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Changes in the Characteristics of the Bone Marrow During Therapy for Acute non-Lymphocytic Leukemia: Relationship to Response to Remission Induction Therapy*

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Abstract—*The bone marrows of patients with acute non-lymphocytic leukemia being treated with 'high dose' cytosine arabinoside remission induction therapy were sampled prior to the initiation of chemotherapy, after* 6 *days of therapy and again* 7 days *after the conclusion of therapy. These studies demonstrated that the marrows of patients who would enter remission (CR patients) contained less leukemic cells prior to therapy than patients who would fail to enter remission because of persistent leukemia (resistant disese, or RD patients). A comparison of the day* 6 *and* 7*-day post-therapy marrows with the pretherapy marrow demonstrated that while the % reduction in leukemic cells was greater for CR patients than for RD patients, the absolute reduction in leukemic cell mass was the same for both groups. While there was no relationship between the percentage of cells in S phase and the pretherapy leukemic cell mass, the greater the pretherapy leukemic cell mass the greater the likelihood that the leukemic cells would be resistant to the metabolic effects of cytosine arabinoside* in vitro.

INTRODUCTION

THE FAILURE of patients with acute non-lymphocytic leukemia (ANLL) to enter complete remission (CR) can be ascribed to the presence of resistant disease (RD) or to death during induction therapy [1-3]. 'Resistant disease' *per se* has been subdivided into 'relative' drug resistance (REDR) and significant drug resistance (SDR) on the basis of the effects of remission induction therapy on the number of leukemic cells in the bone marrow 7 days after the completion of therapy [4]. We have reported that the pretherapy leukemic cell mass is a significant prognostic factor for patients being treated with remission induction therapy consisting of large doses of cytosine arabinoside (HDaraC) [5] and for first relapse patients treated with cytosine arabinoside/anthracycline antibiotic therapy [6].

The present report explores in depth the relationship between the pretherapy leukemic cell mass, the effects of remission induction therapy on leukemic cell mass, and the outcome of remission induction therapy with HDaraC. This study has demonstrated that HDaraC therapy produced the same absolute reduction in leukemic cell mass for the three different therapeutic outcome groups. Only for patients entering CR was the leukemic cell mass reduced to the level at which regrowth of normal hematopoietic elements occurred. Additionally, the percentage of cells in S phase was independent of

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the pretherapy leukemic cell mass and cellular sensitivity to araC tended to be less for patients with a high pretherapy leukemic cell mass than for patients with a low leukemic cell mass.

MATERIALS AND METHODS

Patients with acute non-lymphocytic leukemia (ANLL), as defined by the French-American-British working party [7], were eligible for this study and were treated with the Intergroup Leukemia protocol for high-dose cytosine arabinoside (HDaraC) therapy. There were 78 patients treated and studied at the time of initial diagnosis and 102 patients in first, second or third relapse. Patients ≤70 yr old were treated with a single course of 3 g/m² of cytosine arabinoside q 12 hr for 12 doses while patients ≥70 yr old received 2 g/m² [8, 9]. Table 1 provides the outcome of remission induction therapy for these patients.

The outcome of treatment was characterized as complete remission as defined by Cancer and Acute Leukemia Group B [10], or remission induction failure, which in turn was divided into failure because of resistant disease (RD or persistent leukemia) or death during induction ('other' failure) [1]. Patients were classified as RD failure if the day 13 marrow was cellular (>5% on biopsy or >1 of 4+ cellularity on aspirate) and contained leukemic cells or if leukemic cells repopulated the marrow after HDaraC therapy produced severe marrow hypoplasia. Where indicated, the RD category was divided into relative drug resistance (REDR) and significant drug resistance (SDR) subgroups, with severe marrow hypoplasia being produced in the former but leukemic cells repopulating the marrow while for the latter patients' marrow hypocellularity was not produced. This division of RD patients into two subcategories was made only on the basis of the day 13 marrow results and ultimate treatment outcome without knowledge of the pretherapy or day 6 bone marrow characteristics. Patients were defined as 'other' failures (i.e. failure not clinically ascribable to RD) if they expired early in therapy (<day 13) or if they died while their marrow was extremely hypoplastic. The distinction between RD failures and 'other' failures is important since the clinical sensitivity of the latter patient's leukemia to HDaraC is inevaluable because had the patients survived they may have entered CR (and hence had araC-sensitive leukemia) or may have produced to have RD. When assessing the reliability of a drug sensitivity assay it is important to include only those patients whose drug sensitivity is clinically evaluable [11]. This report concentrates only on CR and RD patients since the clinical relevance of the antileukemic effects of chemotherapy can only be determined from the effects of therapy for these two patient groups.

Table 1. Outcome of therapy

	CR (%)	RD (%)	Other failure (%)
All patients	54 (30)	69 (38)	57 (32)
No prior therapy	30 (38)	17 (22)	31 (40)
Relapsed patients	24 (24)	52 (51)	26 (25)

Assessment of the bone marrow characteristics of patients

Pretherapy bone marrow aspirates were available for 94 patients who had either a CR or RD outcome. One patient's marrow aspirate was a dry tap. Pre-therapy marrow biopsies were obtained for 66 of these patients. The percentage abnormal cells in the aspirate was determined by the local investigator. For patients with FAB types M1-M3 only myeloblasts and promyelocytes were considered to be abnormal cells. For FAB M4 and M5 monocytic and monocytoid cells were also considered to be abnormal. For FAB abnormal M6 erythroid elements together with myeloblasts and promyelocytes were considered to be abnormal.

Marrow biopsy cellularity was estimated by eye by the local investigator by reference to a biopsy cellularity reference chart as previously described [12]. The leukemic cell mass represents the product of the percentage of abnormal cells in the marrow aspirate and the estimated cellularity of the biopsy.

All data were recorded before the outcome of therapy was known.

[³H]T*dR labeling index and cellular sensitivity to cytosine arabinoside*

Standard [³H]TdR autoradiographic procedures were used to estimate the percentage of pretherapy marrow cells in S phase [5, 13]. Leukemic cell sensitivity to araC was estimated by measuring both the immediate effects and persistent (or delayed) effects of araC on DNA synthesis. The former represents the percentage inhibition of DNA synthesis detected when cells were incubated simultaneously with araC and [³H]TdR while the persistent effects represent a comparison of the [³H]TdR incorporation of control cells and cells which were incubated with araC for 1 hr, washed free of the drug and incubated for three additional hours in araC-free medium before the addition of [³H]TdR [5, 14].

Statistical methods

For the purpose of this study, the previously untreated and relapsed patients were analyzed

both together and separately. The data for first, second and third relapse patients were combined in the initial analysis to ensure more meaningful statistical results. These analyses demonstrated that the relationship between the pretherapy, day 6 and 7-day bone marrow characteristics and the outcome of therapy were the same for previously untreated and relapsed patients. Hence, for simplicity's sake, only the pooled data are provided in this paper.

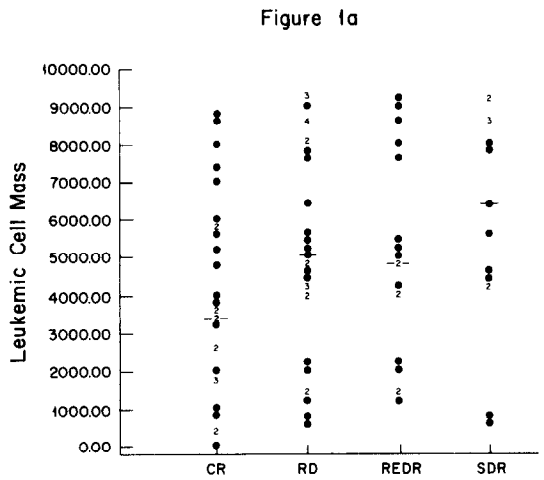
Since the distribution of the bone marrow data in the analysis was not known, the Mann-Whitney test was used to compare the data values in patients with different responses to the remission induction therapy.

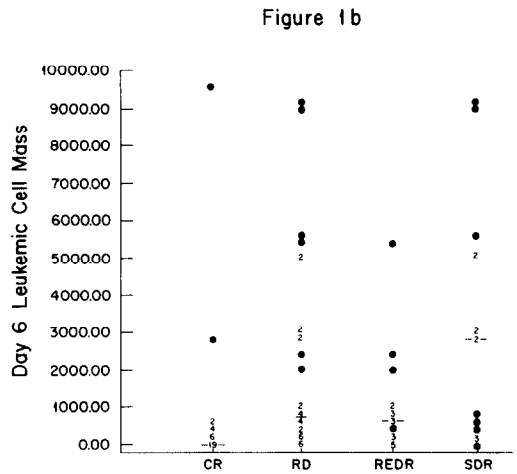
The correlations between pretherapy leukemic cell mass and properties of leukemic marrow cells are given both in terms of Pearson correlation coefficients and (for the same reason as above) both Kendall and Spearman rank correlation coefficients.

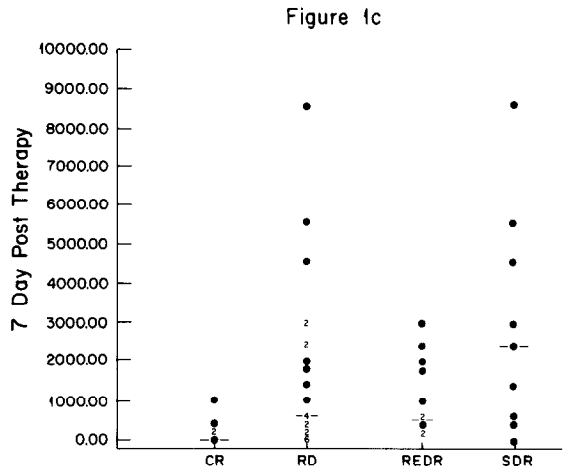
RESULTS

Relationship between pretherapy, day 6 of therapy and 7-day post-therapy bone marrow characteristics and the outcome of remission induction therapy

Prior to the initiation of remission induction therapy, after 6 days of therapy and 7 days after the







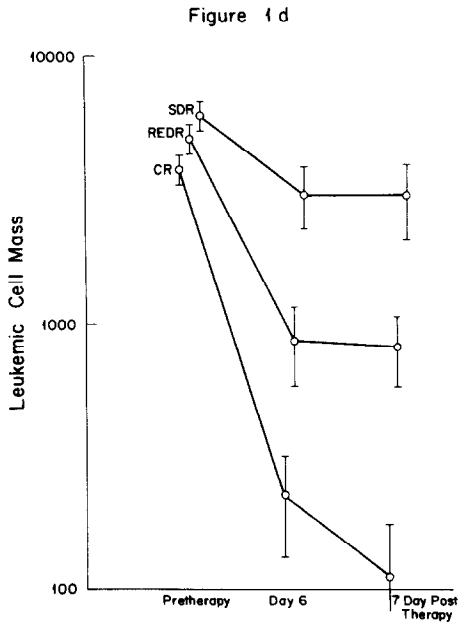


Fig. 1. Relationship between leukemic cell mass (percentage of abnormal cells × biopsy cellularity) and treatment outcome. (a) Pretherapy. (b) day 6 of therapy. Resistant disease treatment failures are presented twice: as one group (RD) and then divided into two subgroups (REDR and SDR). Numbers = No. of values coexistant at the same point; bars = median value. (c) 7 days after the end of therapy. (d) Serial changes in leukemic cell mass during and immediately after therapy. Bars indicate mean ± S.E. Median pretherapy LCM: CR = 3375, REDR = 4808, SDR = 6370. CR vs REDR, P = 13; CR vs SDR, P = 0.01; REDR vs SDR, P = 28; median day 6 LCM: CR = 63, REDR = 551, SDR = 2475. CR vs REDR, P = 0.003; CR vs SDR, P = 0.0001; REDR vs SDR, P = 0.04; median 7-day post-therapy LCM: CR = 8, REDR = 455, SDR = 2475. CR vs REDR, P = 0.001; CR vs SDR, P = 0.008; REDR vs SDR, P = 0.04.

conclusion of therapy the bone marrow of patients who would enter CR contained fewer leukemic cells than the marrow of patients who would not enter remission because of persistant leukemia. These data are provided in Fig. 1. The median pretherapy leukemic cell mass for CR patients was 3375, while it was 4917 for RD patients ($P = 0.015$; Fig. 1a). After 6 days of therapy the median leukemic cell mass of CR patients was 68, the corresponding value for RD patients being 722 ($P = 0.001$; Fig. 1b). Seven days after the conclusion of therapy the median leukemic cell masses of CR and RD patients were 10 and 600 respectively ($P = 0.001$; Fig. 1c).

Subdivision of RD patients into REDR and SDR subgroups demonstrated that the pretherapy and day 6 marrow leukemic cell mass of patients who were REDR failures was intermediate between that of CR patients and those who were SDR failures for both the pretherapy and day 6 specimens (Fig. 1a-c). For example, the pretherapy median leukemic cell mass for CR patients was 3375, for REDR patients it was 4808 and for SDR patients it was 6370. The same was true for the 7-day post-therapy marrow but since we used this marrow assessment to divide RD patients into REDR and SDR subgroups, this observation was a self-fulfilling prophecy. Similar differences were seen when the biopsy cellularities and percentage of abnormal cells of CR, REDR and SDR patients were compared (data not presented). These data demonstrate that the relative differences in the pretherapy marrow between CR, REDR and SDR patients were maintained throughout remission induction therapy and that the RD group could be divided into two subsets which maintained their differences throughout therapy (Fig. 1d).

Serial bone marrow changes during remission induction therapy for CR, REDR and SDR patients

Figure 2 presents the changes in leukemic mass during remission induction therapy from two different perspectives: as a percentage of the pretherapy leukemic cell mass and as the absolute difference in leukemic cell mass (Fig. 2a-d). Six days after the start of therapy the leukemic cell mass of patients who would enter CR was reduced to 21% of the pretherapy mass while 7 days after the end of therapy it had fallen to 11% of the initial value. For SDR patients, the percentage reduction in leukemic cell mass was significantly less than that of CR patients, having fallen only to 53% of the pretherapy value at 6 days ($P = 0.0005$ for CR vs RD) and 56% 1 week later ($P = 0.0008$ for CR vs RD). As before, the REDR patients represented an intermediate group, with the percentage leukemic cell mass falling to 29 and 25% of the pretherapy value 6 and 13 days after the start of therapy respectively.

While HDaraC therapy produced different percentage reductions in the leukemic cell mass of CR, REDR and SDR patients, it produced the same absolute reduction in leukemic cell mass for the three different outcome groups, with median reductions of 3312, 4247 and 3550 respectively after 6 days of therapy and 3367, 4388 and 3895 when the 7-day marrows were compared to the pretherapy marrow (Fig. 2c, d). Given the virtually identical absolute reduction in leukemic cell mass for the three different treatment outcome groups, the differences in the percentage reduction in leukemic cell mass for CR, REDR and SDR patients must be a reflection of the differences in initial leukemic cell mass.

Serial changes in marrow characteristics for individual patients

Between the start of therapy and the end of therapy (day 6) the leukemic cell mass fell in every patient who would enter CR (Fig. 1d) while the percentage of abnormal cells increased in 1/34 patients who would enter CR and the biopsy cellularity increased in none. In contrast, for patients who would prove to be SDR failures the leukemic cell mass increased in 2/14 patients during 6 days of therapy, the percentage of abnormal cells increased in 5/19 patients and the biopsy cellularity increased in 2/15 patients. For REDR failures the leukemic cell mass increased in 1/13 patients, the percentage of abnormal cell increased in 3/19 patients and the marrow cellularity in 1/16 during 6 days of therapy. Therefore the first 6 days of therapy produced a reduction in the number of leukemic marrow cells in virtually all patients who would enter CR. In contrast, there was a group of SDR and REDR patients for whom either the leukemic mass *per se* increased during therapy or at least the relative number of leukemic cells increased (percentage of abnormal cells).

During the week after the end of therapy (between day 6 of therapy and 7 days after the end of therapy) similar changes occurred in the bone marrows of all three outcome groups. Considering CR patients, in 3/12 patients the 'leukemic cell mass' increased between days 6 and 13. The percentage of 'abnormal' cells was greater in the 7-day post-therapy marrow than in the day 6 marrows in 18/31 patients and the biopsy cellularity increased in 4/17 patients. For SDR patients the leukemic cell mass increased between day 6 and 7 days after the end of therapy in 5/8 patients, the percentage of abnormal cells

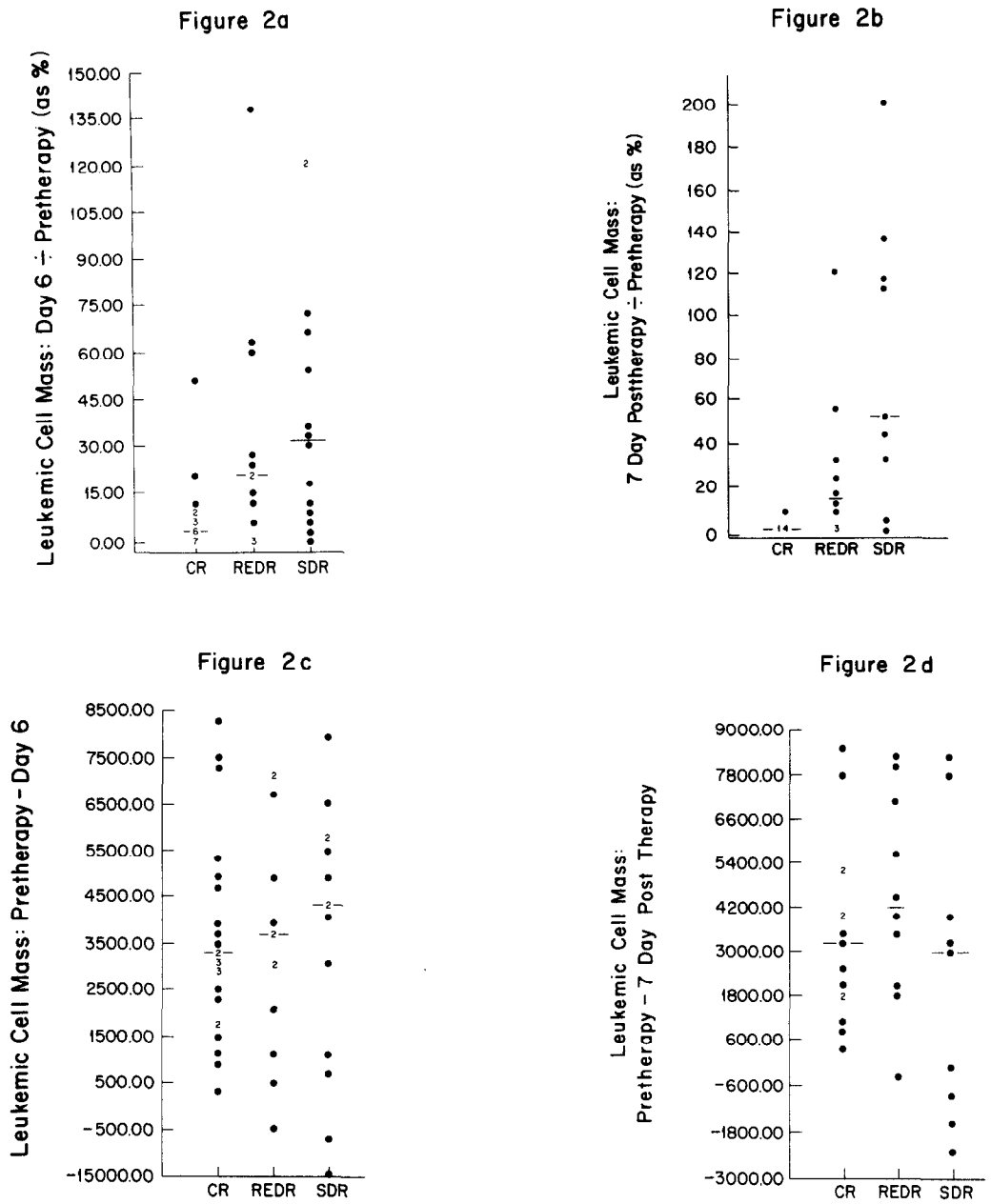


Fig. 2. Effect of HDaraC therapy on leukemic cell mass (LCM). (a) % change in LCM after 6 days *of therapy: median % reduction was* 79% *for CR patients,* 71% *for REDR and* 47% *for SDR patients respectively. CR vs REDR,* P = 0.01; *CR vs SDR,* P = 0.005. *(b) % change when the pretherapy and* 7*-day post-therapy marrows are considered: median % reduction for CR, REDR and SDR patients were* 89, 75 *and* 44% *respectively. CR vs REDR,* P = 0.002; *CR vs SDR,* P = 0.0008; *REDR vs SDR,* P = 0.11. *(c) Absolute change in LCM immediately after* 6 days *of therapy—difference between pretherapy and day* 6 *LCM. (d) Absolute change in LCM when the pretherapy and the* 7*-day post-therapy marrows are considered. Bars indicate S.E. of the mean.*

increased in 9/17 patients and the biopsy cellularity in 7/10 patients. For REDR patients the leukemic cell mass increased in 4/12 patients. The percentage of abnormal cells increased in the marrow of 7/18 patients and the biopsy cellularity increased in 11/19 patients. Hence regrowth of hematopoietic elements began quite promptly in a substantial number of patients and it was not possible to distinguish between the regrowth of normal elements (in CR patients) and leukemic elements (in RD patients) on morphologic grounds.

Relationship between pretherapy leukemic cell mass and percentage of cells in S phase and cellular sensitivity to cytosine arabinoside

[^{3}H]TdR labeling indices were measured for 27 patients whose pretherapy leukemic mass had been estimated. The correlation coefficient for the relationship between the leukemic cell mass and

the percentage of cells in S phase was not significant ($r = 0.2752$). No statistically significant correlations were detected between leukemic cell mass and the percentage of cells in S phase when patients were divided into the three treatment outcome groups.

The possible relationships between pretherapy leukemic cell mass and cellular sensitivity to araC were also explored and are provided in Table 2. Considering all the patients together regardless of treatment outcome, a weak but statistically negative correlation between leukemic cell mass and the immediate sensitivity of leukemic cells to araC at 0.3 μg and the persistence of araC effects at 3 μg/ml ($r = 0.3483$, $P = 0.02$ and $r = -0.2658$, $P = 0.06$ respectively) were detected. When the patients were divided into CR, REDR and SDR subgroups significant negative relationships were found to exist between the pretherapy leukemic cell mass of CR patients and the persistence of araC effects (at 3 μg/ml) and for SDR patients between leukemic cell mass and the immediate effects of araC (0.3 μg). Inspection of Table 2 demonstrates that significance was detected only when non-parametric statistical tests were employed and that the correlations were substantial (0.75–0.8).

DISCUSSION

The data presented in this paper demonstrates that significant differences existed between the leukemic cell mass of CR and RD patients at all times studied: pretherapy, after 6 days of HDaraC therapy and 7 days after the conclusion of chemotherapy. By subdividing RD patients into REDR and SDR subsets we found that these two groups, together with CR patients, represent what appears to be a continuum of pretherapy leukemic cell mass which ranges from the low pretherapy leukemic cell burden of CR patients to the high pretherapy leukemic cell burden of SDR patients, with the leukemic cell burden of the REDR patients falling between that of the CR and SDR patients. HDaraC therapy produced the same average reduction in leukemic cell mass for the three different outcome groups. Given these observations, it appears that the pretherapy leukemic cell mass accounts for the difference in treatment outcome (CR, REDR or SDR), with a single course of HDaraC therapy producing an inadequate reduction in leukemic cell mass so that normal hematopoietic elements cannot repopulate the marrow.

The overall similarities of the effects of HDaraC on the leukemic cell mass of CR, REDR and SDR patients considered as a group, however, was not reflective of the substantial differences in the effects HDaraC therapy on individual patients. The initial effects of therapy (pretherapy to day 6) on CR patients showed some variation, with leukemic cell mass reduction ranging from slight to substantial. HDaraC effects on the leukemic cell mass of REDR and SDR patients was also variable, with the between-patient variability being greater than for CR patients and with the variability being the greatest for the SDR patients. In fact the leukemic cell mass actually increased during therapy in 1/13 REDR patients and 2/14

Table 2. Correlations between pretherapy leukemic cell mass and properties of leukemic marrow cells

Patient groups		0.3 μg/ml araC: immediate*		3.0 μg/ml araC: persistent†
ALL‡	$n = 42$	-0.3483 (0.02)[a]	$n = 33$	-0.2658[b]
CR	$n = 12$	-0.2744	$n = 7$	-0.5470[c]
REDR	$n = 6$	0.0322	$n = 4$	-0.3783

Non-parametric correlation coefficient and P value	
Kendall	Spearman
[a]-0.2833 (0.007)	-0.3837 (0.01)
[b]-0.2308 (0.06)	-0.3527 (0.04)
[c]-0.6190 (0.05)	-0.7857 (0.04)
[d]-0.6444 (0.009)	-0.7455 (0.01)

n = No. of patients studied.

*Immediate inhibitory effects of araC on DNA synthesis.

†Persistence of inhibitory effects after removal of cells from araC-containing medium.

‡ALL patients = all patients treated regardless of outcome of remission induction therapy. Values are Pearson's correlation coefficients. Values in parentheses indicate statistical significance (if any). Values for persistence of araC effects at 0.3 μg/ml and immediate effects at 3 μg/ml are not included since none were statistically significant.

SDR patients, demonstrating apparent leukemic cell resistance. The percentage of abnormal cells increased during therapy (to day 6) in 1/34 CR patients, 3/19 REDR patients and 5/19 SDR patients, demonstrating, at the very least, that for these patients the initial effects of HDaraC therapy were greater on the residual normal marrow elements than on the leukemic cells.

Figure 3a

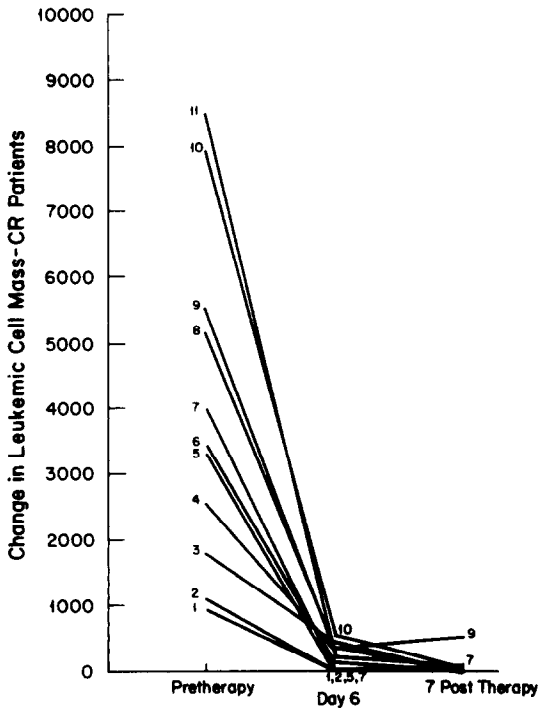


Figure 3b

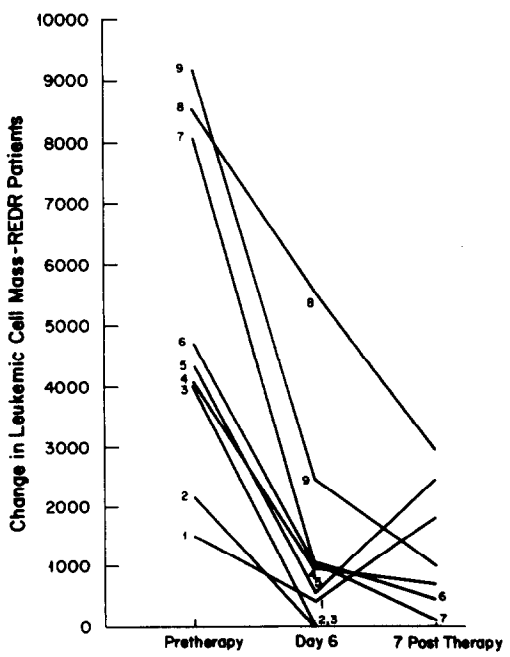


Figure 3c

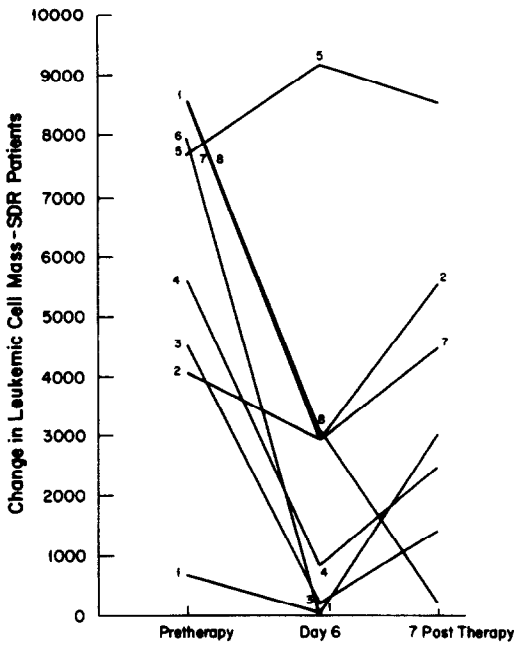


Fig. 3. Changes in the leukemic cell mass of individual patients during therapy (representative examples are given). (a) CR patients. (b) REDR. (c) SDR patients. Numbers indicate individual patients; lines connect the values of individual patients.

Considering the marrow changes which occurred during the 7 days after the cessation of chemotherapy, once again significant between-patient variability was observed with the variability increasing from CR to REDR to SDR patients. The 'leukemic cell mass' increased during the week after the end of HDaraC therapy in 4/17 patients who would subsequently enter CR. Undoubtedly these cells represented early regenerating normal hematopoietic elements whose appearance was indistinguishable from the pretherapy leukemic cells. The day 6 bone marrow of four of the 34 patients who entered remission contained <5% 'abnormal' cells while the marrow of the patients 7 days later contained >10% 'abnormal' cells. If the day 6 marrow had not been evaluated in these patients, it might have been assumed that these patients entered remission without an intervening aplastic phase. Regrowth of leukemic cells in the week after the end of therapy occurred in 4/12 REDR and 5/8 SDR patients. Once again the between patient variability in regrowth rate was the greatest for SDR patients.

Of special interest was the observation that while the studies described here emphasize the effect of the pretherapy leukemic cell mass on treatment outcome, the substantial between patient differences in the effects of araC demonstrate that other factors must also play a role in determining the outcome of therapy. We

have previously reported that the percentage of pretherapy cells in S phase [14, 15] and the sensitivity of the leukemic cells to araC also play a role in determining the outcome of therapy [5, 14]. The data provided here demonstrate that the proportion of pretherapy cells in S phase was unrelated to the leukemic cell mass. The metabolic sensitivity of the leukemic cells to araC was only weakly correlated with leukemic cell mass. Clearly between patient differences in these determinants of response as well as in plasma araC levels may have contributed to the observed between patient differences in response to HDaraC therapy.

We have previously reported that a second course of remission induction therapy has different effects on REDR and SDR patients with the therapy being likely to induce CR in the former and only hypoplasia (REDR) in the latter [2]. The detailed studies described here make these observations understandable since given that chemotherapy produces the same average effects on the leukemic cell mass of patients regardless of the initial tumor mass, a course of therapy should lower the leukemic cell mass of REDR patients to the point that their tumor cell mass is comparable to that of CR patients before therapy and it should reduce the leukemic cell mass of SDR patients to that of prethcrapy REDR patients. Hence, a second course of therapy is likely to produce a CR in REDR patients and REDR in SDR patients. Given these 'mass' effects, whether or not a patient requires one of two courses of conventional remission induction should also be unrelated to remission duration since at the start of maintenance therapy patients who entered CR after one course of therapy and those that entered after two courses of therapy should begin this second phase of therapy with similar residual leukemic cell masses.

Finally, recent reports have suggested that the administration of low doses of araC to patients with ANLL results in CRs which are not preceded by a period of marrow aplasia [16]. The observations reported here demonstrate that the aplastic phase may be quite transient and may not be detected if the usual approach of performing a bone marrow examination 1 week after the end of chemotherapy is taken.

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