



Fanconi Anemia: Myelodysplasia as a Predictor of Outcome

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ABSTRACT: *The adverse potential of the development of myelodysplastic syndrome (MDS) in Fanconi anemia (FA) was examined in a retrospective study of 41 FA patients who had bone marrow morphology and chromosomes reviewed by a single group. Thirty-three patients had adequate cytogenetic studies, and 16 (48%) had one or more abnormal studies: nine initially, and seven more on follow-up. Cytogenetic clonal variation was frequent, including disappearance of clones, clonal evolution, and appearance of new clones. The estimated five-year survival with a cytogenetic clone is 0.40, compared to 0.94 without a clone. Morphologic myelodysplasia (MDS), independent of a cytogenetic clone, was found in 13/41 patients (32%). The estimated five-year survival with MDS is 0.09, versus 0.92 without MDS. Leukemia developed in three patients whose initial cytogenetic clones prior to leukemia were t(1;18), t(5;22) and monosomy 7; the one with t(1;18) also had MDS. Our results focus on marrow morphology, and suggest that morphologic MDS may be more important than classical cytogenetics in prediction of an adverse outcome. © Elsevier Science Inc., 2000. All rights reserved.*

INTRODUCTION

Fanconi anemia (FA) is an autosomal recessive disorder manifest by a variety of characteristic congenital anomalies and a high incidence of bone marrow failure [1, 2], as well as an increased rate of malignancies, including leukemia and solid tumors [3]. Although the underlying biochemical defect in FA remains elusive, there appear to be at least eight different genes responsible for the FA phenotype [4]. Myelodysplastic syndrome (MDS) is not uncommon in FA patients, and its presence tempts physicians to recommend potentially curative but also potentially risky bone marrow transplantation (BMT). This is reasonable if there is an HLA-matched sibling (SIB) donor, but it is less compelling in the face of an alternative donor such as a mismatched family member or a matched unrelated donor (MUD), where the anticipated survival is reduced from >70% to <25% [5]. Data on the incidence of MDS in FA

are sparse, and the range includes 11%, 14%, and 34% of patients in three separate cross-sectional studies [6–8].

In general, MDS is classified according to the French–American–British (FAB) criteria [9], using morphologic criteria which are usually associated with pancytopenia and a hypercellular marrow. Although the diagnosis of MDS in non-FA patients often includes a marrow cytogenetic clone in addition to specific morphologic findings, a cytogenetic clone in FA might not have the same significance as in non-FA patients. The presumed underlying defect in DNA repair in FA might itself contribute to the appearance and persistence of hematopoietic clones. It is important to identify which criteria of clonality and/or MDS might be predictive of an adverse outcome, that is, cytogenetic clonality per se or the morphologic features of the marrow, and to reserve risky and experimental therapies for patients who have the appropriate adverse prognostic characteristics.

The distinction between morphologic MDS and clonal cytogenetics in FA is not clear from the literature. Only three of the reported 69 cases of FA with MDS did not have a clone, which may reflect the bias of the reporting [summarized in 3, 10, 11]. This distinction is also not apparent from the International Fanconi Anemia Registry (IFAR) data, in which acute myelogenous leukemia (AML) and MDS were combined, thus precluding an analysis of the outcome of MDS itself, either morphologic or cytogenetic [8]. Among the 69 literature cases of FA with MDS, ten developed leukemia within one-and-a-half years of de-

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tection of a cytogenetic clone, while 59 did not develop leukemia at up to 13 years. There were 25 deaths in the cytogenetic clonal group without leukemia at up to six years. Eleven were from infection, five from BMT complications, two from hemorrhage, and one each from renal cancer, renal failure, and MDS with Sweet syndrome.

The literature reports of FA indicate that there is cytogenetic clonal fluctuation [12]. One patient with morphologic MDS did later develop a cytogenetic clone, and four who had cytogenetic clones developed new clones prior to the appearance of leukemia. Thirteen of 22 who had serial marrow chromosome studies and who did not develop leukemia also had the appearance of new cytogenetic clones. Clones often disappeared, reappeared, evolved, or were replaced by entirely new clones.

Chromosome 1 was involved in 40% and chromosome 7 in 20% of the ten patients who did develop leukemia, and 31% and 26%, respectively, of the 59 patients who did not develop leukemia. Thus, there was no specific chromosomal clone which was strongly associated with the later development of leukemia.

We previously reported 17 patients, in whom three of 11 (27%) with adequate cytogenetic studies had clones, one of whom had morphologic MDS. Three others had MDS with normal chromosomes. None of the patients had developed leukemia or died within up to two years of follow-up [12]. We now describe longer follow-up of those patients, and include an additional 24, leading to 41 patients seen by only two clinical physicians, with bone marrows examined by only two individuals, thus substantially narrowing the window of subjectivity. We have focused on morphologic MDS as an independent variable, and suggest that it is the single most important predictor of adverse outcome.

METHODS

Patients had FA proven by detection of increased blood lymphocyte chromosome breakage with diepoxybutane and/or mitomycin C. Patients were seen by BPA from 1980 to 1998, and by RAD from 1992 to 1998. They include all FA patients seen at the hospital of record for each physician, with only the requirement that they have representative bone marrow material which was reviewed by BPA and/or MTE. No patient had leukemia at the time of entry. Forty-one patients are included in this analysis; 31 had marrow slides reviewed by one hematopathologist (MTE), and the other ten marrows had been previously examined by BPA but were no longer available for MTE to evaluate. Cytogenetic studies were usually performed at the center where the bone marrow was obtained. All patients had bone marrow chromosomes examined, although these studies were eventually successful on at least one occasion (i.e., 20 to 50 adequate cells) in only 33 patients. Karyotypes were interpreted based on ISCN guidelines [13]. Cytogenetic clonality was diagnosed if two or more cells had the same abnormality, while clonal chromosome loss required three affected cells. Single cell abnormalities were also considered clonal if they had been previously identified as clonal abnormalities in that patient. Patients

for whom marrow cytogenetic studies were inadequate were analyzed separately. Follow-up information was obtained from the personal practices of BPA or RAD, and from the current physician for the patients. The results reported in this paper expand upon the earlier report of the first 17 cases, and focus on the importance of morphologic analyses [12].

The features of morphologic MDS are specific for each lineage. Erythroid characteristics include megaloblastosis, multinuclearity, nuclear fragments, increased immature erythroblasts, and ring sideroblasts. Myeloid dysplasia involves increased immature forms, hypo- or hyper-granulation, and hyposegmentation. Dysplastic megakaryocytes are small, hypo- or hyper-lobulated, or have an increased nuclear/cytoplasmic ratio. In our study, the major criterion for MDS was overt dysplasia; that is, at least two cell lines with dysplasia in at least 20% of the cells. Intermediate criteria for MDS included suggestive dysplasia; that is, only a single lineage which met criteria. Minor criteria for MDS were neutrophilic myeloperoxidase (MPO) deficiency, increased marrow dual esterase (DE) positivity, periodic acid Schiff (PAS) positive erythroblasts, or $\geq 15\%$ ring sideroblasts [14, 15]. Morphologic MDS was only diagnosed if there were one major, or one intermediate plus one minor, criterion. For the purpose of this particular study, too few samples had cytochemical studies, and thus MPO, DE, or PAS results were not included, but they are mentioned because the ideal study should examine those features. The diagnosis of morphologic MDS required involvement of at least two cell lines.

The primary outcome for our study was death from any cause, since there were too few cases of leukemia in the generally brief follow-up period. Survival probabilities were calculated using the Kaplan-Meier method. Mortalities of two groups were assessed using normal approximation at the 0.05 level of significance [16].

RESULTS

There were 41 patients in this analysis—20 males and 21 females. The age at which the first evaluable marrow study was performed ranged from two-and-a-half to 37 years. Twenty patients had either morphologic MDS, a cytogenetic clone, or both, while 14 had neither, and seven had no MDS but were unevaluable for cytogenetics. Nine of those with MDS, clones, or both died (45%), whereas none of those with neither feature died; this difference is significant ($P = 0.011$). The estimated five-year survival probability from the earliest abnormality with MDS and/or a cytogenetic clone was 0.24, compared to one for those patients with neither MDS features nor a clone (Table 1 and Fig. 1). Thus, the classical classification of MDS, which includes clonal cytogenetics, has a poor prognosis in FA. However, our study also examined clonal cytogenetics and morphology of MDS independently in order to identify the most important risk factors.

Cytogenetics

Thirty-three patients had adequate bone marrow cytogenetic studies on at least one occasion. Ten patients had a

Table 1 Outcomes in Relation to Clonality and Morphologic MDS

	Risk of MDS and/or Clone						Risk of MDS		Risk of MDS and Clone			Risk of MDS or Clone		
	MDS and/ or Clone		No MDS	Risk of Clone			MDS+	MDS-	MDS+	MDS-	MDS+	MDS-	MDS+	MDS+
	No MDS or Clone	No MDS Clone?	Clone+	Clone-	Clone?	Clone+								
Total no.	20	14	7	16	25	8	13	28%	9	14%	7	7	3	1
Dead	9	0	1	7	3	2	8	2	6	0	1	1	1	1
% of Total	45%	0%	14%	44%	12%	25%	62%	7%	67%	0%	14%	14%	33%	100%
<i>P</i>		0.011	0.32		0.033	0.655		0.001		0.002	0.112		1	0.537
AML no.	3	0	0	3	0	0	1	2	1	0	0	2	0	0
% of Total	15%	0%	0%	19%	0%	0%	8%	7%	11%	0%	0%	29%	0%	0%
Median Survival (Yrs)	3.5	>10	>9	4.5	>10	>10	3	>10	5	>10	>10	>7	>5	1
2-Yr Probability of Survival	0.63	1	0.85	0.76	0.94	0.71	0.56	0.92	0.76	1	0.85	0.82	0.60	0
5-Yr Probability of Survival	0.24	1	0.85	0.40	0.94	0.71	0.09	0.92	0.31	1	0.85	0.82	0.60	0

Clone+ = meets criteria for cytogenetic clonality. MDS+ = meets criteria for morphologic MDS. Clone? = inadequate cytogenetics. *P* values refer to the data in that column compared with data in the first column of each group.

Abbreviation: AML, acute myelogenous leukemia.

clone in the first marrow examined, providing a 30% cross-sectional incidence, while six developed a clone on follow-up, leading to a total of 16, or a 48% cumulative rate. The clones which were identified are listed in Table 2. The age at which a clone was first documented ranged from four to 27 years. Chromosome results were available on more than one occasion in 15 patients, 14 of whom had a clone in at least one study. There were several patterns of clonal fluctuations in ten patients. Six patients had normal cytogenetic studies on their first marrow, and developed a clone between one and six years later (KA, RH, TL, JM, AM, and JP). Four patients had normal chromosome studies on at least one occasion after a clone had been detected (KA, KF, JM, and TS). In three patients, the original clone reappeared (KA, KF, and TS), two patients had clonal evolution (DD and KF), five had persistence of the original clones (TG, LK, AM, KO, and MP), and in two patients the original clone was either replaced by a new clone, or a new independent clone appeared in addition to the original (CD and AN). AN is especially interesting in that he developed an independent clone while the original clone disappeared. One of the original clones then reappeared later, with additional related clones. This previously reported patient had at least four different clones [12]. The patients with persistent clones subsequently developed MDS, while the two patients whose clonal abnormalities disappeared and then reappeared without clonal evolution have not developed MDS so far (KA and TS).

Seven of the 16 (44%) patients with a cytogenetic clone died at a median of three years (range one to seven years) after the appearance of the first clone, while nine patients who are alive with a clone have been followed for a median of two years (range one-half to seven years) (Table 1 and Figure 2). There were only three deaths among the 25 (12%) patients who either did not have a clone or whose cytogenetics were inadequate, all within one year. The

five-year probability of survival after detection of a clone is 0.40, compared to 0.94 without a clone, and 0.71 with unevaluable cytogenetics. The causes of death were AML in two patients at one and three years after the clone was documented, complications from matched unrelated (MUD) BMTs in two patients at two and five years, and complications of MDS in three patients at one, five and seven years. The patient with a clone who died from AML within a year did not have MDS, while all other patients who died did have MDS (see following). The deaths in the three patients without a documented clone were from complications of BMT in two (one SIB and one MUD), and of MDS in one. The death rate among those with clones was significantly different from the rate in those without clones (*P* = 0.033).

Figure 1 Probability of survival in FA patients with classical MDS, that is, morphologic MDS and/or a cytogenetic marrow clone. — MDS with or without a clone (20). - - - Neither MDS nor a clone (14). - - - - No MDS, clone not evaluable (7).

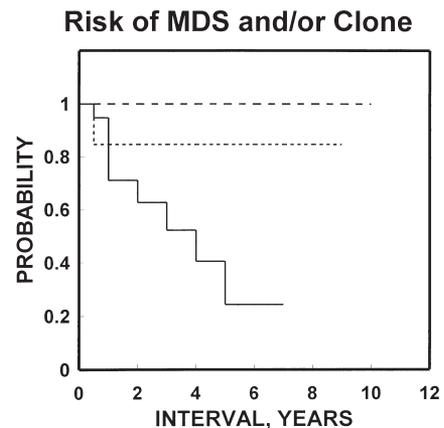


Table 2 Abnormal Karyotypes in FA Patients

KA:	1990	46,XX[25]	
	1994a	46,XX,del(13)(q12q14)[8]/46,XX[23]	
	1994b	46,XX[20]	
	1996	46,XX,del(13)(q12q14)[2]/46,XX[16]	
CD:	1997	46,XX,del(13)(q12q14)[2]/46,XX[36]	
	1992	46,XY,der(2)t(1;2)(q21;q33)[8]/46,XY[1]	
	1994	46,XY,der(2)t(1;2)(q21;q33)[19],dup(1)(q12~q21q24)[6]/46,XY[10]	
	1995	46,XY,der(2)t(1;2)(q21;q33)[6],dup(1)(q12~q21q24)[5]/46,XY[9]	
	1996	46,XY,der(2)t(1;2)(q21;q35~q37)[12],dup(1)(q21q32)[6]/46,XY[2]	MDS
	1997	46,XY,der(2)t(1;2)(q21;q36)[11]/46,XY[4]	
DD:	1998	46,XY,der(2)t(1;2)(q21;q36)[11]/46,XY[4]	
	Case 3 in (12)		
	1997a	46,XX,add(21)(q22)[18]/46,XX[1]	
	1997b	46,XX,add(21)(q22)[18]/46,XX[1]	
	1998a	46,XX,add(21)(q22)[9]/46,idem,del(13)(q21q22)[11]	
KF:	1998b	46,XX,add(21)(q22)[9]/46,idem,del(13)(q21q22)[10]/46,XX[1]	
	1986	46,XX,(q?),+mar[19]/46,XX[5]	MDS
	1991a	46,XX[20]	
	1991b	46,XX,add(1)(p11),add(2)(q33),-6,+13[19]/46,XX[12]	
TG:	1991c	46,XX,add(1)(p11),add(2)(q33),add(6)(p11)[9]/46,XX[22]	
	1995a	46,XY,der(11)t(1;11)(q23;q23)[4]/46,idem,del(6)(p21)[2]/46,XY[14]	
	1995b	46,XY,der(11)t(1;11)(q23;q23)[2]/46,idem,del(6)(p21)[10]/46,XY[8]	
	1996a	46,XY,der(11)t(1;11)(q23;q23)[4]/46,idem,del(6)(p21)[3]/46,XY[13]	
	1996b	46,XY,der(11)t(1;11)(q23;q23)[6]/46,idem,del(6)(p21)[1]/46,XY[13]	
	1997a	46,XY,der(11)t(1;11)(q23;q23)[6]/46,idem,del(6)(p21)[14]	MDS
LG:	1997b	46,XY,der(11)t(1;11)(q23;q23)[2]/46,idem,del(6)(p21)[16]/46,XY[2]	
	1989	46,XX,t(q?;q?) [20]	
RH:	1990	N/A	AML
	1996	46,XX[20]	
LK:	1997	46,XX,add(14)(p11.2)[4]/46,XX[16]	
	1991a	46,X,-X,+mar[6]/46,XX[9]/46,X,(X;3)(p22.2;q13)	
	1991b	46,X,der(X)t(X;3)(p22.2;q13),+3[20]	
	1993	46,X,der(X)t(X;3)(p22.2;q13),+3[43]/46,X,der(X)t(X;3)(p22.2;q13),del(7)(p15)[1]/46,XX[1]	MDS
	1994	46,X,der(X)t(X;3)(p22.2;q13),+3[20]	
	1995	46,X,der(X)t(X;3)(p22.2;q13),+3[32]	
TL:	1997	46,X,der(X)t(X;3)(p22.2;q13),+3[29]	
	1997	46,XX[20]	MDS
JM:	1998	46,XX,del(7)(q31.2)[6]/46,idem,add(1)(p36.1)[9]/46,XX[5]	
	1993	46,XX[9]	
	1996	46,XX,inv(16)(p11.2q11.1)[20]	
AM:	1997	46,XX[20]	
	1991	46,XY[16]	
	1992	46,XY[16]	
	1993	46,XY[20]	
	1996a	47,XY,+i(1)(q10)[3]/46,XY[17]	
AN:	1996b	47,XY,+i(1)(q10)[2]/46,XY[18]	
	1997	47,XY,+i(1)(q10)[15]/46,XY[6]	MDS
	1991	46,XY,dup(1)(q12q31)[20]/46,XY,der(18)t(1;18)(q12;p11.3)[3]/46,XY,del(6)(p21p24)[2]/46,XY[14]	MDS
	1992	46,XY,add(4)(p15.4)[23]/46,XY[2]	
	1993a	46,XY,add(1)(p21.1)[6]/46,XY[2]	
	1993b	46,XY,der(18)t(1;18)(q12;p11)[19]/46,idem,del(12)(p12.1)[2]	
	1994	46,XY,der(18)t(1;18)(q12;p11)[2]	AML
Case 1 in (12)			
KO:	1993	49,XX,+X,+8,+21[50]	
	1996	49,XX,+X,+8,+21[20]	MDS(RARS)
JP:	1991a	46,XY[30]	
	1991b	46,XY[16]	
	1993	46,XY[30]	
	1997a	46,XY[30]	
	1997b	45,XY,-7[9]/46,XY[11]	
	1998	N/A	AML

(Continued)

Table 2 Continued

MP:	1997	46,XX,dup(1)(q21q25)[3],dup(1)(q21q42)[2],del(7)(q31)[15],del(11)(q21q25)[19],add(17)(q25)[2],der(20)t(1;20)(q10;q13.3)[20][cp22]	MDS
	1998	46,XX,dup(1)(q21q42)[3],del(7)(q31)[3],del(11)(q21q25)[3],der(20)t(1;20)(q10;q13.3)[3][cp10]	
TS:	1991a	46,XY,del(3)(q22q24)[2]/46,XY[11]	
	1991b	46,XY[12]	
	1992	46,XY,del(3)(q22q24)[2]/46,XY[8]	
	1993	46,XY,del(3)(q22q24)[2]/46,XY[44]	
	1994	46,XY[39]	
	1995	46,XY[21]	
	1998	46,XY[20]	
	Case 2 in (12)		

Three patients (CD, AN, and TS) were reported previously in [12]. The occurrence of morphologic MDS or AML is indicated on the right, at the year in which it occurred.

Abbreviations: MDS, myelodysplastic syndrome; AML, acute myelogenous leukemia; N/A not available; RARS, refractory anemia with ring sideroblasts.

The major clones are listed in Table 2. Chromosome 1 was involved alone or in combinations in seven patients; chromosome 7 in four patients, chromosome 6 or 13 in three patients; chromosomes 2, 3, 11, 21, and X in two patients each, and the others in only a single patient. AML developed in three patients, with t(1;18), t(5;22), and monosomy 7, at three years, one year, and nine months, respectively. Two patients with del(7)(q31) have not developed leukemia at six and 12 months. Since there are only 16 patients with clones, the numbers are too low to draw conclusions with regard to the leukemogenic implications of specific clones.

Morphologic Myelodysplastic Syndrome (MDS)

All patients had adequate bone marrow material which could be analyzed. Thirteen (32%) of these patients had morphologic MDS diagnosed on one or more occasions. In three, MDS was noted on the first available specimen; in the other ten, MDS was documented to have evolved following a marrow examination which did not show MDS. The interval from the first non-MDS marrow to morphologic MDS ranged from one to seven years (mean three, median two). Among the 28 patients who have not had MDS, follow-up marrows have been done for up to 10 years (mean and median four). One of the three patients who developed AML did have MDS for three years, although all three had a cytogenetic clone detected prior to overt AML.

Eight of the 13 (62%) patients with MDS died within five years of detection of the MDS; only two of 28 (7%) without MDS died, both within the first year (Figure 2, Table 1). Survivors with MDS have been followed for a median of two years (range one to five years), and those without MDS for a median of two years (range one-half to 10 years). The five-year probability of survival after MDS is only 0.09, while it is 0.92 without MDS. The death rate with MDS is very significantly higher than the rate without MDS ($P = 0.001$). The causes of death in the MDS-positive group are listed above for the six patients who also had a cytogenetic clone. One patient who had MDS without a clone died following an MUD BMT, and one died from complications of MDS. The deaths in the two patients without MDS were AML at one year, and following a SIB BMT at six months. Three patients had successful

HLA-matched SIB BMTs within two years of their MDS-negative bone marrow examination.

MDS plus a Cytogenetic Clone

A total of nine patients had both MDS and a clone. Among three who survive to date, MDS preceded the clone by six months in one, and MDS followed the clone in the other two by one and four years. In three of the six who are deceased, MDS and the clone were concurrent, while clonality preceded MDS in one patient by one year, and in the other two patients by three years. No patient with both MDS and a clone was alive at five years; the poor prognosis associated with the combination ($P = 0.002$) was primarily related to the MDS component.

All combinations of the presence or absence of cytogenetic clones and the presence or absence of morphologic MDS were also analyzed (Table 1 and Fig. 2). The estimated survivals were worse in combinations with MDS than those without, although the numbers of patients in some groups were small. The results suggest that morphologic MDS conveys a bad prognosis, and is more important than clonal cytogenetics. Patients with both MDS and clonal cytogenetics had the worst prognosis.

DISCUSSION

This report is the first in which a relatively large number of FA patients was monitored by a single group of physicians and hematopathologists, providing a consistency of interpretation of laboratory findings. The primary outcome for our analysis was death from any cause, since the number of cases of leukemia so far is only three, too small for statistical correlates.

Half of those in our series who had one or more adequate cytogenetic studies have had a clone identified; this number might increase with time, and with additional repeat marrows. Cytogenetic clonal fluctuation was common, although this may be an epiphenomenon, due to the small numbers of metaphase cells which are analyzed in a classical marrow cytogenetic study; namely, 20 to 30 cells. New techniques such as fluorescence in situ hybridization (FISH) offer the prospect of examination of a large number of interphase cells, which will provide statistical power to the meaning of a "clone," particularly in cases in which

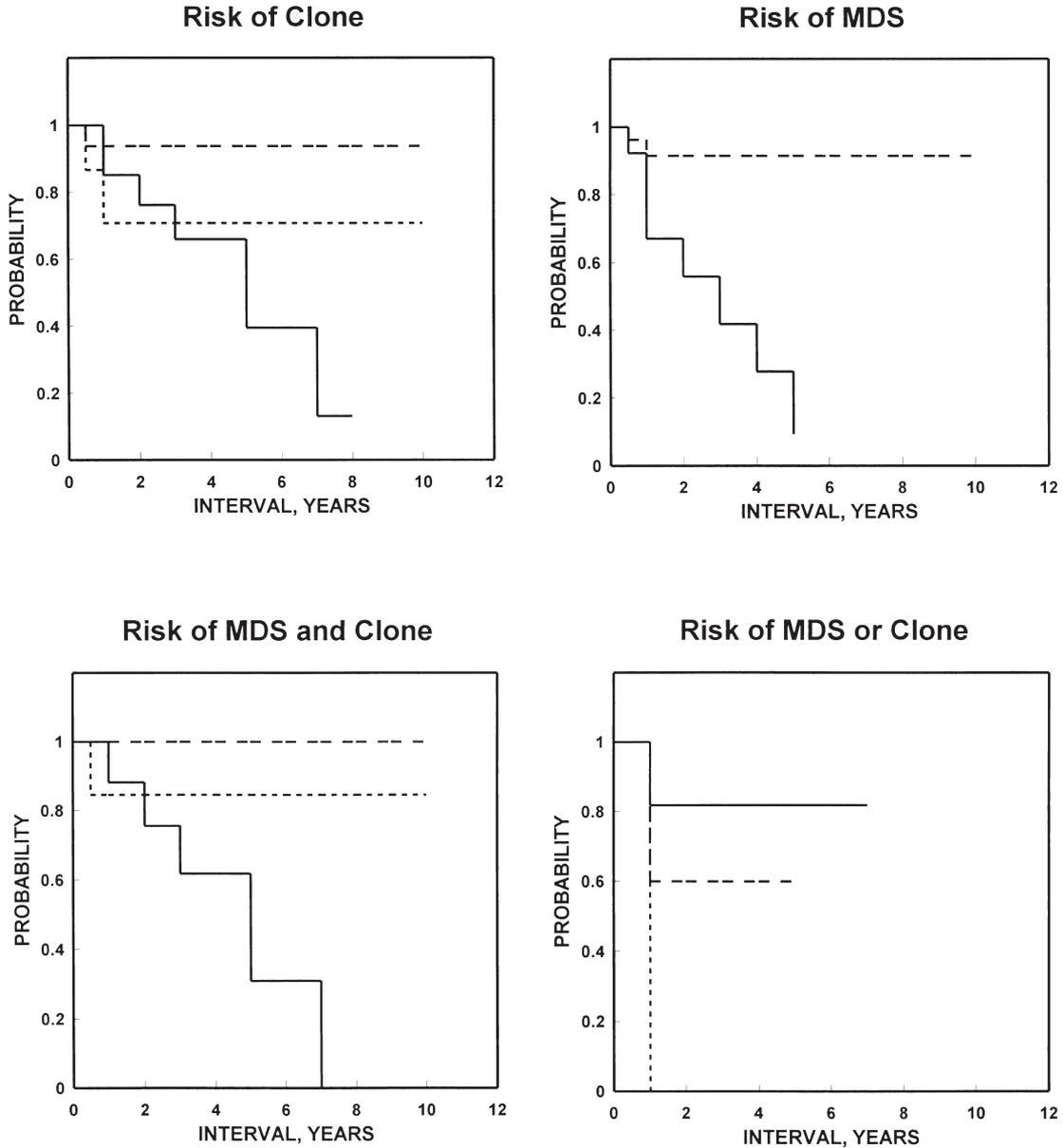


Figure 2 Probability of survival in FA patients with and without all combinations of MDS or a marrow clone. Upper left, ——— Clone-positive (16). - - - Clone-negative (17). - - - Clone not evaluable (8). Upper right, ——— MDS-positive (13). - - - MDS-negative (28). Lower left, ——— MDS-positive and clone-positive (9). - - - MDS-negative and clone-negative (14). - - - MDS-negative and clone not evaluable (7). Lower right, ——— MDS-negative and clone-positive (7). - - - MDS-positive and clone-negative (3). - - - MDS-positive and clone not evaluable (1).

an abnormality has been identified using classical cytogenetics which can now be pursued with FISH. FISH may also be useful for examination of candidate chromosomes, such as 1, 6, 7, or 13 according to our data, or those often involved in non-FA MDS, such as 5 or 20, etc. Use of more sophisticated techniques may also increase the number of patients found to have a clone. In a recent study of an FA patient, Thurston et al. found that FISH was able to identify monosomy 7 19 months prior to its detection by classical cytogenetics [17]. Nine other FA patients did not have monosomy 7 by either cytogenetics or FISH and will be monitored closely.

Since identification of a clone is in part dependent on technique, the significance of its presence or absence requires further scrutiny. We chose to define a patient as “clonal” if they ever had a cytogenetic clone using conventional marrow cell cultures, but this does not exclude the possibility that all patients are “clonal,” if the proper study were performed. Failure to see a clone, or failure to obtain material suitable for cytogenetic analysis, should not be construed as proof that a patient is “nonclonal.”

The prognostic implication of the duration of a documented clone is unclear, since patients have been followed for more than seven years with or without a clone,

and deceased and surviving patients were also followed for equal lengths of time. The prognosis of the type of clone is also not clear. Only four of our 16 patients with clones had involvement of chromosome 7. The one with monosomy 7 (JP) developed AML nine months after that clone was noted; the one with 7p- in one cell (LK) developed MDS and died four years later; one with del(7)(q31) (MP) died with MDS within one year; and one with del(7)(q31) (TL) had MDS without leukemia at one year. The other clones seen in our patients who developed leukemia were t(1;18) and t(5;22); however, most of the clones which we saw have been associated with leukemia in other contexts. There is also no predictive value of clonal fluctuation, except to indicate that it does happen, perhaps as a result of the insensitivity of classical cytogenetic analyses.

The presence of morphologic evidence for MDS is more strongly associated with a poor prognosis than is the presence of a cytogenetic clone in the absence of morphologic MDS. More than half of those with MDS died within five years of the appearance of MDS. Those who survive with MDS are also within five years of the detection of the MDS, while patients without MDS have been followed for up to ten years. Only two died without overt MDS: one from AML and one following an SIB BMT for aplastic anemia. These observations suggest that stable or even progressive aplastic anemia without MDS might be managed conservatively, with BMT considered only if there is an HLA-matched sibling donor.

The development of MDS may be heralded by improving blood counts and a decrease in androgen-dependence [12, 18]; this was seen in our case AN [12, other data not published]. Such improvement implies that a careful examination of the bone marrow is indicated, and may not be a cause for celebration. Although cytogenetic clones are often associated with morphologic MDS, our data so far suggest that the marrow morphology is a more important determinant of outcome than is the cytogenetic result. The diagnosis of morphologic MDS should be made according to stringent criteria, as defined in Methods, and additional prospective studies such as ours will be useful in the determination of critical adverse risk factors in FA. Future studies need to address clonality with more sophisticated methods such as FISH, and to examine cytochemical markers of MDS, as well as expression of specific oncogenes. Choices with regard to experimental and potentially risky treatments may be facilitated by determination of the detailed risk profile of the patient.

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