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Myelodysplastic Syndromes

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Chromosome Abnormalities in Myelodysplastic Syndromes

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DURING THE PAST decade, our understanding of the group of diseases defined as "preleukemic" myeloid disorders has increased significantly. Clinically, the myeloproliferative entities have been separated from the myelodysplastic syndromes (MDS), and the latter have been subdivided into a workable FAB classification.[1] Biologically, it is clear that the MDS subtypes (refractory anemia [RA], RA with ringed sideroblasts [RARS], RA with excess of blasts [RAEB], RAEB in transformation [RAEB-t], chronic myelomonocytic leukemia [CMML]) represent a continuum, with overt leukemia as the ultimate result in a significant proportion of cases. At every stage, these appear to be clonal disorders arising from a marrow stem cell, with the degree of clinical severity reflecting, at least to some degree, the rate at which the clone is expanding. Although MDS-like disorders do occur in children, this is typically a disease of older individuals, making therapy particularly difficult, and perhaps helping to explain, in an aging population, the apparent increase in frequency in recent years.

Chromosome data, along with biochemical studies, have helped to establish the clonal nature of these disorders, as well as their relationship to the frank leukemias that they precede.[3,4] Cytogenetic information has also proved of diagnostic and prognostic value, generally keeping pace with the more detailed clinical characterization.[2,5-8] This brief review will attempt to summarize our present knowledge concerning specific chromosome alterations in MDS, with, wherever possible, related information on genes that may be involved in the pathogenesis of these disorders. It will also indicate current thinking concerning the prognostic significance of various types of karyotypic abnormalities, in both primary and therapy-related MDS. More detailed review of the chromosomal data can be found in other recent sources[9,10]; the limited goal of this summary is to provide an indication, including some personal experience, of how cytogenetic studies are now contributing to both clinical and basic efforts to better understand this difficult group of diseases and some prospects for the future.

ChromosomeAbnormalities in Primary Myelodysplastic Syndromes

In most series reported to date, a chromosomally abnormal clone has been demonstrable in the bone marrow of 40% to 60% of patients with MDS unrelated to previous therapy?.[11] These have ranged from highly aneuploid karyotypes, with multiple structural alterations, to clones characterized by a single chromosome abnormality. In general, clones with complex karyotypes having multiple changes have been more frequent in the more advanced FAB subtypes of MDS (RAEB, RAEB-T, CMML), and have been associated with a poor prognosis, as compared to patients with either a single abnormality in the clone or no demonstrable karyotypic change.[2,5-11] This has been true whether the particular outcome being determined was progression to frank leukemia or overall length of survival. For example, in our own series,[11,12] which now includes more than 250 primary MDS patients, median survival with a complex karyotype was only 3 months following initial study, compared to approximately 12 months for patients with single abnormalities or a normal karyotype. Also, a higher percentage of patients with complex karyotypes have progressed to acute leukemia (62%) versus the other two groups (45%), but the difference is not as striking, perhaps reflecting the very short survival of many patients with multiple cytogenetic abnormalities.

In most series, MDS patients with a normal karyotype have had a slightly better outcome than patients with any chromosomal abnormality, single or multiple.[2,5-11] It may be, in fact, that some individuals with refractory anemia (RA, RARS), a normal karyotype, and a very pro-

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longed indolent course are not appropriately classified as **MDS** and grouped with other RA patients in which there is definite clinical and cytogenetic evidence for a dysplastic myeloid clone expanding in the bone marrow.'

It is true, however, that some **MDS** patients with a normal karyotype have acquired a chromosome abnormality during the course of their disease, and additional cytogenetic changes have also been documented in serial studies of patients who had a karyotypically aberrant clone from the **outset.**[6-14] In both circumstances, this clonal evolution has typically been associated with clinical progression and early death. Interestingly, such karyotypic evolution has generally been less frequent than in some other myeloid disorders, most notably chronic myelogenous **leukemia.**[10,15] There is also no clear evidence, in **MDS,** that the presence of some normal cells in association with a chromosomallv abnormal clone in the marrow is of prognostic **significance.**[6-10]

Recently, we and others have begun to investigate in more detail, both clinically and biologically, the circumstances in which a karyotypically abnormal clone in the bone marrow of an **MDS** patient has a single alteration, either gain, loss, or translocation. This represents approximately 20% to 30% of all patients with primary **MDS,** or half of those with an abnormal karyotype. Five single abnormalities appear most common: loss of all or part of a chromosome 7, an extra copy of chromosome 8, an isochromosome for the long arm of chromosome 17, and deletion of the long arm of chromosome 5 or chromosome 20. Other less common isolated abnormalities include deletion of the short arm of chromosome 12 (12p−), deletions and translocations involving band 11q23, and loss of the Y **chromosome.**[2,6-12] There have also been scattered reports of other small deletions (eg, 2p−, 8p−, 9p−), as well as gain of chromosome 14 and loss of 22, all occurring as single **alterations.**[10,16-19] Conversely, a number of the specific chromosome rearrangements commonly associated with various types of myeloid leukemia, such as t(9;22), t(8;21), t(15;17), t(9;11), and inv(16), are almost never observed in **MDS,** supporting the view that these forms of acute leukemia are not preceded by a preleukemic phase.

Summarized below are some recent findings and suggestions concerning five of the isolated alterations commonly seen in **MDS,** with respect to prognostic significance (Table **1)** and also possible gene involvement that might ultimately have diagnostic or therapeutic implications.

Monosomy 7/del(7q)

Several studies now indicate that a marrow clone with this single abnormality in primary **MDS** indicates a poor prognosis, nearly as ominous as clones with multiple karyotypic **alterations.**[2,6,10,12,15] For example, in our small series of nine patients with monosomy 7 or del(7q) as the only abnormality, only one survived for more than 15 months (median = 8 months), and six of nine progressed to acute leukemia, all within 1year.

Partial or complete monosomy for chromosome 7 also occurs commonly in complex karyotypes in both **MDS** and de novo acute myeloid **leukemia,**[10,15] particularly when the disease is therapy-related (see below). In some cases, this takes the form of an unbalanced t(1;7) **translocation,**[20] which also results in the loss of 7q. The relevant portion of chromosome 7 has been narrowed to band 7q22, but none of the genes currently mapped to this region have been shown to be definitely involved."

It is interesting that monosomy 7 appears to be the most common abnormality in pediatric **MDS,** and in some cases has been associated with familial patterns of **disease.**[22-24] In several instances, these have been families with the increased chromosomal fragility and other characteristics of Fanconi's anemia or its
but in other familial cases there was no evidence of a recognized fragility **syndrome.**[24] It has been suggested that the latter could reflect either an inherited tumor suppressor gene defect or perhaps a "subclinical" chromosomal fragility syndrome,[22,25] but there is no **firm** evidence to support either hypothesis at this time. Further

Table 1. Prognostic Significance of Single Chromosome Abnormalities in Primary MDS

Favorable	Unfavorable
del (5q)	−7/del (7q)
del (20q)	+8
	iso (17q)

study of these pediatric cases may shed light on the chromosome 7 defects in the adult disease.

Trisomy 8

Limited data on this single abnormality in primary MDS suggest that it has only a slightly better prognosis than the monosomy 7/del(7q) group.[6,12] In our series of 14 patients, for example, the median survival was 10 months after chromosome study, and 6 cases progressed to frank leukemia within a year.

Trisomy 8 is the most common single chromosome abnormality seen in de novo acute myeloid leukemia (AML), and also occurs nonrandomly as an additional chromosome change in the blast crisis of Ph-positive chronic myelogenous leukemia (CML).[10,15] Although there has been some suggestion, in the latter circumstance, that trisomy 8 may be associated with altered expression of the *C-MYC* gene, this has not been confirmed, and there are no data directly relevant to altered expression of this or any other gene in the marrow cells of MDS patients with trisomy 8.

Iso(17q)

This karyotypic abnormality, in which a normal chromosome 17 is replaced by an isochromosome for the long arm (Fig 1), may well carry the same poor prognostic significance in MDS patients as monosomy 7/del(7q) and trisomy 8. However, even fewer data are currently available.[12,26] We have followed five patients with this abnormality as the only karyotypic change, and the outcome appears similar to that of the two previous subgroups. The median survival after chromosome study has been 10 months, with 3 cases progressing to acute leukemia.

The iso(17q) alteration occurs quite commonly in a variety of hematopoietic and nonhematopoietic neoplasms, usually in association with additional karyotypic alterations.[11] Other rearrangements involving the short arm of chromosome 17 (17p) have also been described in MDS.[10,15,17,27] In several tumors, including colon cancer and the blast crisis of CML, it has recently been demonstrated that the iso(17q) abnormality is consistently associated with loss

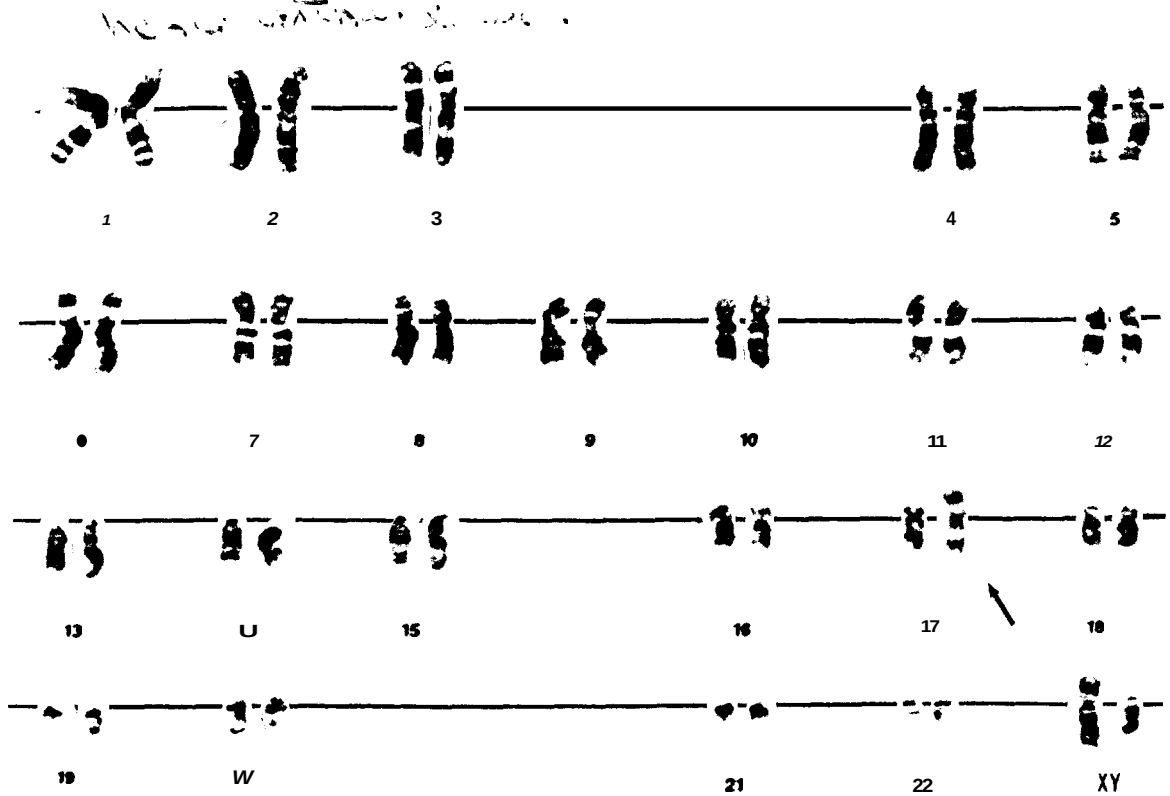

Fig 1. Karyotype of marrow cells from a patient with primary MDS. An iso(17q) is the only abnormality (arrow). In other tumors, this cytogenetic change has been associated with loss of function of the p53 gene.

of function of the p53 gene, which maps to band 17p13, through deletion of the short arm in the isochromosome and submicroscopic alteration of the gene on the other 17 chromosome.[28,29] There is increasing evidence that p53 functions as a tumor suppressor gene in many cell lineages, contributing to abnormal cellular proliferation when, through one mechanism or another, normal function of the gene is abrogated within the cell.

It is still unclear in the iso(17q) anomaly whether other genes on the short arm of 17, or on the long arm, which is present in extra dosage, are also involved." Considerable research on defects in the p53 gene in a variety of human tumors is currently under way, including the possibility of replacement of normal gene function as a therapeutic approach.

Del(5q)

This is the only chromosome abnormality in MDS that is correlated with a specific clinical entity. Patients with the "5q – syndrome" have only this karyotypic change in their marrow cells and typically present with refractory macrocytic anemia, thrombocytosis, and nonlobulated megakaryocytes.[31,32] Many of these patients follow an indolent course for a number of years with little or no evidence of clinical progression. Thus, this karyotypic abnormality, occurring alone and associated with the typical refractory anemia syndrome, appears to be one of the most prognostically favorable forms of MDS.[6,9,10,12,31,32]

We have observed, however, 11 patients with only a 5q– abnormality who presented initially with a more advanced stage of MDS (RARS, RAEB, or RAEB-T). **Six** of these patients died within **6** months of study, 5 having progressed to acute leukemia. It is unclear whether these cases represent end stages of a previously undiagnosed long-term "5q – syndrome" or whether concomitant submicroscopic genetic alterations in the hemic clone, such as mutation of a RAS resulted in more aggressive disease from the outset. Although not all studies have shown as striking a difference in the clinical course of 5q– patients relative to the FAB subtype,[6,9,10,31,32] it is clear that some individuals with this isolated cytogenetic abnormality have a much less favorable prognosis than those with the clinically typical "5q– syndrome."

Loss of all of chromosome 5 or a portion of the long arm is, like monosomy 7/del(7q), also a common finding in complex karyotypes in **MDS** and in AML arising de novo, particularly therapy-related cases."." There has been considerable effort in recent years to identify the relevant gene(s) involved on 5q, particularly at band 5q31.[32-35] Many colony stimulating factors and interleukin genes have been mapped to 5q, as well as the genes of other growth factors and their receptors, but the function of none of these has been shown to be consistently altered in the resultant neoplasms. Detailed molecular analysis of the 5q– anomaly has demonstrated submicroscopic inversions and duplications adjacent to the deleted region of the chromosome.[36] This has led to speculation that the many myeloid-related genes mapped to this area may not themselves be oncogenic, but may, in some fashion, confer unusual instability on cells differentiating along a myeloid lineage and thus increase the probability of a specific tumorigenic alteration in this portion of the genome.[37] The rare reports of a clinically typical "5q– syndrome" preceding a detectable chromosome anomaly' are consistent with this concept. One current candidate for the critical leukemogenic locus is the early growth response gene (EGR1), which is also within this region and codes for a nuclear binding protein.[35] It is currently being investigated as a possible tumor suppressor gene whose loss of function could be important in myeloid tumorigenesis.

Del(20q)

This abnormality, which occurs nonrandomly in myeloproliferative preleukemic disorders (eg, polycythemia vera, myelofibrosis) as well as in dysplastic syndromes, appears to be associated with a relatively favorable prognosis when present as an isolated alteration in MDS.[6,12] Again, the published data are very limited, but in our series of 8 patients, for example, the median survival was more than **24** months after study. Three MDS patients with a 20q– abnormality progressed to leukemia within a year, but the remaining five lived for 2 to 4 years, dying of other causes.

The 20q– alteration is also observed not only

in myeloproliferative disorders but in de novo acute myeloid leukemia, with or without additional karyotypic changes.[10,12,15] As with the other abnormalities discussed earlier, attempts have been made to identify the relevant genes involved in this deletion, without definitive results to date. It has recently been suggested that the HCK proto-oncogene, which maps to this region and codes for a tyrosine kinase involved in myeloid differentiation, may be important, because lack of HCK transcripts has been correlated with a 20q− deletion in several cases of AML (C. Willman, personal communication).

As mentioned earlier, a number of other karyotypic changes have also been reported to occur as solitary alterations in primary MDS. These include deletions of 12p, translocations and deletions involving chromosome band 11q23, loss of the Y chromosome, and occasionally other alterations.[2,6-12,15-19] In none of these instances are there currently sufficient data to warrant any statement concerning prognostic significance, and although some potentially relevant genes have been mapped to the involved chromosomal regions, there is no definite evidence to associate any of them with the pathogenesis of the neoplasm. Clearly, these various nonrandom single abnormalities warrant further investigation, both to determine their value in patient management and to attempt to identify critical genes involved in the pathogenesis of myeloid and other disorders.

Chromosome Abnormalities in Therapy-Related Myelodysplastic Syndromes

As discussed elsewhere in this volume, therapy-related myelodysplastic syndromes (t-MDS) have become increasingly recognized as unwelcome sequelae of successful treatment of a primary malignancy with chemotherapy and/or radiation in both adults and children. Typically, t-MDS is much more aggressive clinically than primary MDS, and these biological characteristics are reflected in the karyotypes. At least 80% of individuals with t-MDS have a chromosomally abnormal clone in the bone marrow, and in the vast majority of cases these contain multiple abnormalities.[2,10,15,19,38-41] All of the nonrandom alterations discussed earlier are observed, in various combinations, but most characteristic are monosomy 7/del(7q) and monosomy 5/del(5q) (Fig 2). The 12p− abnormality noted above is also common, as are the t(1;7) translocation and rearrangements involving chromosome band 11q23. Not infrequently, one also observes in the karyotypes of therapy-related disease additional indications of extensive genomic damage and instability, such as ring chromosomes, dicentrics, and acentric fragments. On occasion, there may also be cytogenetic evidence of more than one clone arising from separate individual cells in the badly damaged microenvironment of the bone marrow.[13] Any combination of these various types of karyotypic alterations strongly suggests previous exposure of the patient to large doses of clastogenic agents, and also indicates, as noted, a very poor prognosis with respect to prompt progression to frank leukemia and generally short survival.[2,10,15,19,38-41]

These observations in patients with known exposure to high doses of genotoxic agents have prompted considerable speculation concerning the possibility that smaller exposures to similar agents, occupational or environmental, might be of etiologic importance in myeloid leukemia and preleukemia unrelated to previous therapy. In studies of AML, it has been possible to elicit a history of such exposures, in the workplace, home, or elsewhere, in some groups of patients, and this appears also to correlate with complex karyotypes containing monosomies or deletions of chromosomes 5 and 7.[42-45] The situation is less clear with respect to MDS.[45,46] In a study that included a group of age- and sex-matched controls without hematological disease, 46% of primary MDS patients gave a history of occupational or environmental exposure to potentially genotoxic agents, but the exposure rate in the control population was similarly high (40%). There was also no correlation, within the MDS group, between a history of such exposure and the specific cytogenetic findings.[46] This question of the role of nontherapeutic genotoxins in the etiology of "primary" MDS needs further investigation, with more detailed epidemiological and molecular studies to complement the chromosomal findings.

DISCUSSION AND CONCLUSIONS

At present, cytogenetic studies are of value in the continuing efforts to understand and to

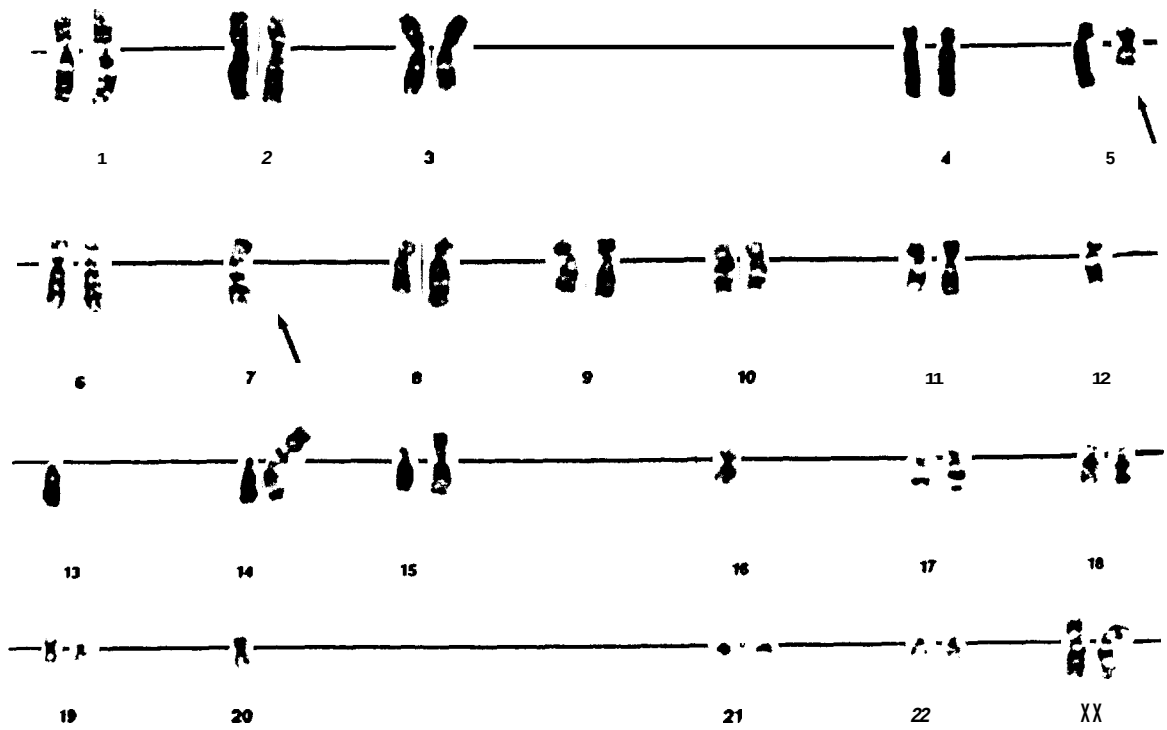

Fig 2. Representative karyotype from a patient with therapy-related MDS (t-MDS), illustrating abnormalities of chromosomes 5 and 7 (arrows), as well as other changes. Patients with such complex karyotypes have a poor proqnosis, in both primary MDS and t-MDS.

manage the heterogeneous group of difficult disorders that we now classify as MDS. The clonal nature of these diseases is well established, and the continuum through the various stages of MDS to frank leukemia is widely accepted. **A** major issue for the near future is the identification of the specific somatic genetic changes that underlie the expansion and evolution of the preneoplastic hemic clone. **As** in all neoplasia, cytogenetic studies are providing valuable clues to the location of relevant growth regulatory genes, and, in some cases, to the mechanisms by which their function is altered. We now recognize that chromosome abnormalities can indicate important changes in gene dosage, either additions or deletions, as well as changes in location and/or structure that can alter gene function.[47] To date, as indicated above, there is very little firm evidence concerning the specific genes involved in MDS, but the nonrandom karyotypic changes are being actively studied at the molecular level. and some recent successes with the human leukemias and lymphomas suggest that important results will also be forthcoming with respect to MDS. The hope is, of course, that such information will not only elucidate the basic mechanisms underlying these disorders but also provide additional useful tools for diagnosis, for monitoring disease in treated patients, and, ultimately, for new therapeutic agents.

It must also be recognized, as already suggested, that not all of the genetic alterations relevant to these diseases will be visible at the karyotypic level. There is already evidence, for example, that mutations in genes of the **RAS** family, not associated with demonstrable chromosome changes, are relatively common in MDS, and may: in fact. have negative prognostic implications.[33,34] Complete elucidation of the sequence of molecular changes underlying the development of these disorders will have to include such submicroscopic abnormalities. as well as those readily visible under the microscope.

In addition to these explorations of somatic genetic changes in **MDS** cells. the possibility of

inherited gene defects playing a role should also continue to be considered. As noted earlier, there is limited evidence suggesting that in some instances of pediatric MDS, often characterized by monosomy 7, there may be a familial factor involved. In some cases this has been associated with a recognized "chromosomal fragility" syndrome, particularly Fanconi's anemia (FA) or one of its variants.[23,48] In a few instances, patients with other "fragility" syndromes (eg, Bloom's syndrome, ataxia telangiectasia) have had a dysplastic preleukemic phase before progressing to acute myeloid leukemia, but lymphocytic neoplasms, with characteristic chromosome changes, are much more common in these patients, perhaps reflecting the more severe immune dysfunction in these disorders as compared to FA.[10,15,49] There are also examples of familial pediatric MDS, including monosomy 7, that do not fit any of the recognized instability syndromes and where increased chromosomal fragility has not been demonstrable in standard assays.[22,24,50,51] These cases could involve either a classical tumor suppressor gene or the inheritance of a gene that confers some degree of "subclinical" genomic instability, making random genetic and karyotypic errors more likely." The two possibilities are not mutually exclusive, and could be different in different families. At present, there is no hard evidence to support either hypothesis.

It is also possible that in adult MDS, either primary or therapy-induced, some minor inherited defect in DNA "housekeeping" could predispose certain individuals to developing the disease. There is beginning to be evidence that some members of the population, for example, are particularly susceptible to chromosome damage by alkylating agents such as bleomycin,[52] and these individuals may well be at greater risk of developing hematopoietic and other neoplasms when exposed to certain genotoxic agents, either therapeutically or under other circumstances. This is a field that is currently under active investigation, and it will be of interest to determine how frequently one can demonstrate some "subclinical" constitutional defect in DNA synthesis, DNA repair, or the mitotic apparatus itself in individuals who develop MDS.[25,52,53]

In addition to contributing to these efforts to understand better the fundamental nature of myelodysplastic disorders, chromosome studies also continue to have a useful role in current attempts to manage these difficult disorders clinically. As noted, the karyotype has been shown to be an independent prognostic indicator, second only to the FAB subtype as a predictor of progression to leukemia and of overall survival. As the cytogenetic data are extended and refined, every physician attempting to evaluate and utilize current therapies for MDS should have the benefit of such information, as well as other parameters, in making decisions concerning patient management.

MDS appears to be increasing in our aging population, and response to treatment is generally unsatisfactory. This has stimulated a variety of therapeutic approaches ranging from very aggressive regimens, including bone marrow transplantation, to less cytotoxic treatments using biological agents that influence the growth and differentiation of hemic cells. The latter may require many months before any effect is apparent.[54-56] At present, although not necessarily predicting response, chromosome studies can help to indicate which patients with MDS are likely to survive long enough to be adequately evaluated with the longer-term therapies, and which patients, if to receive more than supportive care, must be treated rapidly and aggressively. During therapy, karyotypic data can also be utilized to monitor the size of the neoplastic clone in the bone marrow, as one indicator of response.[57] Eventually, molecular approaches may provide better tools, but for the near term it appears that cytogenetic studies of these disorders will continue to provide useful information of practical clinical value.

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