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Chromosome abnormalities in secondary myelodysplastic syndromes

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Specific chromosome abnormalities occur in most cases of secondary myelodysplastic Syndromes (MDS), broadly defined to include acute nonlymphocytic leukaemia (ANLL). To explore their relation with the type of prior cancer and its treatment, and their use in predicting response of the secondary MDS to therapy, 216 patients from the literature were analyzed. Abnormal karyotypes were grouped into 10 nonoverlapping categories, depending first upon the presence of abnormalities of chromosomes 5 and 7 (-5, 5q-, -7, 7q-), then upon specific rearrangements seen in *de novo* ANLL, and finally upon other structural or numerical abnormalities. Karyotype correlated with type of prior cancer ($p = .002$). -5, -7 and additional whole chromosomes were associated primarily (67-86%) with prior haematologic malignancies, and the specific rearrangements and 5q- groups (70-71%) with prior solid tumors. Karyotype also correlated with prior therapy ($p = .0009$). -5, -7 and 7q- were highly (> 85%) associated with chemotherapy (alone or with radiotherapy); the 5q-, specific rearrangements, normal, and "other" structural abnormalities groups were often (29-60%) associated with radiotherapy alone. Finally, karyotype also predicted achievement of complete remission (CR); 5q- and -5 were associated with the lowest CR rate (13%), specific rearrangements and other structural abnormalities with the highest (65%). Prospective studies are required to determine if karyotype is an independent risk factor.

As more patients with cancer have been successfully treated with radiation and/or chemotherapy, there have been increasing numbers of reports of secondary myelodysplastic syndromes (MDS), including acute nonlymphocytic leukaemia (ANLL), occurring among such patients (1-2). To date, relatively few of these patients have had cytogenetic studies done when they developed the secondary MDS. Only five sizeable series of banded chromosome studies have been published (3-10). In these studies it has been suggested that karyotype may be related to type of prior malignancy, and/or type of prior treatment. It has also been suggested that

karyotype may be the major predictor of response to treatment of the secondary MDS. Because of the small numbers of patients studied in each series the conclusions have been tenuous. This review considers the relation of karyotype to the type of prior disease, the nature of prior treatment, and the response to therapy of the secondary MDS in 216 patients from the above 5 published series.

Materials and methods

For purposes of this review, the 5 studies, comprising 232 patients with secondary MDS following therapy for a

primary disease, were carefully examined. Cases reasonably successfully analyzed by the techniques were included. Cases which were analyzed at the Fourth international Workshop on Cytogenetics (4th IWCL) from the University of Minnesota, the Finnish Cancer Registry, were listed with their respective sources (Table I).

TABLE I
Patient characteristics in five studies

	Chicago
References	3-10
Number of cases	62
% male	49
Age at secondary MDS (yrs)	
Median	55
Range	6-71
Mos from initial treatment/diagnosis	
Median	56
Range	10-71
First disease (cancer) (%)	
Hodgkin's disease	37
Malignant lymphoma	16
Multiple myeloma	8
Other haematologic ca.	
Breast	6
Ovary	3
Uterus/cervix	6
Lung	3
Colorectal	8
Other solid tumor	6
Benign	
Prior therapy (%)	
Radiation	
Minimal (R)	
Major (RR)	16
Chemotherapy	
Single (C)	11
Combination (CC)	21
Combined modality	
R + C	
R + CC	8
RR + C	
RR + CC	35
Treatment for secondary MDS (%)	
Intensive	32
Minimal	22
None	44
Response to intensive treatment	
% Complete remission	30
Duration (mos)	
Median	20
Range	6-48
Survival (mos)	
Median	
Range	0-48

* Only secondary ANLL. ** Original

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methods

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primary disease, were carefully examined. Only those 216
cases reasonably successfully analyzed with banding tech-
niques were included. Cases which were included in the
Fourth International Workshop on Chromosomes in Leu-
kemia (4th IWCL) from the University of Chicago, the
University of Minnesota, the Finsen Institute and France
were listed with their respective submitting institution
(Table 1).

Patient characteristics which were available for most
of the cases are summarized in Table 1. The series dif-
fered in the type of patients included. The 4th IWCL and
Minnesota series included only cases meeting the criteria
for a diagnosis of ANLL (11). In each series there was
a slight predominance of females, and the median age
ranged from 55 to 63. The median time from the primary
disease (or its treatment) to the diagnosis of the secondary

TABLE 1

Patient characteristics in five studies of banded chromosome analyses in secondary MDS

	Chicano	French	Finsen	4 th IWCL*	Minnesota ¹	Total	
References	3-5	6	7,8	9	10		
Number of cases	63	55	42	36	20	216	
% male	49	49	45	44	40	47	
Age at secondary MDS (yrs)							
Median	55	60	63	55	59	—	
Range	6-76	13-89	22-75	18-78	22-76		
Mos from initial treatment/diagnosis to secondary MDS							
Median	56	72**	48	58	76	—	
Range	10-192	24-288	12-120	7-204	35-182		
First disease (cancer)(%)						No.	%
Hodgkin's disease	37	22	36	22	20	62	29
Malignant lymphoma	16	11	21	11	10	31	14
Multiple myeloma	8	13	5	11	5	19	9
Other haematologic ca.	7	4	2	3	10	7	3
Breast	6	16	10	22	15	28	13
Ovary	3	5	24	6	15	16	7
Uterus/cervix	6	4	5	0	5	9	4
Lung	3	7	5	3	5	7	3
Colorectal	8	4	0	0	0	7	3
Other solid tumor	6	15	7	11	15	20	9
Benign	5	5	0	11	0	10	5
Prior therapy (%)							
Radiation						10	5***
Minimal (R)	3		10	19	10	15	7
Major (RR)	16	18***	5	8	10	17	8
Chemotherapy						20	9***
Single (C)	11		14	17	25	24	11
Combination (CC)	21	36***	9	14	5	31	14
Combined modality						25	12***
R - C	7		0	0	15	4	2
R - CC	8		5	0	5	8	4
RR - C	5	45***	7	6	0	6	3
RR - CC	35		36	36	30	56	26
Treatment for secondary MDS (%)						55	25***
Intensive	32		45	53	75	73	34
Minimal	22	unknown	12	13	10	28	13
None	44		43	28	10	58	27
Response to intensive treatment							
% Complete remission	30		47	26	53	38	
Duration (mos)							
Median	20	unknown	5	15	3	—	
Range	6-43		1+ - 34+	6-19+	2-11		
Survival (mos)							
Median	7	3	9	3+	5	—	
Range	0-43	1-16	0-39	0-21	0-39		

* Only secondary ANLL, ** Original data provided in years, *** Amount of prior therapy not specified.

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TABLE 2
Karyotype groups, prior disease and prior therapy

	-7	Normal	5q-	-7 & 5q-	Karyotype Groups*					Misc. 5 & 7
					-5	-7 & -5	Adds	7q-	Specific	
Number of cases	52	31	21	18	16	14	12	12	10	9
% of total	24.0	14.4	9.7	8.3	7.4	6.5	5.6	5.6	4.6	4.2
Frequency by series (%)										
Chicago	32	3	13	14	10	10	3	6	3	3
French	24	11	9	5	9	5	7	7	4	5
Finsen	31	26	5	10	2	5	2	5	0	7
4th WCL	11	31	6	6	8	6	0	3	11	3
Minnesota	10	5	20	0	5	5	25	5	10	0
First disease (%)										
Haematologic malignancy	67	35	29	78	69	86	75	42	20	p = .0002
Hodgkin's disease	33	26	10	44	19	57	58	25	0	
Malignant lymphoma	19	10	10	28	19	21	8	8	10	
Multiple myeloma	13	0	5	6	25	0	8	8	0	
Other	2	0	5	0	6	7	0	0	10	
Solid tumors	27	55	71	22	25	14	25	50	70	
Breast	8	13	19	0	19	14	17	8	20	p = .0009
Ovary	0	19	10	11	0	0	0	17	0	
Other	19	22	43	11	6	0	8	25	50	
Benign	6	10	0	0	6	0	0	8	10	
Prior therapy (%)										
Radiation	8	35	33	6	6	14	17	0	0	p = .03
Chemotherapy	40	26	33	22	63	14	42	50	21	
Both	52	39	33	72	31	71	42	50	21	
Single modality										
Number of cases	18	16	12	4	8	3	5	3	6	
% extensive (RR or CC)	83	38	58	0	88	67	60	33	33	

* See text for descriptions of karyotype groups.

sociated with extensive therapy while patients with normal karyotypes or specific rearrangements had often (63—67 %) received more limited single modality therapy.

In an attempt to evaluate the interaction of type of prior disease and therapy on the chromosome abnormality, karyotype was correlated with type of prior therapy separately for patients with prior haematologic malignancies and solid tumors (Table 3). In both instances, type of therapy tended to associate with karyotype group ($p = .06$). Among patients with haematologic malignancies, chemotherapy alone had been given to most (64—83 %) patients in the -5 and 5q- karyotype groups, while combined modality therapy had been received by most patients with a -7, a 7q-, other structural abnormalities or a normal karyotype (54—93 %). In contrast among patients with prior solid tumors, only in the -7 group had a majority of patients (57 %) received combined modality therapy; radiation alone was received by almost half of the patients in the normal karyotype, the 5q-, and the "other" structural abnormality groups (42—47 %), and in almost all patients (86 %) in the "specific" abnormality group. Chemotherapy alone had been received by most patients in the 7q- group.

Similarly, karyotype group was correlated with the type of prior disease separately for patients treated with radiation, chemotherapy or combined modality approaches (Table 3). Among patients treated with only radiation, type of initial disease significantly correlated with karyotype group ($p = .03$). A prior haematologic cancer was frequently found only in the -7, -7 and -5, and the additions of whole chromosome groups. In all other groups most patients had had solid tumors. Among patients treated only with chemotherapy, type of initial disease did not correlate with karyotype group. Among patients treated with combined modality approaches, type of first disease correlated only weakly ($p = .06$) with karyotype: most patients had previously had haematologic neoplasms; the major exception was the 5q- group in which 6 of 7 patients had previously had a solid tumor. Although the explanation for these results is unknown one hypothesis is that the type of radiation administered differs more between solid tumors and

haematologic malignancies than does the type of chemotherapy. Certainly, for many solid tumors radiation is more localized than it usually is for Hodgkin's disease or malignant lymphoma — the 2 major prior haematologic malignancies in the series.

Relation between karyotype, patient characteristics, response to treatment and survival

Although the sex distribution (medians 25—58 % male), age at diagnosis of the secondary MDS (medians 53—66 years) and time between initial and secondary diseases (medians 18—70 months) varied somewhat among chromosome groups, overall the differences were not significant (Table 1). When individual groups were compared, time to the secondary MDS was significantly longer in the group with additional whole chromosomes as compared to the group with a normal karyotype (70 vs. 48, $p = .04$).

Only 73 of the 216 patients received intensive treatment for their secondary MDS, limiting detailed analysis of the effect of karyotype on response. However, karyotype appeared to correlate with achievement of complete remission ($p = .04$, Table 5). The response rate 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. Similarly, a low response rate in patients with *de novo* ANLL with abnormalities of chromosome 5 was seen in the 4th WCL (9). The best response rate (65 %) was seen in patients with specific rearrangement, or other structural chromosome abnormalities. Numbers of cases were too small to statistically compare duration of remission (Table 4).

Among the 73 patients receiving intensive treatment for their secondary MDS, the rate of complete remission was not correlated with whether the first disease was haematologic (40 %), a solid tumor (39 %) or benign (25 %). However, response was highly correlated with type of prior treatment ($p = .005$). Among patients treated only with radiation 67 % achieved complete remission, compared to 24 % treated with only chemotherapy and 28 % treated with both modalities. Similar results

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TABLE 3
Interaction of effect of prior disease and prior therapy on karyotype

	Karyotype Groups									
	-7	Normal	5q-	Other structural	-7 & 5q-	-5	-7 & -5	Adds	7q-	Specific
Effect of type of prior therapy among patients with prior haematologic malignancies										
Number of cases	35	11	6	8	14	11	12	9	5	2
Radiation (%)	6	9	0	13	0	0	17	22	0	0
Chemotherapy (%)	40	36	83	25	7	64	8	33	20	50
Both (%)	54	55	17	63	93	36	75	44	80	50
Effect of type of prior therapy among patients with prior solid tumors										
Number of cases	14	17	15	12	4	4	2	3	6	7
Radiation (%)	14	47	47	42	25	25	0	0	0	86
Chemotherapy (%)	29	24	13	25	75	50	50	67	67	0
Both (%)	57	29	40	33	0	25	50	33	33	14
Effect of type of prior disease among patients previously treated only with radiation										
Number of cases	4	11	7	6	1	1	2	2	0	6
Haematologic malignancies (%)	50	9	0	17	0	0	100	100	0	0
Solid tumors (%)	50	73	100	83	100	100	0	0	0	100
Benign (%)	0	18	0	0	0	0	0	0	0	0
Effect of type of prior disease among patients previously treated only with chemotherapy										
Number of cases	21	8	7	6	4	10	2	5	6	2
Haematologic malignancies (%)	67	50	71	33	25	70	50	60	17	50
Solid tumors (%)	19	50	29	50	75	20	50	40	67	0
Benign (%)	14	0	0	17	0	10	0	0	17	50
Effect of type of prior disease among patients previously treated with combined modality therapy										
Number of cases	27	12	—	—	13	5	10	5	6	2
Haematologic malignancies (%)	70	50	14	56	100	80	90	80	67	50
Solid tumors (%)	30	42	86	44	0	20	10	20	33	50
Benign (%)	0	8	0	0	0	0	0	0	0	0

$p = .06$

$p = .06$

$p = .03$

$p = .43$

$p = .06$

TABLE 4
Patient characteristics and response to treatment according to karyotype groups

Karyotype Group		Specific
-5	5q-	10
-7	7q-	30
-7 & -5	-7 & 5q-	53
-7; 7q-		13-73
Normal		58
Additions		15-156
Other structural		7
Other rearrangements		70-96
		71
		6
		2-18+
		6+
		0-19+
		5+

have been reported by others (1). This was correlated with karyotype groups. Patients with different first differences were seen only for -5 (p = .003, Table 5). When response was compared with karyotype groups separately, previously treated with radiation or both, a trend toward significance was seen for patients previously treated with radiation (p = .07, Table C). The data do not suggest that karyotype may be a prognostic factor, especially when the analysis has been less extensive.

Median survival ranged from 12 to 24 months for the various karyotype groups. These results were not statistically different. The -7 group tended to survive longer than the -5 group (p = .06; -7 vs. 5q-, p = .06). When survival was considered in patients in the -7 group, those with only -7 survived a median of 12 months, while those with -7 plus other abnormalities survived a median of 6 months (p = .096). The latter result is essentially identical to that for patients with -7 and -5, and -7 and 5q- (1).

Discussion

This analysis of 216 published

TABLE 5
Response to intensive treatment by karyotype group

Karyotype groups	
-5; 5q-	
-7 & -5; -7 & 5q-	
-7; 7q-	
Normal	
Additions	
Other structural	
Other rearrangements	

* CR = complete remission

have been reported by others (12). When response was correlated with karyotype groups separately for patients with different first diseases, a significant difference was seen only for the solid tumors ($p = .003$, Table 5). When response was correlated with karyotype groups separately for patients previously treated with radiation, chemotherapy, or both, a trend toward significance was seen only for patients previously receiving radiation ($p = .07$, Table 5). The data could be interpreted to suggest that karyotype may be an independent prognostic factor, especially when prior treatment has been less extensive.

Median survival ranged from 3 to 9 months for the various karyotype groups (Table 4). These results were not statistically different. However, the -7 group tended to survive longer (-7 group vs. -5 group, $p = .06$; -7 vs. 5q-, $p = .08$). Interestingly, when survival was considered separately for patients in the -7 group, those with -7 as their only abnormality survived a median of 10 months and those with -7 plus other abnormalities a median of 6 months ($p = .096$). The latter survival is essentially identical to that for patients in the groups with -7 and -5, and -7 and 5q- (median 5 months).

Discussion

This analysis of 216 published cases of secondary

MDS on whom banded chromosome analyses were obtained confirms and extends previously suggested correlations between karyotype and type of prior disease and prior therapy. In particular, 5q- and -7 have previously been correlated respectively with prior solid tumors (5) and prior haematologic malignancies (6), and a -7 has been previously correlated with more extensive prior therapy (6, 10). The interaction of these two factors requires further study with prospective collection of detailed data regarding primary therapy and sophisticated multivariate analyses of results.

Karyotype as classified here also correlated with response to intensive chemotherapy. Patients with abnormalities of chromosome 5, especially a 5q-, rarely achieved remission with conventional induction chemotherapy. Patients with specific rearrangements and other structural abnormalities seen in *de novo* ANLL frequently achieved remission and some of these patients were long-term disease-free survivors. Kantarjian et al., in a preliminary report, also found that karyotype significantly correlated with response to intensive induction chemotherapy and that the specific rearrangements seen in *de novo* ANLL were most often associated with response (13). More patients must be studied prospectively to determine if karyotype is an *independent* prognostic factor. Moreover, it is not clear that the karyotype classification used here is the best one and other approaches should be tried.

TABLE 5
Response to intensive treatment by karyotype group

Karyotype groups	All patients		Patients with only prior radiation		Patients with prior solid tumors	
	NO. cases	CR*	NO. cases	CR	NO. cases	CR
-5; 5q-						
-7 & -5; -7 & 5q-	16	13 %	3	0	8	0
-7; 7q-	19	32 %	2	50 %	6	33 %
Normal	14	43 %	6	61 %	10	20 %
Additions	6	50 %	1	100 %	1	100 %
Other structural; specific rearrangements	17	65 %	9	89 %	13	77 %
		$p = .036$		$p = .068$		$p = .003$

* CR = complete remission.

Although the results from this analysis of previously published series are provocative, the limitations of such an evaluation are obvious. The only way to clearly answer questions regarding the relation of specific chromosome abnormalities to exposure to prior radiation and chemotherapy, to type of prior disease and to response to treatment of the secondary MDS is a large prospective trial where all patients have good chromosome studies, detailed information on prior therapy, and optimal uniform treatment of the secondary MDS.

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Translocation (t non-lymphocytic association

A reciprocal apparently balanced t (p21;q23), was the sole chromosome of suspected acute leukaemia. The exposure to mutagenic agents, preceding lasting 17 months before ANLL-M1 irradiated after surgical removal of a with ANLL-M1. Both patients had

We have found 4 patients with t had a myelodysplastic syndrome at the others survived after different

Comparison of the cytogenetic findings was apparently identical. The clinical features were somewhat included male sex, age over 50, haematopoietic cells in a preleukemia exposure to irradiation occurred in 2 presently be listed as a non-random myeloid cells.

It has become increasingly evident that types of neoplastic cells are characterized by chromosomal abnormalities, particularly numerical (1).

Acute non-lymphocytic leukemia is characterized by highly non-random abnormalities (2). Karyotypic and valuable diagnostic parameters between the different leukaemia subtypes, between several morphologic subtypes of the disease, the significance of karyotyping in