Progress in Acute Leukemia 1975–1978*

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During the three years which have elapsed between the second and third Wilsede conferences, the clinical management of acute leukemia has become almost routine. Every clinic has become the advocate of combination chemotherapy for remission induction and maintenance, early treatment of the central nervous system at least for childhood disease, and an appreciation of the need for supportive care measures and attention to metabolic abnormalities in the preparation for and sustenance of patients during chemotherapy. This has clearly led to the happy prospect of more patients receiving better care and thus a better chance for long-term survival and possible cure from this once uniformly uncured disease.

This confirmity of approach, however, has serious implications concerning therapeutic research in acute leukemia. First, it tends to obscure the fact that most patients continue to die of their disease; and second, it reflects the leveling off of significant advances in treatment for a sufficient time (3 to 5 years) for the average competent physician to "catch up" with the avant garde. Thus it highlights, among other things, the failure of non-specific immunomodulation (with BCG, MER, and the like) to significantly alter the final outcome of leukemia, and the continued urgent need for more, and more specific, new compounds to break through the toxicity barrier, especially during the remission consolidation and maintenance phases. Finally, given the success of primary treatment of "standard" acute lymphoblastic and acute myeloblastic leukemia of children *and* adults, necessarily greater attention is now commanded by the late toxic effects of drugs, and especially that which remains the most devastating malignancy of all: the acute leukemia which follows (is caused by?) previous bone marrow disease and injury.

Current Therapy and Results

The results of recent successful treatment regimens in acute leukemia are reviewed elsewhere in these proceedings by Freeman, Lister, McCredie, Preisler, and Wiernik. For acute lymphocytic leukemia (ALL), the three-drug combination of vincristine, prednisone, and asparaginase will induce

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almost all good risk patients into complete remission (good risk factors being 2–10 years of age, no previous treatment, and the lack of lymphoblast differentiation into those cells which bear T and B cell surface markers). These same drugs will induce remissions in older patients and those with T cell markers in approximately 75 percent of initial trials. The addition of a fourth drug (daunorubicin) increases the effectiveness of the regimen, at least in adults (Lister et al., 1978; Henderson et al., 1978). In both adults and children maintenance treatment and central nervous system prophylaxis appear necessary for optimal results; although the long-term administration of intensive maintenance treatment has led to increased toxicity, late complications, and deaths in remission; and has compared unfavorably in terms of survival with maintenance regimens employing fewer drugs and/or less frequent drug administration (Pinkel, 1978; Simone et al., 1976; Henderson, 1974). On the other hand, short-term intensification during established remissions may be advantageous (Bodey et al., 1976; McCredie et al., 1978; Freeman et al., 1978).

For acute myelocytic leukemia (AML) combinations of cytosine arabinoside and anthracycline antibiotics given in such a manner that myelosuppression is sustained for 10–14 days or more appears central to an optimal response, given present drugs (Yates et al., 1974; Preisler et al., 1977; Silver et al., 1977; McCredie et al., 1976 and 1978) and support techniques. Although most concede its value, the exact role and necessary duration of remission treatment remains uncertain, as does the administration of treatment to the central nervous system in AML.

Using these treatments survivals of greater than 50 percent have been achieved in ALL in children (Pinkel, 1978; Jones et al., 1977) and up to 25 percent in active (i.e., neither secondary nor smouldering) AML and ALL in adults at several centers (Henderson et al., 1977; McCredie et al., 1975; McCredie et al., 1978).

On the other hand, poor risk patients with acute leukemia continue to do poorly. These are the patients with T cell or B cell disease, extensive extramedullary leukemic infiltrates at diagnosis, at the extremes of age, or most strikingly, those with a history either of preexistant bone marrow disease, or chemotherapy and/or radiation therapy antecedent to the development of leukemia. Unfortunately, given our limited ability to treat them successfully, the incidence of poor prognosis patients appears to be increasing. Until adequate therapies are devised, it is still critical that such patients are identified early to prevent 1. their imbalanced inclusion into comparative treatment studies or 2. their inopportune and premature treatment with intensive drug regimens having little chance of inducing benefit. In this regard, it is unfortunate but true that attempts to increase response and survival with superintensive treatment have rarely proved of benefit, while frequently adding morbidity. For such patients the failure to normally reconstitute hematological and immunological function underlies most failures. Accordingly, the development of drugs or other agents with precise specificities for malignant cells and the sparing and/or reconstitution of normal blood cell progenitors appears to be the areas of greatest promise and highest priority in the immediate future.

At the heart of the problem of specificity is the question of the reliable identification of the progenitors of leukemic and normal cells. Numerous previous attempts to identify and monitor these cells, their function, their replication, and their drug sensitivity have been at best only partially successful. The striking acquisition of new knowledge and techniques for measurement of myeloid and lymphoid cells is the most heartening advance of current years in the study and management of leukemia and allied diseases. Antisera specific for stages of differentiation and the identification of specific surface receptors for antibodies, hormones and antigens have permitted in situ identification and in some instances sorting of specific subpopulations of cells, which can then be studied for replicative activity, drug uptake and effects, and clonogeneicity, thus for the first time permitting sensitivity to drugs to be reliably assessed. Given proper reagents and improvements in sorting technology, it may be possible either in vivo or more likely in vitro, to separate malignant and normal cells from cell mixture, e.g., peripheral blood leukocytes or bone marrow cell suspensions. All this is within the capability of current laboratories and their associated clinics within the next 3–5 years.

Once isolated one from another, it will be possible to assess not only the presence of differentiation related (and/or tumor related) markers, but also function, and clonogenicity and drug susceptibility. Proliferation and differentiation to a more mature state is not sufficient to identify a stem cell, the test of which is self-replication simultaneous with the spawning of differentiate functional progeny. (By analogy it has been noted that there are in fact two cells maintaining immunologic memory, both will respond rapidly to recall antigens but while most will form effect cells at the expense of their own survival, one class will in addition self-replicate, thus renewing memory.) It is the latter class of cell that is obviously most significant in long term propagation of any tissue or function, and it is this type of cell toward which the major search must be directed, and with which assays such as those described by Preisler and Rustum (1978), Greaves (1978) and others can be attempted with assurance of benefit. At the same time, alternate assessment of their involvement in a malignancy can be accomplished by detailed cytogenetic analyses, such as those described by Rowley (1978), idiotypic directed antisera (Broder et al., 1975; Fu et al., 1978), or enzyme allotype studies such as those reviewed by Fialkow (1978). Such studies will, doubtless, continue to amaze us with their demonstration of the ontogenetic scope of normal and malignant tissues which appear otherwise homogenous.

Despite its early promise and despite demonstrations of histological and therapeutic activity, immunotherapy has to date not been noted to increase the probability of long-term survival and cure (Hersh, 1978). However, the preliminary studies reported at this conference by Bekesi (Bekesi, 1978; Silver, 1977) suggest that inoculation of enzyme-treated human leukemic cells may be efficacious, perhaps through the mediation of a leukemia associated or specific immune reaction. Both this premise, and the clinical utility of neuraminidase treated cell immunization, remain to be proved, but results to date are impressive, not only in the observed differences between the survivorship of control versus chemotherapy plus neuraminidase-treated-cell

inoculation groups, but also in the shape of the curves which indicate for the latter group that the risk of relapse is diminishing with time. Such survival curves are in contrast to those observed following BCG or MER treatments (Mathe's series remaining a notable exception) and encourage the hope that this form of treatment will effect cures.

The role of bone marrow transplantation in relapsed patients is now obvious. There is no approach in advanced refractory leukemia which can duplicate that which has been demonstrated by the major transplantation groups in terms of response and survival (Gale, 1978; Storb, 1977). It would appear that the worth of engraftment lies in its permission of supralethal drug and/or irradiation dosages, rather than in any immunological effect (e.g., the graft versus leukemia effects postulated by Boranek, 1968) since identical-twin or autologous stem cell grafting coupled to intense cytolytic regimens appear to afford results comparable to allogeneic transplantation (Grace and Gale, 1977; Bruckner et al., 1977; Fefer et al., 1977). This is of major imporance in providing a rationale for transplantation of stored autologous marrow, freed by sorting either of leukemic cells on the one hand, or allogeneic immunocytes responsible for both graft-versus-host and graft-versus-leukemic reactions on the other. Stem cell replacement could thus become available to all patients, rather than remaining restricted to a small minority of individuals with leukemia.

Finally, as always, the therapist looks forward to the development and discovery of new agents especially those with tumor specificity. Science is providing knowledge of receptors, mediators, and the like which control devision and differentiation, and are thus choice targets for chemical attack. One such example of a new semisynthetic agent is metholated polycytidylic acid, one of a series of "antitemplates" synthesized by Bardos and Ho (Ho and Bardos, 1977) in Buffalo, and shown by Chandra et al. (1978) to potently inhibit mammalian DNA polymerases, including reverse transcriptase extracted from human tissue. Preliminary trials in children with recurrent ALL have demonstrated the activity of this compound in a clinical setting (Kornhuber, 1978). The possible utility of this class of agent will be under investigation during the coming months, along with trials of new anthracyclines, vinca alkaloids, and antimetabolites all selected on the basis of reduced major organ toxicity and, thus, greater specificity than their clinically utilized congeners. Also to be tested are naturally synthesized compounds (or activities) such as immune RNAs and interferons. The possibility of using natural metabolic intermediates, induced in the patients own cells by certain inciting principles, e.g., the 2′5′A oligonucleotides described in these meetings by Kern (1978), is a particularly attractive approach combining as it does the potential advantages of tumor *and* host specificity.

The investigations of the past 3 years, and the spirit of current investigations as manifested in these recent Wilsede meetings, augers well for rapid advances in the direction of truly specific and safe treatments for acute leukemia and allied diseases within the near future. They also emphasize the importance of studying human patients directly, rather than by analogy, attesting that "The proper study of man is man".

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