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Rational Approaches to the Treatment of Leukemia*

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A. Introduction

Advances in the treatment of acute myelocytic leukemia (AML) have largely resulted from empirical drug trials in man. Such trials have led to the recognition of drug combinations which produce remissions in more than one-half of the patients who are under 70 years of age (Yates et al. 1973; Preisler et al. 1977; Rees et al. 1977; Jacquillat et al. 1976). While intensive remission induction therapy will produce complete hematologic remissions in as many as 75% of the patients, large numbers of leukemic cells must persist in the patients who enter remission, since the disease recurs in the majority of patients less than 1½ years after remission is induced. The selection of a treatment regimen on the basis of the regimen having produced a high remission rate in a majority of patients (75%, for example) also mandates that this particular regimen is not appropriate for the patients who do not enter remission (25%–45% of patients). Clearly, for this group of individuals the use of a different treatment regimen would have been preferable.

In the Department of Medical Oncology at Roswellj Park Memorial Institute we have been approaching these problems on a two-track basis. On the one hand we have continued to treat patients empirically using our clinical observations to dictate our therapeutic approach. To this end 3 years ago we initiated a treatment program designed to deliver intensive chemotherapy to patients already in remission to reduce and perhaps ablate the leukemic cells remaining in patients who entered complete remission (Preisler et al. 1980, to be published a). At the same time we began to study the factors which determined response to therapy, so that we would be able to determine in advance the appropriate chemotherapeutic regimen for individual patients (Rustum and Preisler 1979a; Preisler, to be published; Preisler et al. 1979b). This paper represents a progress report on our studies.

B. Empirical Clinical Studies

The therapeutic regimen (P970701) illustrated in Fig. la has been used to treat all patients of less than 70 years of age with AML since June 1977 (Preisler et al., to be published a). The regimen illustrated in Fig. 1b (P950501) was used to treat patients between 1975 and 1977 (Preisler et al. 1979b). Table 1 compares the remission induction efficacy of the two regimens. Given the number of patients studied, there is no significant difference in the overall induction efficacy of the two regimens. Figure 2 compares the duration of remission for three groups of patients: those treated with P950501, those treated with P970701, and a subgroup of patients induced into remission on P970701 but who did not receive the consolidation or maintenance portions of P970701 because their private physicians felt that intensive postremission therapy was not indicated. Comparison of the life table plots for remission duration of the three groups of patients demonstrates a highly statistically significant ($P<0.01$) difference in remission duration between patients induced and maintained on P970701 and those patients who received the same remission induction regimen

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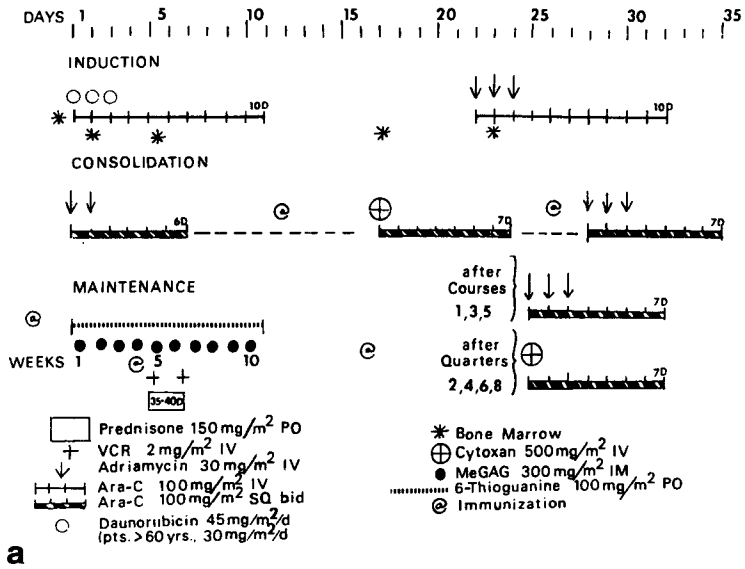
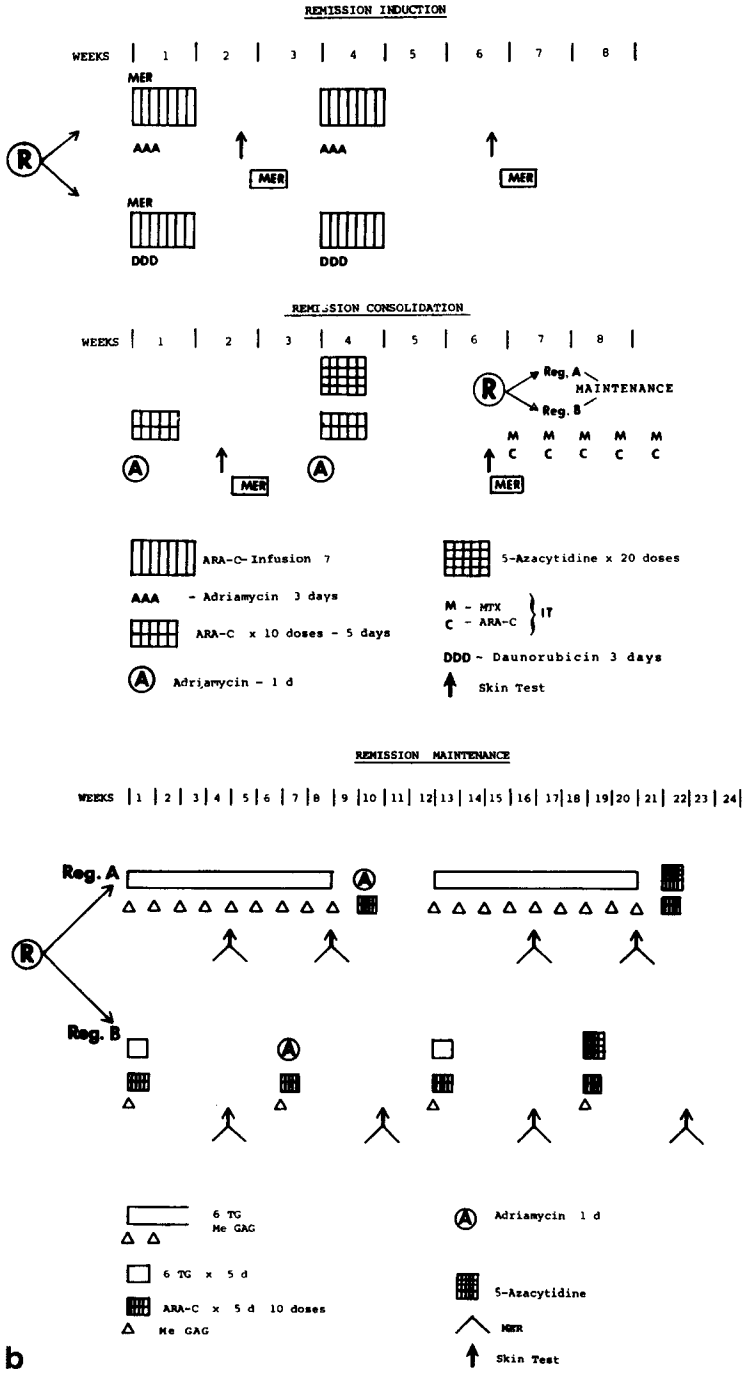


a



b

Fig. 1. a Schema for protocol 970701. **b** Schema for protocol 950501

		Total	≤50	>50≤70
CR/TOT.	P950501	24/36 (66%)	16/20 (80%)	8/16 (50%)
	P970701	52/73 (71%)	29/35 (83%)	24/38 (63%)

Table 1. Outcome of remission induction therapy

but who recieved more gentle maintenance therapy (generally monthly 5-day courses of cytosine arabinoside (ara C) and 6-thioguanine, with or without BCG).

Comparison of remission durations of patients on P970701 and P950501 suggest that the more intensive post-remission induction regimen employed in P970701 resulted in: a reduction in the number of early relapses and a longer median duration of remission with a higher proportion of patients in remission beyond the second year. These observations suggest that early intensive consolidation chemotherapy prolongs remission durations by reducing the number of leukemic cells remaining after remission induction therapy is administered.

It should be noted that P970701 produced severe toxicity with significant thrombocytopenia and granulocytopenia lasting for more than one week's time occurring after each course of intensive chemotherapy administered to patients in remission. The administration of cotrimoxazole to patients has prevented the occurrence of infectious complications (Preisler et al., to be published) and the administration of platelet transfusions every other day to patients whose platelet counts were less than 20,000/μl has prevented hemorrhagic complications.

C. Prediction of Response to Therapy

The outcome of remission induction therapy is determined by both the patients ability to survive remission induction therapy (biological fitness) and by the drug sensitivity of a patient's leukemic cells. Table 2 illustrates the outcome of remission induction therapy given different combinations of biological fitness and drug sensitivity. Needless to say, this construction presumes that adequate serum levels of drug for an adequate duration are achieved during therapy.

To evaluate the ability of an in vitro drug sensitivity assay to predict in vivo drug responsiveness one must be careful to use the outcome of remission induction therapy of only those patients for whom one can assess the in vivo response of leukemic cells to therapy. Hence, patients who die early in the course of therapy or who die during a period of marrow hypoplasia must be considered to be inevaluable, since in both cases it is not possible to determine whether the patient would have entered remission or whether leukemic cells would have persisted or regrown shortly after marrow hypoplasia was induced (Preisler 1978). For these reasons, we consider complete remission to be indicative of in vivo drug sensitivity and either persistence

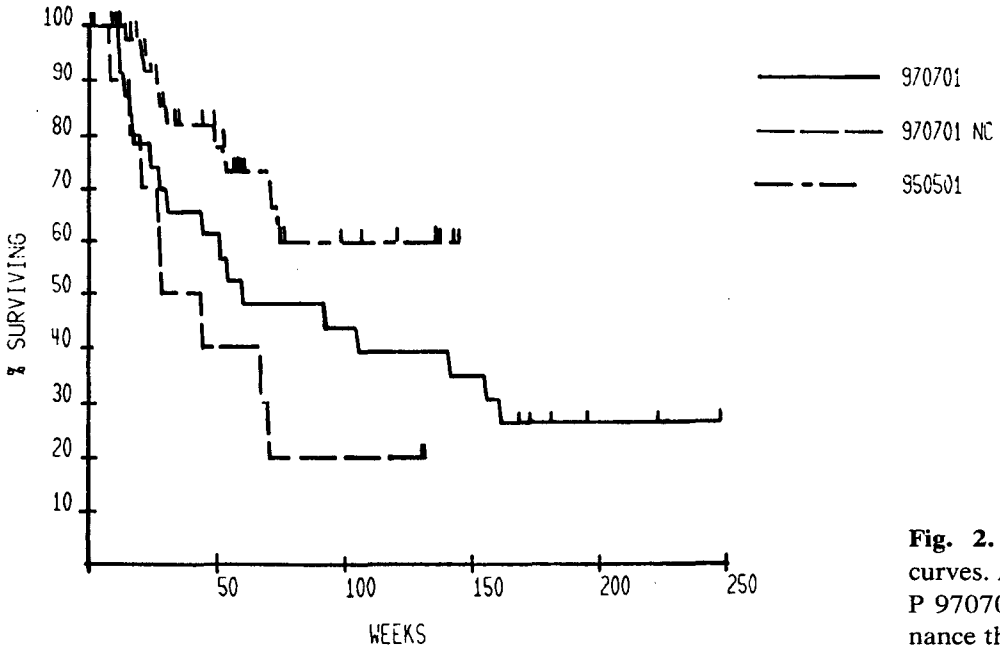


Fig. 2. Remission duration curves. *NC*, same induction as P 970701 but gentle maintenance therapy

Biologically fit[a]	Drug sensitivity	Outcome
yes	yes	Complete remission
yes	no	Persistent leukemia
no	yes	Death early in therapy or while hypoplastic
no	no	Death early in therapy with persistent leukemia

[a] Ability to survive the effects of intensive remission induction therapy.

Table 2. The outcome of remission induction therapy given different combinations of biological fitness and drug sensitivity

of leukemia despite therapy or the regrowth of leukemic cells subsequent to a period of marrow hypoplasia to be indicative operationally of drug resistant disease.

Figure 3 illustrates the method we have employed to determine the sensitivity of leukemic cells to ara C and daunorubicin, and 4 illustrates the relationship between in vitro sensitivity and the outcome of remission induction therapy with these two agents. There is a clear-cut and highly statistically significant relationship between the percent age of clonogenic leukemic cells killed by ara C and DNR and in vivo response to therapy (Preisler 1980, to be published).

D. Comments

Despite recent significant increases in the percentage of complete remissions induced by aggressive remission induction therapy, a significant proportion of patients still fail to enter remission and the majority of patients fail to survive for prolonged periods of time. Empirical approaches to this problem will include the administration of still more intensive remission induction regimens so that patients with disease resistant to currently employed regimens might be induced into remission. More aggressive regimens will, however, result in greater toxicity and in more toxic deaths, deaths which

CRITERIA FOR EVALUATION OF PTS. FOR RELATIONSHIP IN IN VITRO vs. IN VIVO TREATMENT

ESTIMATION OF IN VIVO DRUG SENSITIVITY

1. DRUG SENSITIVE DISEASE = COMPLETE REMISSION
2. RESISTANT DISEASE
   - A. PERSISTANT MARROW LEUKEMIA DESPITE CHEMO RX
   - B. RX PRODUCES MARROW HYPOCELL. BUT ON REGEN. LEUK. CELLS RETURN
3. INEVALUABLE
   - A. PATIENTS WHO DIE EARLY IN COURSE OF RX
   - B. PATIENTS WHO DIE WHILE APLASTIC

CLONAL EST. IN VITRO DRUG SENSITIVITY

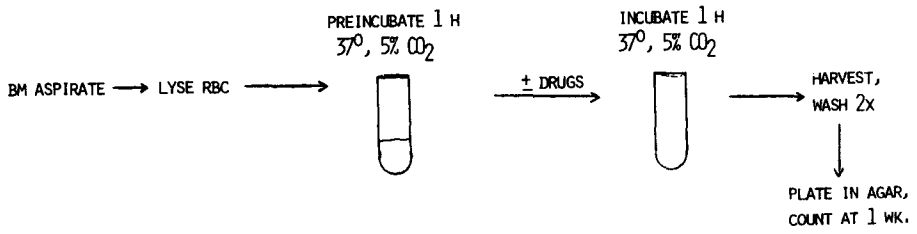
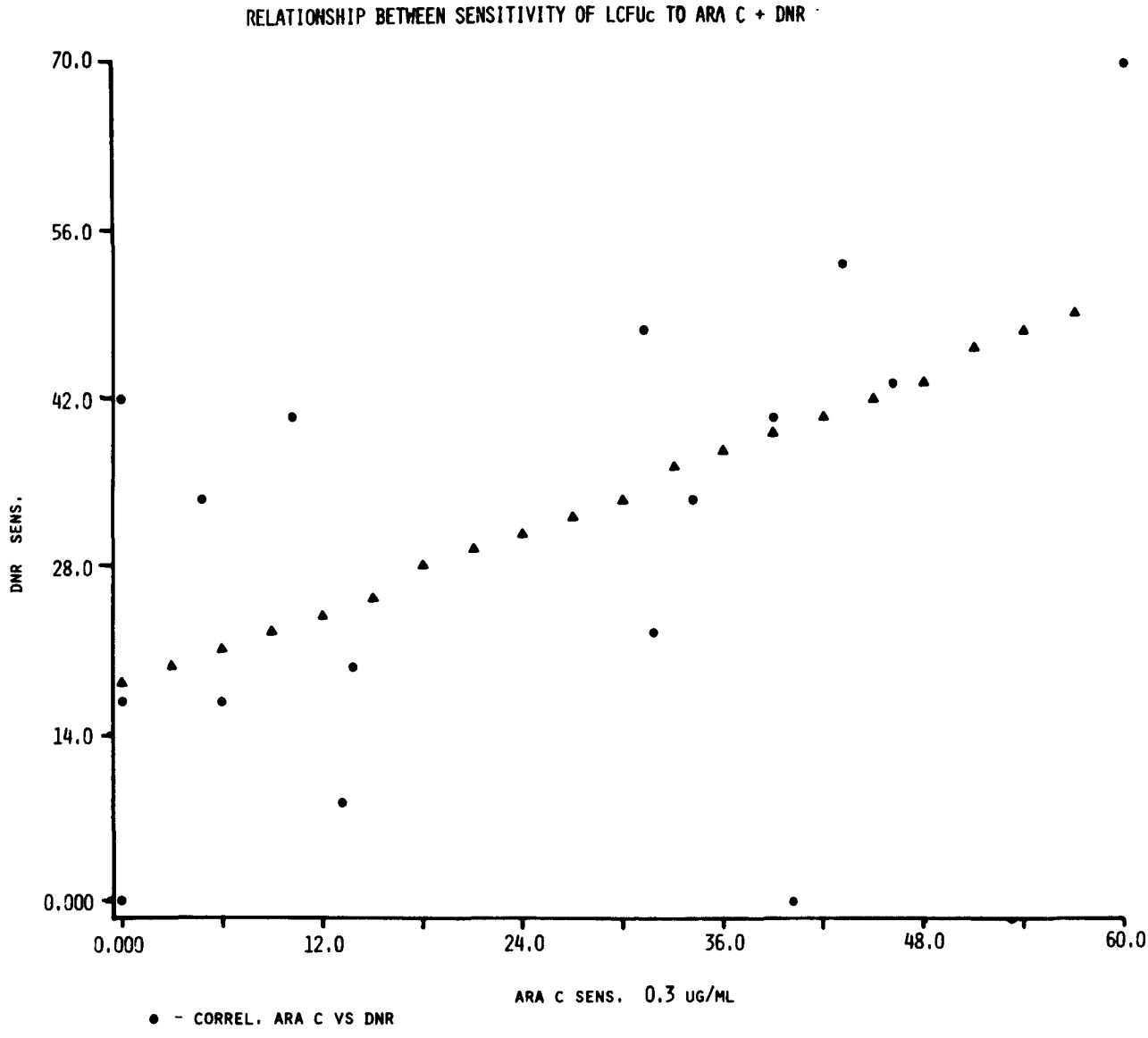


Fig. 3. Drug sensitivity assay



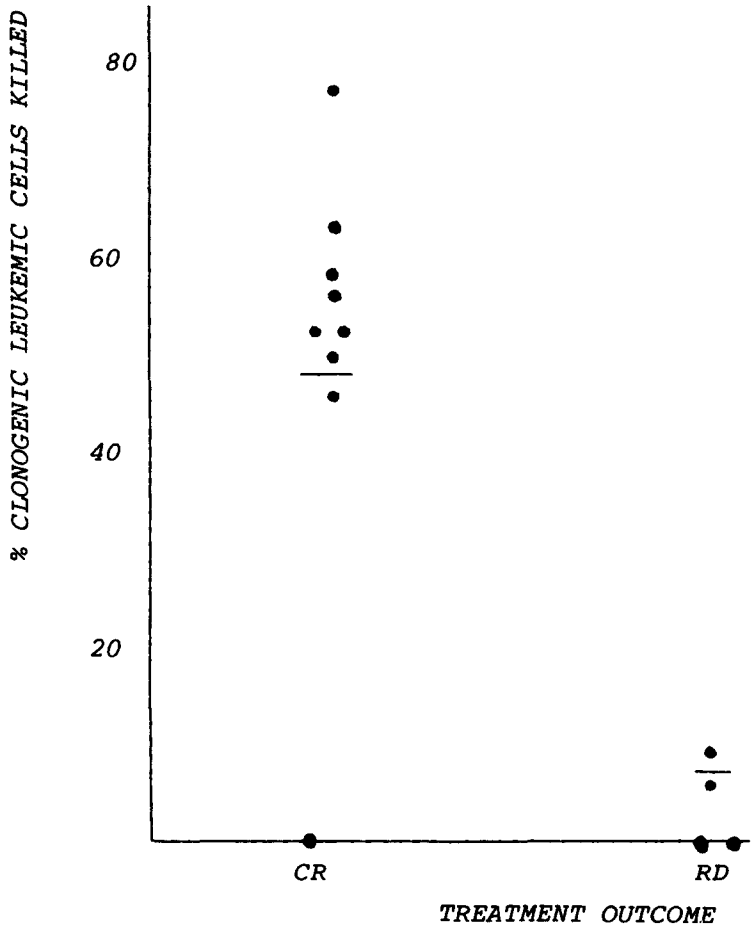


Fig. 4. DNR + Ara C vs. response

may counterbalance the potential benefits of the more aggressive regimens. The development of reliable in vitro drug sensitivity assays would permit the use of remission induction regimens tailored to each patient and, hence, will simplify remission induction therapy, since ineffective drugs will be recognized and will not be administered on the chance basis that they will be therapeutically efficacious.

Until the reliability of in vitro drug sensitivity tests in confirmed, treatment regimens based upon empirical clinical observations will continue to be the main vehicle for improvement in the outlook for patients with AML. It is intuitively clear that intensive remission consolidation regimens appear to be the next step in the evolution of clinical protocols. Since our P970701 appears to have produced promising results, the next phase in our studies will be the administration of a greater number of courses of intensive consolidation therapy employing a greater variety of drugs.

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