q) MDS have greater chances to have advanced disease. More than half of those cases were shown to have an elevated blast cell percentage in the bone marrow (9). The morphological hallmark of the disease is the hypolobulation of megakaryocytes in the bone marrow. Those cells show typically one single round to oval nucleus and account for 30–80% of all megakaryocytes. These cells are not micromegakaryocytes because their size exceeds that of a promyelocyte by far. Still, true micromegakaryocytes might be found in del(5q) MDS in about one-third of cases (9). Apart from megakaryocytic dysplasia, morphological irregularities are not very prominent in the other myeloid lineages in the bone marrow. Therefore, if the dysplastic megakaryocytes are missed in cytology, the disease might not be recognized as MDS. For diagnosis with the microscope, low-power magnification reveals to be the most important aspect in diagnosis of del(5q) MDS.

6.4 Laboratory Values

The typical combination of the 5q– syndrome (i.e., female gender, macrocytic anemia, mild leukopenia, and normal to elevated platelet counts) occurs only in about one out of five patients with isolated 5q– deletion (11). Patients with a higher bone marrow blast count or additional abnormalities tend to have lower granulocyte and platelet counts. The reticulocyte count in del(5q) MDS is almost always reduced, even in patients with additional autoimmune hemolysis (17). Erythropoietin (EPO) levels in the syndrome are usually highly elevated, with a median value of 1000 U/L in a series of 60 patients (11). We have seen patients with EPO levels up to 5500 U/L. Interestingly, because all del(5q) patients eventually become transfusion dependent and many are diagnosed a considerable time after their first transfusion, ferritin levels at the time of diagnosis are often elevated. The median value in 41 patients was found to be 540 ng/mL with a range from 37 to 4830 (11).

6.5 Cytogenetics

Del(5q) is a recurrent chromosomal abnormality in MDS. In fact, as many as 15% of MDS cases will display a deletion of variable length at the long arm of No. 5 chromosome, either as the sole abnormality or in combination with other karyotypic anomalies (18). Isolated del(5q) deletions account for half of this figure, and the 5q– syndrome accounts for about 4% of all MDS cases. This deletion consistently involves a region between the bands q31 to q33, but both proximal and distal breakpoints are variable. Three major deletions have been identified. Their frequency is in the same order as the respective length of the lesion: The most common (and the longest) is del(5)(q13q33), the second most common is del(5)(q13q31), and, finally, less common is del(5)(q22q33). A number of other breakpoints have been reported, some as short as del(5)(q31q33) (19, 20). These short deletions in patients with the typical features of del(5q) MDS (and more precisely, the 5q– syndrome) have defined the minimal commonly deleted region (CDR) of the disease (20). The great variability of breakpoints virtually excludes the possibility that formation of a novel oncogene is responsible for the disease by fusion of the proximal and distal breakpoints. Instead, the constant loss of genetic material from 5q in association with a specific syndrome suggests that the mechanism for tumorigenesis is recessive and that loss of a tumor suppressor gene is responsible for the development of del(5q) MDS. However, the exact mechanism by which the chromosomal deletion leads to the disease is unknown. The majority of the genes mapping within the CDR are expressed in CD34+ cells and might, therefore, be at the origin of the disease. However, no inactivating mutation has yet been identified in any candidate gene (11). Another possibility would be that haploinsufficiency contributes to the development of del(5q) MDS (i.e., a gene dosage effect resulting from the loss of one single allele). An alternate possibility is a gene dosage effect caused by the deletion of multiple genes contained in the 5q region, which are functionally related to hematopoiesis (21). Del(5q) seems to occur very early in the differentiation of hematopoietic stem cells. Nilsson et al. (22) purified pluripotent hematopoietic stem cells (CD34+CD38−) from MDS patients with a 5q- deletion between bands 5q13 and 5q33. Virtually all 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 development. Additional cytogenetic abnormalities like trisomy 8 or trisomy 21 are secondary events that are being acquired at later stages (22).

6.6 Molecular Genetics

The molecular basis of del(5q) MDS has been the subject of extensive investigation. The minimal CDR was identified by Boultwood et al. and assigned to a 1.5-Mb interval at 5q32 flanked by *D5S413* and the *GLRA1* gene (20). This CDR contains approximately 48 genes, including putative tumor suppressor genes like

MEGF1 (FAT tumor suppressor homologue 2) and *G3BP* (Ras-GTPase activating protein-binding protein) (20, 21). This region is distinct from and distal to a 1.5-Mb region at 5q31.1 flanked by the genes interleukin (IL)-9 and early growth response 1 (*EGR-1*) that has been found to be commonly deleted in advanced MDS and AML with del(5q) abnormality (23, 24). The identification of more than one CDR of the del(5q) in association with malignant myeloid disorders suggests that different genes might be pathogenetically relevant. Interestingly, however, nearly all of the deletions in del(5q) MDS are large enough to cover both the MDS and AML del(5q) CDR. Molecular profiling with gene expression analysis using a comprehensive array platform (Affymetrix GeneChip U133 Plus 2.0) has yielded additional insight into the pathophysiology of MDS and the del(5q) subgroup (25). In fact, across the MDS spectrum, the two most upregulated genes were found to be the interferon (IFN)-stimulated genes, *IFITM1* and *IFIT1*. IFN-γ is a cytokine that is supposed to exert an inhibitory role on hematopoietic progenitors in the bone marrow of patients with MDS. The expression profile of del(5q) MDS was significantly different from that of patients with MDS and a normal karyotype. This was, of course, partly due to the fact that the deletion of part of chromosome 5 led to underexpression of the genes encoded on 5q. Approximately 40% of the significant probe sets that show lower expression levels in patients with a del(5q) map to chromosome 5, suggesting a gene dosage effect by the loss of one allele. On the other hand, histone genes within the *HIST1* gene cluster on chromosome 6q21 were expressed at significantly higher levels in del(5q) MDS patients. Some of the patients showed a more than 100-fold upregulation of certain *HIST1* genes (25). Other genes with an increased expression level included actin-binding proteins or myosin-related proteins like *ARPC2, CORO1C*, and *CAPZA2*. Disruption of the actin cytoskeleton and, consequently, deregulation of signal transduction pathways has been implicated in tumorigenesis. Other genes overexpressed in del(5q) MDS were *PF4V1, PPBP*, and *CD61*, which are megakaryocyte/platelet associated (25). Interestingly, a recent study on serum protein profiling in MDS revealed PF-4 to be a highly sensitive and stable marker for the recognition of myelodysplastic syndromes (26).

6.7 Prognosis

Patients with del(5q) MDS are usually considered to have a relatively good prognosis. This is true for those patients who have a medullary blast count of <5% and an isolated del(5q) or a del(5q) with not more than one additional chromosomal abnormality (Figure 6.1) (11, 13, 18, 27, 28). In fact, patients with an isolated del(5q) and a normal bone marrow and peripheral blast count (5q– syndrome) have a median overall survival between 70 and 107 months (11, 13, 14, 18). This should, however, be compared to the survival of the general population at the same median age. At the age of 67 years, the general female population in Germany is expected to live for another 244 months, whereas men generally live 188 months (German Federal Office of Statistics, 2004). This shows that even the favorable 5q– syndrome

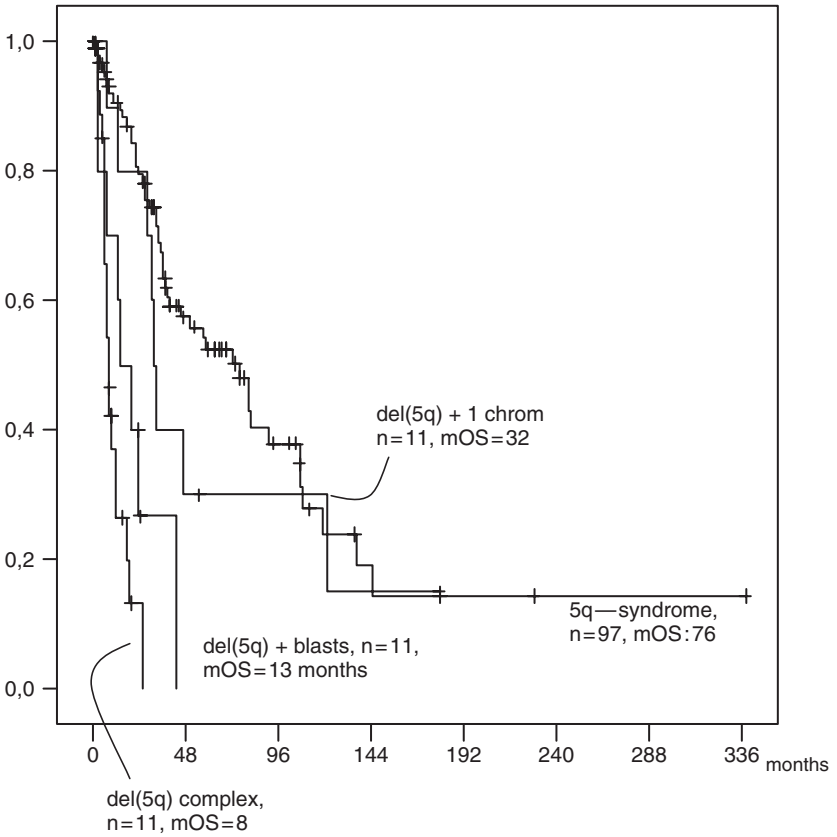

Figure 6.1 Overall survival of patients with del(5q) MDS. Four curves are presented: patients with a bone marrow blast count of <5% (5q– syndrome) and isolated del(5q); patients with a bone marrow blast count <5% and del(5q) plus one additional chromosomal abnormality (del(5q)+1 chrom); patients with isolated del(5q) and a bone marrow blast count >5% (del(5q) + blasts); patients with del(5q) and complex cytogenetic aberrations (del(5q) complex). Median overall survival (mOS) is given in months. No significant difference is found between 5q– syndrome and del(5q)+1 chrom; however, patient numbers are low in the latter group

confers excess mortality compared to the general population. If the patients acquire one additional chromosomal abnormality, the overall survival is reduced to 32–47 months (Figure 6.1) (11, 18). This changes dramatically if the del(5q) comes in association with a complex karyotype. In those cases, the overall survival of the patients is less than 1 year, independent of their medullary blast count (12). Indeed, there is evidence that patients with a complex karyotype involving del(5q) have a worse prognosis than patients with a complex chromosomal abnormality without involvement of chromosome 5. An elevation of the medullary blast count is also an adverse prognostic factor. The median overall survival of 11 patients with an increase in bone marrow blasts and an isolated del(5q) is 13 months (Figure 6.1).

6.8 Therapy

A number of therapeutic approaches have been used in patients with del(5q) disease in the past, generally with little success. Pyridoxine, steroids, and danazol have not shown any effect in a series of patients reported by Mathew et al. (14). More modern approaches are summarized in Table 6.5. A case report has been published in which the use of bortezomib in a patient with del(5q) MDS has resulted in a major hematological response (29).

Erythropoietin or darbepoietin has been given to a small number of del(5q) MDS cases, with some of them showing improvement (30, 31). Its use should be carefully selected, however, because the serum EPO level in this patient subgroup is usually higher than 200–500 U/L, a threshold generally accepted as predictive for EPO responses (32). Indeed, larger series have reported response rates to EPO with or without granulocyte colony-stimulating factor (G-CSF) of only 6–14% (33–36).

The German MDS study group has performed a trial with all-*trans*-retinoic acid (ATRA) in 29 patients with isolated del(5q) with <10% bone marrow blasts. The results were rather disappointing. Overall, 19% of patients showed a reduction in red blood cell transfusions; however, these were not long-lasting and the side effects were serious enough to prompt the authors to conclude that ATRA is not the therapy of choice for this disease entity (37).

Low-dose cytarabine has been used in two small studies for patients with del(5q) MDS, mainly the 5q– syndrome (38, 39). Response rates were 57% and 100%, respectively, with transfusion independence being achieved for up to 30 months. The drug was given at dosages of 20 mg/m^2 twice daily for 14 days as a subcutaneous injection. In most cases, only one course of therapy was given for remission induction. Additional courses were only given in case of relapse, and some of the patients responded again with freedom from transfusion at the time of the second low-dose cytarabine (Ara-C) administration (39). Patients treated with low-dose cytarabine with the above-mentioned schedule will very likely become neutropenic because del(5q) MDS initially often presents with mild to moderate leukopenia. One of our patients experienced life-threatening *Escherichia coli* septicemia after one course of therapy. Therefore, the drug should only be used by experienced hematologists and the patients should be monitored carefully for cytopenias. Supportive therapy with myeloid growth factors might be necessary to prevent serious infection.

Table 6.5 Modern treatment approaches to del(5q) MDS

Erythropoietin and darbepoietin
All-*trans*-retinoic acid
Low-dose cytarabine
Bortezomib
Thalidomide
Lenalidomide
Allogeneic stem cell transplantation

Because of the good overall survival in the 5q– syndrome, hematopoietic stem cell transplantation (HSCT) is considered appropriate only for patients with progressive disease in terms of additional chromosomal abnormalities, peripheral blood cytopenias, or an increase in bone marrow or peripheral blood blast counts (40). Stewart et al. (48) have published a series of 57 patients with del(5q) MDS or secondary AML who underwent HSCT. Seventeen patients had an isolated del(5q) and a blast count of <5%; however, only 5 patients had a low-risk IPSS profile. Hence, 12 of the 17 patients had at least one cytopenia in addition to anemia. Most of the patients with the lower-risk features were referred to the transplantation center because of increasing transfusion dependence. Seven patients with one additional karyotypic abnormality underwent HSCT. Another 30 patients had a poor-risk karyotype, including 12 with chromosome 7 abnormalities and 18 with at least another 2 cytogenetic aberrations. Only 1 of 20 patients with isolated del(5q) relapsed, compared with 15 of 37 patients with additional chromosomal abnormalities. Although patients with additional chromosomal anomalies tended to have more advanced MDS, this result still underlines the unfavorable prognosis of additional karyotypic anomalies in conjunction with del(5q), which is not only true for the natural course of the disease but also in association with HSCT. The nonrelapse mortality, on the other hand, was not statistically significantly different, accounting for 30% in the isolated del(5q) group and 38% in the group of del(5q) with additional chromosomal abnormalities. Although, from a transplantation standpoint, a 30% mortality might not be judged excessive, in patients with an isolated del(5q), 30% of patients would not be expected to die before about 40 months of their natural course (Figure 6.1). Therefore, the decision to proceed with an allogeneic HSCT in patients with isolated del(5q) should be carefully weighed and the patients selected on an individual basis.

Thalidomide is a pleiotropic drug with antiangiogenic, anti-inflammatory, and T-cell costimulatory activity that can effectively treat anemia in MDS, with response rates ranging from 20% to 49% (41). The best results were seen in patients with low-risk or intermediate-1-risk IPSS profiles (42). Strupp et al. (43) reported three cytogenetic responses (19%) out of 16 patients with karyotypic abnormalities, and, interestingly, 2 of those patients had a del(5q) chromosomal abnormality. The first patient had an isolated del(5q)(q22q33) abnormality in 11 out of 20 metaphases and other features of the 5q– syndrome. She was treated with thalidomide doses of 100–400 mg/day and achieved both partial cytogenetic remission (2 out of 20 metaphases remained abnormal) and transfusion independence. Transfusion independence lasted for about 3 years, but the patient eventually had to stop the treatment because of progressive polyneuropathy. The second patient had a complex karyotype including del(5q) and RAEB-T with severe anemia (7.2 g/dL) and thrombocytopenia (22.000/μL). Within 5 months of thalidomide treatment at 200–400 mg/day, this patient achieved transfusion independence (hemoglobin, 12.8 g/dL; platelets, 240.000/μL) and complete cytogenetic remission. However, the patient experienced deep venous thrombosis and pulmonary emboli during treatment with thalidomide. Finally, after 9 months of therapy, he relapsed with RAEB-T and a complex karyotype and died in the further course of the disease.

These observations are of special interest because they show that hematological and cytogenetic remissions might be obtained in del(5q) MDS with an immunomodulatory approach. The consistent activity of thalidomide in MDS provided the rationale for the use of its structural analog lenalidomide in this patient population. Lenalidomide is a 4-amino-substituted thalidomide derivative that has a 20,000–50.000-fold higher activity in suppressing tumor necrosis factor (TNF)-γ, and it is more potent than thalidomide in stimulating T-cell proliferation, natural killer cell activation, and production of IL-2, IL-10 and IFN-α (44). The toxicity profile of lenalidomide is more favorable than that of thalidomide because neither polyneuropathy nor significant constipation or sedation have been reported in MDS patients (45, 46). Most importantly, in the rabbit model most sensitive for thalidomide-associated embryotoxicity, lenalidomide did not show any fetal malformations (44). In the MDS, lenalidomide has been evaluated in a number of clinical studies, the most important being the Lenalidomide-MDS-001, Lenalidomide-MDS-002, and Lenalidomide-MDS-003 studies. In the Lenalidomide-MDS-001 trial, 43 patients with MDS and transfusion-dependent or symptomatic anemia were treated with lenalidomide doses of up to 25 mg. All patients had no response to erythropoietin therapy or were believed to be poor erythropoietin responders because of high endogenous EPO levels. All FAB subtypes could be included, but neutrophil counts were required to be >500/μL and platelet counts >10.000/μL. Responses were defined according to the modified International Working Group criteria (47). Although, according to the natural frequency of del(5q) among all MDS subtypes, one would expect only about 15% of patients with del(5q) in such a trial, 12 out of 43 (28%) of the trial patients displayed a del(5q) chromosomal abnormality. This turned out to be a fortunate event, as 83% of del(5q) patients achieved an erythroid response, defined as a sustained transfusion independence with more than a 2-g/dL hemoglobin increase, compared to 57% of patients with a normal karyotype and 12% of patients with other karyotypic abnormalities (46). Complete cytogenetic remissions occurred in 75% of patients with del(5q). Interestingly, a reduction of bone marrow blast percentages was also observed, as three out of six patients with excess blasts (6–21%) achieved a reduction to ≤5% blasts after treatment. Dose-limiting toxicities were neutropenia and thrombocytopenia of WHO grade 3/4 in 58% and 50%, respectively.

The Lenalidomide-MDS-003 trial (45) was designed to study the effects of lenalidomide in the subgroup of MDS patients with del(5q) cytogenetic abnormalities. The trial included transfusion-dependent del(5q) MDS patients with or without additional chromosomal abnormalities and an IPSS grading of low or intermediate-1. This allowed the authors to study a number of different patient populations with del(5q): the 5q– syndrome, with isolated del(5q), normal blast count, and isolated anemia (e.g., low-risk IPSS), as well as patients with the above features but an increase of medullary blasts of up to 10% and/or two or more peripheral blood cytopenias (e.g., intermediate-1 risk). Also, patients with one additional chromosomal abnormality and a blast count of up to 10% were eligible to participate in the study if the number of cytopenias was <2 (e.g., intermediate-1 IPSS). Finally, patients with a complex karyotype including del(5q) or a chromosome 7 anomaly

in addition to del(5q) were eligible if there was only one peripheral cytopenia and the bone marrow blast count was <5%. As a result of the treatment-related neutropenia and thrombocytopenia observed in the Lenalidomide-MDS-001 trial, patients had to have at least 500/μL neutrophils and >50.000/μL platelets to be eligible for the trial. Furthermore, the initial lenalidomide dose was set at 10 mg orally per day ("continuous schedule") or 21 days out of 28 ("syncopated schedule") with possible dose reductions in case of adverse events to 5 mg po daily or 5 mg po every other day. Among 148 patients included, 111 had an isolated del(5q) abnormality and 37 had additional chromosomal abnormalities. Central cytology and cytogenetic review was performed and 120 patients (81%) were confirmed as suffering from low/intermediate-1-risk MDS. The results of this study confirmed the impressive data of the Lenalidomide-MDS-001 trial. Using an intent-to-treat (ITT) analysis, by week 24, 76% of patients achieved at least a 50% reduction of transfusion need compared to pretherapy levels and 67% of patients became entirely transfusion-free for ≥56 days with a rise in hemoglobin of at least 1 g/dL. The median time to response was 4.6 weeks, and the median rise in hemoglobin at maximum response was 5.4 g/dL. After a median follow-up of 2 years, the median duration of transfusion independence was not reached. Fifty-three patients were still on-study and transfusion-free. Cytogenetic responses were very impressive, indeed. Not only did 45% of patients achieve a complete cytogenetic remission and another 28% reduced the number of abnormal metaphases by at least 50%; the trial did not show any significant statistical difference between patients with an isolated del(5q) and those with one or more additional cytogenetic abnormalities. This result is as important as it is astonishing. The natural course of patients with complex cytogenetic abnormalities including del(5q) is very poor indeed, the median overall survival being 8 months (Figure 6.1), independent of the bone marrow blast count (12). The fact that 50% of patients with this adverse feature went into complete cytogenetic remission heralds a new era in the treatment of MDS, as previously no other drug was able to show such impressive remitting activity in such a poor prognosis subgroup. Furthermore, this result suggests that lenalidomide might alter the natural history of disease in patients with a higher-risk del(5q) abnormality. Red blood cell transfusion independence was also unaffected by age, gender, FAB subtype, or IPSS category. The only two variables in multivariate analysis predicting a better response to the drug were a higher peripheral platelet count (because those patients received a higher cumulative lenalidomide dose) and a lower pretreatment transfusion burden.

The most common adverse events were grade 3/4 neutropenia (55%) and thrombocytopenia (44%), necessitating dose adjustment in 91% of patients on the continuous treatment schedule and 67% of patients on the syncopated treatment regimen. The median time to the first dose interruption or reduction was 22 days, and the median duration of this first interruption was also 3 weeks. A third of the patients had to undergo a second dose reduction or interruption. These results emphasize that patients treated with lenalidomide need weekly complete blood count evaluations during the first 8 weeks of therapy and biweekly blood draws thereafter for at least another 4 months. Other adverse effects of lenalidomide included skin rash, pruritus, diarrhea, muscle cramps, and, rarely, hypothyroidism

and endocrine hypogonadism. In our experience, pruritus is self-limiting but might require oral antihistamines. In more severe cases, a short course (usually less than 14 days) of 10 mg of prednisone can be given to alleviate symptoms. Diarrhea is difficult to tackle and might require dose reduction. Neither loperamide nor other antidiarrheal drugs are very helpful to treat this complication. Muscle cramps are usually self-limiting. Magnesium supplementation did not show any significant effect, and in some instances, quinine sulfate might be used. Hypothyroidism was always associated with high levels of antithyroid antibodies and needed thyroid supplementation therapy. Deep venous thrombosis, a complication feared with combination lenalidomide and dexamethasone therapy in multiple myeloma, occurred in four patients only (i.e., 2.7% of all patients).

Nine patients progressed to higher MDS subtypes or acute myeloid leukemia, and 11 patients died due to disease complications ($n = 8$) or neutropenic infection ($n = 3$). Interestingly, in contrast to the results of the Lenalidomide-MDS-001 trial, no patient acquired secondary chromosome 7 anomalies.

6.9 Conclusion

Myelodysplastic syndromes with a del(5q) chromosomal abnormality are a heterogeneous group of disorders. The deletion at 5q is acquired early during hematopietic stem cell development (22), and secondary chromosomal abnormalities are later events. Del(5q) is the most common chromosomal abnormality in MDS and might present as an isolated abnormality with or without an increase in bone marrow blasts, and in conjunction with one or several other karyotypic anomalies. The natural course of these patient subgoups can be very different. Only patients with an isolated del(5q) and a normal bone marrow blast count ("the 5q– syndrome") have a truly favorable prognosis, although it is worse than that of the age-matched general population (11). As all patients eventually become red cell transfusion-dependent, therapeutic strategies aimed at reducing the transfusion need should be discussed early in the course of the disease. Erythropoietic agents are not very useful, as most patients display high endogenous EPO levels at the time of transfusion dependence. Lenalidomide has consistently shown high rates of transfusion independence in more than two-thirds of patients treated and has also led to complete cytogenetic remissions in 44% of cases. The induction of cytogenetic remission is independent of the cytogenetic complexity (i.e., additional cytogenetic abnormalities). Lenalidomide has been approved in the Unites States for use in low- and intermediate-1-risk MDS according to the IPSS. For patients with a blast count >10% (i.e., IPSS intermediate-2 or high risk) and a reduced platelet count, a course of low-dose cytarabine could be indicated to reduce the leukemic burden, as the cumulative lenalidomide dose that might be administered might be too low to achieve a response. The treatment should then be followed by maintenance therapy with lenalidomide.

With the advent of powerful molecular techniques, including the microarray technology, proteomics, and single-nucleotide polymorphism scanning, the gene or genes responsible for the disease might soon be identified. This would open the door to a targeted therapy on the molecular level.

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