Summary of Clinical Poster Sessions

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The first of six presentations in this poster session to be discussed is that of Preisler and Rustum [1]. This paper demonstrates the efficacy of anthracycline derivatives given as a pulse injection daily for 3 days in combination with a continuous seven day infusion of cytosine arabinoside for the treatment of acute nonlymphocytic leukemia (ANLL). This regimen and regimens similar to it [2] are among the best treatments for this disease at the present time. A number of investigators have achieved complete responses on the order of 65–70% with such treatment [3–5]. Preisler and Rustum attempt to determine whether the intracellular retention of activated Ara-C in vitro by a patient's bone marrow leukemic cells correlates with remission rate and duration. Unfortunately, the authors did not find an improved remission rate in those patients who retained phosphoralated cytosine arabinoside better than others. However, there was a highly statistically significant correlation between phosphorolated cytosine arabinoside retention and remission duration. This is an important finding not only because it may allow one to predict in broad strokes what remission duration is likely to be in a given patient, but the data strongly suggest that the induction therapy given to a patient with ANLL is the most important determinant of remission duration. Others have also suggested this may be so [6]. A number of investigators have recently questioned the value of intensive maintenance therapy in this disease and the results have been variable [7,8]. Perhaps further studies of this kind will allow for more selective and therefore more successful therapy in terms of remission induction and duration of response. Similar work by others [9] suggests that this may already be partly true for solid tumors.

The paper by McCredie et al also concerns ANLL treatment [10]. This paper further confirms the efficacy of the anthracycline-cytosine arabinoside combination with different doses and schedules of the drug. The combination of adriamycin, vincristine, cytosine arabinoside, and prednisone produced a 74% complete response rate at M.D. Anderson Hospital and a 54% complete response rate in the Southwestern Oncology Group. Group studies always give poorer results than studies performed at single institutions that specialize in the treatment of the disease entity in question. Substituting rubidazone [11], a new anthracycline currently undergoing trial in France and in the United States, for adriamycin in older patients produced essentially the same complete response rate as that of the adriamycin containing combination. Therefore, there is no advantage gained by substituting

rubidazone for adriamycin. It is somewhat disappointing that this new anthracycline derivative is not more active than the two (adriamycin and daunorubicin) already in widespread use. A good deal of analog research has occurred in cancer chemotherapy with the hope that refinement of a molecule with proven activity might lead to a greater therapeutic index. Unfortunately, this has not been the case thus far with the anthracyclines, the nitrosoureas, the antipurines and the antipyrimidines, or the actinomycin-mythramicin antibiotics. Perhaps this is not too surprising when one considers that analog research in the aminoglycoside antibiotics and, indeed, in the cardiac glycosides has not yielded a major improvement over the respective parent compound.

The study of McCredie et al. includes a new approach to remission maintenance. The late intensification program at M.D. Anderson Hospital has been reported previously [12]. The present data suggest that roughly half of the patients who undergo this program remain in unmaintained complete remission for significantly longer periods of time than reported with other relatively intensive maintenance programs. The data also suggest that if the patient remains in continuous complete remission for 24 months following the discontinuation of late intensification therapy, he has a 90% chance of remaining in complete remission. We will watch these data with intense interest over the next months and years with the hope that they continue to be as impressive as they are at the present time.

The McCredie paper also describes another novel approach to remission maintenance, use of autologous bone marrow transplantation using marrow collected and stored from patients with ANLL during periods of remission. Too few patients have been entered on this aspect of the study to date to allow full evaluation or even significant optimism at this point. One might not be surprised, however, if this method ends in failure. Spiegleman et al. [13] have shown that even during complete remission reverse transcriptase may be isolated from what appear to be normal granulocytes in the peripheral blood of ANLL patients. Therefore, one might expect that the viral etiologic agent, if there is one, might also be present in the morphologically normal appearing cells used for these autologous transplants. One cannot be too optimistic about transplanting cells that may harbor pathologic time bombs.

The third paper of this series is that of Freeman et al. [14] concerning intermediate dose methotrexate in childhood acute lymphocytic leukemia (ALL). The purpose of Freeman's study is to prevent the development of CNS leukemia without employing cranial radiotherapy by administering relatively high doses of parental methotrexate that will result in therapeutic CSF levels of the drug. Additionally, the goal of the study is to eradicate leukemic cells in other sanctuaries such as the testes. In the study, children are induced with a combination of steroid, vincristine, L-asparaginase and intermediate doses of methotrexate (500 mg/M^2). The methotrexate is followed by citrovorum factor. The idea of this study has merit. More and more undesirable effects of commonly employed methods of CNS prophylaxis (intrathecal methotrexate and cranial irradiation) are coming to light with time [15, 16]. It might have been more reasonable, however, to design the study so

that L-asparaginase was given after the high-dose methotrexate. In this way L-asparaginase might not only be used as a therapeutic agent with activity against ALL but as a methotrexate reversal agent which would obviate the need for citrovorum factor [17]. This might be an important consideration since high dose parenteral methotrexate would still enter CSF and brain, but L-asparaginase would not. Variable amounts of citrovorum factor enter CSF.

The results of this study are of interest. Complete remission was achieved in 96% of patients but there were 7 CNS relapses according to the paper. For reasons that are totally unclear to me, two patients who presented with CNS leukemia are included in this study (one relapsed with CNS leukemia). It would have been perfectly reasonable to exclude patients from admission to the study if they presented with CNS leukemia since one of the goals of the study is to evaluate this regimen for its potential to prevent CNS leukemia.

One can conclude from the study that this method of CNS prophylaxis probably is better than no prophylaxis at all. However, it is not clear that it is equal to or superior to more standard cranial irradiation and intrathecal methotrexate administration. In addition, the fact that intrathecal methotrexate was also given to these patients makes my interpretation of these results even more difficult since others [18] have suggested that intrathecal methotrexate alone may be sufficient.

The paper by Lister et al. [19] concerns 62 adult patients with ALL who received adriamycin, vincristine, prednisone and L-asparaginase in a program based on lessons learned from childhood ALL. The complete response rate in the study was 69%. This is one more paper that indicates that combinations of anthracyclines, vincristine, glucocorticoids, and L-asparaginase and other drugs can produce complete responses in adults with ALL on the order of 70%, as previously reported by Henderson [20] and Capizzi [21]. This study and ones similar to it represent significant advances in the treatment of this disease. Cranial irradiation and intrathecal methotrexate were given as CNS prophylaxis. A standard dose of methotrexate not related to body surface area was used intrathecally in all patients. This makes sense since almost all adults have a CSF volume of approximately 150cc. irrespective of body surface area. Such practice will decrease the number of inadvertant overdoses of intrathecal methotrexate [22]. As maintenance therapy, patients received oral 6-mercaptopurine oral methotrexate and oral cyclophosphamide. I question the usefulness of cyclophosphamide in this regard since data in children from St. Jude's Children's Hospital in Memphis has shown that as one multiplies the number of drugs used during maintenance, one multiplies the complications to be expected and does very little to improve the remission duration [23]. In my opinion, cyclophosphamide is a drug with marginal activity in ALL and is more likely to be hazzardous than helpful. I cannot help but wonder whether the one patient who died at home during an influenza epidemic while in complete remission may not have been a cyclophosphamide casualty. The maintenance therapy was continued for three years and then stopped. I agree with the concept, but would have been more pleased to see half the patients randomized to dinscontinue maintenance and the other half randomized to have treatment continued. That kind of comparative informa-

tion about a crucial question, that is whether or not one can safely take an acute leukemia patient in remission off maintenance therapy at some period in time needs to be developed. The remission duration median of 21 months in this study represents some of the best data of this kind. The fact that 7 patients have already been in continuous complete remission for more than three years is encouraging, but not different from the early observations in other studies of similar design.

In an attempt to identify features on presentation that might influence remission duration, the authors found that age was not a factor as have other investigators. They did find, as have others, that patients with hepatosplenomegaly on admission have, on the average, shorter remission durations than patients with less disease bulk, and they found that patients who have extremely high white counts on admission relapse relatively quickly. Cytochemical and cell surface marker studies gave the same results that have been reported by others for childhood ALL.

This study confirms the fact that adult ALL behaves much the same as childhood ALL and responds to the same kind of therapeutic manipulations. The question then comes up as to whether or not separate studies need to be designed for children and adults with ALL. It would appear from these data and other studies that children and adults might be treated on the same protocols with the same stratifications applied to both.

The paper by Catovsky et al. [24] concerns ultrastructure and cell marker studies in lymphoproliferative disorders. The authors contend, and rightly so, that surface marker studies and electron microscopic studies increase the accuracy of subclassification of the acute leukemias. They carefully define the morphology and cell surface marker study results in various B and T cell disorders. They conclude that these studies are useful and no one doubts this. I do take issue, however, with their idea that prolymphocytic leukemia is a disorder separate and distinct from chronic lymphocytic leukemia (CLL). It seems to me most likely that what has been called prolymphocytic leukemia by these authors is simply middle or endstage CLL. Many patients with CLL end up with lymphocytes in the marrow and peripheral blood that are younger than those which were demonstrated at the time of diagnosis. An occasional patient with CLL terminates with what appears to be a blastic crisis based on the immature nucleolated morphology of the leukemic cells at or near the time of death [25]. I see no scientific or clinical reason for separating this disorder out from CLL since the treatment for Catovsky's prolymphocytic leukemia is not different from that of resistant CLL.

The last paper in this series is by Mertelsmann et al. [26], and it concerns marker studies in hematologic malignancies. The authors characterized malignant cells by terminal deoxynucleotidyl transferase (TdT) activity, CFS-c assays, and cell surface marker studies. They have found, as have others [27] that TdT activity is highly specific for lymphoid neoplasms and that TdT positivity approaches 100% in acute lymphocytic leukemia. In addition, approximately one-third of patients with the blast phase of chronic myelogenous leukemia (CML-BC) have TdT positive blasts. An extremely important observation from this study is that acute leukemia patients whose

blasts are TdT positive almost always respond to vincristine and prednosine, whereas TdT negative patients do not. This correlation of TdT with response remains valid even when the standard morphological examinations are inconclusive. In addition, the majority of the CML-BC patients who responded to chemotherapy were TdT positive. It must therefore be concluded from this study and similar ones [27] that bone marrow TdT assay is a powerful aid in determining type of acute leukemia and in predicting response to therapy. This study also defined 4 cases of morphological acute myelomonocytic leukemia associated with cell marker data consistent with a double stem cell lineage. Other recent evidence suggests a stem cell capable of both myeloid and lymphoid differentiation as the site of the major lesion in some acute leukemias [28]. The fact that myeloid-appearing cells in CML blast crisis can exhibit TdT activity [27] suggests that such a common stem cell may be deranged in many cases of CML-BC. The absence of the Philadelphia chromosome in lymphocytes found in the chronic phase of CML has been considered evidence against a common lymphoid-myeloid stem cell in nature. However, cytogenetic examination of lymphocytes obtained during the chronic phase of the disease from patients who have sustained the chronic phase for 5 to 10 years may shed some light on this important question. In those patients, all lymphocytes would have been formed since the development of the CML, whereas many lymphocytes present at the time of diagnosis would have been formed prior to the advent of the disease with its marker chromosome. Such studies as these and those of Mertelsmann may eventually lead to a better understanding of the origin of some hematologic malignancies.

References

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