Perspectives and Prospectives in the Management of Acute Leukemia*

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The management of and outlook for patients with acute leukemia is strikingly different than it was 10 years ago. The introduction and refinement of empirically based combination chemotherapy in the early 1960's not only demonstrably improved the response and survival of acute leukemia victims, but equally stimulated basic scientists and clinicians alike to view this malady as an entity which could be cured within the foreseeable future. With this stimulus a remarkable amount of careful, and, often, inspired research has been conducted with the idea of better understanding and controlling this illness. In 1975, the task is not to stimulate interest in the pathogenesis and pathophysiology of leukemia, but to determine whether sufficient information is already available to consistently manage the disease, and, if so, how best to integrate current knowledge.

As with most illnesses, although progress has been made in parallel in the clinical and non-clinical spheres, and although clinical protocols have often been rationalized on the basis of pre-clinical studies, it is not clear that any therapeutic advance has directly and totally depended upon non-clinical observations. For example, the systematic determination of schedule dependency, independent mechanisms of action, and pharmacokinetics of individual drugs have provided models for and explanations of the increased effectiveness of drug combinations, but it is hard to imagine that without these studies individual drugs with antileukemic activity would not have been combined in much the same fashion as is the current practice without these ancillary investigations. Indeed historically many of the clinically most successful approaches were conceived and implemented before or concurrent with the non-clinical studies which provided their radionale. Furthermore, many unequivocal conclusions in animals cannot be (or at least as yet have not been) confirmed in man.

For example, studies in vitro of the scheduling of agents have suggested that a certain sequence of drug administration is optimal – and as a corollary, that the opposite sequence may be detrimental. Edelstein and his colleagues have shown that for greatest effect, cytosine arabinoside (ara-C) should preceed daunorubicin (DNR) (1), yet both Omura, et al (2) and Weil, et al. (3) have been unable to demonstrate such a difference in the clinical management of acute myelocytic

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leukemia, while DNR for 3 days plus ara-C for 7 days (3 during, and 4 following) has been as good or better therapy as any evolved to date for this condition (4, 5).

Second, viral reinduction of leukemia has been documented in animals (6) and suggested in man (7), yet the few attempts at anti-virus therapy in patients with leukemia have either met with little or no success or clear evidence of failure (8, 9, 10).

This preamble is not intended as a criticism of basic pre-clinical research, but rather as an explanation of and introduction to the great dilemma of any conscientious clinician, namely when to abandon or modify effective modalities of management based on repeated laborious clinical observations, for new approaches of extreme intellectual attractiveness developed in a non-clinical setting. Such a consideration is most germane to a symposium such as this one, at which reports of significant recent advances in clinical chemotherapy, immunotherapy and combination modalities, empirically based and derivative are interspersed with reports of new insights and techniques of potentially revolutionary scope which have evolved peripheral to or in some cases exclusive of the clinicial arena. If, indeed, our clinical efforts had hitherto proved fruitless, it would be a simple matter to bear with those treatments we have, rather than flying to those we know not of. But clearly this is not our condition at present. Rather, therapy has made major strides in children during the last decade and in adults during the last 5 years. At every age, the most successful programs have been similar or identical (Table 1),

Table I: Remission Induction in acute leukemia*

Drugs	% *Complete Remission*	
	Adults	*Children*
Acute Lymphocytic Leukemia:		
Prednisone (P) + Vincristine (V)	50	88
P + Daunorubicin (D)		65
P + V + D	50–88	89–100
P + V + Asparaginase	74	87
P + V + Mercaptopurine + Methotrexate (POMP)	43–60	50–90
Acute Myelocytic Leukemia:		
Daunorubicin (D)	34	37
Cytosine Arabinoside (ara-C)	16–31	25
POMP	44	75
POMP/PVD	38	71
Ara-C + Thioguanine	35–36	43
Ara-C + D (5 days, 2 days)	43	56
Ara-C + D (7 days, 3 days)	77	–
Adriamycin + Ara-C + V + P	83	

* for references, and additional data, see reference 29.

although, in virtually all instances, age per se has proven to be the most critical determinant of response and survival. At the present time, perhaps 90 percent of children and 70 percent of adults with acute leukemia initially respond to optimal therapy, and up to 50 percent of children can be expected to survive, disease free, for 4 to 5 years or more following diagnosis. The long range effectiveness of treatment in adults is only now being assessed, but within the last 4 years the remission rates and median survival for both acute lymphocytic leukemia and acute myelocytic leukemia treated with the best available protocols has doubled, so that there is hope and optimism that the 2 % 5 year survival rates previously observed (Table 2) will be significantly increased.

Table II: Long term (≧ 5-Year) survival in acute leukemia in adults

Type	Number at Risk	Median Duration of Survival	Number Alive and Disease-Free for ≧ 5 Years
AML	97	5.5	3
ALL	*40*	*8.5*	*0*
TOTAL	137	6.5	3

What then are the clues from non-clinical research that may be so advantageously incorporated into future clinical management that we can abandon or significantly modify current practices? I can see only one at present, but several more are approaching the threshold of clinical experimentation. The available clinical modality is the use of non-cytocidal substances, chiefly bacteria or bacterial antigens, to stimulate natural immunity and/or hematopoiesis. This approach was spearheaded initially in acute lymphocytic leukemia (10), but has shown to more

Table III: Remission maintenance of acute myelocytic leukemia with chemotherapy ± immunotherapy (28)

Maintenance Treatment		No. of Patients	Median Months of Complete Remission
Chemotherapy	Immunotherapy		
OAP (V, P, Ara-C)	BCG	20	21
OAP (V, P, Ara-C)	None	33	11.5
Ara-C + D, Ara-C + TG	BCG + AML cells	23	11
Ara-C + D, Ara-C + TG	None	19	7
MT X ± (V + C)	BCG	22	11
MT X ± (V + C)	None	26	7.5
Ara-C + TG, Ara-C + D, Ara-C + C	Neuraminidase treated AML cells	7	16+
Ara-C + TG, Ara-C + D, Ara-C + C	None	10	5

consistent advantage as an adjuvant to chemotherapy in the remission maintenance phase of acute myelocytic leukemias (Table 3) (11, 12, 13, 14, 15). Dr. Raymond Powles, in this volume, has presented some of the difficulties in defining the mechanism(s) of action of this approach. What is clear is that first, use of the term "immunotherapy" for such approaches is at best premature and second, irrespective of the mode of action such explorations will and should continue both at the laboratory and clinical levels.

On the horizon shimmering with promise and backed by abundant data in animal models are the use of cell kinetics for drug selection, the exploitation of normal biological rhythms for drug scheduling, and the selection of drugs based on intracellular biochemical determinants of drug action. While clinical application of these approaches have been attempted in the past (16–19) with limited success, the obvious deficiencies in the methodology required for on-going studies may have abbrogated any striking clinical benefit. For example, most methods of determining intracellular DNA synthesis are either retrospective and limited to a few key determinations (e. g., radioautography) or are indirect and not specific for the most critical stem cell population (e. g., in vitro thymidine incorporation or spectrofluorometry). Recent progress in cell fractionation and real time analysis procedures, e. g., high-pressure liquid chromatography, should facilitate future studies in these areas.

The use of biological pharmacological stimuli to control cell replication and differentiation is perhaps the most intriguing new avenue for exploration. Without question both naturally produced and synthetic activities can induce strikingly quantitative and qualitative changes in both normal and malignant cell populations in vitro as amply reviewed in this symposium (20–24). How general is this phenomenon, and how effectively these activities can be isolated and successfully delivered to their cellular targets will determine the applicability of such an approach in vivo.

Evaluation of all modes of therapy present and future, would be greatly bolstered by the development of sensitive, specific assays of the extent of idsease involvement. Is initial therapy still appropriate? Must therapy be continued, and for how long? Do foci of leukemic cells (or leukemogenic agents) remain in the marrow, or in extramedullary sites such as the central nervous system or gonads? These are without question the most common questions asked by and of the leukemia therapist, and at present the answer is almost always "wait and see." The greatest frustration for the physician remains that only failure is established with certainty, while the greatest calamity of therapy is the injury or death of a patient through treatment which might not be necessary.

Unfortunatley no suitable asssay is currently available. Light microscopy is capable of assessing orders of magnitude of 10^9–10^{12} leukemic cells in a clinical setting although even within this range the specificity of morphological (and cytochemical) criteria are frequently suspect. Cytogenetic assays may occasionally extend this range, but are fraught with many technical and sampling variables not to mention the fact that approximately half of all leukemic cell lines go unrecognized with current karyotypic techniques. The production of muramidase, polyamines, uric acid, and lactic acid dehydrogenase are at present too non-specific and insensitive for clinical monitoring. For the above examples, and indeed for all

other readily available tests, there is insufficient resolution to assess tumor extent or activity during the increasingly crucial period of complete remission.

There is reason to hope, however, that current research will shortly improve leukemic cell identification. Several of the most promising lines of investigation have been reviewed in this symposium. These include the development and utilization of antisera to leukemic cells, the identification of previously undescribed and possibly more specific metabolites of leukemia cells, and perhaps of greatest immediate value, the development of more rapid and precise techniques of cell separation, e. g., the fluorescence activated cell sorter. These separation techniques may well enhance the sensitivity of all leukemic cell identification procedures, both current, based on morphology, cytochemistry, and immunological characteristics and future, including the identification of oncorna virus footprints. The report in this volume by Greaves and co-workers (25) exemplifies the combination of a highly specific leukemia cell assay with sophisticated cell separation which should aid in clinical management and in the assessment of new treatments.

Finally, I would like to briefly summarize the observations made by my colleague at Roswell Park Memorial Institute, Dr. Alex Bloch, concerning the urinary excretion of cytidine 3', 5'-monophosphate (cyclic CMP). Dr. Bloch has recently identified not only this previously unrecognized cyclic nucleotide, but cytidyl cyclase as well, in murine leukemia L1210. In this model cyclic CMP stimulates rapid cell proliferation, shortening the lag phase of in vitro passaged L1210 from two hours to less than thirty minutes (26). Cyclic CMP is either in low concentration or absent in normal mouse tissues; however it becomes elevated in regenerating liver following partial hysterectomy. Based upon these observations, the urinary excretion of cyclic CMP was evaluated in 6 patients with active leukemia (2 ALL, 3 AML, and 1 CLL), whereas no cyclic CMP could be detected in individuals or pooled urines from normal urine samples, concentrations of 0.27 to 1.31 u moles were observed in the 24 hour urines collected from all leukemic patients (27). In the one patient studied serially, a fall in urine concentration of cyclic CMP paralleled the reduction of bone marrow and blood myeloblasts. Clearly this observation is most preliminary, and any further judgment must await the completion of the controlled assessments currently in progress. Nonetheless it is this type of non-invasive monitering which must be developed if therapeutic trials are to be safely and scientifically conducted.

In summary, the dilemma of the therapist is how far to pursue modifications of the empirical cytotoxic approach to leukemia therapy, and when and how to seek new avenues of leukemia control which have as yet no clinical substantiation. It is encouraging to note the continued interest and accomplishments of laboratory investigators in leukemia research, since despite remarkable progress during the last decade, leukemia remains incurable for the majority of those afflicted.

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