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Summary Overview of Clinical Session

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It is apparent from the recent work presented at this meeting that great strides have been made in the past few years in our understanding of the biology of leukemia, from the molecular to the clinical levels, but, unfortunately, these advances have not yet been translated into improved methods of treatment. As Hardisty recently pointed out [1], the major advances in the treatment of childhood leukemia took place more than 10 years ago, and there has been relatively little progress since then in developing better treatment for patients presenting with disease features which are associated with a poor prognosis; about half of the children and over half of the adults with acute lymphoblastic leukemia (ALL) are still dying of their disease even with the best modern treatment regimens. The best results yet reported in adults with ALL were achieved with a protocol which was designed over 10 years ago [2], and our own attempts as well as those of other investigators since then to improve further the treatment of adults have been unsuccessful [3, 4].

McCredie presented the combined results of treatment of over 900 adults with acute nonlymphoblastic leukemia (ANLL) at five major centers in the United States. The results in terms of long-term survival are disappointing. Overall, only 14% of the patients survived 5 years, but age had an important influence; 19% of the patients under 50 years of age and only 8% of those over 50 survived 5 years. As in the case of ALL, it is discouraging that despite intensive efforts to develop better treatment protocols, the results have remained almost constant during the past decade.

Except for bone marrow transplantation, which I will discuss shortly, there has also been little progress in improving survival in the chronic leukemias. The recent observations that some of the interferons have therapeutic activity in hairy-cell leukemia [5] and chronic myelogenous leukemia [6] are extremely interesting, but this is certainly not a curative form of treatment, and it is too soon to determine whether survival will be extended.

Patients with leukemia usually have between 10^{12} and 10^{13} leukemic cells at diagnosis. Based on the rapidity of cell kill with modern induction programs [7], it seems possible that some of the current intensive treatment regimens are capable of killing this many leukemic cells (or at least the entire fraction of the population which is capable of serving as stem cells) in highly responsive cases of ALL without producing irreversible damage to normal stem cells. However, it is doubtful if any of the regimens yet devised are capable of entirely eradicating the leukemic cells in the less-responsive types of ANLL without causing lethal injury, and I suspect there must be other factors aside from drug-induced cell kill which come into play to account for the long survivors. As has previously been shown, the human promyelocytic cell line HL-60 is a good target for induction of dif-

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ferentiation, and fresh promyelocytic leukemia cells can also be forced to differentiate with vitamin A and D analogues and various chemotherapeutic agents employed in leukemic therapy. Induced differentiation may be one reason for the better therapeutic results in acute promyelocytic leukemia (APL); in our experience about 35% of patients with APL survive over 5 years compared with 10%–15% for the other types of ANLL [8], and other groups have had similar results. The observation that enhanced differentiation of leukemic cells can occur using combinations of low doses of cytostatic drugs and differentiation inducers is intriguing, and hopefully these observations will eventually lead to clinical therapeutic advances. A number of investigators are currently trying to define the most effective combinations of agents for different types of leukemia [9], and we can look forward to learning more about the therapeutic potential of this approach during the next few years.

Mixed opinions were expressed concerning the usefulness of low-dose cytosine arabinoside (Ara-C) or high-dose Ara-C, but the general consensus seemed to be that some of the initial highly favorable claims had been overstated. Although occasionally durable responses have been observed with low-dose Ara-C, the responses occurred erratically and most of them were of short duration. High-dose Ara-C of course causes marrow aplasia quite consistently, but although clinical trials in ANLL have been underway for several years now, a substantial effect on survival has not yet been demonstrated. Several interesting new drugs are currently undergoing clinical trials or will be soon, including homoharringtonine, fludarabine, and several new anthracyclines and antifols. While these drugs have potent antileukemic activity, and it is quite possible some of them may prove to have a therapeutic advantage over the present generation of drugs, I am doubtful whether any of them will lead to a major increase in the cure rate. We are still learning how to use the drugs already available more effectively, but so many modifications of intensive treatment programs have already been tried without appreciably altering the end results that it is doubtful if any further minor changes or substitution of new active compounds will be any more successful. Thus, in my opinion, a more radically different approach is needed if we are to see substantial further improvements in curability.

High hopes were held at one time for various forms of immunotherapy, but the results of clinical trials during the past 2 decades have generally been very disappointing, including recent trials with monoclonal antibodies [10–13]. Immunotherapy alone is unlikely to be curative, but it is still quite possible that highly specific monoclonal antibodies will be shown to be useful therapeutically in targeting cytotoxic agents to tumor cells. The current investigations concerning the role of oncogenes in the pathogenesis of leukemia are enormously interesting and important, and while it is not unreasonable to hope that they may eventually lead to the development of more selective forms of treatment, it is not yet possible to predict if or when therapeutically applicable strategies will evolve from this work.

At the present time, probably the most promising approach for the responsive leukemias is high-dose chemotherapy and total body irradiation followed by rescue with bone marrow transplantation. The dose response curves for some of the cytotoxic agents and ionizing irradiation are very steep, and there is abundant evidence from experimental tumor models that responsive tumors which are incurable with conventional doses of active agents can often be cured simply by substantially increasing the dose. I suspect we are coming sufficiently close to curing some of the "high-risk" patients with ALL, who are now still relapsing and dying on conventional chemotherapy, that the incremental dose increases permissible with bone marrow rescue may tip the balance in favor of cure. The challenge is of course more formidable in the less-responsive types of ANLL, but here too it may be possible to cure some patients who are presently dying of their diseases.

Allogeneic BMT is presently limited to the minority of patients who have human leukocyte antigen (HLA)-identical or partially HLA matched donors, usually sib-

lings, although with further advances in transplantation biology better ways may be found to prevent graft rejection and graft versus host disease, and in the future it may be possible to overcome the present restrictions. It is clear that the results are better if the procedure is done early in the course of the disease before drug resistance has developed [14–19]. Because 40%–50% of the patients with ALL are now probably being cured with conventional chemotherapy, to date most of the bone marrow transplantation (BMT) trials in ALL have been done in second or later remissions. However, more recently, with reliable definition of risk factors, selected children at higher risk of early relapse have been transplanted in first remission. Only about 10%–20% of patients transplanted in third or fourth remission survived 2 years, while the results are better for patients transplanted in first or second remission. The relapse rate has been similar for patients transplanted in first or second remission, probably about 30% overall at different centers, but since those transplanted in first remission have almost exclusively been high-risk patients while those in second remission were in varied risk categories, no valid comparison is yet possible. There seems little doubt that patients transplanted in second or later remissions have a better chance of long-term survival than in comparable patients treated with chemotherapy. There is insufficient experience yet to compare the results of BMT and chemotherapy of patients in comparable (high) risk categories in first remission, but because of our inability to improve the treatment results in such patients with chemotherapy alone during the past 10 years, I predict that BMT will soon be shown to produce a higher proportion of long survivors among these high-risk patients than is possible with chemotherapy.

The majority of allogeneic transplants thus far have been performed in children and adolescents and very few patients over the age of 40 have been transplanted. At my own institution, patients over 20 years of age had a significantly higher early mortality [17], but Karl Blume at the City of Hope has also had very good results in adults with ALL [15].

In ANLL, the results of chemotherapy are sufficiently poor that it is justifiable to accept the risks and early mortality associated with BMT and perform the procedure in first remission. Currently there are several ongoing comparative trials of chemotherapy alone versus allogeneic bone marrow transplantation in patients with ANLL in first remission [3], and during the next several years we should be able to get a firm answer to the question of which gives better results. All of the transplant teams are of course working hard to develop more effective ways to prevent the major complications associated with the procedure and to improve the chemotherapeutic and irradiation eradication regimens, and we can anticipate further improvements in the results with fewer complications during the next few years.

Attempts to cure chronic myelogenous leukemia (CML) with intensive treatment programs have so far been unsuccessful [20], and the results with allogeneic BMT performed during the blastic phase have generally been poor with very few long survivors. However, during the past few years over 100 patients throughout the world with CML in the chronic phase or early in the accelerated phase have had allogeneic transplants, with more encouraging early results [21]. While all the results have not yet been compiled and the follow-up is still too short in most cases to determine the long-term results, it appears that approximately 65% of patients transplanted in chronic phase and perhaps half that percentage in accelerated phase are surviving the procedure and that the marrow remains in complete remission (i.e., free of Ph′+ cells) in most of them. Whereas the median survival from diagnosis for patients with chronic-phase disease is 3–4 years, some patients may live 5–10 years and remain in good health for most of this time. Faced with the hazard of a 35% early mortality incidence associated with the transplant procedure, the patients and their physicians are confronted with a serious dilemma of which course of treatment to choose a when. A reliable staging system has long been needed in CML; such a system is presently under development, and once its validity is confirmed, it should prove help-

ful in advising patients who have suitable donors when to opt for BMT [22]. As in the case of acute leukemia, this option is usually limited to patients under the age of 40, and patients under 25 have a significantly better outcome [21].

The majority of patients with leukemia do not have HLA-identical sibling donors. For younger patients with acute leukemia who lack suitable donors and who are at high risk of failing the best available chemotherapy programs, the most promising approach now available is probably intensive treatment with whole body irradiation and high-dose chemotherapy followed by autologous bone marrow transplantation, using the patient's own remission marrow which has been appropriately treated in vitro to remove residual leukemic cells. The early results in patients with poor-prognosis lymphomas have been encouraging if carried out immediately after primary induction treatment [23]; as expected, heavily pretreated patients do not respond as well. Most of the lymphoma patients successfully treated so far after primary induction therapy had minimal or no marrow involvement with lymphoma prior to treatment, and it is undoubtedly more difficult to eliminate the increased numbers of residual leukemic cells present in the marrows of patients with acute leukemia in first remission. The majority of patients with ANLL as well as the majority of high-risk patients with ALL who achieve remission relapse within the 1st year after doing so [3], and most of these patients probably barely meet the qualifications for complete remission. Using the usual morphological criteria, the marrow can contain between 10^4 and 10^5 leukemic cells/ml and still qualify as a remission [23, 24]; thus, to purge the marrow successfully in patients who are at high risk of early relapse, it is probably necessary to develop purging methods which will kill at least this number of leukemic cells without causing lethal damage to the normal stem cells.

Relatively few patients with acute leukemia have yet been treated with autologous BMT, and, as in the case of the early trials with allogeneic BMT, most of them have been in second or later remissions [25–27]. The results of all the recent trials have not been collected, but it is rumored that the relapse rate has been appreciable in these high-risk patients. However, it is not clear yet whether this is due to failure of the in vitro purging techniques or of failure to eliminate the residual leukemic cells in the patients by the in vivo conditioning programs so far tried. Studies are currently underway at many institutions to develop better purging methods, using physical, immunological, or pharmacological techniques or combined methods [28–33], and it is not unreasonable to expect that improved methods for eradication of leukemic cells both in vitro and in vivo will be forthcoming during the next several years. The maximum tolerable age threshold for autologous BMT is not yet known, but autologous transplants are associated with fewer serious complications than allogeneic transplants, and it may prove possible to treat patients successfully up to the age of 50 years. In the meantime, while these clinically oriented studies are proceeding, the geneticists and molecular biologists will doubtless continue their remarkable advances, and we eagerly anticipate the day when their work will lead to more selective forms of treatment for all types of leukemia.

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