

CYTOGENETIC ABNORMALITIES AND THERAPY-RELATED MYELODYSPLASTIC SYNDROMES IN RHEUMATIC DISEASE

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Objective. To describe the myelodysplastic syndromes (MDS) and cytogenetic abnormalities that occur in patients who have been treated with alkylating drugs for their rheumatic disease.

Methods. Patients with rheumatic disease who developed MDS after current or previous treatment with alkylating drugs were selected for evaluation by chart review and cytogenetic studies.

Results. Eight patients with rheumatic disease (mean age 56.9 years) developed MDS over the study period. Seven had received oral cyclophosphamide and 1 chlorambucil as their main immunosuppressive drug. The mean total cumulative dose of cyclophosphamide or chlorambucil was 118 gm and 6.5 gm, respectively, over a period of 2–10 years. The cytogenetic abnormalities included a deletion of all or part of chromosome 7 in 5 patients, while 4 had a deletion of part of the long arm of chromosome 5. Six of the patients have since died.

Conclusion. Large cumulative doses of cyclophosphamide and chlorambucil were associated with the development of MDS, the occurrence of abnormalities of chromosome 5 and/or chromosome 7 deletions, and a poor prognosis.

The occurrence of myelodysplastic syndromes (MDS) after exposure to alkylating drugs is frequently associated with chromosomal abnormalities, particularly of chromosome 5 and/or chromosome 7 (1–3). These changes are often associated with a poor prognosis (1). Treatment of rheumatic disease with alkylating drugs is associated with the development of MDS and hemato-

logic malignancies (4), and conversely, patients with MDS can develop rheumatic manifestations (5,6). However, to date, no study has described the cytogenetic abnormalities in patients with rheumatic diseases who have developed therapy-related MDS. This study describes the MDS and cytogenetic abnormalities that occurred in a group of patients with rheumatic disease who had been treated with alkylating drugs.

PATIENTS AND METHODS

All patients with rheumatic disease who attend our clinics and receive immunosuppressive drugs are monitored regularly, with monthly complete blood cell counts, for the development of hematologic abnormalities. All patients with rheumatic disease who had received alkylating drugs and were known to have developed MDS over the previous 7 years were included in this study. Their hospital charts were reviewed for information regarding their rheumatologic diagnosis, as well as the type, cumulative dose, and duration of the alkylating drug. Additional information regarding cytogenetic abnormalities, the type of MDS, and the patient outcome was obtained from chart and pathologic review. In each case, treatment with an alkylating drug was initiated because of serious complications of the disease.

The classification of MDS has been previously described (7). Cytogenetic studies were performed on cells from a bone marrow aspirate obtained during a routine workup for the hematologic disorder. In all cases, the bone marrow and karyotype were reviewed by a pathologist and cytogeneticist, respectively.

RESULTS

Table 1 characterizes the patients in this study. Five men and 3 women, with a mean age of 56.9 years (range 36–75 years), developed MDS over the 7-year study period. Their clinical presentations were varied. Five presented with cytopenia on routine laboratory testing. Two patients presented with increasing fatigue related to anemia. Seven patients had received cyclophosphamide and 1 chlorambucil as their main immunosuppressive drug. The mean cumulative cyclophospha-

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Table 1. Characteristics of the study patients*

Patient/age/sex	Rheumatologic diagnosis	Type	Alkylating drug		Type of MDS	Cytogenetic abnormality	Outcome
			Cumulative dose, gm	Duration, years			
1/64/M	Wegener's granulomatosis	CYC	135	6	RAEB-T	7q-	Died
2/36/F	Takayasu arteritis/Cogan's syndrome	CYC	91.2	2	MDS-NOS	7q-	Living
3/64/M	Rheumatoid arthritis/Sjögren's syndrome	CYC	112.5	3	RAEB	5q-, 7q-	Died
4/75/F	Wegener's granulomatosis	CYC	120	2	RAEB-T	Monosomy 7	Living
5/46/M	Goodpasture's syndrome	CYC	110	3	MDS-NOS	Monosomy 7	Died
6/45/M	Cerebral angiitis	CYC	140	4	MDS-NOS	5q-	Died
7/72/F	Polymyositis	CHL	6.5	3	RAEB	5q-	Died
8/57/M	Wegener's granulomatosis	CYC	109	2	MDS-NOS	5q-	Died

* Myelodysplastic syndromes (MDS) are defined in ref. 7. CYC = cyclophosphamide; RAEB-T = refractory anemia with excess blasts in transformation; MDS-NOS = MDS not otherwise subclassified; CHL = chlorambucil.

midose dose was 118 gm (SD 16.6 gm), with a mean treatment period of 4.4 years (range 2–10 years). The chlorambucil-treated patient received a total dose of 6.5 gm. Of the cyclophosphamide-treated patients, 3 had also received 2 other immunosuppressive drugs (methotrexate and azathioprine in 1, methotrexate and cyclosporin A in 1, and chlorambucil [total dose 3.6 gm] and methotrexate in 1) and 1 had received a different immunosuppressive drug (chlorambucil at a total dose 1.4 gm).

The mean time from the start of treatment to the development of MDS was 8.25 years (range 2–19 years). The mean time from the diagnosis of the rheumatic disease to the development of MDS was 10.6 years (range 7–19 years). The mean time from discontinuation

of the alkylating drug to development of MDS was 2.4 years (range 0–4 years).

Figure 1 shows the karyotype of a patient with rheumatoid vasculitis, which necessitated treatment with cyclophosphamide. A total cumulative dose of 112.5 gm of cyclophosphamide was administered over 3 years. He developed refractory anemia with excess blasts 5 years after starting cyclophosphamide. The karyotype shows deletions of part of the long arms of chromosomes 5 and 7 (arrows) as well as 2 chromosomes that could not be identified (markers; bottom left) and monosomies 12 and 17. These abnormalities were present in all cells analyzed.

Cytogenetic abnormalities in chromosome 7 oc-

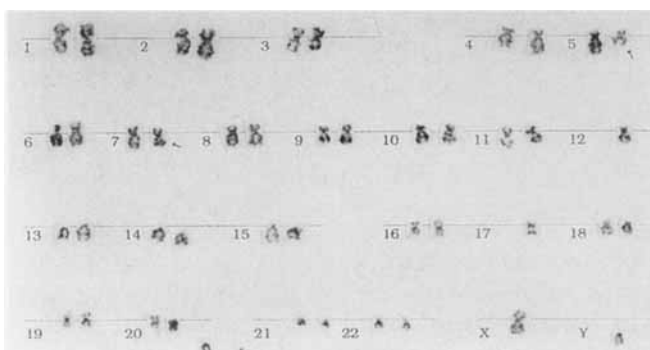


Figure 1. Karyotype from a patient with rheumatoid arthritis and vasculitis, showing deletions of part of the long arm of chromosomes 5 and 7 (arrows) as well as 2 chromosomes that could not be identified (markers; bottom left) and monosomies 12 and 17. These abnormalities were present in all cells analyzed.

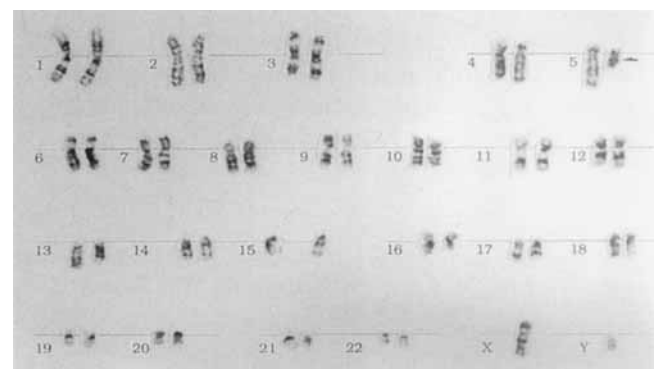


Figure 2. Karyotype from a patient with Wegener's granulomatosis, showing a deletion in part of the long arm of chromosome 5 (arrow).

curred in 5 patients, while abnormalities in chromosome 5 occurred in 4 patients (the patient described above had abnormalities in both chromosome 5 and chromosome 7). The cytogenetic changes described in these patients are characteristic of therapy-related MDS. In contrast, the histologic features were frequently minimal. The outcome was poor, with 6 of 8 patients dying from complications of their MDS. Four of these had changes in chromosome 5.

DISCUSSION

Up to 80% of individuals with therapy-related MDS or therapy-related acute myeloid leukemia have loss of chromosomal material from chromosome 5 and/or chromosome 7 (2,8). In this study, we report the types of MDS and cytogenetic abnormalities that occurred in a group of hospital-based patients with rheumatic diseases after treatment with alkylating drugs. While these patients had different indications for treatment with alkylating drugs, they all had received large doses of alkylating agents. Their outcome was poor, particularly in those patients with abnormalities of chromosome 5, in a relatively young population of patients. This is consistent with another report of a poor prognosis in cancer patients who developed MDS after treatment with alkylating drugs (1). Patients with MDS can develop rheumatic disease manifestations (5,6), with a third of patients developing chromosomal abnormalities (5). To date, as far as we are aware, there have been no reports of cytogenetic abnormalities in chromosome 5 in patients with rheumatic disease. This suggests that the changes documented herein are likely to be a secondary phenomenon related to high cumulative doses of the alkylating drugs (4,8).

We can only speculate as to the duration of risk of MDS following discontinuation of the alkylating drug. In this study, our patients developed MDS up to 4 years after cessation of the alkylating drug, but in patients treated for cancer, there have been reports of MDS developing up to 12 years after treatment (2,8-10). In contrast, one study suggested that there is no increased risk of therapy-related MDS 10 years after discontinuation of treatment (11). The actual risk of developing MDS in our population of patients treated with alkylating drugs is not known; however, followup of our patients is ongoing. We are currently following up 24 patients on a regimen of oral cyclophosphamide and over 100 patients who have received intravenous cyclophosphamide. We are also following up 5 patients being treated with chlorambucil.

Many of these patients have also been treated with methotrexate and/or azathioprine. Azathioprine may increase the risk of some malignancies. However, in rheumatic disease, neither of these compounds has been clearly implicated in the development of MDS (12,13). We can only suggest that patients who have been treated with alkylating drugs and methotrexate or azathioprine should be followed up very closely.

A deletion of the long arm of chromosome 5 (5q-) in patients with refractory anemia was described in 1974, and is now called the 5q- syndrome (8,14,15). The chromosome breakpoints vary. However, there is a region of overlap that is consistently lost (16). This region on 5q contains the genetic information for a large number of growth factors and growth factor receptor genes, which play an important role in normal myeloid growth and differentiation. In addition, the loss of heterozygosity at some loci, leading to oncogene expression, may be important in the development of MDS (16).

The findings of this study suggest that high cumulative doses of alkylating drugs present a risk for the development of MDS, with associated cytogenetic abnormalities of chromosomes 5 and/or 7 in patients with rheumatic diseases. Long-term hematologic monitoring of patients who have received cumulative doses of >100 gm of cyclophosphamide is strongly recommended. The occurrence of hematologic abnormalities in patients with rheumatic disease who have received high cumulative doses of alkylating drugs may herald the onset of MDS. Bone marrow evaluation should include cytogenetic studies because these may have diagnostic and prognostic implications.

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