Leukemias and Myelodysplastic Syndromes Secondary to Drug, Radiation, and Environmental Exposure

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ONE OF THE most feared complications that any physician faces is the induction of a second malignancy as a result of attempts to eradicate a prior one. Often even more disturbing is the induction of a malignancy during the treatment of a nonneoplastic disorder. In either instance, the onset of a treatment-related myelodysplastic syndrome (MDS) or acute leukemia (AL) often substitutes a condition more deadly and more refractory to treatment than the original. This review will focus on the biologic and clinical aspects of treatment-related MDS and AL, as well as the factors that appear to be important in their causation. In addition, we will briefly review the evidence that various environmental or occupational exposures can induce hematologic malignancies.

The incidence of treatment-related leukemia remains difficult to define. Incidence rates are highly variable even within studies of a single primary disease treated in a relatively uniform way. This variability in part results from cohort differences in age, duration of treatment, and length and rigor of follow-up. When other primary diseases are considered, incidence rates not surprisingly become even more disparate, for additional variables such as the number and types of drugs used, their cumulative doses, extent and dose of radiation therapy, and prognosis of the primary malignancy—treatment-related leukemias have less time to develop among patients whose primary cancer causes a rapid death—also come into play. Nonetheless, all investigators agree that the problem is not inconsiderable and is likely to increase in parallel with the increasing success of treatments to prolong survival among patients with cancer.

This review represents an update of information contained in an article published 6 years ago.[1] Major developments that have occurred during that interval include a better characterization of cellular events in treatment- or environmentally-related MDS/AL at the molecular genetic level, a better understanding of the period of time following treatment of the primary disease during which patients are at risk for this complication, and the vigorous application of colony stimulating factors and allogeneic bone marrow transplantation to the treatment of these disorders, Henceforth, we will refer to treatment- or environmentally-related hematologic disorders as the secondary myelodysplastic syndromes (2" MDS) and acute leukemias (2" AL). This designation does not include individuals who are genetically-predisposed to the development of hematologic disorders.

We will approach the subject of this review in the following order: (1) an overview of the problem, (2) signs and symptoms, (3) blood and bone marrow findings, (4) biology, (5) 2" MDS/AL among individual primary malignancies and synthesis of that information, (6) environmental/occupational exposure, (7) treatment, and (8) prevention. We will attempt to generate tentative conclusions when sufficient data allow.

OVERVIEW

Table 1 is a compilation of studies that contain 50 or more patients with 2" MDSIAL. With the exception of the study from Brusamolino et al,[2] in which all patients had a primary diagnosis of Hodgkin's disease, patients in these reports were culled from those treated for several different primary malignancies, either in a single or multi-institutional setting. Some studies examined patients with AL only; others included patients with both MDS and AL. These studies contained adults almost exclusively, and median ages were in the sixth and seventh decades. In all studies, the majority of patients had received either chemotherapy alone or both chemotherapy (CT) and radiotherapy (RT).

Median latency to the development of MDS/AL was quite consistent among studies,

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Table 1. Clinical Aspects of 2° MDS/AL Among Large Series of Patients with Diverse Primary Malignancies

Number of Patients	MDS/AL	Median Age yr (range)	Treatment (no. of patients)	Median Latency‡ mo (range)	Conversion to AL	Median Survival (mo)	FAB Subtypes of AL (no. of patients)	Comments	Reference
55	44 MDS 11 AL	62 (22-75)	RT only (8) CT only (25) RT + CT (22)	48 (12-131)	84% (med, 5 mo)	7	M1 (10), M2 (20), M4 (7)†		
55	20 MDS 35 AL	~50	CT ± RT (55)	50	NS	MDS, 8.4; AL, [illegible]	M1 (8), M2 (8), M3 (0), M4 (11), M5 (1), M6 (6), Unclass (8)	5 cases in the MDS category did not satisfy strict diagnostic criteria	23
56	All AML	58 (18-90)	RT alone (15) CT alone (17) RT + CT (26)	6 (1-20)	NS	5.1	M1 + M2 (26), M3 (4), M4 (9), M5 (7), M6 (3), Unclass (7)		14
65	39 MDS 26 AML	52.5 (<1-81)	RT alone (14) CT alone (25) RT + CT (26)	58 (11-192)	30% (1-12 mo)	AML, 3; MDS-AL, 6; MDS, 4	M1 (0), M2 (9), M3 (1), M4 (3), M5 (2), M6 (4), Unclass (18)	At Minnesota 1° MDS survival = 15 mo; another 21% with 2° MDS evolved to RAEB-T	7
75	75 AML	30-50 (range)	RT only (2) CT only (7) RT + CT (66)	27 (from end of treatment)	73% (med, 7 mo)	Supportive care or < CR, 3; CR, 10	M1 (12), M2 (20), M3 (4), M4 (13), M5 (3), M6 (5), Unclass (18)		2 *
112	57 MDS 55 AL	65 (20-82)	RT only (26) CT only (37) RT + CT (49)	71 (from end of treatment) (7-331)	55%; RA, 14%; RA-S, 50%; CMML, 40%; RAEB, 68%; RAEBT, 77%	7.5; MDS, 10; AL, 5	M1-M2 (25), M3 (3), M4 (16), M5 (3), M6 (6), ALL (2)	For MDS median survival was similar whether conversion to AL or not	15

Abbreviations: RT, radiotherapy; CT, chemotherapy; NS, not stated; RA, refractory anemia; RA-S, refractory anemia with sideroblasts; RAEB, refractory anemia with excess blasts; RAEBT, fractory anemia with excess of blasts in transformation; CMML, chronic myelomonocytic leukemia; FAB, French-American-British classification; AML, acute myeloid leukemia.

*Represents an exception, as it is a multi-institutional collection of patients previously treated for Hodgkin's disease.

†Subtypes included MDS cases which transformed to AL.

‡Time from start of treatment until development of MDS/AL, unless otherwise stated.

ranging between 4 and 5 years. Nonetheless, the range within studies was quite broad, with some MDS/AL developing within a year of the initiation of therapy, and others developing more than 25 years later. Of interest, Pedersen-Bjergaard et al[3] noted a biological difference among cases of 2" MDS/AL appearing between 30 and 60 months after treatment (n = 16), and those appearing before or after this time (n = 15). The former cases more often presented with MDS than AL (88% v 47%); and with an abnormal karyotype (100% v 33%), a hypodiploid modal number (100% v 40%), and combined B and C group chromosome changes (50% v 13%). No responses to treatment occurred in the former group, as opposed to 4 in the latter. Although these data require corroboration, they imply that 2" MDS/AL is a heterogeneous disorder.

As can be seen in Table 1, a large percentage of patients (55% to 84%) presenting with 2" MDS progressed to AL in most studies, a transformation rate generally higher than those reported in large series of 1" (primary) MDS.[4-6] Michels et al[7] observed only 30% of those with 2" MDS progressing to AL; however, an additional 20% had evolved into a refractory anemia with excess of blasts in transformation (refractory anemia [RA] with excess of blasts in transformation [RAEB-t]) (20% to 30% blasts in the bone marrow). Secondary AL is preceded by a MDS much more commonly (30% to 80%) than de novo AML (20%).[8] Median survival was uniformly dismal and not greater than 10 months in either 2" MDS or 2" AL. With the exception of 1" RA and refractory anemia with ringed sideroblasts (RAS), survival in 1" MDS and 2" MDS/AL appears to be similar.[7] However, some investigators have reported a modestly longer survival in 1" MDS, even upon consideration of the poor prognosis groups alone (ie, subtypes other than RA and RAS).[7,10]

Other studies of smaller numbers of patients with 2" MDS/AL have yielded similar results.[11-13]

SIGNS AND SYMPTOMS

Most patients (75% to 100%) with 2" MDS/AL have symptoms at the time of diagnosis.[14-16] Fatigue and weakness are the most commonly reported (50% to 100%). Fevers are present in 25% to 40% of patients, but microbiologically-documented infections are established in less than 50% of patients with fever. Among the most common physical signs of 2" MDS/AL are those associated with anemia (~100%) and with bleeding manifestations (50% to 60%), such as bruising and hemorrhages. Disseminated intravascular coagulation has been described in 2" MDS/AL, but occurs in less than 10% of patients. Less common physical signs, all occurring in less than 10% of patients, include hepatomegaly, splenomegaly, lymphadenopathy, gingival hypertrophy, skin infiltration, and neurological abnormalities caused by central nervous system infiltration. These symptoms and signs are not dissimilar from those of 1" MDS or de novo AL; however, patients with 1" MDS more commonly have splenomegaly,[9] probably because of the higher percentage of patients with chronic myelomonocytic leukemia (CMML) in 1" versus 2" MDS, and patients with de novo AL more commonly have gingival hypertrophy, lymphadenopathy, and splenomegaly.[14]

BLOOD AND BONE MARROW FINDINGS

Blood and marrow findings in the 2" MDS/AL have been examined by a number of investigators.[2,7,15-20] Anemia and thrombocytopenia are extremely common; leukopenia is less so. In series that have included more than 50 patients, investigators have reported mean or median hemoglobins to be less than 10 g/dL.[2,7,15-21] In these same series, the majority of platelet counts have been less than 100,000 x 10^6/L. Among the 56 patients with 2" AL in the report of the Fourth International Workshop on Chromosomes in Leukemia (FIWCL),[14] all had platelet counts less than 100,000 x 10^6/L. Brusamolino et al[2] and Michels et al[7] reported median and mean white blood counts (WBC) of 6,500 (n = 75) and 3,500 (n = 65) x 10^6/L, respectively. Kantarjian et al[15] found that 13% of 112 patients had WBC less than 2,000 x 10^6/L, and 10% had granulocytes less than 500. Pedersen-Bjergaard et al[21] reported that 29 of 55 patients had granulocyte counts less than 1,500.

The morphologic findings in the blood and marrow of these patients are described in Table

Table 2. Collection of Blood, Bone Marrow and Ultrastructural Findings Described Among Series of Patients with Secondary Myelodysplastic Syndromes and Leukemias

	Erythroid Series	Granulocytic Series	Megakaryocytic Series
Light microscopy: Peripheral blood	Anemia, anisopoikocytosis, normoblastemia, basophilic stippling, circulating erythroblasts	Immature myeloid cells with blasts appearing eventually, hypogranular neutrophils, pseudo Pelger-Huet nuclei, basophilia, Auer rods possible, neutropenia, monocytosis	Giant forms and degranulation, thrombocytopenia, circulating micromegakaryocytes and megakaryoblasts
Bone marrow	Erythroblastosis, periodic acid-Schiff-positive erythroblasts possible, dyserythropoiesis, erythroid hyperplasia with megaloblastoid features, ring sideroblasts	Nuclear hyposegmentation, cytoplasmic hypogranulation	Megakaryocytic hyperplasia with atypical forms, numerous micromegakaryocytes, abnormal nuclear contours, mononuclear forms and odd-numbered nuclei decrease in number of granules, decrease in demarcation membranes, large platelets, giant compound granules, micromegakaryocytes
Electron microscopy	Occasional multinucleate forms, abundant intracristal mitochondrial iron, large vacuoles, infoldings of redundant membranes, membrane bound nuclear blebs, intranuclear clefts	Granulocytes: decreases primary and/or secondary granule formation, abnormal granules (irregular shape, large size, internal membranous lamellae, nuclear hyposegmentation) Monocytes: perinuclear bundles of filaments, large size, angulated and extremely large granules	

2. Because no single finding is unique to 2" MDS/AL, a constellation of findings is necessary to diagnose the disorder. Bone marrows are of varied cellularity, but most commonly hypercellular.[7,21] Hypocellular marrows have been seen in approximately 25% to 50% of cases and normocellular marrows in 10% to 25%. Mild to marked reticular fibrosis occurs in 15% to 80%.[7,16,17] Michels et al[7] pointed out that although the marrow appearance resembles refractory anemia with excess blasts (RAEB) in many patients with 2" MDS, the French-American-British (FAB) classification criteria for this diagnosis" are not satisfied because the blast percentage in the marrow is often less than 5%. In addition, although the criteria for RA or RAS are satisfied in some cases, the degree of dysgranulopoiesis and dysmegakaxyopoiesis is greater than would be expected in the de novo forms. For the latter two reasons, as well as the classical (but not universal) trilineage involvement of 2" MDS, the application of the FAB system to 2" MDS has been difficult; many cases are not classified. Nonetheless, when attempts have been made to do so, RAEB and RAEB-T predominate.[15,23]

When more than 30% of the cells in the marrow have been blasts, attempts have been made to classify the 2" AL according to the FAB system for acute leukemia." As shown in Table 1, all subtypes are represented, but FAB subtypes M1-M2 and M4 are most common. However, similar to the situation in 2" MDS, many investigators have commented upon the difficulty of classifying 2" AL according to the FAB criteria, as most of the leukemias demonstrate trilineage involvement and appear to bridge several subtypes. Among other differences between 2" and de novo AML, relatively fewer of the former cases have Auer rods compared to approximately 40% of the latter; and myeloperoxidase and nonspecific esterase positivity is uncommon among 2" leukemias, but present in 90% and 30% of cases, respectively, of de novo AML.[16] Although the overwhelming number of cases of 2" AL are classified as AML, a small percentage of cases are acute lymphocytic leuke-

mia (ALL) or chronic myelogenous leukemia (CML).

BIOLOGY

Although significant efforts have been made to understand the biology of de novo MDS and AL, relatively little effort has been expended on the biology of 2° MDS/AL. In general, de novo and 2° AL are not morphologically or cytogenetically similar, and other aspects of this underlying biology are also likely to be quite different. Although morphologic and cytogenetic aspects of 1° and 2° MDS parallel one another more closely, it cannot be assumed that other biologic similarities exist. Unfortunately, biologic studies of patients with these disorders have often been lumped together and the data unsegregated, thereby disallowing a determination of their unique elements.

Investigations regarding the cell of origin of the malignant clone have largely been done on the primary myeloid disorders. Studies of the glucose-6-phosphate dehydrogenase polymorphism in heterozygous females have suggested a stem cell origin of some, but not all, cases of MDS.[25,26] Using an X-linked restriction fragment length polymorphism (RFLP)-methylation strategy among seven patients with MDS, Tefferi et al[27] found a monoclonal pattern of X inactivation among myeloid, monocytic, and lymphoid cells. Using the same technique, Janssen et al[28] showed a monoclonal pattern of X inactivation in blood or marrow cells among seven of eight patients with MDS. The one patient who demonstrated a polyclonal pattern had a hypoplastic marrow, leading the authors to speculate that the limitations of the technique rather than the differences in the cell of origin were causative. Furthermore, using the technique in which selective oligonucleotide hybridization to *ras* gene sequences amplified in vitro by the polymerase chain reaction, these same authors demonstrated the same mutated *ras* allele in circulating granulocytes, monocytes, and B and T lymphocytes in each of two patients with CMML. On the other hand, experiments by Kere et al[29] suggest heterogeneity of cell lineage involvement among different patients with MDS/AL. In their study of five patients, four of whom had 2° MDS/AL, each had partial or complete monosomy 7 by cytogenetic analysis. Clonality was studied by using chromosome 7-specific DNA probes on DNA derived from specific cell fractions. Lymphocytes of all five patients had two different chromosomes 7; only one chromosome 7 would have been anticipated in the setting of a multipotential stem cell disorder. Nonetheless, the findings of Kere et al[29] may still be reconcilable with those of other investigators, if karyotype abnormalities occur in a more differentiated cell only after the malignant clone is already established.

As in studies of clonality, much of the in vitro bone marrow culture data have been generated from the study of 1° MDS.[30,31] In that disorder leukemic and nonleukemic growth patterns have been noted, the former characterized by absent or reduced colony growth and micro- or macrocluster formation. Leukemic growth patterns have been associated with an abnormal karyotype, a high rate of leukemic transformation, and a shortened survival. Similar growth patterns have been noted in 2° MDS/AL.[3,32,33] Although the in vitro culture data between 1° and 2° disorders has not been rigorously compared, correlations between in vitro growth patterns and clinical and other biologic aspects of the 1° and 2° disorders have not been dissimilar. In a study evaluating patients with 2° MDS/AL only, Pedersen-Bjergaard et al[3] found an inverse relationship between the number of clusters (5 to 50 cells) and the percentage of cytogenetically normal metaphases in the marrow. Mortensen et al[33] examined 39 patients with 2° MDS and noted a significant connection between increased cluster growth and the rate of leukemic transformation. Specifically, 14 of 18 patients with increased cluster growth progressed to AL within the first year of study compared to only 6 of 21 with normal or decreased cluster growth. Sequential studies additionally demonstrated that a change in growth pattern from normal or decreased to one that was increased was also predictive for leukemic transformation (six of nine patients). However, cluster growth patterns were not associated with survival.

Studies in 1° MDS have shown reduced or absent colony formation of multipotent progenitors and of subsets of committed progenitor

cells, abnormalities in regulator production by marrow accessory cells and in regulator responsiveness of multipotent and committed progenitors, and changes in the composition of marrow matrix.[30,31,34-36] Whether these observations can be extrapolated to 2" MDS/AL remains largely speculative.

The molecular genetic study of 1" MDS and 2" MDS/AL is evolving rapidly, although the significance of the findings is uncertain. An area of the genome that is often deleted in 2" MDS/AL, the long arm of chromosome 5 (see below), is known to contain numerous genes whose function, or lack thereof, could be implicated in pathogenesis. Specifically, genes encoding for interleukin 3 (IL3), IL4, IL5, granulocyte-macrophage colony-stimulating factor (GM-CSF), the platelet-derived growth factor receptor, the β-adrenergic receptor, the endothelial cell growth factor, the myeloid cell-membrane antigen CD14, and the DNA-binding zinc-finger protein EGR1 have all been mapped to the 5q arm, most at bands 5q23-31.[37] More detailed studies of the molecular structure of these genes have been limited. Boultwood et al[38] failed to find any structural rearrangements of the GM-CSF gene among 76 patients with MDS.

The role of oncogenes is being intensively investigated in MDS, particularly the *ras* gene (H-, N-, and Ki-*ras*) and its mutations at codons 12, 13, and, 61. One of the three *ras* genes has been mutated in up to 40% of cases.[39,40,41] In a sequential study of 15 patients with 1") MDS, Melani et al[42] noted that *ras* mutations not present at diagnosis did not subsequently appear even when significant hematologic abnormalities evolved; on the other hand, activated *ras* genes could be present over time without deterioration of the hematologic picture. There have been relatively few studies of the *ras* gene among patients either at risk for 2" MDS/AL or with these disorders. In blood and marrow DNA among 70 patients previously treated for lymphoma but with no evidence of hematologic abnormalities, 13% were found to have *ras* gene mutations.[43,44] There was no obvious difference in the frequency of *ras* gene mutations among those receiving radiation therapy alone, chemotherapy alone, or combination therapy. In addition, age or the amount of treatment administered did not influence their frequency. Of interest, 11% of normal individuals (no previous therapy or malignancy) were also found to have *ras* gene mutations. Pedersen-Bjergaard et al[45] reported only one *ras* gene mutation among 13 patients with 2" MDS/AL. In sum, only preliminary conclusions are possible: (1) *ras* mutations are insufficient to cause hematologic abnormalities, (2) *ras* is not universally present among MDS and is therefore unlikely to be an initiating event, (3) *ras* mutations do not necessarily confer a proliferative advantage, and (4) disease progression can occur in the absence of a *ras* mutation.

The protooncogene c-myb produces a peptide product P-75, which is found in high concentration in myelodysplastic cells of all lineages at each stage of maturation.[46] Although P-75 content declines appropriately in myelodysplastic cells with differentiation, it nonetheless remains disproportionately elevated relative to normal hematopoietic elements at equivalent stages of maturation. The cause or significance of this observation is presently unknown.

As resistance to cytotoxic agents is a common clinical problem in MDS and AML, Holmes et al[47] have investigated the role of mdr1 (p-glycoprotein) gene amplification and mRNA expression. Sixty-six patients with MDS or AL were screened. No cases of gene amplification were observed; 45% of those tested had an increase in mdrl mRNA expression. The only case of 2" MDS/AL did not show an increase in mRNA expression. These data suggest that other mechanisms of drug resistance must also be present.

Several investigators have reported immunologic abnormalities in MDS, almost exclusively in the 1" disorder. Both total numbers of T lymphocytes and the T4 subset are reduced in number, and T8 lymphocytes have been variably reported to be decreased, normal in number, or increased.[30,31,48,49] Among T4 lymphocytes, there is decreased response to mitogens, decreased colony formation, decreased production and responsiveness to interferon gamma (IFN-γ) decreased DNA repair, and increased radiosensitivity.[30,31,48] Natural killer cells are reduced in number and both produce and respond suboptimally to IFN-α.[30,31,50,51] B lymphocytes have been reported to be both decreased and increased in

number. Humoral mechanisms appear to be intact; however, abnormalities of immunoglobulin production, such as hypergammaglobulinemia, the presence of monoclonal antibody, and autoantibodies are frequently cited.[30,31,49] B lymphocytes may also be deficient in the Epstein Barr virus receptor.[30] Additionally, there appears to be ineffective interactions between B and T lymphocytes."

Among granulocytes, qualitative and/or quantitative defects in one or more of the constituents of the primary (myeloperoxidase, elastase) and/or secondary (lactoferrin) granules exist.[30,52,53] A decrease in leukocyte alkaline phosphatase has also been reported.[54] There are several defects in neutrophil function—chemotaxis, adhesion, phagocytosis, and bactericidal activity are all affected.[30,48,53,54] Of interest in this regard, the gp130 gene important in neutrophil chemotaxis has been mapped to an area of the long arm of chromosome 7 often deleted in MDS (HGM10) (see also "Cytogenetics" below). Expression of myeloid and monocyte antigens are often abnormal.[30,53,54] Macrophages from patients with MDS and media conditioned by them are capable of suppressing the growth of normal CFU-GM.[55]

Erythrocytes can display abnormal iron metabolism, decreases in enzyme activity (pyruvate kinase, 2-3-diphosphoglyceromutase), reappearance of HbF, imbalances in globin chain synthesis, and changes in membrane antigens.[30,54] Platelets may exhibit functional or cytochemical abnormalities.[30]

The relevance of these data regarding lymphocytic, phagocytic cells, erythrocytes, and platelets to 2" MDS/AL is largely unexplored.

Cytogenetics

Clonal chromosome abnormalities, often of a complex nature, have been identified in most cases of 2" MDS/AL. Results from the largest single institution studies have reported clonal chromosome abnormalities in 76% to 97% of cases.[15,56-60] Losses of part or all of chromosomes 5 and 7 have been considered the characteristic findings, in some institutions reported in almost 90% of cases of 2° MDS/AL.[61] Other institutions have reported involvement of these two chromosomes in 50% or so of cases.[15,59] A review of 216 cases from five larger series in 1986 found these abnormalities in 142 (66%) of the cases.[62] The most common single abnormality was −7 (39%) followed in frequency by del(5q) (18%) and −5 (14%). Although the same abnormalities have been reported in primary MDS/AL, their frequency is clearly higher in 2° MDS/AL.

In the majority of series, chromosome 7 is the most frequently involved, being abnormal in as many as 65% of cases.[60,62] Most commonly reported is −7, seen in as many as 56% of cases in some series.[62] Although often seen as part of a complex karyotype, it is the most frequent sole abnormality in 2" MDS/AL.[59,62] Deletions of 7q are seen in 5% to 10% of cases. These are interstitial with the proximal breakpoint usually restricted to a fairly narrow region at band 7q22 and the distal breakpoint varying from q32 to q36.[60,63,64] Although monosomy 7 or del(7q) have been most commonly described, in recent years recurring unbalanced translocations that also result in loss of the long arm have been reported: t(1;7)(p11;q11)[65]; t(5;7)(q11.2;p11.2)[66]; t(7;17)(p11;p11).[67] Unbalanced translocations may be more common than previously recognized due to the frequent complex nature of these karyotypes. Cytogenetic studies thus suggest that a critical region in pathogenesis in many cases of 2° MDSIAL is on the long arm of 7q. Although genes of potential importance have been mapped to 7q (eg, those for erythropoietin, p glycoprotein 1/multiple drug resistance 1 and p glycoprotein 3) none has yet been shown to be implicated.[68]

In most reported series chromosome 5 is the second most frequent chromosome *involved, being abnormal in as many as 50% of cases.[62] An interstitial deletion of the long arm is most common, reported in 12% to 27% of larger series.[58,59,62] The proximal breakpoint is usually between 5q31 and 5q22 and the distal breakpoint between 5q31 and 5q35.[56,60] The second most frequent abnormality involving chromosome 5 is monosomy 5, reported in 7% to 20% of cases.[58-60,62] As with chromosome 7, in recent years recurring unbalanced translocations resulting in loss of part of the long arm of 5 have been reported: t(5;7)(q11.2;p11.2)[66]; t(5;17)(p11;p11).[67,69] The critical region in chromosome 5 has been suggested to be from band 5q22 to 5q31.[60] Genes of potential importance have been mapped to the distal region of chromo-

some 5, including in particular those for hematopoietic growth factors and their receptors, but none has yet been clearly implicated in the pathogenesis of 2" MDS/AL.[70,71]

Chromosome 17 has often been the third most frequently involved chromosome reported in the larger series of 2" MDS/AL, being seen in 14% to 18% of cases.[60,72,73] Abnormalities usually involve translocations; bands 17p11-p13 have been most commonly rearranged, followed by band 17q21. Interestingly, one of the most frequent recurring translocations seen in both secondary and primary AML is the t(15;17)(q22; q11-21).[62,74]

Other chromosomes often reported to be abnormal in 2" MDS/AL include numbers 21 and 11. Abnormalities of the long arm of 21 were the fourth most frequent finding in the Danish series (14% of cases); rearrangements involving 21q22 were most common.[60] Recently a recurring translocation involving 21q22 has been reported: t(3;21)(q26;q22).[61,75] Unlike most of the recurring rearrangements reported in 2" MDS/AL, this translocation has not yet been reported in 1"MDS/AL. Other recurring abnormalities involving 21q22 include the t(8;21)(q22; q22)[62,74,76] frequently noted in de novo AML but also noted in de novo MDS and following occupational exposure to mutagenic chemicals."

Rearrangements of 11q23 have increasingly been recognized in 2" MDS/AL.[60,78-81] They occurred in 10% of the cases from Denmark. Although the most frequent rearrangement has been t(9;11)(p21;q23) numerous other recurring translocations seen in de novo acute leukemia have been reported including t(6;11)(q27; q23); t(11;19)(q23;p13); t(11;17)(q23;q21-25); and t(4;11)(q21;q23). In addition a t(2;11)(p21; q23) has been reported to be commonly associated with 2" MDS/AL.[82]

Other chromosomes frequently reported to be abnormal in larger series include chromosomes 3, 8, 9, 12, 18, and 19.[1,58,59] LeBeau et al[56] have suggested that chromosomes 1, 4, 5, 7, 12, 14, and 18 are the only ones significantly more frequently involved in 2" compared to 1"MDS/AL. However, determination of the specificity of involvement of various chromosomes in 2" MDS/AL will probably not be possible until detailed banding studies have been undertaken on more patients, allowing precise identification of the chromosome regions involved, and subsequent prospective trials comparing the frequency of the specific abnormalities in primary and secondary cases have been performed.

A number of specific structural chromosome abnormalities other than those involving chromosomes 5, 7, 11, 17, and 21 have been suggested to be associated with 2" MDS/AL. These include t(1;3)(p36;q21)[83,84,85]; a deletion of 12p11-p13[59,86-88] and rearrangements of band 19q13 or p13.[86] However, it is increasingly being recognized that essentially all of the specific structural rearrangements seen in de novo AML can also be found in secondary MDS/AL, alone or in conjunction with abnormalities of chromosomes 5 and 7. As discussed above t(15;17)(q22; q11-21), t(8;21)(q22;q22), and t(9;11)(p21;q23) have been found in most series of 2" MDS/AL. The other common rearrangement seen in de novo AML that has been reported in many series of 2" MDS/AL is inv(16)(p13q22) or del(16)(q22).[58,74,76,79,81,89]

As specific chromosome abnormalities in 2" MDS/AL are increasingly identified, a better understanding of their biological and clinical significance will be possible. However, certain chromosome abnormalities in 2" MDS/AL have already been reported to be significantly associated with the patient's type of prior disease or treatment and the presenting clinical and pathologic features of the 2" MDSIAL. Monosomy of chromosomes 5 and 7 and additional whole chromosomes (67% to 86%) have been associated more commonly with prior hematological malignancies.[62,73,90] Deletions of 5q and the specific rearrangements reported in de novo AL (eg, t[15;17][q22;q21], t[9;11][p21;q23], t[8; 21][q22;q22] and del[16][q22]/inv[16][p13q22]) have been associated more frequently with prior solid tumors.[62]

Monosomy of chromosomes 5 or 7 and deletions of 7q have been highly associated (>85%) with prior chemotherapy (alone or with radiotherapy).[59,62] Chromosome 5 and 7 abnormalities of any type have been significantly more frequently seen in patients receiving prior alkylating agents than in those not having received them; they have also been significantly more frequently associated with the presence of a myelodysplastic phase.[60] Deletions of chromo-

some 5q, specific rearrangements seen in primary AML, normal karyotypes and "other" structural abnormalities have been more frequently associated with radiotherapy alone[62] or chemotherapy other than long-term alkylating agent treatment. 11q23 rearrangements have recently been associated with a lack of a preceding MDS, short hiatus from initial treatment to secondary leukemia, prior treatment with epipodophyllotoxin and no long-term alkylating agent treatment.[60,78]

The interaction of the type of prior disease and prior therapy with the specific chromosome abnormality requires further study with prospective collection of detailed data regarding primary treatment and multivariate analyses of results. The influence of specific chromosome abnormalities on clinical and pathological characteristics of the 2" MDS/AL has also been inadequately studied. However, karyotype has been correlated with response to chemotherapy and survival as discussed below in the section on treatment of 2" MDS/AL.

SECONDARY MYELODYSPLASTIC SYNDROMES AND LEUKEMIAS AMONG INDIVIDUAL PRIMARY DISEASES

An overview of the biology and clinical aspects of 2" MDS/AL that this review has thus far provided gives relatively little guidance to the individual practitioner in regard to risk assessment for a patient with a particular malignancy. This section attempts to correct this deficiency. Nonetheless, let the reader beware; in many of the primary malignancies discussed, the treatments have evolved, and the risk of 2" MDS/AL quoted may have little relevance to present day therapies. Furthermore, variables that are identically named in the tables may have been differently defined between studies; comparison between these studies would be therefore inappropriate. In addition, duration of follow-up and statistical analysis of data tend to be different between studies; either situation may lead to disparate results. With these several caveats in mind, the brief discussion below can then allow only a superficial overview of the leukemogenic potential of treatment approaches used in various diseases. Especially in regard to reports cited in the tables, we point out differences between studies that appear to be more similar than they are, so the reader can better place their results in perspective.

Hodgkin's Disease

There have been several large studies of the risk of 2" MDS/AL in Hodgkin's disease.[16,32,91,92-104] The six studies summarized in Table 3 represent either the largest and/or the most informative. All the studies with the exception of van Leeuwen et al[92] looked exclusively at the incidence of 2" AL; if 2" MDS were considered in these studies, relative and actuarial risk would be higher. In general, the use of RT alone, even intensively—usually defined as extensive RT to at least one side of the abdomen—resulted in few or no cases of 2" MDS/AL. The overwhelming majority of the cases resulted in the setting of chemotherapy use, almost always involving an alkylating agent. Combined modality therapy did not elevate risk in the studies cited, although this conclusion has not been universal.[97] Relative risk was usually greater than 100-fold and actuarial risks ranged between 1% and 10% over a period of 7 to 10 years. Glicksman et al[93] reported the highest actuarial risk of 26% in a study with a relatively short median follow-up of 46 months. The subset with this risk had received either MVPP/MOPP induction and a lengthy maintenance chlorambucil program.

The studies cited in Table 3 often include sizeable subsets of patients who have received considerably more therapy than one ideally wishes to give to the patient with Hodgkin's disease. Reasons for this observation include both the previous use of maintenance therapy and of more prolonged courses of treatment than is now the norm. In addition, patients who relapse and require additional therapy are also included in these tables. As the risks of the former group of patients are not directly relevant to present-day therapy and the risks of the latter group become less important in the setting of trying to prevent death from recurrent Hodgkin's disease, the risk to those receiving front-line therapy for six cycles (or such therapy after failure of initial radiotherapy) is of most compelling interest. Unfortunately, there is relatively little information on this topic.

After six cycles of MOPP (mechlorethamine, vincristine, procarbazine, prednisone) Blayney et al[100] cite less than a 2% risk for 2" AL at 10

Table 3. Secondary Myelodysplastic Syndromes and Leukemias Following the Treatment of Hodgkin's Disease

No. of Patients	Treatment (no. of patients)	No. of AL	Median Follow-Up (mo)	Median Latency (mo)	Relative Risk	Percentage Actuarial Risk (yr)	Comments	Reference
659						0 (7)	Subgroup at increased risk: age > 40 years	91
						6.2 ± 3.4 (7)		
			NS	NS	NS	6.4 ± 2.1 (7)		
						7.7 ± 2.9 (7)		
693							Subgroups at increased risk: 40-59 yr; NM v nitrosourea: maintenance with Chl	93
			46	72	691	26.2 ± 11.1 (NS)		
					234	9.0 ± 6.1 (NS)		
					101	2.0 ± 1.4 (NS)		
					0	0	RT not an additive hazard	
744	RT only (273)						Increased risk with increased intensity of treatment; age > 40 yr; splenectomy	92
	CT only (48)	6 secondary MDS						
	Combined modality (234)	16 secondary AL	77	68	45.7	5.1 ± 1.2 (10)		
	Salvage RT and CT (187)							
	No RT or CT (2)							
947	RT alone (136)	0				0 (10)	Subgroups at increased risk: salvage treatment needed; age > 30 yr	32
	CT alone (175)	2	24-144	50.5	NS	2.2 ± 1.6 (10)		
	Combined Modality (394)	8				6.2 ± 3.4 (10)		
	Salvage Treatment (242)	4				4.8 ± 2.5 (10)	Tendency for ABVD patients to have less AL	
1,329	RT alone (307)	0				0 (12)	Subgroup at increased risk: older age groups, salvage CT necessary	94
	CT alone (96)	1				1.4 ± 2.3 (12)		
	RT + MOPP (335)	9	114	55	NS	10.2 ± 5.2 (12)		
	RT + ABVD (180)	0				0 (12)		
	RT + other (411)	9				4.8 ± 1.6 (12)		
2,591	No intensive Tx (1,394)	0			0		NM+ PCB resulted in RR = 50-100; NM used alone was not associated with AL	95
	Intensive RT, no intensive CT (696)	1	NS	NS	7	NS		
	Intensive CT, no intensive RT (360)	14			140			
	Intensive CT + RT (141)	5			125			

Abbreviations: NS, not stated; RT, radiotherapy; CT, chemotherapy; AL, acute leukemia; Chl, chlorambucil; NM, nitrogen mustard; PCB, procarbazine; MOPP, mechlorethamine, vincristine, procarbazine, prednisone; MVPP, mechlorethamine, vinblastine, procarbazine. prednisone; ABVD. Adriamycin, bleomycin, vinblastine, dacarbazine.

years. However, this observation is based on small numbers; other investigators have found considerably higher actuarial risks after MOPP (eg, see Valagussa et al Table 3), but the number of MOPP cycles received is not clearly stated. The evidence appears convincing that **ABVD** (doxorubicin, bleomycin, vinblastine, dacarbazine) is less leukemogenic than MOPP, but risk is not absent.[32,94]

Readers should be aware that studies cited in Table 3 are not directly comparable. Type, length, and intensity of treatment varies between studies, as does length of follow-up and methods of statistical analysis. Furthermore,

patients receiving "salvage therapy" are a very mixed group. For example, a salvage patient may have received only six cycles of chemotherapy after failure of radiotherapy, or multiple cycles of additional chemotherapy following initial chemotherapy and radiotherapy. Yet other studies lumped "salvage" patients with other treatment groups.

Non-Hodgkin's Lymphoma

Table 4 lists some of the larger studies examining the risk of 2" MDS/AL resulting from the treatment of non-Hodgkin's lymphomas (NHL). In general, the actuarial risks among these studies were 5% to 10% up to 10 years from the initiation of therapy.

Alkylating agents again represent the primary contribution to risk. The role of radiation therapy is less clear, as one study[105] supports its contribution to risk and another does not.'" The former study, however; used, in part, low-dose irradiation — total body or hemibody irradiation — a therapy that may paradoxically be more leukemogenic than its high-dose counterpart (see "Synthesis").

Whether these actuarial risks are representative of those subsequently to be encountered in present-day regimens is unclear. The treatment strategies in the studies represented in Table 4 often consisted of long-term maintenance programs containing alkylating agents and, as cited above, one study used low-dose irradiation. The latter strategy has never been popular and the former strategy has increasingly fallen into disfavor. On the other hand, present-day regimens do tend to be more aggressive and use higher doses of drugs, including alkylating agents, than in the past.

In a literature review of case reports of 2" MDS/AL following the treatment of non-Hodgkin's lymphoma, 104 cases were cited.'" Of these, 15 were either concurrent with or developed within 1 year of the diagnosis of NHL. The selection inherent to case reports does not allow one to conclude that patients with NHL are intrinsically prone to develop MDS/AL, but these data suggest such a hypothesis. Nonetheless, the contribution of therapy seems unequivocal.

Multiple Myeloma

Table 5 lists some of the largest studies to data addressing the risk of 2" MDS/AL among treated patients with multiple myeloma. Over-

Table 4. Secondary Myelodysplastic Syndromes and Leukemias Following the Treatment of Non-Hodgkin's Lymphoma

No. of Patients	Treatment (no. of patients)	No. of MDS/AL	Median F/U (range)	Median Latency (range)	Relative Risk	Percentage Actuarial Risk (mo)	Comments	Reference
261*	Modified LSA2L2	6	Range of f/u: 3-9 yr	– 3 yr	NS	7.8 (84)	No stable plateau in actuarial risk yet reached	154
517	NS, but 7/9 developing AL has TNI. TBI or HBI	9	52 mo (0-264)	68 mo (18-120)	105	7.9 ± 3.2 (120)	Increased risk (case-control analysis): RT + CT *v* RT or CT alone, higher radiation dose, higher cumulative dose of cyc, longer duration of cyc use	105
602	NS, but all patients developing AL received alkylating agents	9	NS	51 mo (26-81)	76	8.0 ± 3.3 (108) (group receiving alkylating agent only)	Increased risk: *two* or more combination CT regimens. Regimens; No increase: CMT *v* CT alone. No apparent plateau in actuarial risk	106

Abbreviations: NS, not stated; RT. radiotherapy; CT, chemotherapy; cyc, cyclophosphamide; CMT, combined modality therapy; TNI, total nodal irradiation; TBI, total body irradiation; HBI, hemibody irradiation.

*Children with NHL and T-cell leukemia/lymphoma.

Table 5. Secondary Myelodysplastic Syndromes and Leukemias Following Treatment of Multiple Myeloma

No. of patients	Treatment (no. of patients)	No. of AL	Median F/U	Median Latency (mo)	Relative Risk	Percentage Actuarial *Risk* (mo)	Comments	Reference
364	Melphalan (125) M-CYC-BCNU (123) M + CYC + BCNU (116)	5 3 6	NS	NS	230	19.6 (50)	MDS seen in other patients No significant difference in risk of AL between treatments	158.225
648	Melphalan (NS) Cyclophosphamide (NS)	12 (includes MDS)	97 mo (for 5-yr survivors)	85.5	NS	10 (96)	Risk was associated with length of melphalan treatment, but not with cyclophosphamide	109
908	Melphalan (NS) BCNU (NS) Cyclophosphamide (NS)	15 1 1	NS	NS	NS	10.1 (120)	Seven additional patients had MDS	107
945	Continuous oral M (274) IV Melphalan ± other AA (671)	7 5	NS	30.1 54.1	NS	13.4 ± 5 (60) 7.4 ± 7 (60)	Less risk of developing AML for pulsed *v* continuous treatment	110

Abbreviations: NS. not stated; CYC. cyclophosphamide; M, melphalan; IV, intravenous; AA, alkylating agent; AML. acute myeloid leukemia.

all, actuarial risk is approximately 10% at 5 to 10 years following the initiation of treatment, but risks as high as 20% has been reported.[107] Cases of MDS have generally not been included in these risk calculations. Although AL (ie, leukemia other than plasma cell leukemia) has been regarded by some as part of the natural history of multiple myeloma, there is little evidence to support this[108]; cases of MDS/AL occurring after the treatment of multiple myeloma can therefore be assumed to result from that treatment.

Investigators have attempted to determine whether the scheduling or mode of delivery of melphalan, still the mainstay in the treatment of this malignancy, affects risk. Initially, there does not seem to be a significant difference in the risk of 2" MDS/AL whether oral melphalan is given on a daily basis or for a few consecutive days every 4 weeks.[109] McIntyre et al[110] found IV bolus melphalan to be less leukemogenic than continuous oral treatment; however, a low rate of leukemogenesis with IV melphalan has not been found by others."'

Again, caution is advised in extrapolating these data to present-day treatments. It has been the norm in reports detailing risk of 2" MDS/AL that patients were treated until the time of relapse or progression; presently, therapy is generally discontinued at an earlier time, a treatment strategy that could have considerable effects on risk. Furthermore, the treatments represented in Table 5 and other reports are only the initial ones received by the patient; as there was likely to be substantial crossover among treatments during the patient's course, figures must be viewed as rough estimates of the leukemogenic potential of the cited therapy.

Ovarian Cancer

Table 6 lists three of the larger studies examining the risk of 2" MDS/AL following the treatment of ovarian cancer with either chemotherapy or radiation therapy. Actuarial risks ranged between 5% and 10% at 5 to 10 years following diagnosis. Neither the use of radiotherapy alone or in combination with chemotherapy appeared to contribute significantly to risk in these or other studies.[112]

The risks represented by studies in Table 6 and those of others[112-114] are risks, for the most part, resulting from the use of single alkylating agents, either alone or in sequence. The most commonly used of those agents were melphalan and cyclophosphamide. Although the chemotherapeutic approach to all stages of ovarian cancer is in a state of flux, the use of single agents rather than combination chemotherapy

Table 6. Secondary Myelodysplastic Syndromes and Leukemias Following the Treatment of Ovarian Cancer

Number of patients	Treatment (no. of patients)	Number of AL*	Median Follow-up	Median Latency mo (range)	Relative Risk	Percentage Actuarial Risk (mo)	Comments	Reference
553	Dihydroxybusulfan	7	NS	50 (21-58)	125	7.6 ± 3.0 (60)	No dose-dependent risk for development of AML; irradiation was not a major leukemogenic factor	160
3,363	No RT or CT (595)	0	5.7 y	5.6 y	93 (among 1,794 women treated with CT)	0 ± 0 (120)	Women receiving melphalan were 2-3 times more likely to develop leukemic disorders than women receiving CYC; CMT did not increase risk above CT alone	166
	RT Only (955)	2				0.1 ± 0.1 (120)		
	CT Only (1,179)	21				8.6 ± 2.2 (120)		
	RT + CT (549)	12				8.3 ± 2.4 (120)		
5,455	CT + RT	4	NS	41.5 (30-90)	36.1 (CT ± RT) 171.4 (patients surviving ≥ 2 years)	NS	Analysis of historical control group of 13,309 showed no AML, even among 6,596 receiving RT	226
	CT alone	9						

Abbreviations: NS. not stated; RT, radiotherapy; CT, chemotherapy; CYC, cyclophosphamide; CMT, combined modality therapy; AML, acute myeloid leukemia.

*Data of Greene et al[188] include 7 cases of MDS.

is becoming less traditional. How the latter therapy, which often includes one or more alkylating agents, will affect incidence rates of 2" MDS/AL in this malignancy is presently unclear. Although the use of regimens with cisplatin, an agent that binds to DNA, is expected to be associated with low rates of leukemogenesis, based on experience with this chemotherapeutic agent in other malignancies, further follow-up is required.[114]

Breast Cancer

Three of the more important studies examining the incidence of 2" MDS/AL among women treated for breast cancer are listed in Table 7. Actuarial risk has been small (<2%), even at 10 years. Risk, when it occurs at all, has been attributable to the use of alkylating agents, although the study by Fisher et al[115] did find an increased relative risk for the use of radiotherapy alone —either to the breast or regionally (chest wall, axilla, internal mammary, and supraclavicular areas). Other investigators have discounted any risk of radiotherapy on leukemogenesis in this malignancy.[112,116-118] The weight of the latter studies and the fact that only four ALs were identified in the study by Fisher and colleagues[115] presently suggests that radiotherapy as applied in breast cancer has either a minor or absent role in leukemogenesis. The studies cited in Table 7 have usually involved women receiving adjuvant therapy or chemotherapy as a first course of treatment for 12 to 24 months. The trend toward shorter courses of adjuvant therapy may well decrease risk even further.

Nonetheless, high rates of 2" MDS/AL have been reported following adjuvant treatment or the treatment of advanced/metastatic disease.[119-121] Generally, however, these studies have used drugs not commonly used (chlorambucil, dibromoducitol, prednimustine) and at a duration and/or schedule that is either longer or uncommon, respectively, by present-day standards.

Lung Cancer

There have been no large reports of 2" MDS/AL following the treatment of lung cancer that postdate our last review of this area.' Even though an actuarial risk of 5.8% at 5 years among 243 patients following the use of single agent busulfan for up to 2 years was not particularly surprising,[122] two other large studies have produced among the highest actuarial risks

Table 7. Secondary Myelodysplastic Syndrom and Leukemias Following Treatment of Miscellaneous Disorders

Disease (no. of patients)	Treatment (no. of patients)	Number of AL	Median Follow-up (yr)	Median Latency (mo)	Relative Risk	Percentage Actuarial Risk (mo)	Comments	Reference
Breast (666)	*CMF × 12 (450)*	0	> 10	Not applicable	0	0		167
	CMF × 6 (216)							
Breast (8,483)	*Surgery alone (2,068)*	*2(+1 CML)*	*	51.5	2.6 (AL)	0.27 ± 0.05 (120)	Age (<50 or >50): n	effect on incidence of	115
	RT alone (1,116)	4(+2 CLL)		78.9	10.3 (AL)	1.39 ± .49 (120)	AL. Groups with an	l without leukemia:
	Melphalan (5,299)	26(+1 CLL,7 MDS)		50.8	24.0 (AL)	*1.68 ± .33 (120)*	*Similar in amount c*	M received; intensity
							of therapy; but diffe	ent in days on ther-
							apy (AL > control).	*Actuarial risk has sta-*
Breast (21,708)	CT ± RT (13734)	24	4.2 PY	NS	.5	0.7 ± 0.2 (120)	bilized after five yea	s
[SEER database]	Surgery only (7974)	7	8.5 PY			0.1 (120)	*Specific details of trea*	*ment and its length*	118
Brain (2,656)	BCNU (1,628)	2	(see comment	8,31		NS	were not known	
	Other CT (582)	0	column)				Only 2% of patients u	der observation for	130
	No CT (446)	0					> 2 years	
Polycythemia vera (431)	Phlebotomy alone (134)	1	5.5			NS		
	^{32}P + Phlebotomy (156)	9	5.4	≤8.8	3		Risk greater for higher	aily dose of CHL and	132
	CHL + Phlebotomy (141)	16	6.1		13		more days on thera	

Abbreviations: NS, not stated; RT, radiotherapy; CT, chemotherapy; M, melphalar :HL, chlorambucil; PY, patient years; CMF, cyclophosphamide, m inte, 5-FU; CML, hc c myelogenous leukemia; CLL, chronic lymphocytic leukemia.

*40% followed for a minimum of 7 years, 35% for a minimum of 2.8 years, remainder f median follow-up of 3.2 years.

noted in any primary malignancy; furthermore, the 2" MDS/AL has occurred with a very short latency. Specifically, among 158 patients with small cell lung cancer treated with VAM-POCC or POCC **(VP-16** [etoposide], Adriamycin [doxorubicin; Adria Laboratories, Columbus, OH], methotrexate, procarbazine, vincristine, cyclophosphamide, and CCNU [lomustine]) for up to **13** months, 3 developed AL, producing an actuarial risk of 25 ± **13%** at **3.1 years.**[123] Chemotherapy exposure was not different between the leukemic and nonleukemic groups. Median latency was **32** months. Among **796** patients with small cell lung cancer treated with CCNU, cyclophosphamide, vincristine ± VP-16, methotrexate, and doxorubicin for up to 18 months, **6** developed 2° MDS/AL, leading to an actuarial risk of **14 ± 6.9%** at **4** years.[''] Median latency was 20 months. Several hypotheses could be advanced to explain these findings: lung cancer patients are at greater inherent risk to develop 2" MDS/AL; the high actuarial risk and short latency are deceptive due to rapid deaths induced by this malignancy; the use of two or more alkylating agents in the cited studies is the primary culprit. The actual reason remains uncertain. There presently are no traditional regimens for non–small cell or small cell lung cancer, although aggressive and lengthy intervals of treatment remain the norm.

Testis Cancer

Testis cancer is another primary malignancy in which the risk of leukemogenesis following treatment appears to be low. Redman et **al**[125] reported 5 leukemias (3 AML, **2** CMML) developing among 722 analyzable patients. Two patients had received RT alone, and **3** had received chemotherapy. The latter had all received alkylating agents; cisplatin was also used in two of the three regimens. Actuarial risk was 1.3% at 10 years. Present-day regimens tend to be platinum-based without the use of alkylating agents. Using such regimens, Nichols et **al**[126] noted no cases of 2" MDS/AL among **654** patients treated with an average of four courses of therapy. Although the development of 2" MDS/AL following the use of a cisplatin-based regimen alone is not unprecedented in testicular **cancer,**[127,128] its incidence must be small. Secondary MDS/AL in testis cancer must be differentiated from hematologic neoplasia associated with primary mediastinal germ cell tumors. The latter hematologic disorders are distinguished by their high percentage of acute megakaryoblastic leukemias, their occurrence shortly after or simultaneous with the diagnosis of the mediastinal germ-cell tumor, their association with the rapid onset of clinical symptoms, and the general lack of abnormalities in chromosomes 5 or 7.[129]

Other Primary Malignancies

The incidence of **2"** MDS/AL in other primary malignancies has been less well studied than those reviewed above. The reasons for this fact are likely to include the uncommon use of alkylating agents-clearly the most important factor in leukemogenesis—in past or present-day therapies for some malignancies, and the short median survival associated with others, thereby not allowing its emergence.

Of relevance is the study of **2"** MDS/AL in brain tumors by Greene et **al**[130] because the agent implicated in leukemogenesis in that study-carmustine (BCNU)—is still commonly used in these disorders (Table **7).** Treatment arms included surgery alone, surgery and RT, surgery and BCNU, or surgery and both BCNU and RT. Acute leukemia was reported only in patients who received BCNU (2 of **1,628).** Due to the rapid and considerable mortality associated with CNS tumors (only **290** patients were under observation for 2 or more years), it is thus likely that more **2"** AL would have been observed, if the treatment had been more successful.

Methyl-CCNU is no longer used in the adjuvant therapy of stomach, colon, or rectal cancer, but the report by Boice et al[131] has established it as a leukemogenic agent in that setting. Actuarial risk was **4%** at **6** years among **2,067** patients treated with a methyl-CCNU–containing regimen. Relatively few patients were given fluouracil (5-FU) in the absence of methyl-CCNU, a closer approximation to present-day therapies. However, there is presently no evidence implicating 5-FU in human or animal leukemogenesis.

Because of the unexpectedly high incidence

of 2" MDS/AL, a study by the Polycythemia Vera Study Group[132] was instrumental in defining present day approaches (Table 7). The 431 patients on study were randomized to receive either phlebotomy alone, radioactive phosphorous and phlebotomy, or chlorambucil and phlebotomy. Chlorambucil was given intermittently but indefinitely. Increased rates of 2" AL were seen with the use of both ^{32}P and chlorambucil, with the latter producing the highest relative risk. However, there was no statistically significant difference in survival between the groups. The increase in risk of 2" AL without concomitant benefit led to the abandonment of alkylating agents in this disease and the use of ^{32}P among elderly patients only. Of interest, polycythemia vera may illustrate a primary malignancy whose biology is influential in affecting subsequent rates of 2" leukemogenesis. For example, exposure of patients with polycythemia vera and chronic lymphocytic leukemia (CLL) to the same cumulative doses of ^{32}P results in very different rates of leukemogenesis (14% *v* 2.5%, respectively).[133] Polycythemia vera is known to have little inherent risk to evolve to AL in the absence of radiotherapy or chemotherapy.

A number of reviews detailing case reports of AL in diseases such as CLL,[134,135] Waldenstrom's macroglobulinemia,[136] sarcomas,[137] and bladder cancer[138] have appeared and case reports of leukemias developing after virtually any primary malignant disease not yet mentioned can be found?' In nearly all such cases, the patients have been exposed to CT with or without RT. Presently, the absence of information regarding the number of patients at risk prohibits a determination of the significance of these reports. Gynecologic malignancies other than ovarian have been instrumental in better defining the risk of radiotherapy in leukemogenesis, a topic that will be addressed below.

Nonneoplastic Diseases

The influence of chemotherapeutic agents on the development of 2" MDS/AL in nonneoplastic disease has been confused by the theoretical supposition that the immunosuppression inherent in many of these disorders (eg, rheumatoid arthritis, lupus, and other collagen vascular diseases; chronic glomerulonephritis and other renal diseases, the inflammatory bowel diseases) would alone allow the emergence of AL. However, considerable evidence suggests that AL does not normally evolve from these immune disorders.[139-141] In his review of malignancies developing in patients with depressed immunity, Penn[142] found the incidence of NHL and select solid tumors to be increased, but there was no increase in the incidence of AL among adult patients in the absence of prior CT.

Even when patients with nonneoplastic disease have been administered chemotherapeutic agents, an excess of AL has not always been found.[143-145] Nonetheless, the large number of reported cases of AL following cytotoxic therapy for these diseases implicates these drugs as causative agents.[146-150] Not surprisingly, alkylating agents such as chlorambucil, cyclophosphamide, melphalan, and busulfan are most often associated with leukemogenesis in this setting. Louie and Schwartz[146] compiled 108 cases of neoplasms complicating cytotoxic therapy (in the majority of cases, alkylating agents) of nonmalignant disease and compared their distribution to 94 cases of neoplasms complicating nonmalignant disease in which cytotoxic therapy was not used. Although 26% of the neoplasms in the former group were AML, only 3.2% of neoplasms in the latter group were. Unlike the situation in many primary malignancies, calculations of relative risk and actuarial risk have not generally been performed in the nonneoplastic disorders. Therefore, although the ability of cytotoxic agents to cause 2" MDS/AL among patients with nonneoplastic disorders is well established, the "cost" of this feared complication relative to the benefit that these drugs provide to a broad spectrum of patients has not been delineated.

Childhood Cancer

There are two large studies investigating the incidence of 2" MDS/AL in children following the treatment of a primary malignancy. Tucker et al[151] reporting for the Late Effects Study Group, noted the occurrence of 22 cases of 2" AL among 9,170 2-or-more-year survivors of childhood cancer, resulting in a relative risk of 14. The actuarial risk of developing leukemia for the entire cohort was 0.8% 20 years following diagnosis. Median latency was 3.5 years.

Among 3,365 children treated for malignant solid tumors at the St Jude Children's Research Hospital (Memphis, TN), Pui et al[89] reported 12 2° MDS/AL. Latency was 14 to 189 months following diagnosis of the primary malignancy. Actuarial risk was 0.6% at 10 years. Even these risks of therapy-related myeloid disorders may be inflated, because up to *25%* of children with "secondary" cancers may have a genetic predisposition to additional cancer development, independent of preceding treatment.[152,153] A child's seemingly lower risk of developing a secondary myeloid disorder may not be surprising. Younger adults may be at lower risk for secondary leukemogenesis than older adults (see below), and this fact suggests a reason that children may be at even lesser risk. Furthermore, the study of Pui et al[89] found that even among children, those younger than age 12 were at relatively lesser risk than older children. However, the data from the above two studies were collected over several decades in several different primary malignancies. Therefore its comparability to the adult data reviewed in the preceding sections and its relevance to the present-day treatment of children is suspect.

A disease that is treated relatively comparably among children and adults is Hodgkin's disease. In the study of Tucker et al[151] 1,036 children with Hodgkin's disease had a 4.2% actuarial incidence of 2° leukemia at 20 years following treatment. Relative risk of AML was 140. In the study of Pui et al[89] the actuarial risk of 2° MDS/AL at 10 years following the diagnosis of Hodgkin's disease was 1.3% among 447 patients. As neither the treatment groups nor the number of patients treated within such groups is delineated, direct comparability to adult studies is not possible. In general, however, actuarial risks have been less or similar at equivalent rates of follow-up (see Table 3). A clearer answer to this question of childhood risk has been provided by Valagussa et al[94] who noted at 12 years among 1,329 patients an actuarial risk of 0.06% among children (age < 17 years), of 2.7% among those aged 17 to 40, and of 7.0% among those 40 or older, regardless of treatment modality and type of therapy.

Of considerable concern is the high rate of AML among children who have been treated for T-cell malignancies. Among 733 consecutive children treated for newly diagnosed ALL at the St Jude Children's Research Hospital between 1979 and 1988, 13 developed AML.[78] Five programs of intensive chemotherapy were used, of which four included an epipodophyllotoxin (ie, VP-16 and/or VM-26 [teniposide]). Median latency was 3 years (range, 1.2 to 6 years). At 6 years, the actuarial risk of AML was 4.7% (confidence intervals 2% to 10%); however, among the 98 children with T-cell disorders, the actuarial risk was 19.1% (confidence intervals 6% to 47%). Several aspects of the AMLs were atypical; only 3 of the cases were preceded by a preleukemic phase; there was no evidence of loss of all or part of either chromosomes 5 or 7; and among the 9 of 10 patients whose sequential cytogenetic studies revealed entirely different karyotypes at the time of diagnosis of AML, 8 had abnormalities of the 11q23 region. Because the 11q23 region has been suggested to be preferentially involved in the malignant transformation of pluripotential stem cells able to differentiate into either lymphoid or myeloid blasts, its involvement may be important to the pathogenesis of AML in this setting. Ingram et al[154] using a modified LSA_2L_2 protocol among 261 children with NHL or T-cell leukemia/lymphoma, also noted a high rate of secondary leukemogeneis.

Children are probably at lesser risk than adults for 2° MDS/AL, at least after the treatment of Hodgkin's disease. Nonetheless, in regard to T-cell disorders, rates of leukemogenesis thus far described are as high as any for adults after the treatment of each of a variety of primary malignancies.

Synthesis

Attempting to synthesize the data above to arrive at some summary statements is a precarious undertaking. Because these studies are both toxicity-related and collected over years, information from randomized trials is infrequently available. Between studies, cohorts of patients are likely to differ in a number of ways, including age, sex, diet, heredity, hormonal status, immunological status, preexisting diseases, and degree of exposure to environmental carcinogen ~each of;these variables could influence results. Furthermore, as we have pointed out repeatedly when comparing trials in individual

primary malignancies, a drug could be administered at different doses, by different routes, and over widely variable periods of time. A particular drug could be given alone, in association with other drugs, or preceding, concurrent with, or following irradiation. In addition, the size of the study, competing causes of death (especially from the primary malignancy itself), and the duration of follow-up, all of which could have considerable effects on the numbers of 2° MDS/AL observed and the outcome of statistical analyses, were highly variable. Last, the nature of follow-up procedures, the identification of cases, and the manner in which the data were analyzed was not uniform. With these several caveats, then, we consider the following questions.

Which drugs appear to confer risk for development of 2" MDSIAL? Many of the alkylating agents have been clearly implicated in the development of 2" MDS/AL. These include the nitrogen mustards meclorethamine, chlorambucil,[93,119,132,155-157] cyclophosphamide,[105] and melphalan[113,115,155,158,159]; the epoxide dibromoducitol[120]; the nitrosoureas BCNU[130] and methyl-CCNU[131]; the alkyl alkone sulfonates busulfan[122] and dihydroxybusulfan,[160] and the nonclassic alkylating agent procarbazine.

Anecdotal reports of leukemia following the use of virtually any other alkylating agent can be found, but each has been less firmly established as a leukemogen, either because of its relatively infrequent use, or its customary use in combination regimens, thereby not allowing its contribution to this complication to be easily discerned. These agents derive from several of the alkylator classes above, and include thiotepa,[138,161] CCNU, streptozotocin,[162] hexamethylmelamine, and dacarbazine. Ifosfamide has quickly come into widespread use, but no data yet exist on its leukemogenic potential. Investigators should consider each of these lesser used alkylators as a leukemogen, until evidence establishes otherwise.

More recently, cisplatin and the epipodophyllotoxin VP-16 have also been implicated as leukemogens. Cisplatin, for several years a standard agent in testis cancer, is also commonly used in a number of other malignancies, including lung and ovary. Anecdotal reports of 2" MDSIAL in these malignancies following the use of cisplatin without the concomitant use of an alkylating agent continue to accrue.[114,163,164] Secondary myeloid disorders following the use of VP-16 in both hematologic and solid primary malignancies are also becoming more common.[78,165] A unique aspect of the 2° MDS/AL following VP-16 use has been the frequent involvement of the 11q arm; the possible generation of a secondary leukemia following the treatment of a primary one with VP-16 may represent a special situation (see ***Childhood Cancer)*** and merits continued vigilance. On the other hand, the strong reporting bias inherent in the infrequent retrospective reports of a 2° MDS/AL following cisplatin and VP-16, together with the widespread use of these agents, infer that the two are weak leukemogens. In addition, Nichols et al[126] have observed no 2" MDS/AL among 654 patients with testicular or retroperitoneal germ-cell tumors treated with cisplatin therapy (± VP-16), despite follow-up in some patients for over 10 years.

There is even less compelling evidence that other classes of chemotherapeutic agents are leukemogens. Reports of 2" MDS/AL following treatment with fluorinated pyrimidines (5-FU), cytidine analogues (cytarabine), the antifolates (methotrexate), the purine derivatives (6-mercaptopurine, 6-thioguanine), the plant alkyloids (vincristine and vinblastine), the antitumor antibiotics (dactinomycin, mitomycin, bleomycin), the anthracyclines (daunorubicin, doxorubicin, mitoxantrone), and hydroxyurea have been infrequent to rare.

In summary, the risk of leukemia following treatment with chemotherapeutic agents is overwhelmingly attributable to the use of the classic alkylating agents and the nonclassic alkylating agent procarbazine.

Is one alkylating agent more leukemogenic than another? As a drug is uncommonly used alone and often in combination with other probable chemical leukemogens and/or RT, the leukemogenic potential of one drug relative to another is difficult to determine. In addition, available information is sometimes conflicting.

The most persuasive evidence indicating that one drug may be more leukemogenic than another derives from the comparison of melphalan and cyclophosphamide. In a report[166] of 3,363 1-year survivors of ovarian cancer who

were treated in five randomized clinical trials, 1,794 were treated with chemotherapy, over one-half of whom received either melphalan or cyclophosphamide as the only alkylating agent. The 10-year cumulative risk of acquiring a leukemic disorder was 11.2% after treatment with melphalan and 5.4% after cyclophosphamide treatment. Women receiving melphalan were two to three times more likely to develop leukemia disorders than were women receiving cyclophosphamide. In a Connecticut case-control study by Curtis et al[118] 20 leukemic disorders were identified between 1973 and 1985 among 14,860 women with breast cancer who had survived at least 18months. Chemotherapeutic regimens including melphalan were associated with a significantly higher risk of 2° MDS/AL than those including cyclophosphamide. The greater leukemogenic potential of melphalan is also suggested by the 28 cases of leukemia among 5,299 melphalan-treated patients in the National Surgical Adjuvant Breast and Bowel Project trials of adjuvant therapy,[117] and its absence among 666 cyclophosphamide-methotrexate-5-FU treated patients in the adjuvant trials of Valagussa et al.[167] Cuzick et al[109] reported 12 patients with 2° MDS/AL among 648 patients in the Medical Research Council's first two trials in multiple myeloma. Treatment with melphalan was found to be a risk factor for 2° MDS/AL; treatment with cyclophosphamide was not.

Stott et al[122] have also suggested that busulfan may be more leukemogenic than cyclophosphamide. In a study of the postoperative adjuvant therapy of lung cancer, AL developed in those receiving busulfan, but not in those receiving cyclophosphamide.

Comparisons of the leukemogenic potential of other drugs have yielded conflicting information. The introduction of nitrogen mustard alone for the treatment of Hodgkin's disease in the late 1940s resulted in only a small increase in the incidence of 2° AL. With the introduction of MOPP, however, in the mid-1960s, the increase in incidence has been dramatic.[168] Single studies containing small subgroups of patients who received either nitrogen mustard or procarbazine have yielded inconsistent results. Boivin et al[95] demonstrated that the use of procarbazine with or without nitrogen mustard resulted in a relative risk of 50 or greater of developing AL, but the use of nitrogen mustard without procarbazine resulted in no AL (short observation period in the latter group). On the other hand, none of the 95 patients who received PAVe (procarbazine/melphalan/vinblastine) as adjuvant therapy following irradiation for Hodgkin's disease developed AL during a median follow-up of 6 years; the difference in AL incidence between this group and a similarly treated group receiving MOPP as adjuvant therapy was of borderline significance.[169] In addition, a small number of patients receiving procarbazine and vinblastine as adjuvant therapy for 2 years in a trial of the European Organization for Research and Treatment of Cancer (EORTC) did not develop AL if combination chemotherapy was not subsequently used during a relapse.[170] In summary, historical evidence suggests that procarbazine is more leukemogenic than nitrogen mustard; evidence from trials in which small subgroups have been exposed to one drug or the other is conflicting. Whether the leukemogenic potential of both drugs are additive or synergistic cannot be known on the basis of available information.

In addition, there is conflicting evidence regarding the relative leukemogenic potential of the nitrosoureas and nitrogen mustard. Among patients with Hodgkin's disease, Pedersen-Bjergaard and Larsen[102] found the risk of 2° MDS/AL to be similar for drug combinations including nitrogen mustard, BCNU, or CCNU. Alternatively, Cancer and Leukemia Group B (CALGB) reported among patients with Hodgkin's disease that nitrogen mustard-containing combinations caused significantly more AL than nitrosourea-containing regimens.[93]

Finally, two investigators have reported a very high risk of leukemogenesis following treatment with infrequently used agents. Among 71 patients with advanced breast cancer treated with a regimen containing prednimustine as the only alkylating agent, Andersson et al[121] reported a cumulative risk for AL of 25.4 * 10.3%, 37 months after the start of chemotherapy. Prednimustine is the C-21 prednisolone ester of chlorambucil. In a study of 1,460 patients who were treated on 15 protocols for metastatic breast cancer with dibromodulcitol,[117] the risk per person in the high-dose subsets was

as high as 8%, despite a median survival in this population of only 16 months. Dibromodulcitol is a halogenated hexitol whose primary mechanism of action appears to be alkylation.

Are two or more alkylating agents in combination or in sequence synergistic or additive? The data available to answer this question are largely indirect and weak. Nonetheless, those data suggest that the cumulative dose of multiple alkylating agents may be important in determining the risk of leukemogenesis.

The combined use of two alkylating agents is common in lung cancer, and the actuarial risk of developing 2" MDS/AL is among the highest in all primary malignancies. Among patients ranging in age from 49 to 74 years, Pedersen-Bjergaard et al[124] noted a short latency to development of AL and an actuarial incidence of 14% at 4 years among patients with lung cancer given combination CT regimens including CCNU and cyclophosphamide. Similarly, Chak et al[123] using combination CT regimens including procarbazine, cyclophosphamide, and CCNU, in a group of lung cancer patients having a median age of 58 years, noted an actuarial incidence for 2" MDS/AL of 25% at 3 years. Bradley et al[171] among 8 patients with lung cancer and a median age of >60 years, noted the development of AL in 1 and MDS in another after treatment with a regimen containing both cyclophosphamide and CCNU. Although the combination of two alkylating agents in these regimens might explain the unusually high actuarial risk, an alternative explanation may be the older age of these patients (see below). Subgroup analysis in Hodglun's disease, in which the use of two alkylating agents is also the norm, demonstrates the highest risk, comparable to that in lung cancer, in older patients exposed to chemotherapy.

The use of a variable called the alkylator score by some investigators has also provided indirect evidence that the cumulative dosing of multiple alkylating agents is important in leukemogenesis. The alkylator score is a composite indicator of the individual's total exposure to alkylating agents. The drug dosage for each patient is classified as being in the lower (score = 1), middle (score = 2) or upper (score = 3) third of the cumulative dose for that particular agent. Scores of individual agents are then summed for each patient to produce the alkylator score, usually ranging between 1 and 12. In the study of Greene et al[166] 1,794 women with ovarian cancer were exposed to alkylating agents, usually in combination or in sequence. Thirty-three of the 35 cases of 2" MDS/AL occurred among patients receiving alkylating agents. There was a positive relationship between the cumulative dose of alkylating agents received and the risk of 2" MDS/AL. Among those with medium to high alkylator scores, the actuarial risk at 10 years was 11% to 13%; among those with low scores, actuarial risk was 1.7%. In the report of Tucker et al[151] 22 cases of 2" AL were identified among 9,170 2-or-more year survivors of childhood cancer. Again the risk of 2° AL rose with an increasing alkylator score. These types of analyses are somewhat weakened by the assumption, one that we have questioned above, that the relative efficacy of each alkylating agent in causing 2" MDS/AL is the same.

Does ***the duration of chemotherapy or the amount of chemotherapy delivered influence the development of 2° MDS/AL?*** Most investigators have not tried to separate the independent influence of cumulative dose and duration of therapy or have found the two so highly correlated, that their separation was not possible. Unless otherwise stated, we will consider these two variables to be similar for the purposes of this discussion.

A number of studies in several different primary diseases have noted a direct association between duration of treatment or amount of drug given and the incidence of 2" AL. In Hodgkin's disease, after estimating equivalent doses among different alkylating agents, Pedersen-Bjergaard et al[11] summed the doses of all alkylating agents received by each of 320 patients. Patients administered the equivalent of 6 or less courses of MOPP had at 10 years an actuarial risk of 2" MDS/AL of 6.4%. Actuarial risk was 11.3% and 37.5% among those receiving the equivalent of 7 to 12 cycles and more than 12 cycles of MOPP, respectively. Also in Hodgkin's disease, Glicksman et al[93] reported a greater incidence of AL among those given maintenance therapy than among those not so treated. Other investigators[32,94,104] have noted an

increased incidence of AL following the use of salvage CT.

In NHL, Greene et al[105] found in a case-control study of 2° AL that cases with AL received significantly more cyclophosphamide than did controls (71,700 v 23,300 mg), and that the mean duration of cyclophosphamide therapy was significantly longer in those developing AL (28.5 v 10.5 months). *Also* in NHL, Pederson-Bjergaard et al[106] observed a significantly higher risk of 2° AL among retreated patients than in patients requiring one regimen only.

In a case-control study of breast cancer, Curtis et al[118] identified 20 leukemic disorders among 14,860 survivors of at least 18 months between 1973 and 1985. In comparison to patients with no exposure to alkylating agent therapy, the relative risk of 2° MDS/AL associated with less than 18 months of therapy was 8.8, and with greater than 18 months of therapy, 14.7 ($P = 0.001$). Among 1,460 patients with metastatic breast cancer treated on 15 protocols with dibromodulcitol, 23 cases of 2° MDS/AL occurred.[120] Both the risk/person and the risk per patient-year increased significantly with an increasing cumulative dose of dibromoducitol. For example, the risk/person was 0.3% at cumulative doses of 4 grams, but was 6% among those receiving 16 g or more.

Among a population in which most of the chemotherapy consisted of cyclophosphamide alone, Haas et al[112] conducted a case-control study to determine whether the development of leukemia was associated with the treatment of ovarian and breast cancer. There was a general trend to higher relative risks with increasing doses of cyclophosphamide. In a study of ovarian cancer alone, Pedersen-Bjergaard et al[106] found that the risk of developing 2° AL was significantly increased among the 114 patients who had received a cumulative dose of dihydroxybusulfan exceeding 200 mg (n = 9) as compared to 439 who had received less than this amount (n = 4). In addition, Greene et al[155] observed among a large cohort of ovarian cancer patients that 11 of 12 cases of 2° AL developed in those with a "high" exposure to chemotherapy (>700 mg of melphalan or >2,000 mg of chlorambucil).

In polycythemia vera Berk et al[132] demonstrated within a group treated with chlorambucil that the relative risk of AL was four times greater with average daily doses of more than 4 mg than with lesser doses, or five times greater when the drug was given more than 50% of the time when the patient was on study as compared to less than 50% of the time. In multiple myeloma, of the 11 cases of 2° AL reported by Gonzales et al[173] among 476 patients treated with melphalan with or without other alkylating agents, 10 occurred in a subgroup receiving melphalan for 2 or more years. Similarly, Wahlin et al[111] reported 4 AL among 71 patients treated with multiple myeloma, and all occurred in patients receiving melphalan for more than 2 years.

Finally, we refer the reader to the discussion above regarding the alkylator score, an indirect measure of cumulative dose. In both the studies of Tucker et al[151] and Greene et al[155] an increasing alkylator score was associated with an increasing risk of 2° MDS/AL. In the former study, involving 9,170 2-or-more survivors of childhood cancer, total dose seemed to be a more important parameter of risk than duration of treatment.

There are a lesser number of studies, some involving large numbers of patients, that show no correlation between CT dose or duration and the development of 2° AL.[101,115,123] Conflicting results are not unexpected, given the caveats presented at the beginning of this section. Furthermore, the influence of a lengthened survival confounds this discussion, as prolonged survival due to repetitive courses of successful CT would be expected to allow the emergence of 2° MDS/AL. Nonetheless, the current weight of evidence from a number of primary malignancies treated with several different alkylating agents suggests that the dose or duration of CT is of importance for the development of 2° MDS/AL.

Does the schedule of administration influence the incidence of 2° MDS/AL? There are few data that bear on this question. In a series of consecutive studies of multiple myeloma within the CALGB,[110] 247 patients received daily oral melphalan and 671 received "pulsed" IV melphalan at 4 to 8 week intervals. At 5 years, the actuarial estimate for the occurrence of 2° AL was 13.4% for the oral regimen versus 7.4% for the pulsed IV therapy; confidence intervals

overlapped. There was no attempt to compare cumulative dose.

In two consecutive trials of multiple myeloma performed by the Medical Research Council, 12 of 648 patients developed 2" MDS/AL.[109] In the initial trial, melphalan was given daily; in the second, melphalan was given daily for 7 days every 4 to 6 weeks. A significant relationship was found between the length of melphalan treatment and the occurrence of 2" MDS/AL. However, when melphalan treatment was broken down into two variables—months of daily treatment and months of intermittent treatment, each method of administration was similar in its ability to induce 2" MDS/AL.

In sum, the potential influence of scheduling exists for only one drug used in one disease, and even in this instance, the paucity of data does not allow definitive conclusions.

Are alkylating agents and radiation therapy additive or synergistic in their abilities to induce 2" MDS/AL? This question begs another, ie, is radiation alone a leukemogen? Among the studies providing positive evidence, Kato and Schull[174] reported a cohort of 79,856 atomic bomb survivors who received an average dose of 22 rads and were at risk an average of 24 years. The relative risk of developing AL in those receiving 200 or more rads was 15. Darby et al[175] found a three-fold increase in mortality from leukemia following a single course of x-ray treatment during 1935 to 1954 among greater than 14,000 patients with ankylosing spondylitis. Although the mean dose of radiation was 13.20 Gy, the greatest risk of leukemia was in a group of patients with a mean marrow dose of 1 to 2 Gy.[176] The absence of a linear dose-response relationship between RT and the development of leukemia was suggested. Boice et al[177] conducted a case-control study on a cohort of over 150,000 women with invasive cancer of the uterine cervix. The relative risk of AL and CML associated with radiotherapy was 2.0. Risk increased with increasing radiation dose until average doses of about 4 Gy were reached and then decreased at higher doses.

The latter two studies present an apparent paradox: the higher the dose of radiotherapy delivered, the less the chance for subsequent development of leukemia. Animal studies have suggested a possible explanation for these unexpected results. In animals, an initial rise in tumor induction occurs at low dose levels, reaches a peak at intermediate dose levels, and declines at high dose levels. It is likely that high dose levels induce cell death, whereas lower dose levels induce genetic alterations that predispose to or cause leukemia.

In general, although the studies cited above and others[178,179] implicate radiation alone as a causative agent in leukemogenesis, relative risks (uncommonly greater than 5) have tended to be manifold less than those obtained in studies involving alkylating agents. This fact, in addition to the paradoxical finding in the setting of most primary malignancies that high doses of radiation to small volumes of bone marrow tend not to be leukemogenic, may explain the considerable evidence suggesting that patients treated with a combination of RT and CT have little or no additional risk of developing AL as compared to patients treated with CT alone. This conclusion has been reached over a broad range of primary malignancies, including Hodgkin's disease,[32,91-93,95,99,101,103] NHL,[106] breast cancer,[112,118] ovarian cancer,[56] testicular cancer,[125] and gastrointestinal malignancies.[131]

Is ***the extent of radiotherapy important in the development of 2" MDS/AL?*** Not all studies have failed to find a deleterious interaction between alkylating agent therapy and radiotherapy. In a case-control study of 517 patients with NHL, Greene et al[105] found that patients treated with both radiation and chemotherapy were at significantly greater risk for 2" AL than those treated with single modality therapy. The average radiation dose to the active bone marrow was significantly greater for cases than for controls (11.8 v 4.9 Gy). Unlike most other studies, extensive use was made of total body and hemibody irradiation in their study. Akin to the situation in atomic bomb survivors or patients in the British spondylitic series in which large volumes of bone marrow were exposed to relatively low cumulative doses of RT, the investigators hypothesized that the extensive use of total body or hemibody irradiation was responsible for the elevated risk.

In a study of 441 patients with clinical stage I, II, III Hodgkin's disease who were prospectively treated with three or six cycles of MOPP and supra- and/or infradiaphragmatic irradiation

(40 Gy), Andrieu et al[97] found that the extent of irradiation was the only significant explanatory variable of 2" AL risk. Risk of 2" AL ranged from 2.7% for supradiaphragmatic irradiation to 9.1% for subtotal or total nodal irradiation. In general, this result is in discordance with several other studies showing little or no additive effect of irradiation in Hodgkin's disease, although extent of irradiation has been uncommonly broken into subgroups. As activity in the residual nonirradiated bone marrow is increased proportionately to the volume of irradiated marrow, the authors hypothesized that exposure of precursor cells in these hyperactive areas to alkylating agents may increase the risk of leukemogenesis. Other investigators have also reported an association between extent of irradiation and risk of leukemia.[115,180]

In summary, low-dose irradiation to a large volume of bone marrow is likely to increase the risk of leukemia. There is conflicting information regarding the risk associated with high-dose irradiation to a large volume of marrow, but the weight of evidence presently suggests that the risk is low or absent.

which subgroups appear to be at greatest risk of developing 2" MDSIAL, ? We have previously discussed the risks of leukemia associated with subsets receiving large cumulative doses of alkylating agents or low doses of radiotherapy to an extensive volume of bone marrow. Those data will not be reiterated here.

There is some evidence to suggest that the older patient is at increased risk, at least in the setting of Hodgkin's disease. A number of studies in this type of lymphoma[32,91-94,104,172] have shown that patients older than 40 years (older than 30 years in one study) are at higher risk for development of 2" MDSIAL. For example, Aisenberg[104] reported an actuarial risk of 33% at 12 years in patients older than 40 years following treatment with cytotoxic therapy and Pedersen-Bjergaard et al[172] reported an actuarial risk of 31% at 10 years in this age group. In malignancies other than Hodgkin's disease, there is no evidence that advancing age is predictive of increased risk.[112,115,118,131] However, most of these studies have included a cohort of patients whose median age was considerably higher than that commonly found in studies of Hodgkin's disease. If there is an age threshold above which risk increases, the advanced age of patients in the latter studies may not have allowed a distinction in risks to be discerned.

The risk of 2" MDS/AL among children may even be less than that of adults who are younger than 40 years old. Moreover, younger children may be at less risk than older children (see ***Childhood Cancer).***

Uncommonly, other subgroups have been reported to be at increased risk for 2" MDS/AL, such as splenectomized patients with Hodgkin's disease– and those with certain primary malignancies. For example, following treatment with radioactive phosphorous, a cohort of patients with polycythemia vera has been found to be at significantly higher risk for development of acute leukemia than a cohort with CLL, despite comparable treatment and follow-up.[133]

Is there any indication that a plateau in incidence of 2" MDSIAL is reached several years after the administration of treatment? Not unexpectedly, the present answer to this question relies almost solely on data from those treated for Hodgkin's disease, or with adjuvant therapy for breast cancer; prolonged observation over years has been possible in these settings. When median follow-up has been less than 10 years, many investigators have reported that the cumulative risk of 2" MDS/AL continues to rise over a decade of observation.[32,91,104,118,131] More recently, results from a few studies with a longer median duration of follow-up have suggested that although cumulative risk continues to rise during the first decade of observation, it also peaks during this period; no cases are observed 10 years after treatment. Andrieu et al[97] followed 441 patients with Hodgkin's disease for a median of more than 10 years. All 10 cases of 2" AL developed during the 34th and 123rd month of follow-up; there were no cases of leukemia after 123 months. Blayney et al[100] followed 192 patients with Hodgkin's disease for a median of 15 years. The risk of 2" MDS/AL peaked 6 years following treatment; no cases were observed after 11 years. Among the 320 patients with Hodgkin's disease followed for up to 15 years, Pedersen-Bjergaard et al[172] noted a steady increase in risk of 2" MDS/AL from 1 to 10 years following the initiation of treatment; there were no further cases after 10 years. In a study of the adjuvant therapy of breast cancer by the NS-

ABP,[115] the incidence of 2" MDS/AL was constant during the 5 years after the completion of therapy; no new cases were reported after this time.

On the other hand, van Leeuwen et al[92] in a report of 744 patients with Hodgkin's disease, noted a decreasing incidence of 2" MDS/AL after 10 years (the risk of 2" MDS/AL was highest 5 to 10 years following treatment), but no plateau in the cumulative risk following this time. In the studies demonstrating no risk of 2" MDS/AL 10 years following treatment, limited numbers of patients have been available for follow-up during the second decade of observation; this fact may explain the discrepancy in results between the study of van Leeuwen and the others cited above.

In summary, although the peak incidence of 2" MDS/AL in the first decade of observation seems well established, its frequency after this time period remains less clear.

ENVIRONMENTAL/OCCUPATIONAL EXPOSURE

There are few specific chemicals that have been implicated in leukemogenesis. Thus far, the chemical most strongly linked to its development has been benzene. Benzene is the parent compound of the aromatic group. Its ability to serve as a solvent for a broad range of solutes, as a starting material for synthetics in the chemical industry, and as a cleaner, has resulted in its widespread use. It is known that hematological abnormalities occur at the previously legislated exposure limit of 10 parts per million (ppm)[181] (current exposure limit is 1 ppm). There is also known to be an increase in the frequency of chromosome aberrations in blood lymphocytes among workers chronically exposed to benzene concentrations of 5 to 25 ppm.[182,183] Studies by Rinsky et al[184] and Aksoy[185,186] suggest that cumulative benzene exposure is associated with the development of leukemia as well. Rinsky et al[184] performed a retrospective cohort mortality study of 748 workers who had been exposed to benzene in the manufacture of rubber hydrochloride; relative risk for AL was five to 20 times greater in subsets of exposed workers than in the general population. Aksoy[185,186] found a similar relative risk among 2,800 shoe workers in Istanbul who used benzene. Aksoy collected 53 cases of 2° MDS/AL presumably caused by chronic exposure to benzene and noted a preceding pancytopenic period in 13 of 53 patients (24.5%). The interval from pancytopenia to the diagnosis of AL ranged from 6 months to 6 years. The exposure period to benzene ranged from 4 months to 25 years (mean, 10.2 years).

Ethylene oxide, a direct acting epoxide and an alkylating agent, is also thought to be a leukemogen. In humans, exposure to ethylene oxide has been demonstrated to be associated with cytogenetic changes. Hogstedt[187] noted 8 cases of leukemia among 733 ethylene oxide-exposed workers compared to an expected 0.8 cases. Ethylene oxide is an important intermediate product in the chemical industry and is also used for sterilizing medical products, hospital equipment, and food.

Of great concern to the health professions is the finding of mutagenicity in the urine of oncology nurses and pharmacists handling antineoplastic drugs.[188] No direct link between this observation and leukemogenesis has been established, however. In an attempt to identify other specific chemicals and exposures that may place the population at risk, case-control studies of MDS patients have been conducted. Among a list of 70 specific chemical and substance exposures, Farrow et al[189] found that MDS patients reported a significantly greater exposure to petrol and diesel fumes or liquids. Petrol and diesel fumes, and exhausts from petrol and diesel engines, contain a large number of chemicals, one of which is benzene. Goldberg et al[190] elicited information about exposures to chemicals, solvents, asbestos, and insecticides through both occupation and hobby from 52 patients with 1" MDS. Although there was a 46% exposure rate among MDS patients, the control group had a similarly high exposure rate of 40%. These data reinforce the impression that ferreting out the specific exposures most responsible for leukemogenesis will not be an easy task.

Agricultural employment (eg, farmers) has been linked to leukemia—CLL rather than the acute leukemias—but the observation has not been consistent.[188,191] Agricultural workers are exposed to pesticides, herbicides, oils, paints, and solvents, as well as viruses, fungi, and other potentially pathogenic microorganisms. The responsible factor or factors, if any, are unknown.

The nonrandom occurrence of similar abnormalities of chromosomes 5 and 7 among patients with 2° MDS/AL resulting from prior CT or RT, and among patients with 1° MDS and de novo AML occupationally exposed to chemical solvents, insecticides, or petroleum products provides inferential evidence that there are many leukemogens that are as yet uncharacterized. Up to 70% of patients with both 1° MDS/AL and occupational exposures (exposure to chemical solvents, insecticides, or petroleum products) have had chromosome 5 and/or 7 chromosome abnormalities,[192,193] a percentage similar to that of patients with 2° MDS/AL.[14] Patients with 1° MDS, but without known exposures to occupational hazards, and those with de novo AML, have generally had a considerably lesser frequency of chromosome 5 and 7 abnormalities—approximately 20% to 30%.[14,192,193]

We have previously discussed the leukemogenic potential of radiation when used as a therapeutic modality. However, exposure to ambient radiation or radiation used for diagnostic purposes may also have similar potential. In general, Forman et al[194] found no increase in cancer mortality near nuclear installations in England and Wales during the period 1959 to 1980; however, leukemia among those less than age 24 represented a possible exception. Significant controversy has been generated by the study of Gardner et al[195] who reported that a raised incidence of leukemia among children near the Sellafield nuclear plant (United Kingdom) was associated with paternal employment and external dose of whole body radiation during work at the plant before conception. The highest relative risks—sixfold—were for fathers whose total radiation doses were 100 mSv or greater before the date of their child's conception or were 10 mSv or greater during the 6 months before conception. These results seem incongruous with those establishing no risk of leukemia among children of atomic bomb survivors.[196] Nonetheless, if it is of importance to leukemogenesis that the dose received be accumulated over time or within a short interval prior to conception, the results of Gardner and those regarding children of atomic bomb survivors may not necessarily be in conflict.[197] Radon exposure has also been suggested to be a causative factor in leukemia,[198] but this observation remains controversial.[199]

Regarding radiation used for diagnostic purposes, Evans et al[200] have estimated that approximately 1% of all cases of leukemia result from diagnostic radiology. However, the investigators voiced caution about their conclusions because of the subjectivity and uncertainty in any estimate of the risks induced by radiation at these relatively low doses. Nonetheless, a threshold dose below which there are no leukemogenic effects of radiation has not been proved in either humans or laboratory animals.[201] Sadamuri et al[202] reported 12 cases of leukemia among 20,000 to 33,000 persons injected with Thorotrast in Japan. Thorotrast, a 25% colloidal solution of thorium dioxide that emits about 90% of its energy as alpha radiation, was used as a radiographic contrast agent for bronchography, arteriography, and hepatolienography between 1930 and 1955. The median latent period was 35 years.

A link between leukemia incidence and exposure to strong electromagnetic fields has been hypothesized.[188,191] However the association has been inconsistent and the possible mechanisms obscure.

TREATMENT

Prognostic Factors

Variables predictive of response to treatment or survival are important to the clinician for many reasons. Their combination aids in determining both the prognosis of an individual patient and the therapeutic aggressiveness with which the disease should be approached. Furthermore, knowledge of these prognostic factors allows the clinician to better assess the comparability of treatment studies.

There have been several large studies of prognostic factors in 1° MDS.[203-207] Although a large number of these factors have been identified, a few have been found repeatedly to significantly and adversely influence survival—an increasing percentage of blasts in the bone marrow, advanced age, a low platelet count, and severe anemia. Cytogenetics of 1° MDS have not been incorporated into the analysis of these larger studies.

Kantarjian et al[15] and Pedersen-Bjergaard et al[60] have conducted two of the larger studies of

prognostic factors in patients with 2" MDSIAL. Their findings have not been dissimilar to those in 1" MDS. In the former study of 112 patients, the median age was 65 years. *Sixty* of the 112 patients received intensive therapy, and another 12 were treated with low-dose cytarabine. A factor adversely affecting achievement of complete remission (CR) was the presence of MDS versus AL. Factors adversely affecting survival were advancing age and increasing number of blasts in the bone marrow. The study of Pedersen-Bjergaard et al[60] included 91 patients with 2" MDS/AL. Generally, MDS was treated with supportive care or nonaggressive approaches, and AL was treated with intensive therapy. The multivariate analysis disclosed that survival was adversely affected, if the primary malignancy was still active (ie, not in CR), the primary malignancy was not lymphoma, or the platelet count was low at the time of diagnosis of 2" MDS/AL. The most important factor predicting response to intensive chemotherapy was the absence of a preceding myelodysplastic phase. For the subgroup of 62 patients with MDS, an increasing percentage of blasts in the bone marrow and a low hemoglobin adversely affected survival.

Both of these studies have also found karyotypic features to be independent prognostic factors. Kantarjian et al[15] reported low rates of CR in those patients with abnormalities of chromosomes 5 and/or 7 (13%), but significantly higher response rates in those with normal karyotypes (54%) and those with chromosomal abnormalities most common to de novo AML, such as t(8;21), t(15;17), and inv(16) (5 of 5 CR). Indeed, in their multivariate analysis, they found karyotype to be one of the most important prognostic factors associated with achievement of CR. They also found cytogenetic pattern (t(8;21), t(15;17); inv(16); or normal versus other abnormalities) to be an important prognostic factor for survival. In 36 patients with overt AL treated with intensive chemotherapy, Pedersen-Bjergaard et al" found a low CR rate among those with chromosome 5 or 7 abnormalities (27%) as compared to those with other abnormalities (45%) or a normal karyotype (80%). Their multivariate analysis found the number of chromosome aberrations to be an independent prognostic factor for survival among the 62 patients presenting with 2" MDS as opposed to 2" AL.

Other investigators have also noted that cytogenetic abnormalities in 2" MDS/AL are predictive of clinical outcome. After collecting 216 cases of 2" MDS/AL from the literature, Bloomfield[62] analysed the association between achievement of CR and cytogenetics in 73 patients who had been intensively treated. Response rate (CR) was lowest in patients with abnormalities of chromosome 5(5q- or -5), regardless of whether abnormalities in chromosome 7 were also present; only 13% responded (2 of 16). More favorable CR rates were seen in patients with monosomy 7 or a deletion of its long arm (32%), a normal karyotype (43%), a karyotype containing additional chromosomes as the only abnormality (50%), or a karyotype containing other structural abnormalities, including the recurring specific rearrangements associated with de novo AML (65%). Fenaux et al[76] have also reported high response rates in patients with the specific chromosome abnormalities common in de novo AML. Pui et al[78,89] have noted a high response rate in patients with the common recurring abnormalities associated with de novo acute leukemia, but few long-term remissions.

Most reports are thus consistent in showing low response rates for patients with abnormalities in chromosome 5 and 7 and higher CR rates in those with normal karyotypes and the specific recurring translocations often seen in de novo AML. Insufficient data are available comparing response rates and durations for specific cytogenetic subtypes of secondary and primary MDS/AL when treated with similar intensive regimens. Large prospective trials of intensively and optimally treated patients, well studied both for prior treatment and for clinical and pathologic characteristics of their 2° MDS/AL, are required in order to conclusively evaluate the utility of specific chromosome abnormalities in selecting therapy.

Nonaggressive Approaches

A variety of nonaggressive approaches have been applied to the myelodysplastic syndromes. The vast majority of patients in such trials have had 1" MDS. Even when patients with 2" MDS/AL have been included, their responses

have uncommonly been segregated from the remainder of the cohort. Nonetheless, few of the therapies have been beneficial, and it is unlikely that patients with 2" MDS respond in a manner that distinguishes them from those with the 1" disorders. As there have been several recent reviews of therapy in 1" MDS,[6,31,208] only a brief overview of many of the nonaggressive approaches will be provided.

Although occasional responses have been noted, therapy with vitamins (folic acid, vitamin B12, pyridoxine), immunosuppressive drugs (glucocorticoids, cyclosporine, antithymocyte globulin), and androgens (including the attenuated synthetic androgen danazol) have been generally ineffective. Furthermore, the risk-benefit ratio of many of these therapies has been distressingly high. Vitamin D3, despite its ability to cause differentiation of leukemic cells in vitro, has shown little efficacy in vivo and has proven unacceptably toxic.

Retinoic acid has also been shown to have differentiating effects on leukemic cells in vitro and to inhibit their clonal growth. Good responses with 13-cis-retinoic acid-defined as a clear improvement in at least two blood cell parameters with or without a decrease in some marrow blasts—have occurred in less than 5% of patients. In a randomized study of 13-cis-retinoic acid versus placebo in 68 patients with MDS, Koeffler et al[209] noted no significant difference in responses or progression-free survival between the two treatment groups. Nine of these 68 patients had 2" MDS/AL. Among the observed side effects were skin and hepatic toxicity.

The beneficial effects of low-dose cytarabine (LoDAC) have been attributed to its differentiating effects by some, and to its cytotoxic effects by others; however, the latter explanation is thought to be more plausible. Summarizing the published data, Cheson et al[210] noted a similar CR rate of less than 20% among 170 patients with 1" MDS and 69 patients with 2" MDS. Median duration of CR—10.5 months—was identical for both groups. Achievement of CR did not prolong survival. Despite the "nonaggressive" nature of this approach, 90% of patients suffered myelotoxicity and 15% died from treatment-related complications. A randomized prospective evaluation of LoDAC versus supportive care was conducted by the Eastern Cooperative Oncology Group and the Southwest Oncology Group."' One hundred and fifteen patients were evaluable. Crossover from the supportive care arm to the LoDAC area was permitted after 2 months of documented progressive disease. The overall response rate to a single cycle of LoDAC was 8%. Although patients in the LoDAC arm demonstrated a significantly longer time to progression, there was no significant difference in overall survival—8.7 months for LoDAC versus 6.9 months for supportive therapy. Patients on the LoDAC arm had a higher rate of infection.

The antimetabolite 5-azacytidine represents a more recent approach to treatment. It causes DNA hypomethylation, an activity that correlates with the induction of differentiation in leukemic cells. Silverman et al[212,213] have conducted phase II trials of this agent given by the intravenous or subcutaneous route. In their two studies, CRs have been seen in approximately 10% of patients; lesser degrees of improvement have been found in 35% to 55% of patients. Median survival was 49 weeks among the 44 evaluable patients receiving intravenous 5-azacytidine. Ten percent to 20% of patients had 2" MDS, but their responses were not separately reported. The major toxicity was nausea and vomiting. The role of 5-azacytidine in the treatment of MDS remains to be defined.

One of the more exciting developments in recent years has been the application of hematopoietic growth factors (HGFS)—glycoproteins that regulate proliferation and differentiation of malignant cells—to the treatment of MDS. Once again, experience has been largely confined to those with 1" MDS. In fact, the number of 2" MDS cases treated has been so limited that extrapolation of results of present studies to this patient group must be done with caution. Most studies thus far have used either granulocyte-macrophage colony stimulating factor (GM-CSF) or granulocyte-colony stimulating factor (G-CSF). Results have been similar whether the preparation was G-CSF or GM-CSF or whether the vector for GM-CSF was yeast or Escherichia coli. Summarizing data from 95 cases of MDS treated with one of these two HGFs, Cheson[6] noted an improvement in neutrophil count in 81 of 95 cases (85%) and in

platelet count in 10 of 95 (11%). Monocytes, eosinophils, and lymphocytes increased at a percentage between these two extremes. Although the reticulocyte count increased in 30%, this increase led uncommonly to a decrease in transfusion requirements. Deterioration rather than amelioration of disordered hematopoiesis is, of course, a concern with the HGFS, and leukemic progression has been described in up to 20% of treated patients. Although leukemic progression has generally been confined to those with a high percentage of marrow blasts pretreatment, many patients with high marrow blast counts have been treated without incident. Most frequent side effects have included fever (GM-CSF), bone pain, and a flu-like illness.

Vadhan-Raj et al[214] reported a CR following the use of GM-CSF in a 63-year-old woman with refractory anemia with excess of blasts (RAEB) occurring after 22 courses of melphalan for a preceding diagnosis of ovarian cancer. She received three 2-week cycles of 60 to 120 $\mu g/m^2$ of GM-CSF by continuous intravenous infusion. Significant increases were noted in WBC and granulocyte counts, platelets, and hemoglobin levels. Despite discontinuation of the GM-CSF therapy after three cycles, the hematologic remission lasted for 11.5 months. Several lines of evidence (cytogenetic studies, assays for hematopoietic precursor cells, premature chromosome condensation analysis, and DNA studies for restriction fragment-length polymorphism-methylation analysis) suggested suppression of the abnormal clone and a selective growth advantage of normal elements. Of interest, reinstitution of GM-CSF therapy at the time of relapse did not reverse disease progression.

This excellent response unfortunately seems to be atypical of those of most 1" MDS patients and the few 2" MDS patients that have been reported. In an earlier report by Vadhan-Raj et al[215] of eight patients with MDS, three had 2" MDS and were treated with GM-CSF at the same schedule. Although one of these patients demonstrated a multilineage response, the other two showed hematologic responses among white cells only. After the infusion was discontinued, the WBC returned to base-line levels. Based on cytogenetic studies, clonal hematopoiesis was maintained.

Clinical trials of interleukin-3—a glycoprotein that promotes the survival, proliferation, and development of both multipotential hematopoietic stem cells and of committed progenitor cells—are also in progress. Among nine patients reported by Ganser et al[216] all had increases in neutrophils. Platelet responses were seen in two of four profoundly thrombocytopenic patients, and one patient experienced a temporary decrease in red blood cell transfusion requirements. The only patient with 2" MDS had a significant increase of blast cells in the marrow from 2% to 20% in contradistinction to the other eight patients in this study. As the heterogeneity of response established by this latter result and those of Vadhan-Raj[214,215] point out, considerably more experience will be necessary to better define the role of HGFs in 2" MDS/AL.

Combination Chemotherapy

When aggressive approaches have been applied to patients with 2" MDS/AL, combination chemotherapy regimens commonly used in de novo AL have been the norm. More recently, the use of high doses of cytarabine has gained popularity in the treatment of 1" and 2" MDS and of acute leukemias with a preceding myelodysplastic phase. Table 8 provides an overview of treatment outcomes among patients with 2" MDS/AL treated with either anthracycine-cytarabine containing regimens or high doses of cytarabine. Response rates have been variable, ranging from 15% to 52%, and are a likely reflection of the small number of patients treated and the heterogeneity of the cohorts. Median survival was usually less than 6 months; even among those who achieved CR, median survival was less than 1 year. One or more of the studies found that one or more of the following variables was predictive of a better outcome: good performance status, preceding use of RT only as therapy for the primary malignancy, and the absence of abnormalities of chromosomes 5 and 7. The latter two are likely to be related, as patients who have received radiotherapy alone have a lesser incidence of chromosome 5 or 7 abnormalities.[15,60,62]

In summary, combination chemotherapy can be justified for good performance status patients who have "favorable" karyotypes. Even in

Table 8. Combination Chemotherapy in the Treatment of Secondary MDS/AL

No. of Patients	Description of Cohort	Treatment (induction)	CR(%)	DFI or Survival (med:mo)	Comments	Reference
60	Secondary MDS/AL; median age = 65; 72%: CT ± RT; 44%: 5 or 7 abnormalities	OAP + anthracycline	19/60 (32%)	S: − 12 (CR) S: − 2 (no CR)	Only 13% of patients with chromosomes 5 or 7 abnormalities achieved CR	15
42	Secondary AL; median age = 55; 74%: CT ± RT	Anthracycline + cytarabine	17/42 (40%)	DFI: 10	Those previously treated with RT alone did better	227
20	Secondary AL; median age = 55; 100%: CT ± RT; 35%: 5 or 7 abnormality	Daunorubicin, cytarabine, and 6-thioguanine	5/20 (25%)	DFI: 1,4+,6,7+,16; S: − 2		13
17	Secondary AL; median age = 52; 82%: CT ± RT	Cytarabine (15/17), anthracycline (15/17) + others	7/17 (41%)	DFI: 3 mo; S: 4; (CR: 10; mo CR: 2)	Those previously treated with RT alone did better	228
34	Secondary AL; median age = ?; 97%: CT ± RT; 72%: 5 or 7 abnormalities; all had primary HD	Daunorubicin, cytarabine ± VP-16, or high-dose cytarabine only	5/34 (15%)	DFI: 2,3,3,5,10		16
23	Secondary AL; median age =?; 87%: CT or RT; 13%: occupational exposure	2-3 gm/m² of cytarabine x 12 doses	12/23 (52%)	NS	CR rate better than another cohort with transformation of 1° MDS to AL	229
17	Secondary MDSIAL; median age = 53; 94%: CT ± RT; 94%: 5 or 7 abnormalities; 47%: primary malignancy still active	1-3 gm/m² of cytarabine x 12 doses	8/17 (47%)	DFI: 5 mo; S: 6.5 (CR); S: 1.0 (no CR)	0-1 PS: 7/7 CR, ≥ 2 PS: 1/10 CR; longest remission (>30 m) in patient with t(15;17)	57

Abbreviations: NS, not stated; RT, radiotherapy; CT, chemotherapy; CR, complete remission; DFI, disease-free interval; S, survival; 5 or 7 abnormalities, chromosome 5 or 7 abnormalities; OAP, vincristine, cytarabine, prednisone; PS, performance status.

this group, however, results remain inadequate; entry of these patients into innovative clinical trials is strongly encouraged.

Bone Marrow Transplantation

Allogeneic bone marrow transplantation is presently the only therapeutic approach for 2" MDS/AL that produces a prolonged disease-free survival. There are transplanted patients with these disorders who remain without evidence of disease over 8 years from the receipt of their allografts. These patients are presumed to be cured, although late recurrences following transplantation have been described in 1" MDS.[217]

As has been the custom for other treatment approaches, 1" and 2° MDS have often been treated uniformly. Nonetheless, there have been more consistent attempts to segregate the data regarding 2" MDS/AL, as the latter patients might be expected to have more toxicity resulting from the transplant procedure. For example, as a result of preceding chemo/radiotherapy for the primary malignancy, patients with 2" MDS/AL may be at higher risk both for nonhematologic organ toxicity, such as interstitial pneumonitis, and graft-versus-host disease.

Bandini et al[218] collected from the literature 16 patients with 2° AL who had been transplanted with HLA-identical sibling donors. Of the 9 who were transplanted without prior attempts to induce their leukemias into remission, 4 died of toxicity, 2 relapsed after achieving CR, and 4 were alive without evidence of

disease between 18.5 and 56 months following transplant. Of 5 patients who had attained a CR following induction therapy for 2" AL, 3 died of toxicity, and 2 remained alive at 13 and 57 months. Both patients who did not respond to induction therapy achieved CR following transplant and were alive at 18 and 25 months.

The experience of De Witte et al[219,220] has not been dissimilar to that outlined by Bandini et al[218] with the exception that patients not responding to previous induction attempts all died (3 of 3). Conditioning regimens consisted of chemotherapy alone or chemotherapy and total body irradiation. Of the 10 patients without induction attempts prior to transplant, 3 died of toxicity, 3 relapsed, and 4 were alive without evidence of disease at 1.5 to 72 months. Of the 7 patients who had achieved a CR/PR prior to transplant, 3 died of toxicity and 4 were without disease at 6 to 44 months. These data and those reviewed by Bandini[218] preliminarily suggest that there is no advantage in trying to induce a remission of 2" MDS/AL before allogeneic bone marrow transplantation (ABMT)—ABMT represents acceptable front-line therapy for these patients.

Applebaum et al[221] treated 59 myelodysplastic patients with high-dose cyclophosphamide and total body irradiation followed by ABMT from either an HLA-identical or HLA-partially matched donor; 6 of them had previously untreated 2" MDS/AL. Two of these 6 died of toxicity, 1 relapsed, and 3 had no evidence of disease at unspecified times. Among all patients, the product-limit estimate for disease-free survival 3 years following transplant was 45%. The small group of patients with 2" MDS, then, responded to treatment comparably to those with 1"MDS. The disease-free survival of Applebaum et al[221] is comparable to those of other investigators who have performed ABMT in 1" MDS.[217]

Although Longmore et al[222] also noted an excellent actuarial disease-free survival of 56% among their 12 patients with 1" MDS followed for a median of 2 years, the other 11 patients with 2" MDS/AL did not fare as well—the actuarial disease-free survival was 27% at a median follow-up of 5 years. However, confidence intervals overlapped. Conditioning regimens consisted of TBI and cyclophosphamide with or without cytarabine. Six of the 11 patients had not been previously treated for 2" MDS/AL. Five died of toxicity, 1 died of Hodgkin's disease, 2 relapsed, and 3 were alive without disease between 2.5 and 8.5 years. There were more toxic deaths among patients with 2" MDS/AL (36%) than among those with 1° MDS (8%).

A number of variables have been proposed to explain the tendency of patients with 2" MDS/AL to do less favorably than 1" MDS in some studies.[222,223] These include advanced age, a greater percentage of abnormal karyotypes, the presence of a greater number of blasts in the marrow, marrow fibrosis, and a higher incidence of toxic deaths. However, due to the small number of treated patients, each of these potentially adverse prognostic factors requires additional corroboration.

Gribben et al[224] have performed double autologous bone marrow transplantation in patients with AL who had a preceding history of MDS and successfully achieved a CR following induction therapy. All five patients relapsed within 1 year of the procedure. The applicability of this treatment approach to patients with 2" MDS/AL who do not have a donor for an allogeneic transplant, therefore, remains uncertain.

PREVENTION

Development of 2" MDS/AL is undeniably a major complication of cancer treatment. However, the arbitrary alteration of a regimen successful against a primary malignancy, in order to mitigate this complication, is unwarranted. Data from Pedersen-Bjergaard and Larsen[102] place the mortality caused by 2" MDS/AL in its proper perspective. In a series of 391 patients with Hodglun's disease, there were 12 deaths due to 2" MDS/AL; however, 104 deaths were due to progressive Hodgkin's disease or complications due to treatment other than AL.

Of more concern at present is the use of potentially leukemogenic regimens in the adjuvant setting. The possibility that any additive curative benefit could be eliminated or overwhelmed by development of 2" MDS/AL must be closely monitored.

Evidence is suggestive that either longer duration of therapy or greater cumulative doses of a

leukemogen is important to secondary leukemogenesis; the trend toward shorter induction and maintenance intervals should mitigate its incidence. As age may also be an important factor in the development of 2" MDS/AL following CT, the leukemogenic potential of equally effective regimens should be carefully considered when the clinician is choosing therapy for an older patient. Finally, clinicians must continue to focus attention on both cytogenetic analyses and occupational histories among patients with 1" MDS, as their combination is likely to provide epidemiologicclues about chemical carcinogenesis in the environment and the workplace.

SUMMARY

The median latency of 2" MDS/AL is 4 to 5 years. A high percentage of patients with 2" MDS/AL convert to 2" AL. Survival of either is less than 1year.

A constellation of morphologic abnormalities from all 3 cell lines produces a unique appearance. Both 2" MDS and 2" AL are difficult to classify by the FAB system. With the exception of the identification of karyotypic abnormalities, the biology of 2" MDS/AL remains largely unexplored. Alterations of chromosomes 5 and 7 predominate, but other associated cytogenetic abnormalities are being increasingly recognized.

A synthesis of data regarding 2" MDS/AL resulting from the treatment of several primary malignancies generates the tentative conclusions that (a) many of the alkylating agents, and the nonclassic alkylating agent procarbazine, are leukemogens; (b) melphalan is a more potent leukemogen than cyclophosphamide. None of the other alkylating agents has been clearly established to be more or less potent than another; (c) increasing duration or amount of alkylator-based chemotherapy increases the risk of leukemogenesis; (d) low doses of radiation delivered to large volumes of bone marrow are weakly leukemogenic. High doses of radiation delivered to small volumes are not. Due to the latter, there is minimal additive risk for 2" MDS/AL among studies using alkylator-based chemotherapy and radiotherapy, either concurrently or sequentially; (e) the older patient (>40) is at increased risk for 2" MDS/AL, at least in Hodgkin's disease. Children may be at lesser risk than adults, and younger children at lesser risk than older children; (f) the risk of 2° MDS/AL peaks within the first decade after treatment for the primary malignancy. The incidence rates during the second decade are low.

Identified occupational/environmental risks for 2" MDS/AL include benzene, ambient and diagnostic radiation exposure, and perhaps ethylene oxide. The similarities in karyotype abnormalities among leukemic cells of those whose occupations expose them to chemical hazard, and those who are exposed to cytotoxic agents, suggest that many more environmental leukemogens have yet to be discovered.

Karyotype is an important prognostic factor for both achievement of CR and for survival. Nonaggressive treatment approaches have not proven useful, although the use of hematopoietic growth factors offers promise in this area. Combination chemotherapy is justified in patients with adequate performance statuses and "favorable" karyotypes. Allogeneic bone marrow transplantation is currently the only curative approach, and can be applied without attempts to first reduce the leukemic burden.

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