



## Identification of a group of AML/MDS patients with a relatively favorable prognosis who have chromosome 5 and/or 7 abnormalities

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### ABSTRACT

**Background and Objectives.** Patients with AML, RAEB-t, or RAEB and abnormalities involving chromosomes 5 and/or 7 (-5, -7) generally, but not always, have poorer prognoses than patients with a normal karyotype. Our objective was to see whether the occasional relatively favorable outcome in -5/-7 patients is a random event or, rather, reflects true heterogeneity in -5/-7.

**Design and Methods.** We examined 3 factors known to be prognostic in AML for their prognostic significance in 400 -5/-7 patients treated at the M.D. Anderson Cancer Center from 1980-1998 for AML or MDS. The outcome of comparative interest was survival as assessed by log-rank test.

**Results.** There was evidence that outcome was better in -5/-7 patients with a simple (rather than complex) karyotype, with > 1 normal metaphase (rather than only metaphases containing -5/-7), and without an antecedent hematologic disorder. More importantly, the 10% of the patients with a simple karyotype, > 1 normal metaphase, and no antecedent hematologic disorder not only had a better outcome than the other -5/-7 patients but had essentially identical outcomes to the 669 AML/MDS patients with a normal karyotype treated at M.D. Anderson during the same period.

**Interpretation and Conclusions.** The results indicate that the -5/-7 group should not *a priori* be regarded as having an unfavorable prognosis, and more generally suggest the need to refine prognosis within each of the cytogenetic subsets of AML.

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It is clear that patients with acute myeloid leukemia (AML) characterized by monosomy of chromosomes 5 and/or 7 (-5, -7) or by deletion of long arms of these chromosomes (5q-, 7q-) have, *on average*, worse outcomes following anthracycline + ara-C regimens than patients with AML and a normal karyotype.<sup>1,2</sup> The prognostic significance of -5, 5q-

-7, and/or 7q- (-5/-7) appears to be the same in patients with refractory anemia with excess of blasts (RAEB) or RAEB-t given AML-type chemotherapy as in AML patients.<sup>3</sup> The words *on average* are important. Indeed, several time-to-death or time-to-relapse analyses in patients with -5/-7 indicate that a small minority of patients with these perhaps most prognostically unfavorable of abnormalities do relatively well.<sup>1,2,4,5</sup> This observation could reflect either random fluctuation or a true lack of homogeneity within the -5/-7 group. This paper explores whether factors predictive of longer survival can be identified in this group.

### Design and Methods

Four hundred adults with newly-diagnosed AML (265 patients), RAEB-t (79 patients) or RAEB (56 patients) and -5, 5q-, -7, or 7q- received treatment in our institute from 1980-1998. Standard criteria were used to establish the presence of these abnormalities.<sup>6</sup> Specifically, 5q- was considered present only if two or more cells showed this abnormality and the same applied for 7q-. -5 was considered present only if three or more cells showed this abnormality and the same applied for -7. If a cytogenetic abnormality associated with a better prognosis, e.g. t(8;21), inv(16), was present in addition to an abnormality of chromosomes 5 and/or 7, the patient was considered to have the better prognosis abnormality and was not included in this data set. The patients had a median age of 62 years. Only 3 had 7q 32 breakpoints. In 19% of the AML and 32% of the MDS patients, the leukemia or MDS was considered a result of chemotherapy for a prior malignancy. Regimens given to the patients were: '3+7'-like to 33 patients, high-dose ara-C + anthracycline to 142 patients, high-dose ara-C + fludarabine to 214 patients, and miscellaneous to 33 patients.

Based on previous results in all patients with AML, we examined 3 characteristics as potential prognostic factors in the -5/-7 group. These 3 factors were: (i) presence of a complex rather than a simple karyotype, (ii) presence or absence of > 1 cell with a normal karyotype in addition to the clone with -5, 5q-, -7, or 7q-, and (iii) presence or absence of an antecedent hematologic disorder (AHD). A complex abnormality was defined as one in which two or more separate clones, defined using standard criteria, were present while an abnormality was considered simple regardless of the number of changes present provided only one clone was involved. An AHD

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was defined as a documented abnormality in blood count (Hb < 12 g/dL, neutrophil count < 1,500/ $\mu$ L, WBC > 15,000/ $\mu$ L, or platelet count < 150,000/ $\mu$ L) present for at least one month prior to presentation at M.D. Anderson. Time-to-event analyses were done using the Kaplan-Meier method. Curves were compared using the log-rank test.

## Results

Three hundred and fifty-nine of the patients (90%) were dead after a median follow-up time of 35 weeks (range 4-564) in the living patients (Figure 1). Three hundred and eighty-two of the patients (96%) failed initial induction or post-remission therapy, i.e. died during this therapy, failed to enter CR or had disease recurrence after an initial CR. The CR rate was 40%. Once in initial CR the median disease-free survival time was 23 weeks with recurrences documented in 77% of the patients and deaths in CR occurring in 12%.

Despite these generally poor outcomes, there were suggestions that patients with simple abnormalities lived longer than patients with complex abnormalities ( $p < 0.001$ , Figure 2), that patients with  $\geq 1$  normal metaphase admixed with abnormal metaphases lived longer than patients with no normal metaphases ( $p = 0.03$ , Figure 3), and that patients without an AHD lived longer than patients with an AHD ( $p = 0.04$ , Figure 4). Results were the same when disease-free survival became the endpoint. The better results in patients with simple abnormalities resulted from better disease-free survival once in CR ( $p < 0.001$ ) rather than from a higher CR rate (40% in both simple and complex groups). Patients with  $\geq 1$  normal metaphase and patients without an AHD had better outcomes due equally to a higher CR rate and longer disease-free survival in CR.

Although the differences between patients in each of the 3 groups appear trivial (although statistically significant), differences became more marked when we used all 3 factors to divide the 400 patients into 8 groups. Seven of the 8 groups had largely identical survivals but the group with simple abnormalities,  $\geq 1$  normal metaphase, and no AHD not only lived longer than the other 7 groups (Figure 5) but also had a similar survival to that of the 669 AML/MDS patients with a normal karyotype given the same chemotherapy regimens during the same time period (Figure 6). Conclusions were essentially the same when disease-free survival or disease-free survival in CR was the endpoint. CR rate varied between 28% and 55% in the seven worse -5/-7 groups (the legend to Figure 5 defines these), was 71% in the better -5/-7 group and was 68% in the normal karyotype group. Median age in the better -5/-7 group was 56 years and was 58 years in the patients with a normal karyotype. Eighteen percent of the former and 10% of the latter had a poor pre-treatment performance status (Zubrod >2). Thirty-six percent of the patients with a normal karyotype had had an AHD.

## Discussion

Our results indicate that complexity of karyotype, an AHD and/or residual normal metaphases are prognostic in patients with -5, 5q-, -7, or 7q-. While these

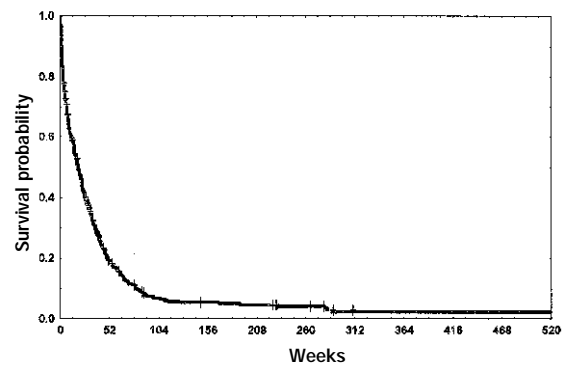


Figure 1. Probability of survival in 400 patients in the -5/-7 group. Median is 18 weeks.

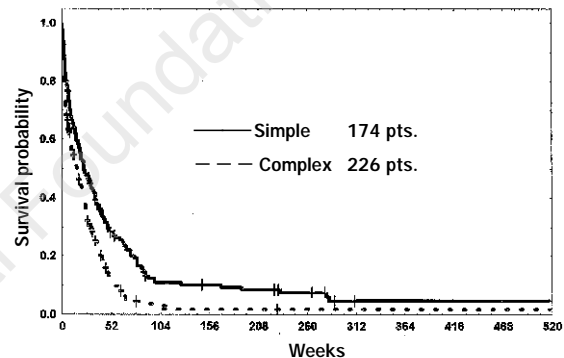


Figure 2. Probability of survival in the 400 patients according to presence (226 patients) or absence (174 patients) of complex abnormalities.  $p$  value < 0.001.

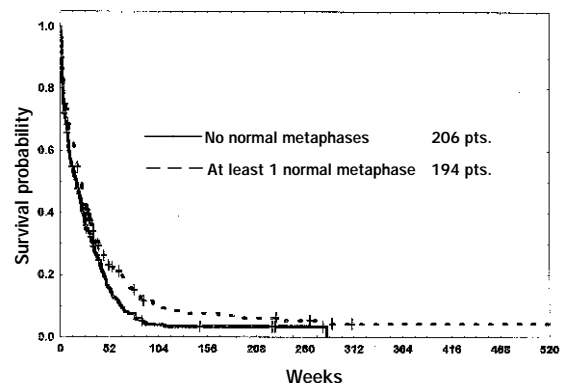


Figure 3. Probability of survival in the 400 patients according to presence (194 patients) or absence (206 patients) of  $\geq 1$  normal metaphase.  $p$  value = 0.03.

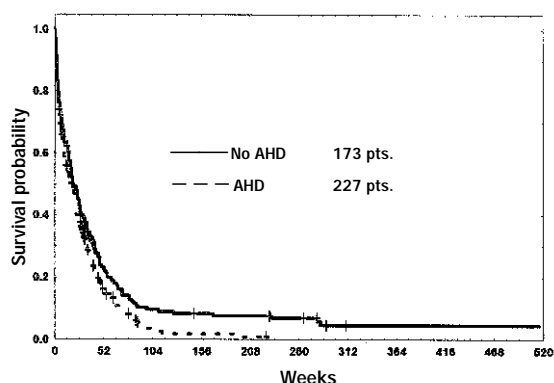


Figure 4. Probability of survival in the 400 patients according to a history (227 patients) or lack of history (173 patients) of an AHD.  $p$  value = 0.04.

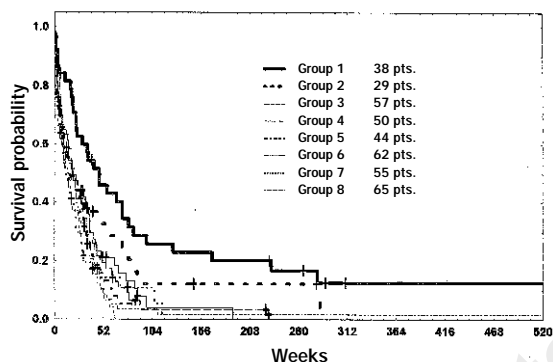


Figure 5. Probability of survival in the 400 patients according to Group.

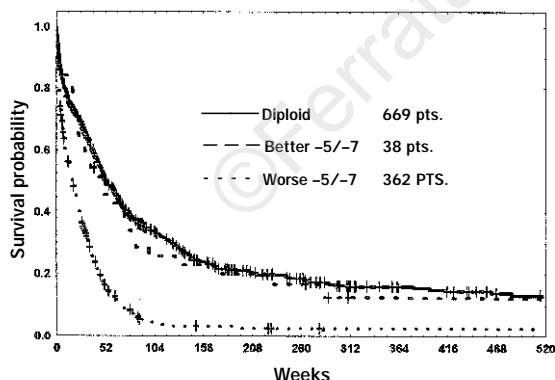


Figure 6. Probability of survival in patients with -5/-7, simple abnormalities,  $\geq 1$  normal metaphase, and AHD, other -5/-7 patients, and patients with a normal karyotype ( $p < 0.001$ ).

factors are well known to be associated with prognosis in AML, it is less clear that they have a prognostic value within the subset of patients with -5/-7. Swansbury *et al.* have pointed out that patients with del 7q as their sole cytogenetic abnormality live longer than other patients in the -5/-7 group.<sup>2</sup> Only 11 patients

Table 1.

Group	Patients	Complex or Simple	> 1 Normal metaphase	AHD
1	38	Simple	Yes	No
2	29	Simple	No	No
3	57	Simple	Yes	Yes
4	50	Simple	No	Yes
5	44	Complex	Yes	No
6	62	Complex	No	No
7	55	Complex	Yes	Yes
8	65	Complex	No	Yes

were so classified, constituting about 10% of their -5/-7 patients. Similarly, 10% of our -5/-7 patients would be considered to have a favorable prognosis, although the number of such patients in our series is 3 times higher than that in the series of Swansbury *et al.*, thus making survival estimates more reliable. Our definition of a simple abnormality will undoubtedly strike some as unusual. Standard systems would consider as complex many of the karyotypes we considered as simple. We would point out that all clinical classification systems are arbitrary and that the purpose of any such system is to produce a clinically relevant stratification, which our system does.

We believe that these results illustrate the limitations of cytogenetics as a prognostic factor in AML/MDS. Specifically, patients with -5/-7 should not be regarded *a priori* as having relatively poor prognoses since a small (10%) subset of them have a prognosis identical to that of patients with a normal karyotype. Since the normal karyotype group is also likely heterogeneous, it follows that a not insignificant number of patients with -5/-7 has a better prognosis than some patients with a normal karyotype, e.g. those with an AHD. This information has obvious implications not only when planning therapy but also when analyzing results of clinical trials. Specifically, a therapy could conceivably be thought of as useful in -5/-7 disease when favorable results with the therapy could merely reflect inclusion of a relatively large number of patients with favorable prognosis -5/-7 disease. Finally, our results indicate the need to refine prognostic expectations<sup>7,8</sup> within each of the cytogenetic subsets of AML/MDS.

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EHE and MJK collaboratively suggested the analysis and interpreted the data. EHE and SP wrote the paper and SP also collected the data. The authors wish to thank Tania Petts-Jones for her expert secretarial assistance.

**Disclosures**

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**Manuscript processing**

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**Potential implications for clinical practice**

- ◆ Not all patients with AML and monosomies of chromosomes 5 and/or 7 or deletions of the long arms of those chromosomes should be assumed to have extremely poor prognoses.
- ◆ As a corollary, there may be considerable heterogeneity within each of the various cytogenetic subsets of AML.

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