Therapy-Related Myelodysplastic Syndrome and Acute Myeloid Leukemia in Children: Correlation Between Chromosomal Abnormalities and Prior Therapy


We have studied 20 children with therapy-related myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) who were 3 months to 16 years old at diagnosis of their primary neoplasm and 1 to 24 years old at diagnosis of their secondary neoplasm. The median interval from initial treatment for the first malignancy to diagnosis of therapy-related MDS or AML was 46 months (range, 12 to 116 months). Twelve patients had chromosomal abnormalities resulting in loss of material from the long arm of chromosomes 5 and/or 7, three patients had abnormalities of chromosome 11 band q23, one patient had both classes of abnormalities, three patients had other abnormalities, and one patient had a normal karyotype. Ten of 12 patients with chromosome 5 and/or 7 abnormalities had been exposed to an alkylating agent, and two of three patients with 11q23 abnormalities had been exposed to an epipodophyllotoxin. The patient with both classes of abnormalities had been exposed to both types of therapy. We conclude that abnormalities of chromosomes 5 and/or 7 are common in children with therapy-related MDS or AML. The proposed relationships between exposure to alkylating agents and abnormalities of chromosomes 5 and/or 7 and between exposure to epipodophyllotoxins and abnormalities of 11q23 are supported in this pediatric series.

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MYELODYSPLASTIC syndromes (MDS) and acute myeloid leukemia (AML) can occur as late complications of chemotherapy and/or radiotherapy. Most of the literature on this subject pertains to adult patients. However, these disorders are a significant problem in children as well, affecting at least 1% of childhood cancer patients overall. For pediatric Hodgkin's disease (HD) patients, at least 4% develop therapy-related myeloid leukemia.

Based on combined data from the pediatric and medical literature, two subgroups of patients with therapy-related MDS or AML have been identified on the basis of characteristic chromosomal abnormalities. The first and best-described group includes patients with abnormalities of chromosomes 5 and/or 7. The aberrations include whole chromosome loss, as well as deletions and unbalanced translocations resulting in loss of material from the long arms of these chromosomes. In addition, rare patients have balanced translocations involving chromosome 5 at band q31 (M.M. Le Beau, unpublished observations), which is the critical region on this chromosome. These individuals typically had been exposed to alkylating agents with or without radiotherapy, have a myelodysplastic phase preceding acute leukemia, and have trilineage bone marrow (BM) dysplasia. It is usually difficult to classify these patients according to the French-American-British (FAB) system.

The second group includes patients with abnormalities of chromosome 11 at band q23. The rearrangements include translocations and deletions, but always involve a chromosomal breakpoint within band 11q23. These patients usually have been exposed to epipodophyllotoxins, namely, etoposide (VP-16) or teniposide (VM-26). It has been proposed that the association be expanded to include all topoisomerase II-reactive drugs including epipodophyllotoxins, anthracyclines, and actinomycin D, usually in combination with cisplatin or an alkylating agent. Most often these patients present acutely, without a myelodysplastic phase, with acute myelomonocytic leukemia (AMMOL) or acute monocytic leukemia (AMOL) consistent with FAB subtypes M4 and M5.

There are relatively few pediatric patients with therapy-related MDS or AML for whom cytogenetic information has been reported. Our objectives in this study were to determine the frequencies of specific cytogenetic abnormalities in pediatric patients with therapy-related MDS and AML, and to examine the relationship between exposure history and karyotype.

MATERIALS AND METHODS

Patients. Patients from the authors’ institutions who were 16 years old or less at diagnosis of a primary malignancy, who were diagnosed with a secondary MDS or AML in the 10-year period between April 1, 1981 and March 31, 1991, and who had adequate studies included. One patient for whom cytogenetic studies were attempted was not included because the quality of the
material was not sufficient for complete analysis. We are not aware of any other patients from these institutions who developed therapy-related MDS or AML, but who did not have material submitted for cytogenetic studies. Two patients were reported previously and are included in this report in greater detail; patient 5 was in a large series of patients with therapy-related MDS and AML composed primarily of adults, and patient 16 was in a series of patients with secondary malignancies after BM transplantation.

Morphologic analysis. Diagnosis of MDS or AML was based on morphologic and cytochemical studies of peripheral blood (PB) smears and BM aspirates and biopsy specimens obtained before therapy for the secondary hematologic disease. Whenever possible, the FAB Cooperative Group criteria were used to subclassify the disorder.

Cytogenetic analysis. Cytogenetic analysis was performed by G-banding using a trypsin-Giemsa or a Wright’s staining technique, or by Q-banding using a quinacrine fluorescence technique. Cells were obtained from aspirated BM and/or PB before initiation of therapy for the secondary hematologic disorder, or, in one case (patient 5), at relapse of the secondary disease. Metaphase cells were examined from direct preparations and/or short-term (24- and 48-hour) unstimulated cultures. Chromosomal abnormalities are described according to the International System for Human Cytogenetic Nomenclature.

RESULTS

Clinical findings. There were 20 patients including 13 males and seven females qualifying for inclusion in this series. Information regarding the primary malignancies and therapeutic exposure histories is summarized in Table 1. The clinical and hematologic features at diagnosis of the secondary malignancies and outcome are summarized in Table 2.

Patients 1 and 7 had underlying genetic conditions that may have predisposed them to the development of both primary and secondary malignancies. Patient 1 had intrauterine growth retardation and had multiple congenital anomalies including an imperforate anus. Extensive analyses of multiple tissues showed a chromosome instability disorder that could not be classified as one of the previously described chromosome breakage syndromes (B. Hirsch, 1970).

Table 1. Primary Malignancies and Therapeutic Exposure Histories for 20 Children With Therapy-Related MDS or AML

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Table 2. Clinical Features, Initial Hematologic Findings, and Outcome for 20 Children With Therapy-Related MDS or AML

| Patient | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 |
|---------|---|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|----|
| Sex     | M | M | M | M | M | M | F | M | M | M | M | M | M | M | M | M | M | M | M | M |
| Secondary disease | AML | AML | AML | AML | AML | AML | AML | AML | AML | AML | AML | AML | AML | AML | AML | AML | AML | AML | AML |
| Age at onset (yr) | 1.5 | 2 | 2 | 4 | 6 | 7 | 8 | 9 | 10 | 16 | 15 | 15 | 18 | 19 | 5 | 7 | 24 | 13 | 10 | 19 | 13 |

Abbreviation: ND, not done.

Patients 3, 7, and 13 were on therapy for their primary malignancies at the time of diagnosis of the secondary disease; thus, the hematologic values may have been influenced by the therapy. Patient 16 had a red blood cell transfusion before the laboratory values were obtained.

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unpublished observations). Spontaneous chromosome breaks and rearrangements were markedly increased in PB and BM, whereas the number of sister chromatid exchanges in PB was normal. The patient acquired a t(4;7)(q23;q34) in a subpopulation of BM and PB cells before developing her primary solid tumors and at a time when she was hematologically normal. Of interest is the fact that her therapy-related AML arose in this abnormal cell line. Patient 7 had neurofibromatosis type 1.

The median age at diagnosis of the primary malignancy in our series was 5 years with a range of 3 months to 16 years. Six patients had acute lymphoblastic leukemia (ALL), five patients had HD, two patients had non-Hodgkin’s lymphoma (NHL), and one patient each had Wilms’ tumor (WT), rhabdomyosarcoma (RMS), primitive neuroectodermal tumor (PNET), neuroblastoma (NB), and osteosarcoma (OS). In addition, one patient (patient 1) with a chromosome breakage disorder had two previous malignancies including WT and NB, and one patient (patient 7) with neurofibromatosis had three previous malignancies including WT, ALL and PNET.

Of the seven patients with ALL (including patient 7), five had adequate immunophenotyping: three were T-cell lineage (patients 3, 7, and 17), one was early B-cell lineage (patient 13), and one was non-T cell based on a negative sheep erythrocyte receptor study (patient 8). Four of the patients with ALL had cytogenetic studies at diagnosis; all of these had clonal abnormalities that were different from those observed at diagnosis of the secondary hematologic malignancy. Patient 3 had a del(6q) and a +7; patient 7 had a del(6q) alone; patient 13 had a hyperdiploid karyotype with 51 chromosomes; and patient 17 had a del(6q) and a t(14;?14). One of the two patients with NHL (patient 14) was studied and had a B-cell immunophenotype and a characteristic t(8;14)(q24;q32).

Seventeen of the 20 patients had received an alkylating agent as therapy for the primary neoplasm. Five patients had received epipodophyllotoxins. Another patient (patient 18) also had received epipodophyllotoxins 10 months before a firm diagnosis of therapy-related MDS was established; however, in reviewing the history, there was clinical evidence that the secondary process began before this therapy. Fifteen patients had received radiotherapy.

The epipodophyllotoxin drug schedules varied in the five patients who had received this therapy. All epipodophyllotoxin was administered intravenously, and in conjunction with other antineoplastic agents. Patient 2 received one 4-day course of etoposide at a dose of 3.3 mg/kg/d. Patient 6 received six 1-day courses of etoposide at a dose of 150 mg/m² and seven 5-day courses at 100 mg/m²/d; the courses were administered at 4-week intervals. Patient 13 received 15 doses of etoposide at 165 mg/m²/dose on days 28 and 42 of successive 56-day cycles. Patient 14 received three 5-day courses of etoposide at 100 mg/m²/d and three 2-day courses at 100 mg/m² every 12 hours; the courses were separated by 4-week or 8-week intervals. Patient 16 received 34 doses of teniposide at 150 mg/m²/dose at intervals ranging from 1 to 4 weeks, and received 360 mg/kg of

teniposide divided into two daily doses as part of a transplant conditioning regimen.

The patients were 1 to 24 years old (median, 10 years) at diagnosis of their secondary hematologic neoplasm. The median interval from initial treatment for the first malignancy to diagnosis of therapy-related MDS or AML was 46 months with a range of 12 to 116 months. Ten of 20 patients presented with an MDS; six eventually developed frank leukemia. The remaining 10 patients presented with an acute leukemia. All but one patient had presenting white blood cell (WBC) counts less than 20 x 10⁹/L.

The patients were treated for therapy-related MDS or AML in a variety of fashions. Intensive combination chemotherapy and/or BM transplantation was used either initially or at some point in the course of the disease for 15 patients, while the remaining five patients (patients 7, 9, 13, 16, and 18) received palliative therapy only. Only three patients (patients 4, 11, and 14) are alive at the time of this report. The remaining 17 patients died at a median of 7 months from diagnosis.

**Morphologic findings.** The marrow findings could be re-evaluated in seven of the 10 patients who presented with MDS. Six had BM dysplasia involving two or three lineages, and one had severe hypoplasia. Some of the cases were difficult to classify by the FAB criteria because of prominent multilineage dysplasia without increased numbers of type I and type II blasts. However, when based on the percentage of blasts in the BM in the six patients with dysplasia, the morphology could be classified as refractory anemia in two patients (patients 9 and 12), refractory anemia with excess blasts in three patients (patients 3, 7, and 18), and refractory anemia with excess blasts in transformation in one patient (patient 19). The patient with hypoplasia (patient 11) later developed an acute leukemia with FAB-M1 morphology, but this was evident in only one of four marrow aspiration sites.

Ten patients presented with AML without an apparent antecedent myelodysplastic phase. Morphology could be re-evaluated in all of these patients. Five were most consistent with FAB subtype M2 (patients 1, 2, 6, 8, and 17), and one was classified as M1 (patient 15); multilineage dysplasia was frequently observed. Three patients presented with myelomonocytic or monocytic leukemia with FAB subtypes M5B (patient 13), M5A (patient 14), and M4 (patient 16); these patients did not appear to have involvement of the erythroid and megakaryocytic series. Finally, patient 20 presented with an acute leukemia characterized by undifferentiated blast cells, accompanied by dysplasia in the maturing granulocytes. Twelve percent of the blasts were myeloperoxidase positive. The myeloid surface markers My7 and My9 were negative, while the T-cell markers Leu 9 and T11 were positive on more than 95% of the blasts. Thus, this patient was considered to have a mixed-lineage leukemia.

**Cytogenetic findings.** The complete karyotypes of 19 patients at the time of diagnosis and one patient (patient 5) at relapse of therapy-related MDS or AML are given in Table 3. The dominant cytogenetic feature was the presence of abnormalities of chromosomes 5 and/or 7, without
abnormalities of chromosome 11 band q23, found in 12 of the 20 patients (patients 1 through 12). Eight of the 12 patients had abnormalities of chromosome 7, three patients had abnormalities of chromosome 5, and one had abnormalities of both chromosomes 5 and 7. Four of these patients (patients 5, 8, 10, and 11) had complete loss of one copy of chromosome 7. Three patients (patients 4, 6, and 7) had interstitial deletions affecting the long arm of one chromosome 7. One of these patients (patient 6) also had an unbalanced translocation resulting in loss of the long arm of chromosome 5 [-5, -17, +der(5)(5;17)(q11;q11)]; this is a recurring abnormality in de novo and therapy-related malignant myeloid diseases. Two patients (patients 9 and 12) had an unbalanced translocation resulting in loss of the
long arm of chromosome 7 [-7,+der(1) t(1;7)(p11;p11)]; this is another recurring abnormality in de novo and therapy-related malignant myeloid diseases.26 One patient (patient 1) had an interstitial deletion of the long arm of one chromosome 5; this arose in a pre-existing abnormal subpopulation of cells with a t(4;7) (q23;q34), which was present before developing her primary solid tumors and at a time when she was hematologically normal. One patient (patient 3) had loss of the long arm of chromosome 5 as a result of formation of a dicentric chromosome. Finally, one patient (patient 2) had a balanced translocation involving the critical band on chromosome 5 (band 5q31).

Three patients (patients 13, 14, and 15) had an abnormality of chromosome 11 involving band q23, without abnormalities of chromosomes 5 or 7. The abnormality in all three cases was the same, namely, t(11;19)(q23;p13), which has been observed previously in de novo lymphoid and myeloid hematologic malignancies,28 as well as in therapy-related AML.15,27

Another patient (patient 16) had abnormalities of the long arms of both chromosome 7 homologues, as well as an abnormality of 11q23; these abnormalities were present in the same clone. One chromosome 7 was involved in a balanced translocation involving chromosome 7[t(1;7)(q32;q32-34)] and the other in an unbalanced translocation involving unidentified chromosomal material [t(7;?) (q22;?)]; the latter abnormality effectively results in monosomy for the long arm of chromosome 7 distal to the breakpoint in 7q22. The abnormality of chromosome 11 was a balanced translocation involving chromosome 3 [t(3;11)(q25;q23)].

Three patients had other abnormal karyotypes that did not involve chromosomes 5 or 7, or band q23 of chromosome 11 (patients 17, 18, and 19). Notably, patient 18 had a gain of chromosome 11, which has been observed in de novo lymphoid and myeloid hematologic malignancies,28 post-transplant lymphoma,29 and in therapy-related AML.15,30 Patient 19 had a balanced translocation between chromosomes 1 and 21 in all metaphase cells examined; it is possible that the t(1;21) is a constitutional abnormality in related MDS and AML in our series had abnormalities of chromosomes 5 and/or 7 had a median interval of 46 months (range, 12 to 114 months) and the three patients with 11q23 abnormalities had a median interval of 41 months (range, 17 to 107 months).

The karyotypes of 30 patients with therapy-related MDS or AML after a diagnosis of cancer before the age of 17 years have been reported previously. Eighteen of these were reported in two series from one institution (St Jude Children’s Research Hospital, Memphis, TN),5,17 and the remainder were reported as single cases39,40,43 or as small groups of patients.41,42 In contrast to our findings, only five of 30 pediatric patients (17%) in the previous reports had chromosome 5 and/or 7 abnormalities, while 17 (57%) had 11q23 abnormalities. This finding may be due in part to a greater use of epipodophyllotoxins in the treatment protocols at St Jude Children’s Research Hospital during the past decade, in comparison with the practices at our hospitals. It is also possible that patients with 11q23 abnormalities have been reported preferentially.

In our series, three of five patients with ALL as a primary malignancy who had immunophenotyping had T-cell disease. In contrast, T-lineage leukemia represents only 20% of all childhood ALL.35 This supports the finding at St Jude Children’s Research Hospital that development of secondary AML is more likely in pediatric patients with a T-cell phenotype than a non-T-cell phenotype.13 In contrast to the data from St Jude in which all of these patients had received an epipodophyllotoxin,15 none of our patients with T-cell leukemia had received epipodophyllotoxins or had 11q23 abnormalities. This finding suggests that the risk of secondary myeloid disease may be increased after T-cell ALL whether or not epipodophyllotoxins are used. The risk may be greater in T-cell patients due to exposure to more chemotherapy compared with non-T-cell patients.

It is clear that some T-cell leukemias have the ability to switch to a myeloid process both in vitro and in vivo.37

However, this does not appear to have occurred in most of the pediatric patients with therapy-related MDS or AML reported here and elsewhere in the literature36; six of the seven patients with T-cell leukemia followed by MDS or AML for whom cytogenetic studies had been performed at diagnosis of both the primary and the secondary malignancies have had completely different clonal chromosomal abnormalities, suggesting the development of an independent neoplastic process.

The proposed relationship between epipodophyllotoxins and therapy-related myelomonocytic or monocytic leukemia with 11q23 abnormalities is supported by our data. Three of four patients with an 11q23 abnormality (including one patient who also had 7q abnormalities) had been exposed to an epipodophyllotoxin, and had a monocytic component to their disease. In contrast, only three of 13 patients with abnormalities of chromosomes 5 and 7 (including one patient who also had an 11q23 abnormality) had received an epipodophyllotoxin. These findings support the suggestion that secondary leukemia characterized by an 11q23 abnormality is associated with prior therapy with epipodophyllotoxins. In patients with abnormalities of chro-
moresomes 5 and/or 7, all but two had received an alkylating agent and all but three had received radiotherapy. If these relationships remain firm, cytogenetic studies may help to ascertain which drugs are responsible for the secondary malignant process in patients who have been exposed to multiple agents.

The patient with an 11q23 abnormality without a history of treatment with an epipodophyllotoxin had been exposed to an anthracycline. This is further evidence that 11q23 abnormalities are associated with exposure to topoisomerase II-reactive drugs including epipodophyllotoxins, anthracyclines, and actinomycin D. However, there is little previous supporting data implicating either actinomycin D or anthracyclines in the development of therapy-related MDS or AML. Also, the mechanisms of action of these agents are distinct from those of epipodophyllotoxins.

Two patients had underlying conditions that may have predisposed them to the development of the secondary myeloid disease. In these cases there were obvious signs that alerted the clinicians to the presence of a congenital disorder. In addition, each of these patients had multiple malignancies before the diagnosis of MDS or AML. It is possible that these patients would have developed MDS or AML in the absence of prior therapy. For the remaining 18 patients there was no evidence of a predisposing factor other than the primary malignancy and its treatment. Nevertheless, it is important for the pediatric oncologist to be vigilant for those children with cancer who may be more likely to acquire a therapy-related or secondary hematologic malignancy.

The clinical outcome in our series of children with therapy-related MDS and AML was poor. Only three patients are alive at 1, 12, and 68 months, while the remaining patients died at a median of less than 1 year from diagnosis. Of the 30 pediatric patients in the literature, only six were alive at the time of the report and all of these living patients had a short follow-up ranging from 1 to 13 months. Thus, we cannot correlate specific chromosomal abnormalities with survival. As treatment for therapy-related MDS and AML improves, cytogenetics may play a greater role in assigning prognosis and in determining the therapeutic plan.

ACKNOWLEDGMENT

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