Leukemia: A Model for Drug Development

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Abstract

Early attempts at preclinical model development for cancer drug development relied heavily on mouse leukemias and lymphomas to detect agents with antitumor activity. These models were applied clinically, and the concepts of combination chemotherapy, remission induction, and maintenance treatment all developed in leukemia. Subsequently, the predominant impact of cytogenetics on probability of response to treatment and survival was first illustrated in leukemia. The power of a single drug to change the natural history of a disease was noted in acute myelogenous leukemia, in which a previously incurable disease was rendered potentially curable with 1-β-D-arabinofuranosylcytosine. Additional studies illustrated the exquisite relationship between karyotype and response to specific agents. The ability to achieve a high proportion of complete remissions and to control the complication of intravascular coagulation, acute promyelocytic was noted with all-trans retinoic acid. The concept that new drug activity would only be demonstrated in patients with minimal prior therapy has been challenged by the curative potential of a number of agents in far-advanced hairy cell leukemia. In addition, fludarabine monophosphate (Fludara) was sufficiently active in advanced refractory patients that approval for this agent in chronic lymphocytic leukemia was granted by the Food and Drug Administration without comparative clinical trials. Fludara was initially a drug with limited therapeutic range, but has been shown to be active in indolent lymphoproliferative disorders. Understanding of the multiple biochemical actions of this agent has led to its use in combinations with 1-β-D-arabinofuranosylcytosine in acute myelogenous leukemia and myelodysplastic syndrome and with DNA active agents such as novantrone and cyclophosphamide in other lymphoproliferative disorders. The understanding of the various actions of this drug gives rise to a wide range of possibilities for biochemical modulation with agents active in solid tumors. The evolution of this understanding of the new role of Fludara has occurred over a period of 10 years. A drug with similar potential in the next decade is compound 506U78, an analogue of arabinosyl guanosine. This agent has potent activity in acute T-cell leukemia. Because it shares many of the activities of Fludara in interfering with enzyme systems important in DNA and RNA synthesis and DNA repair, it is likely that this agent will also have a wider scope than is presently obvious. The unique accessibility of leukemia cells for study has allowed hematologists to understand more fully the range of activities of new agents and has led to important new concepts in the area of drug development.

Introduction

In the early phases of development of chemotherapy for malignant disease, leukemias and lymphomas played a pivotal role. These tumors were not only sensitive to a variety of agents but provided animal models from which many of the principles of chemotherapy were established. The outstanding work of Skipper et al. developed the principles of dose and schedule dependency in mouse models of leukemia and lymphoma (1). The pivotal role of leukemia as a model for drug development was accelerated by the outstanding developments in combination chemotherapy achieved in childhood ALL (3). These principles, developed by Drs. Frei and Freireich and illustrated in this Festschrift in the presentation by Dr. Emil Frei (2), were seminal in the development of the intellectual underpinning of chemotherapy in malignant disease generally (3). Leukemia was initially considered to be a window into the understanding and treatment of cancer. These diseases have a number of important characteristics that allow a detailed study of the biology of cancer. In most cases, first it is a stem cell disorder with variable morphology and natural history. There is increasing evidence of not only cytogenetic heterogeneity but molecular specificity to clinical syndromes and the probability of response to particular chemotherapeutic agents. Of increasing importance is the observation that monoclonality in minimal residual disease in acute leukemia or in early stages of CLL does not equate to a disease process.

In recent years, leukemia has lost its position at center stage in the drug development of oncology for a number of reasons. Because of developments in solid tumor chemotherapy, the window to cancer is now bidirectional. Drugs being developed predominantly in solid tumor oncology are now being applied in the leukemia area. The initial optimism that existed in the 1960s and 1970s that leukemias could be cured with systemic chemotherapy and biological therapy has been replaced by the reality of early, steady progress without dramatic breakthroughs, except in a few situations. For example, in hairy cell leukemia, the proliferation of new agents such as human leukocyte IFN, recombinant α-IFN, 2-deoxycoformycin, and 2-chlorodeoxy-
denosine has transformed this disease from one that was fatal in 60–70% of cases to one in which the majority of patients seem able to live out a normal life expectancy (4).

A major reason for a lack of focus on leukemia in the national and international oncology community has been that leukemias are uncommon diseases that require high levels of specialized, intensive, and expensive support for their management. Many of the drugs that are active in leukemia do not cross over to show substantial activity in solid tumors. Being a small proportion of cancers in general, leukemia provides a small market for the pharmaceutical industry, which has shifted emphasis to the development of agents that are effective in common solid tumors such as lung, breast, colorectal, and prostate cancers. Thus, leukemia at a national and international level, both in the public and private sectors, has a low clout index. However, although leukemia is a low-incidence tumor, this does not equate with a low biological interest. Leukemia remains a pivotal tumor for the discovery of a number of concepts of oncology treatment and for the rational design of chemotherapeutic strategies.

**AML Therapeutic Dissection of Leukemia Biology**

Despite the dramatic impact of combination chemotherapy with agents such as 6-mercaptopurine, methotrexate, vincristine, and prednisone in combination in childhood leukemia developed in the early 1960s, there was no effective strategy for the management of adult AML. In the middle of 1965, when Drs. Frei and Freireich first developed the Adult Leukemia Program in the Department of Developmental Therapeutics at the MDACC, a combination of 6-mercaptopurine, methotrexate, vincristine, and prednisone in relatively young patients with AML showed a response rate of approximately 50% but was not found to be curative (5). Combination of 6-mercaptopurine with methyl-mercaptopurine riboside and other combinations were also ineffective. In 1969, ara-C was first introduced as a single agent in the initial management of adult AML. Applying the principles of prolonged exposure of the cells to ara-C by continuous infusion (a concept developed by Skipper et al.; Ref. 1), ara-C as a single agent was found to have a complete response rate of approximately 40% in a variety of schedules. The drug was well tolerated and was found to be more effective in younger patients. The striking difference of this approach when compared to earlier regimens was that a number of patients who achieved CR remained in CR indefinitely (5). Thus, ara-C was defined as the first and only drug found to be curative (5). Combination of 6-mercaptopurine with cyclophosphamide were associated with a somewhat high complete response rate, but a decrease in the cure fraction was seen as the dose of ara-C was modified to approximately 50% of its dose as a single agent (5).

The modern era of chemotherapy in adult AML was ushered in when the anthracycline daunorubicin, the activity of which was discovered in European studies, was combined with ara-C. The 3/7 regimen was developed by the Cancer and Leukemia Group B in 1973 (6), and the DOAP regimen (daunorubicin, vincristine, ara-C, and prednisone) was developed in 1971 at the MDACC (7). Subsequently, because there was a temporary hiatus in the availability of daunorubicin, doxorubicin was combined with vincristine, ara-C, and prednisone in the ADOAP regimen (8). The combinations of anthracyclines and ara-C were associated with a higher complete response rate and a longer survival (Table 1).

In 1978, it was obvious that a number of patients treated up to 10 years previously were still in continuous CR. An analysis was undertaken to identify characteristics associated with the eventful cure of AML in patients treated between 1965 and 1973. The results were published in an article from the MDACC in which 20 patients who had been in continuous CR for more than 5 years were highlighted (5). Previously, only 16 patients were reported in the literature to have been in continuous CR for more than 5 years. A number of disease features were identified to be important in this small subset of patients. As expected, younger age was important. More importantly, a number of patients had −C, +D, +E, −G in their cytogenetic analysis, and seven of the patients had an increase in eosinophils. Until the advent of anthracyclines, no patient with APL was cured, but combinations of daunorubicin or Adriamycin with ara-C were found to be associated with long-term survival in APL (Table 1). Subsequently, we have come to appreciate that the abnormal eosinophils seen in these patients were typical of patients with a pericentric inversion of chromosome 16 (inv16) (9). Auer positive patients with −C, +D, +E, −G were patients with a translocation between chromosomes 8 and 21 [t(8;21); Ref. 10], and APL is associated with t(15;17) (11). Thus, many of the cures in this patient population occurred in specific cytogenetic and morphological subsets of patients. Some patients had a normal karyotype noted with unband cytogenetics. Partly as a result of these observations, cytogenetic studies were routinely applied to all MDACC patients with AML from 1975 onward.

The importance of cytogenetic parameters as predictors of response and survival has been extended. When dose intensity of ara-C regimens was explored with a high-dose ara-C regimen, a higher CR rate was noted when high-dose ara-C was used in salvage settings (12). In our studies, the patient subsets who responded to high-dose ara-C after relapse were those with inv16 and t(15;17) and some diploid patients. The regimen was not effective in t(15;17) or in other cytogenetic abnormalities (Table 2). Subsequently, Cancer and Leukemia Group B conducted a study of high-dose ara-C as intensification in remis-
and conventional-dose ara-C, intermediate-dose ara-C, and high-dose ara-C were compared. The high-dose ara-C regimen in younger patients was associated with a significant improvement in CR duration and long-term survival (13). Subsequently, Bloomfield has identified that the improvement in CR duration was noted only in inv16 and t(8;21) and in some diploid patients (14). There was no improvement in survival in t(15;17). Thus, there is the unique relationship that occurs between ara-C and curability of inv16 and t(15;17). Closure of this loop has been established, now that it has been noted that the products of the breakpoints in chromosome 16 and chromosome 21, namely CBF-β and AML1, come together to form a joint complex that is important in normal hematopoiesis. The reason why ara-C is exquisitely active in these two subsets of disease should provide exciting insights into the relationship between chemotherapeutic agents and specific genetic abnormalities.

**APL: Serendipity Revisited**

The clue that anthracyclines were important in APL was provided by the high response rate initially noted in 1973 by Prof. Jean Bernard when APL was treated with single-agent daunorubicin (15). This morphological subset of AML, which occurs in 5–10% of patients, was initially described in 1953. The activity of daunorubicin was striking, but many patients died from the complications of intravascular coagulation and bleeding. The bleeding manifestations led to attempts to provide systemic anticoagulation for these patients. However, Chinese physicians were frustrated by limited blood transfusion resources that contributed to a high mortality rate in patients with APL treated with chemotherapy. This led to the search for new approaches to the management of this subcategory of disease characterized by the t(15;17). Laboratory investigators evaluated the use of retinoids in HL60, a leukemia cell line that was initially thought to be APL. (It is of interest that this cell line, developed from a MDACC patient, is now identified not to be APL and does not have the t(15;17) abnormality.) The Chinese investigators showed striking differentiation of HL60 in cell culture, leading to a clinical study of ATRA in the management of APL (16). A high CR rate in patients treated with ATRA was reported. Although this was a seminal observation, it was not until Degos et al. presented their data on patients treated in France with the Chinese preparation at the American Society of Clinical Oncology in 1990 (17) that the Western World became convinced that this was indeed a major observation. Subsequently, molecular biologists have found that the important breakpoint in chromosome 17 affects the retinoic acid receptor α gene (18). Whereas the ATRA effect and the genetic abnormality have been brought together, the exact mechanism by which ATRA causes differentiation of the leukemic cells has not been established.

Although ATRA alone has a very high complete response rate in previously untreated patients and in relapsed patients who have previously received chemotherapy, patients become resistant to ATRA either because of pharmacological reasons with inability to sustain blood levels of ATRA over time or by the development of other mechanisms of resistance. Thus, studies have now been undertaken combining daunorubicin or idarubicin with ATRA either simultaneously or sequentially (19). These studies have not only improved the CR rate (up about 90% in some studies) but have also demonstrated that the majority of patients who achieved CR stay in CR. Our results are illustrated in Fig. 2. Thus, APL, a disease in which 3/7 type regimens and postremission therapy using ara-C and anthracyclines were associated with a long-term survival fraction of approximately 1 in 3, is now associated with a long-term survival fraction of 60–70%.

Dr. Eli Estey conducted a study of high-dose ara-C by continuous infusion as a single agent as an initial therapy in AML and found that it was ineffective in t(15;17) patients (20). This study highlighted that whereas ara-C is a very important single agent in AML in general, it does not seem to play a major role in APL and confirmed our earlier observation that before anthracyclines became available, ara-C regimens were not associated with cure of any APL patients at MDACC treated before 1970. The reasons behind the unique association between anthracyclines and APL are unknown.

Amazingly, Chinese investigators have come up with yet another unique observation that arsenic trioxide can cause long-term sustained remissions as a single agent in APL (21). Whether the arsenicals will have particular associations with the breakpoints in chromosomes 15 or 17 or interaction with retinoids awaits elucidation.

**Fludarabine: Snakes and Ladders in Clinical Research**

A number of purine analogues were synthesized by Dr. Montgomery et al. at Southern Research Institute in the 1970s (22). Initially, ara-A was used as an antiviral agent, and studies were conducted investigating ara-A as a chemotherapeutic agent. However, limited solubility of ara-A and rapid deamination by adenosine deaminase were associated with failure of the drug to develop an effective chemotherapeutic agent. Changes in the structure of the purine analogues have led to two major

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### Table 1 Results of early protocols in AML at MDACC, 1965–1972.

<table>
<thead>
<tr>
<th>Category</th>
<th>Patients</th>
<th>CR (%)</th>
<th>Died (%)</th>
<th>Resistant (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miscellaneous single agents</td>
<td>19</td>
<td>11</td>
<td>58</td>
<td>32</td>
</tr>
<tr>
<td>6MP&lt;sup&gt;a&lt;/sup&gt; combination</td>
<td>60</td>
<td>37</td>
<td>50</td>
<td>13</td>
</tr>
<tr>
<td>Ara-C ± VP&lt;sup&gt;b&lt;/sup&gt;</td>
<td>62</td>
<td>39</td>
<td>47</td>
<td>15</td>
</tr>
<tr>
<td>Ara-C combination (cyclo. TG)</td>
<td>96</td>
<td>34</td>
<td>43</td>
<td>23</td>
</tr>
<tr>
<td>DNRA&lt;sup&gt;c&lt;/sup&gt; + ara-C</td>
<td>16</td>
<td>69</td>
<td>19</td>
<td>13</td>
</tr>
<tr>
<td>Total</td>
<td>250</td>
<td>37</td>
<td>44</td>
<td>19</td>
</tr>
</tbody>
</table>

<sup>a</sup> 6MP, 6-mercaptopurine.  
<sup>b</sup> VP, vincristine and prednisone.  
<sup>c</sup> Cyclo., cyclophosphamide.  
<sup>d</sup> DNR, daunorubicin.

### Table 2 Dose intensification of ara-C

<table>
<thead>
<tr>
<th>Karyotype</th>
<th>Conventional ara-C</th>
<th>Salvage HDAC</th>
<th>HDAC intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>t(8;21), inv 16</td>
<td>Cures 50% CR</td>
<td>+ +</td>
<td></td>
</tr>
<tr>
<td>t(15;17)</td>
<td>No cures &lt;5% CR</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Diploid</td>
<td>Cures ± 25% CR</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>No cures &lt;5% CR</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>
new drugs. The first is fludarabine, which has a fluorine atom attached to the purine ring and a phosphate added to the sugar of the arabinose sugar moiety to improve solubility. The other is 2-chlorodeoxyadenosine, which uses a deoxyribose sugar and a chlorine atom affixed to the purine ring (Fig. 3).

Fludarabine was initially developed as an agent likely to be effective in rapidly proliferating tumors. It has well-known effects in inhibiting DNA synthesis and is active in a number of leukemia cell lines. Because of the marked difference in metabolism between mouse and man, when the drug was used in Phase I studies, it was found to be one of the few drugs in which the initial Phase I dose level was too high, and a decrease in the dose administered to humans was necessary (23). The drug was found to cause myelosuppression and to have potent immunosuppressive qualities. Phase II studies were performed in solid tumors and demonstrated no activity. However, Phase I-II studies had demonstrated substantial activity in lymphoma and CLL (24, 25). As is customary in Phase I clinical trials in acute leukemia, the dose achieved was substantially higher than that in the chronic leukemias, lymphomas, and solid tumors. At a dose ≥96 mg/m²/day for 5 days, striking neurotoxicity was noted, with patients developing blindness, paralysis, and coma (26). This led to the discontinuation of almost all of the clinical trials using fludarabine in the United States. Because Dr. Michael Grever and our group had noted striking activity with this drug in CLL and lymphoma at doses of 20–30 mg/m²/day for 5 days with no neurotoxicity, our Phase I-II study of fludarabine in hematological malignancies was continued at a maximum dose of 30 mg/m²/day for 5 days (27, 28). The striking activity of fludarabine in CLL was confirmed. Of interest, fludarabine was also highly active in patients with low-grade lymphoma and Waldenström’s macroglobulinemia but had little or no activity in intermediate- or high-grade lymphomas (25). This is a striking anomaly for a drug that had demonstrated activity against a wide variety of enzymes important in DNA synthesis and DNA repair and has yet to be explained. The exquisite sensitivity in the low-grade lymphoproliferative disorders is also unexplained. Fludarabine causes apoptosis, but why the effect is selectively noted in this particular subset of diseases, characterized by a low growth fraction, is still a puzzle. Increasing evidence suggests that the drug may work by inhibition of protein synthesis by incorporation into RNA rather than by its effect on DNA replication (29).

The approval of fludarabine for use in CLL is an example of the new relationship with the FDA. Accepting that there was no effective treatment for CLL in patients who were refractory to alkylating agents, the FDA approved the licensing of fludarabine in 1991 with two Phase II clinical trials, one conducted by the Southwest Oncology Group, and one conducted by the MDACC. No comparative data were considered necessary. The dramatic clinical activity with responses seen in 30–55% of patients and with restoration of normal hematopoiesis in patients achieving a CR was sufficient to satisfy the FDA that this drug should be approved for relapsed patients. The history of fludarabine illustrates that truly effective drugs can be discovered in patients who have had extensive prior therapy and are refractory to all other effective agents and calls into question the strategy that is in vogue to give Phase I drugs increasingly to patients with better and better prognoses.

Biochemical Modulation: Now a Reality

Interesting interactions of fludarabine have been noted in conjunction with other chemotherapeutic drugs. Gandhi and Plunkett made the observation in K562 cells that preincubation with fludarabine markedly enhanced the formation of ara-C triphosphate (30). This has now been confirmed in other human cell lines and also in the cells of leukemia patients studied with the fludarabine/ara-C combinations (31). It seems that fludarabine triphosphate decreases deoxynucleotide pools by inhibiting the ribonucleotide reductase and also has a direct stimulating effect on deoxycytidine kinase, the enzyme active in the formation of the triphosphate form of ara-C. This has led to fludarabine/ara-C combinations being used widely in poor-prognosis patients with AML and myelodysplastic syndrome since 1990, with impressive results (32). The long-term survival of such patients treated with fludarabine/ara-C in 1991–1995 is better than that observed in previous studies (Fig. 4).

The ability of fludarabine to inhibit DNA repair in damage caused by drugs such as alkylating agents, cisplatinum, and radiation has led to a number of other combinations. Fludarabine has now been combined with cyclophosphamide in patients with CLL and low-grade lymphoma. In the CLL studies, the response rate is significantly higher than that of fludarabine alone in previously treated patients (33). An Eastern Cooperative Oncology Group study of fludarabine and cyclophosphamide used in low-grade lymphoma is associated with a 100% response rate (34). In addition, it seems that fludarabine used in conjunction
with other agents causing apoptosis, such as mitoxantrone, has led to the new development of an extremely effective regimen in low-grade lymphoma (35). Fludarabine and ara-C inhibit repair of DNA damage caused by novantrone in AML cells in patients treated with a fludarabine, ara-C, and mitoxantrone protocol. The combination of fludarabine with mitoxantrone and dexamethasone has been developed by Dr. Fernando Cabanillas, Dr. Peter McLaughlin, and their colleagues in the MDACC lymphoma group and is now identified as a major new regimen in previously treated and frontline patients with low-grade lymphoma. In previously treated patients, most of the 51 patients were able to achieve a complete (47%) or partial (47%) response rate. The regimen is now being compared in a frontline comparative trial with an alternating triple therapy regimen with equivalent response rates and at least an equivalent ability to achieve bcr negativity for bcl2 rearrangement in low-grade lymphoma.

Cisplatinum causes cytotoxicity in malignant cells by forming DNA cross-links (36). The ability of fludarabine to inhibit repair of these cross-links has been demonstrated in a number of experiments. This has led to the development of the combination of fludarabine, ara-C, and cisplatinum in lymphoma, and clinical studies have been conducted at the MDACC and elsewhere (37). In addition, inhibition of repair of radiation damage has led to the development of a combination of fludarabine and radiation to give boosts to residual tumors in patients with bulky head and neck tumors that have not initially responded to 5 weeks of radiation therapy. Other potential agents that can be modulated by fludarabine include gemcitabine and many agents that have DNA-active effects. The range of potential combinations of fludarabine in hematological malignancies and solid tumors is illustrated in Table 3.

Thus, whereas fludarabine has initially been demonstrated to be active not only in indolent lymphoproliferative disorders, the range of possibilities that is now presented by understanding of the mechanisms of action of this drug is impressive (Table 3). The interactions with other agents lead to the possibility of combination chemotherapy protocols in which fludarabine acts as a modulator of the effect of other agents rather than a direct cytotoxic agent. Tight integration of understanding of the clinical behavior of the combinations with biochemical pharmacology laboratory collaborators has led to this rapid expansion of research opportunities.

### Table 3  Future Fludara combinations in hematological malignancies and solid tumors

<table>
<thead>
<tr>
<th>Hematological malignancies</th>
<th>Solid tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>F + gemcitabine (AML, NHL&lt;sup&gt;a&lt;/sup&gt;)</td>
<td>F + gemcitabine (pancreas)</td>
</tr>
<tr>
<td>F + hyper-CVAD (ALL)</td>
<td>F + anthracyclines</td>
</tr>
<tr>
<td>F + melphalan</td>
<td>F + radiation</td>
</tr>
<tr>
<td>F + CHOP (NHL)</td>
<td>F + radiation</td>
</tr>
<tr>
<td>F + cyclo. (Wald.&lt;sup&gt;b&lt;/sup&gt;)</td>
<td>F + IL2&lt;sup&gt;c&lt;/sup&gt; (CLL)</td>
</tr>
</tbody>
</table>

<sup>a</sup> F. Fludara.
<sup>b</sup> NHL, non-Hodgkin’s leukemia.
<sup>c</sup> Cyclo., cyclophosphamide.
<sup>d</sup> Wald., Waldenström’s macroglobulinemia.
<sup>e</sup> IL2, interleukin 2.

### Compound 506U78: Fludarabine Revisited?

Whereas analogues of adenine and cytosine have been prominent in the clinic, analogues of guanosine have not been widely explored. This is partly due to the limited solubility of some of these molecules. Scientists at Glaxo Wellcome have developed compound 506U78, which is the methoxy derivative of arabinosyl guanosine, a drug synthesized in 1964 (38). Compound 506U78 acts as a pro-drug of arabinosyl guanosine, with the methoxy radical being rapidly cleaved off in plasma by adenosine deaminase. Activity of 506U78 has been demonstrated predominantly in a variety of cell lines. The activity of 506U78 against T-cell lines is markedly higher than that against stem cell or B-lymphocyte lines (39). Preclinical toxicology suggested central nervous system depression as the most likely toxicity.

A Phase I clinical trial was initially conducted in pediatric patients and subsequently conducted in adults (40). The dose varied from 5 to 75 mg/kg. Antitumor activity was reported in this Phase I study at all dose levels, and neurotoxicity was dose-limiting. Two of 22 pediatric patients had some neurotoxicity at doses between 30 and 60 mg/kg. Sixteen (47%) of 34 adult patients, however, experienced grade 3 or 4 neurotoxicity. Strikingly, half of the evaluable patients with T-cell ALL or lymphoblastic lymphoma achieved a complete or partial response, as did a number of patients with other T-cell diseases. Some responses were noted in B-lineage ALL, B-CLL, and B-cell non-Hodgkin’s lymphoma, but not in patients with AML. One patient with chronic myelogenous leukemia blast crisis with T-cell transformation had a dramatic and prolonged response.

Thus, compound 506U78 has marked activity in T-cell diseases, and there is evidence of activity in B-lymphocytic disease. No evidence of activity in myeloid disorders has been demonstrated to date, and neurotoxicity is dose-limiting. The resemblance to fludarabine with a limited spectrum of clinical activity and a dose-limiting neurotoxic profile is very suggestive of fludarabine at a similar stage in its development. When evaluating the mechanisms of action of compound 506U78, it is obvious that there is a striking correlation between the intracellular levels of ara-GTP and response (41) that is similar to that demonstrated with ara-CTP levels and response in AML (42).
The mechanisms of action and the possibility of modulation with other drugs such as fludarabine suggest that the next stage of development will be in combinations (43). In vitro studies suggest that enhancement of intracellular ara-GTP levels may be achievable with pretreatment of fludarabine in a variety of cells.

Leukemia: Still An Attractive Target

Repeated observations demonstrated that whereas leukemias are numerically less frequent than solid tumors, a wealth of important information on mechanisms of drug action can be obtained in this tumor type. Development of some rational combinations is possible only in the situation of leukemia. The ability to frequently sample malignant cells and to look for evidence of biochemical activity and for damage to molecules such as DNA makes leukemia an attractive target for new drug development. It is my opinion that no drug should be developed along an exclusively solid tumor pathway without a companion study in leukemia, looking at possible mechanisms of action that can be applied not only to leukemia patients but in an intellectually synergistic fashion with solid tumors. A continued theme throughout the development of agents effective in leukemia is demonstrated by one of Dr. Freireich’s many credos, namely, “it is easier to declare a drug to be inactive than to discover its true activity.” Expansion of the scope of new agents both in leukemias and solid tumors cannot be accomplished without the concept of developmental therapeutics developed by Drs. Frei and Freireich in the 1960s. This was, in fact, the model for translational research programs in cancer and led to an era of unparalleled success during the period of 1965 to 1980. Although progress in the management of acute and chronic leukemias has come at a slower pace than had been hoped, the steady stepwise incremental improvement in survival in all of the leukemias is testimony to the power of a good idea and the ability of a single individual, Dr. Emil J Freireich, to attract and retain a group of students committed to exploring the ideas espoused by him throughout his professional career.

References


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