BRIEF REPORT
Patients With Fanconi Anemia and AML Have Different Cytogenetic Clones Than De Novo Cases of AML

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Specific cytogenetic clones might distinguish patients with unrecognized Fanconi anemia (FA) who present with acute myeloid leukemia (AML) from those with sporadic AML. Cytogenetic reports in literature cases of FA and AML were compared with de novo cases enrolled on CCG-2961. Gain of 1q, gain of 3q, monosomy 7, deleted 7q, gain of 13q, and deleted 20q were more frequent in FA AML; t(8;21), trisomy 8, t(9;11), t(6;9), and inversion 16 were exclusive to de novo AML cases. Observation of the FA AML cytogenetic clonal patterns should raise suspicion of an underlying leukemia predisposition syndrome and influence management. Pediatr Blood Cancer

Key words: acute myelogenous leukemia; cytogenetics; clones; Fanconi anemia; sporadic AML

INTRODUCTION

Fanconi anemia (FA) is an inherited bone marrow failure syndrome characterized by varying degrees of bone marrow failure, birth defects, and high risks of myelodysplastic syndrome (MDS) and malignancies [1]. FA patients have a more than 500-fold higher risk of acute myeloid leukemia (AML) than the general population [2–5], and AML was the initial presentation in approximately one-third of published FA cases with AML [6]. We hypothesized that unique bone marrow cytogenetic clones may distinguish patients with FA and AML from patients with de novo AML. We compared the types and frequencies of bone marrow cytogenetic clones in patients with FA and AML reported in the literature with data from cases with de novo AML enrolled on Children's Cancer Group protocol 2961 (CCG-2961).

METHODS

A systematic review of the FA literature from 1927 through 2011 was performed using the search string "acute myeloid leukemia" or "leukemia" combined with "Fanconi anemia" and "cytogenetics" or "clone." The diagnosis of leukemia for each case was accepted from the descriptions and conclusions of the authors. The de novo AML cohort was composed of patients <21 years old enrolled on CCG-2961 between 1997 and 2002 [7]. Bone marrow cytogenetic reports were tabulated in Excel spreadsheets (Excel 2007); each chromosome was scored for monosomy, duplication or derivative; each arm was scored for deletion/addition of extra unknown material, or inversion. Recurring translocations were recorded separately. All cytogenetic reports were independently reviewed by a cytogeneticist (S.B.O.), applying ISCN 2009 nomenclature wherever possible [8]. Denominators were those patients in whom karyotypes were reported. Fisher's exact test was used to compare the frequency of each aberration (Stata 11); $P \leq 0.05$ was significant.

RESULTS

There were 162 cases of FA AML reported in the literature; 146 were <21 years of age, and 46 of these (32%) had cytogenetics described in the reports. The CCG group included 892 cases of de novo AML, all <21 years old, of whom 559 (63%) had adequate cytogenetic studies. Although more CCG than literature subjects had karyotypes documented ($P < 0.001$), the proportions of abnormal karyotypes were similar, 87% in the FA AML literature, and 78% in the CCG group ($P = 0.2$). The FA cases were older than the de novo patients at diagnosis of AML, median 14 years, range 0.5–20, compared with a median of 9 years, range 0–20.9 ($P < 0.001$). The ratio of males to females was similar, 1.4:1 and 1.1:1 respectively. In eight of the 46 FA literature cases, the AML clone was first noted in a "preleukemic" phase (not otherwise described).

Chromosomes 1, 3, and 7 were more frequently involved in clones in FA AML patients than in de novo AML cases (37%, 19%, and 36% in FA compared with 12%, 6%, and 11% in CCG respectively, $P < 0.001$). Conversely, chromosomes 8 and 16 (11% and 8%) were exclusively affected in de novo AML patients ($P < 0.001$), while chromosome 11 was more frequent in the de novo cases.

The frequencies of reports of specific clones differed between FA AML and CCG (Table I). Gain of 1q, monosomy 7, and gain of 3q were much more frequent in FA AML ($P < 0.001$), as were deletion 7q, gain of 13q, and deletion 20q ($P = 0.02$). In contrast,

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TABLE I. Frequencies of Specific Cytogenetic Clones in FA AML and De Novo AML

	FA AML, 46		De novo AML, 559		
Chromosome	N	%	N	%	*P*-value
More frequent in FA AML					
+1q	10	22	7	1	<0.001
−7	8	17	14	3	<0.001
+3q	5	11	5	1	<0.001
7q−	5	11	16	3	0.02
+13q	2	4	1	0	0.02
20q−	2	4	3	1	0.05
More frequent in de novo AML					
t(8;21)	0	0	88	16	0.001
Trisomy 8	0	0	62	11	0.01
t(9;11)	0	0	52	9	0.03
inv(16)(p13q22)	0	0	48	9	0.04
t(6;9)	0	0	9	1.6	1

t(8;21), t(9;11), t(6;9), inv(16)(p13q22), and trisomy 8 were exclusive to de novo AML patients. Thus, the specific type of clone distinguished the two groups.

We previously analyzed the time to recovery of the absolute neutrophil count (ANC) to >1,000/μl after induction chemotherapy in the CCG cohort, and speculated that the group with no or delayed ANC recovery (more than 2 standard deviations beyond the mean of 40 days) may be enriched with FA patients [9]. We have now examined the association of specific cytogenetic clones with the time to ANC recovery in this de novo AML cohort (Table II). There was a trend toward slower recovery with 7q− in the FA AML group, but no other correlations with specific clones in FA. Among the unique clones in de novo AML, t(8;21) was associated with more rapid ANC recovery, while t(9;11) and t(6;9) were more frequent in those with delayed or no recovery. Trisomy 8 and inv(16)(p13q22) did not distinguish the normal from the poor responders.

DISCUSSION

This study compares cytogenetic data in FA AML with data in de novo AML patients. The specific involved chromosome may distinguish patients with FA AML from de novo cases, since chromosomes 1, 3, and 7 were more frequently abnormal in FA, similar to a previous report [10]. Conversely, abnormal chromosomes 8 and 16 were exclusive to de novo AML. The specific clone might also distinguish FA AML from de novo AML. Gain of 3q was found primarily in FA AML patients, consistent with previous reports of 3q26-q29 abnormalities with MDS or AML [11–14]. In addition, +1q, −7, 7q−, +13q, and 20q− were more frequent among FA AML patients. In contrast, t(8;21), t(9;11), t(6;9), and inv(16) and trisomy 8 were found only in de novo AML; t(8;21) was more frequent among patients with de novo AML with good ANC recovery.

A strength of our study is that the CCG 2961 cohort constitutes the largest pediatric AML cytogenetic dataset. A limitation is that the literature data included leukemia cases reported between 1974 and 2011, while the CCG 2961 data were from patients enrolled from 1996 through 2002. In addition, the actual slides in the FA AML literature cases could not be reviewed, and terminology has changed over time [8]. To compensate for this, all cytogenetic *reports*, but not *slides*, were independently interpreted by a cytogeneticist (S.B.O.). Although the known diagnosis of FA is an exclusion criterion from enrolling on standard COG AML trials, it remains possible that some patients, with subtle phenotypes, had unrecognized FA. FA AML literature cases as well as the de novo AML cohort may be affected by reporting or enrolment biases. Finally, the prognostic significance of clonal evolution could not be evaluated due to insufficient data, since the data in the literature were reported at diagnosis of AML.

In conclusion, the cytogenetic clonal patterns in FA AML differ from the patterns in de novo AML. Presence of +1q, −7, +3q, 7q−, +13q, or 20q− in a newly diagnosed patient with AML should lead to consideration of FA as an underlying diagnosis. Conversely, t(8;21), trisomy 8, t(9;11), t(6;9), trisomy 8, and inv(16) would not warrant testing for FA unless it is clinically indicated.

This report, with all the limitations intrinsic to published, historical data, is a hypothesis-generating analysis. Our results require validation from additional multi-center data and centralized cytogenetic analyses. Prospective screening of all patients with de novo AML for FA could identify the prevalence of FA in that group. Identification of undiagnosed cases of FA with AML

TABLE II. Association of Clones With ANC Recovery in Patients With De Novo AML

	Good ANC recovery (<60 days, N = 442)		Delayed or no ANC recovery (>60 days or never, N = 117)		
	N	%	N	%	*P*-value
More frequent in FA AML					
−7	11	2.5	3	2.6	1
7q−	9	2.0	7	6.0	0.054
+1q	6	1.4	1	0.9	1
+3q	3	0.7	2	1.7	0.28
+13q	1	0.2	0	0	1
20q−	3	0.7	0	0	1
More frequent in de novo AML					
t(8;21)	77	17.4	11	9.4	0.033
Trisomy 8	44	10.0	18	15.4	1
t(9;11)	35	7.9	17	14.5	0.047
inv(16)(p13q22)	41	9.3	7	6.0	0.35
t(6;9)	4	0.9	5	4.3	0.023

might alter management strategies, including chemotherapy or earlier stem cell transplantation, using FA-specific preparative regimens.

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