MEDICAL GRAND ROUNDS

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OBSTACLES TO THE CONTROL OF ACUTE LEUKEMIA

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I. INTRODUCTION

Acute leukemia is a group of neoplastic disorders of hematopoiesis in which abnormal clones of immature leukocytes progressively accumulate, leading to death from bone marrow or other vital organ failure if treatment is unsuccessful. The overall yearly incidence is about 3.5 cases/10^5 inhabitants (1); i.e., about 80 cases are annually observed in the Dallas-Fort Worth area. This number will increase as Metroplex hospitals accept patients from an increasingly larger referral area.

This review will summarize recent information pertinent to etiology, classification, diagnosis, and therapy of acute leukemia, with emphasis on the lymphocytic and granulocytic types -- the former the most common malignancy of children, and the latter increasing in frequency with age through at least the 8th decade. A major focus will be an analysis of the variability of prognosis.

II. ETIOLOGY

Although several unequivocal risk factors have been identified and are tabulated below, in the vast majority of cases of human acute leukemia no predisposing factors can be identified. At least 4 factors can provoke similar diseases in animals; epidemiologic observations suggest that the same factors may contribute to human leukemia.

A. Chemical Factors

1. Animal models. 7,12-dimethylbenz(a)anthracene (DMBA) causes leukemias in mice and rats (2). The widely used L1210 murine leukemia originated in a DBA strain female mouse following skin paintings with methylcholanthrene (3).

2. Human acute leukemia

   a. Benzene

      (i) Heavy exposure causes aplastic anemia followed in a small proportion of cases (perhaps 20%) by acute leukemia (4).

      (ii) A 10-fold excess risk of AGL was found in a 30 year followup of rubber workers exposed to benzene levels that were thought to be well within safe limits at the time surveys were made (5).

   b. Alkylating agents - Patients treated with these agents for multiple myeloma, Hodgkin's disease and other lymphomas, carcinoma of the ovary, breast cancer, and non-neoplastic connective tissue disorders have an increased risk of developing acute myelomonocytic leukemia (6). Leukemia is more common in patients who develop prolonged periods of pancytopenia after chemotherapy.

   c. Other marrow toxins may rarely lead to AGL after a period of aplasia.

(i) Chloramphenicol (7)

(ii) Phenylbutazone (8)

B. Radiation

1. Animal models - Leukemogenesis in mice is sharply dependent on the dose and fractionation of radiation (9). For single exposures of photons, a peak incidence at about 300 r is observed. If a given dosage is fractionated, the incidence of leukemia is much lower than the incidence obtained when the dose is given all at once. Dependence on fractionation is not seen with neutron irradiation (9).

2. Human "experiments"

a. Atom bomb survivors - ALL, AGL and CGL occurred in excess among exposed survivors. ALL predominated in children, while CGL was commoner in adults. Latent periods of 2-3 years, with peak incidence 5-10 years after irradiation, were observed. Excess leukemia was seen in persons exposed to as little as 5-20 rad. The overall risk was estimated as 0.5-1 death/10^6 person years/rad exposure (10,11).

b. Pioneer radiologists - Since these individuals received multiple small doses of radiation, while the atom bomb survivors were exposed all at once, it has been possible to compare the effects of fractionated and single doses. The leukemogenic effect per rad of intermittent (fractionated) exposure in the radiologists may not have been less than the effect of a single exposure in the atom bomb survivors (10,11). Uncertainties in total dose estimates leave some doubts about these conclusions.

c. Ankylosing spondylitis - At least a 10-fold increase in leukemias (CLL excluded) was seen in those patients who received spinal irradiation. The excess risk increased with age of the patient at the time of exposure (12).

3. Problem of threshold - no clear threshold dose has been demonstrated. This problem is critical in the calculation of risks of diagnostic radiation.

4. Susceptible groups - Excess leukemia per rad exposure is higher following prenatal radiation than following postnatal irradiation (10,11). The peak incidence of leukemia after prenatal irradiation occurs in the fifth postnatal year (13).

C. Viruses

1. Animal models - Type-C enveloped RNA-containing viruses (retraviruses) cause naturally occurring leukemia in chickens, wild mice, cats, cows and gibbon apes (14). These important discoveries establish that retraviruses are one cause of naturally occurring leukemia in a variety of warm-blooded animals. In many instances, however, no evidence can be found to associate spontaneous leukemias in these animals to RNA tumor

viruses (15). Therefore, naturally occurring, morphologically similar hematopoietic neoplasms have more than one cause.

2. Human leukemia/lymphoma

   a. The weight of evidence is against an etiologic role for any known retravirus (16).

   b. Epidemiologic, immunologic and virologic evidence strongly supports an etiologic role for the Epstein-Barr virus (EBV) in African Burkett's lymphoma. Proof of such a role is impossible for ethical reasons. Hyperholoendemic malaria is a probable etiologic cofactor, and the International Agency for Research in Cancer is sponsoring a prospective study of the effect of eradication of malaria on the incidence of Burkett's lymphoma in Tanzania (17). Interestingly, EBV does not appear to be involved in 2-5% of African Burkett's lymphoma or in 85% of cases of morphologically and clinically identical disease in temperate climates (17). This is a possible example in human neoplasia of more than one cause of a single clinicopathologic entity.

   c. Recurrence of leukemia in donor cells in patients receiving bone marrow transplants for the therapy of acute leukemia suggest the possibility of a leukemogenic "agent" in these patients (18-20). No such agent has actually been isolated, and these provocative findings are open to other interpretations as well.

D. Genetic Factors

1. The murine viral leukemia model is instructive. Several genes must sequentially operate, or fail to operate, before leukemia surfaces: (21)

   a. The genes for the virus itself (21);

   b. A gene (Fv-1) that permits or restricts expression of the viral genes (21);

   c. Genetic susceptibility at the target all level favoring neoplastic transformation (22);

   d. At least 2 genes linked to the major histocompatibility locus that control immune responses to virus-infected cells (23).

2. An x-linked recessive lymphoproliferative syndrome has been described that appears directly traceable to failure to control expression of EBV (24). The consequences of this failure include fatal infectious mononucleosis, American Burkett's lymphomas, immunoblastic sarcomas and plasmacytomas. Other consequences include aplastic anemia, agranulocytosis, lymph node necrosis, and hypogammaglobulinemia.

3. The identical twin of a child with ALL has a 20% chance of developing the same disease within 1 year (25). The risk for other siblings is only slightly greater than the risk in the population at large. These figures

strongly support the role of a genetic or gestational factor in the genesis of ALL.

4. Familial acute leukemia has been rarely but repeatedly observed, raising the possibility of interacting genetic and environmental factors (26). A simple mendelian genetic transmission is usually not demonstrable.

5. Chromosomal abnormalities - Patients with trisomy 21 (Downs syndrome), and the autosomal recessive Fanconi and Bloom's syndromes have an increased risk of developing acute leukemia. Heterozygote carriers of the Fanconi and Bloom defects may also be at excess risk (27). The basis of these 2 defects is not known, although these patients frequently have karyotypic abnormalities and their chromosomes are exceptionally fragile in vitro.

6. Hereditary immunodeficiencies - Patients with the Wiskott-Aldrich syndrome, and ataxia-telangiectasia are at increased risk of developing lymphoproliferative tumors (28).

7. Susceptibility or resistance to acute leukemia may be linked to certain loci in the HL-A region (29) or in other weak histocompatibility loci (30).

E. Conclusions regarding etiology

1. Each of the 4 factors well-known to contribute to naturally-occurring animal leukemia have also been associated with occasional or exceptional cases of human leukemia/lymphoma.

2. In the vast majority of patients, none of these 4 factors can be identified. Equally important, none has been excluded. Therefore, each possibility deserves further research.

3. Different factors or agents can cause pathologically similar tumors in animals and man. It is unlikely that a single approach to control or prevention of morphologically similar acute leukemias will be found.

III. DIAGNOSIS AND CLASSIFICATION

A. Bone marrow aspiration/biopsy is required for diagnosis and for unequivocal diagnosis must demonstrate:

1. Hypercellularity

2. More than 50% blasts or other immature leukocytes.

B. Morphologic classification is required for planning treatment and projecting prognosis.

1. ALL

a. Abnormal cells have a high N/C ratio, agranular cytoplasm, indistinct nucleoli, and a coarser pattern of chromatin than is usually seen in AGL blasts.

b. Cells do not stain for myeloperoxidase or sudan black.

2. AGL

a. Abnormal cells have, on the average, more cytoplasm than ALL cells. Fine to coarse granules distinguish the cytoplasm. In 15% of cases, Auer rods can be found in the cytoplasm of some of the blast cells. The nucleus contains 2 or more distinct nucleoli and a very fine network of chromatin.

b. At least 5% of the abnormal cells stain for myeloperoxidase or sudan black.

3. AGL (AML) variants - Seven variants have been recognized (31,32) (Table 1). Frequently, 2 malignant cell types coexist, suggesting that AGL is really a disease of a pluripotent erythrocyte-phagocyte-megakaryocyte precursor. Prognosis in these different forms does not differ strikingly, but promyelocytic and monocytic leukemia have definite clinical correlates.

4. Unclassifiable or undifferentiated acute leukemia - This term is applied when histochemical studies are negative and morphologic criteria for the diagnosis of ALL are absent. Special techniques may permit classification as ALL or AGL (Section XIV, Table 9).

IV. CLINICAL FEATURES common to all types of acute leukemias fall into 3 groups:

A. Bone marrow failure due to replacement with leukemic cells.

1. Anemia - fatigue, weakness, shortness of breath.

2. Neutropenia - fever, infections, stomatitis, sore throat.

3. Thrombocytopenia - petechiae, mucosal bleeding.

B. Organ/tissue infiltration with blast cells.

1. Hepatosplenomegaly - usually modest.

2. Lymphadenopathy - usually modest.

3. Bone pain.

4. Arthralgias; frank arthritis is commoner in children.

5. CNS symptoms: headache, papilledema, cranial nerve palsies (meningeal leukemia). Commonest in ALL, especially when WBC >25,000.

6. Extramedullary tumor masses: myeloblastomas (chloroma or granulocytic sarcomas) in virtually any site; testicular masses in treated ALL. Skin nodules and gingival infiltrates are particularly common in acute monocytic leukemia.

TABLE 1

AGL MORPHOLOGICAL VARIANTS

Designation	Morphology	Clinical Features	Reference
M1	Myeloblasts		31
M2	Myeloblasts ⟶ myelocytes		31
M3	Hypergranular promyelocytes	DIC response to anthracyclines	31,92
M4	Myeloblasts ⟶ monoblasts		31
M5	Monoblasts ⟶ monocytes	Skin nodules, gingival swelling, acute renal failure	31,92
M6	Dysplastic erythroblasts, myeloblasts		31
M7	Megakaryoblasts		32

7. Leukostasis - Extremely high counts of blast cells lead to sludging in and injury to small vessels, with consequent perivascular hemorrhages. Any organ can be affected, but the major targets are:

   a. CNS - obtundation progressing to coma. Funduscopy reveals florid hemorrhages, Roth spots.

   b. Lung - Adult respiratory distress syndrome.

C. Metabolic problems are usually associated with increased cell turnover.

1. Weight loss.

2. Hyperuricemia.

3. Hypokalemia - often associated with AGL. May be due to kaliuresis from renal tubular injury, but other mechanisms may operate as well (33). Lysozyme excreted in large amounts in myelomonocytic and monocytic leukemia may contribute to tubular injury and consequent hypokalemia (33).

4. Hypocalcemia - from hypoalbuminemia, uremia, massive phosphate release after treatment, or hypomagnesemia (33).

5. Hypercalcemia - Uncommon (2.5%). Commoner in ALL than AGL. Mechanism unclear. Poor prognostic sign (33).

6. Hyperphosphatemia - may follow extremely rapid cell lysis, usually in ALL or childhood lymphomas (33).

7. Hypomagnesemia - Probably from poor nutrition (33).

8. Lactic acidosis - may or may not be associated with hypoxic states (33). Responds to bicarbonate and specific antileukemic therapy.

9. Cytotoxic or antibiotic drugs may cause a variety of electrolyte disorders (33).

10. Acute renal failure from a combination of dehydration, urate nephropathy, and leukemic infiltration of the kidneys may contribute to electrolyte and acid-base disorders. Patients with acute monocytic leukemia may be particularly prone to develop acute renal failure during remission induction (92).

11. Disseminated intravascular coagulation is particularly common with the hypergranular form of acute promyelocytic leukemia and is due to release of activators of coagulation (proteases) from the granules in the leukemic cells (34).

V. CAUSES OF DEATH IN THE ERA OF TREATMENT (1,35).

A. Infection alone - 60-70%.

B. Hemorrhage alone - 10-15%.

C. Infection plus hemorrhage - 9% (35).

D. Organ failure (35).

1. Heart failure - 4%.

2. Liver failure - 2%.

3. Renal failure - 1%.

VI. IMPORTANT DIFFERENTIAL CONSIDERATIONS AT THE TIME OF DIAGNOSIS

A. Subacute granulocytic leukemia (36) - This disorder is characterized by ineffective hematopoiesis with various cytopenias and by an excess of myeloblasts in the marrow. This excess falls short of the diagnostic requirements for acute leukemia defined above. Symptoms and signs relate primarily to bone marrow failure. The disorder may remain stable for months to a few years, evolve into frank acute leukemia, or lead to death from refractory cytopenias. These patients are usually over age 50 and respond poorly to chemotherapy. They may do well for months with red cell transfusions alone. Patients who progress to AGL can be treated as outlined in Section XI.

B. Blastic transformation of chronic granulocytic leukemia (37). Clues include frequent or immature eosinophils or basophils in the peripheral blood, thrombocytosis, or a massive spleen. This disease can take lymphoblastic, myeloblastic or morphologically unclassifiable forms (32). Diagnosis can be confirmed by a karyotypic analysis of marrow cells which demonstrates the Philadelphia chromosome. Therapy is difficult:

(i) Lymphoblastic crisis - a trial of vincristine and prednisone is warranted (38). (Section XIV.A.1.b.).

(ii) Myeloblastic crisis - no therapy is satisfactory. We use a multi-agent chemotherapy program, (TRAMPCO), with little success so far (34).

C. Lymphosarcoma cell leukemia - This poorly standardized term describes a variety of lymphocytic leukemia characterized by moderate to large lymphocytes with immature or cleaved nuclei, with or without nucleoli. Thus, these cases can be misinterpreted as ALL. However, these cases represent the leukemic extension of a lymphocytic lymphoma. The clinical presentation may include lymphadenopathy; hepatosplenomegaly; vascular, lymphatic or hollow viscus obstruction from mass disease; fever, sweats, weight loss and various cytopenias from marrow replacement. The overlap with CLL is extensive and poorly defined (40). Therapy should be guided by the results of lymph node biopsy (41); for example:

(i) Nodular or well-differentiated lymphoma - alkylating agents.

(ii) Diffuse poorly differentiated lymphoma - a combination regimen such as vincristine, cyclophosphamide and prednisone, with the addition of Adriamycin and/or bleomycin for rapidly advancing disease (42).

VII. THERAPY OF ACUTE LEUKEMIA - GENERAL PRINCIPLES

A. Available resources for the care of acute leukemia should include:

1. An experienced hematologist.

2. Experienced nursing personnel or clinical specialists.

3. Experience and laboratory facilities for the management of infections.

4. Blood bank support, including the capability for platelet and granulocyte transfusions.

5. A private room to minimize nosocomial infections.

B. For planning and reviewing complicated therapy, flow sheets are very helpful.

C. Maintenance of patency of veins is vitally important. Frequently changed butterfly needles are preferable to indwelling catheters unless rapid fluid replacement is necessary.

D. Treatment can be divided into 5 phases.

1. Supportive care at diagnosis to manage:

a. The crushing blow of catastrophic illness.

(i) Psychological burden.

(ii) Financial burden. The first year of therapy of AGL typically costs $15,000-30,000 (43).

b. The complications of bone marrow failure.

c. The consequences of increased cell turnover

(i) Urate nephropathy.

(ii) Need for high renal clearance of potassium and phosphate ions.

d. Special problems demanding prompt attention:

(i) Leukostasis (WBC >150,000/ml).

(ii) Disseminated intravascular coagulation.

2. Remission induction - combination chemotherapy to reduce the burden of leukemic cells from 10^{12} or more to 10^{9} or less. A remission is defined as a morphologically normal bone marrow with fewer than 5% blast cells, a normal white count, normal platelet count, a hemoglobin greater than 11 grams %, and no evidence of extramedullary leukemia.

3. Supportive care for drug-induced bone marrow aplasia

4. Eradication (prevention) of CNS disease. This is primarily a problem in ALL (44).

5. Maintenance (prolongation) of remission - combination chemotherapy to prevent relapse. The early months of this phase are commonly termed "consolidation", "reinforcement" or "intensification" therapy. These terms acknowledge the fact that leukemic stem cells invariably remain at the termination of successful remission induction therapy.

VIII. THERAPY OF ALL (45)

A. Remission induction:

1. In children is highly successful. About 90% of patients achieve remission within 4 weeks on a regimen including:

a. Weekly vincristine, 1.5 mg/m^2 IV

b. Daily prednisone, 40-60 mg/m^2 p.o.

c. Addition of a third agent may prolong remissions but does not increase the frequency of remission (46). (Table 2).

TABLE 2

REMISSION INDUCTION THERAPY, ALL

Induction Therapy	Number of Patients	Proportion in Remission at 24 Months
1) Vincristine/Prednisone	47	60%
2) 1) plus daunorubicin	45	75%

(From ref. 46)

2. In adults is less successful. About 50% achieve remission on vincristine and prednisone. The addition of either of 2 other drugs increases the remission rate to about 75%:

a. An anthracycline antibiotic (daunorubicin or Adriamycin). With daunorubicin and intrathecal methotrexate, 78% complete remissions were seen in one adult series (47).

b. L-asparaginase (48).

B. Prevention of meningeal leukemia - "total therapy" (49).

1. The rationale of this therapy stemmed from observations that relapse of ALL in the CNS was exceedingly common: 50% of children and 40% of adults who achieved remission developed their first relapse in the meninges (44,50).

2. Three types of therapy have been used with equivalent results (47,51). Therapy is given shortly after remission induction is completed.

   a. Craniospinal irradiation (2400 R) (51).

   b. Cranial irradiation (2400 R) plus 5 doses of intrathecal methotrexate (6-12 mg per injection) (51).

   c. Intrathecal methotrexate alone (47).

3. The results of prophylactic therapy of the CNS in prospective randomized trials show (Table 3).

   a. Prevention of meningeal relapses.

   b. Longer durations of complete remissions in the treated groups.

   c. Improved overall survival in the treated groups.

TABLE 3

ERADICATION OF CNS DISEASE, ALL
(Craniospinal Irradiation, 2400 R)

	No radiation	Radiation
Patients	49	45
CNS relapses	33	2
Second CNS relapses	13*	---

* After control of first CNS relapse with radiotherapy

(From ref. 52)

4. Toxicity includes leukoencephalopathy and other neurologic disorders in a small percentage of children, but the benefits outweigh the risks.

C. Remission maintenance in ALL is partially successful

1. Controlled studies revealed that more drugs do not necessarily mean better therapy (46,53). The combination of weekly IV methotrexate and daily oral 6-mercaptopurine was superior to methotrexate alone. However, the addition of a third or fourth drug to this combination did not reduce the frequency of relapse but did aggravate toxicity. (Table 4).

TABLE 4

REMISSION MAINTENANCE, ALL

	M_1	M_1M_2	$M_1M_2C_1$	$M_1M_2C_1C_2$
Patients	20	44	45	41
% in remission at 18 months	40	86	74	94
Number of times hospitalized	13	9	18	34
Died in continuous remission	1	0	0	2

M_1, methotrexate; M_2, 6-mercaptopurine; C_1, cyclophosphamide; C_2, cytosine arabinoside. Doses adjusted proportionately to keep WBC in 2000-3500/µl range (from references 46, 53).

2. Intensive 4-drug combination chemotherapy delivered on an intermittent schedule may also be an effective yet safe program for maintenance (54).

D. A summary of current therapy is presented in Table 5. More vigorous therapy such as the L-2 program (47), may be appropriate for adults, but this has not been proven.

TABLE 5

CURRENT THERAPY, ALL

1. Remission induction

Vincristine, 1.5 mg/m^2 IV weekly x 4
Prednisone, 60 mg/m^2 p.o. daily x 28
Daunorubicin, 60 mg/m^2 IV daily x 2

2. Eradication of CNS disease

Craniospinal irradiation, 200 rad/day x 12 days or

Cranial irradiation, 200 rad/day x 12 days
Methotrexate, 6-12 mg intrathecally x 5 doses

3. Remission maintenance

Methotrexate, 20 mg/m^2 p.o. once weekly
6-mercaptopurine, 50 mg/m^2 p.o. daily

Adjust proportionately to keep WBC in 2000-3000/µl range.
Do not exceed 50 mg/m^2 methotrexate.

E. Results of therapy

1. In large series, using optimal therapy, approximately 50% of children survive 5 years (46,47,53).

2. Survival of adults with ALL is difficult to ascertain because the sample size from any one center is small. In one series, median survival was 32 months. Survival curves for this study are shown in Figure 1.

FIGURE 1

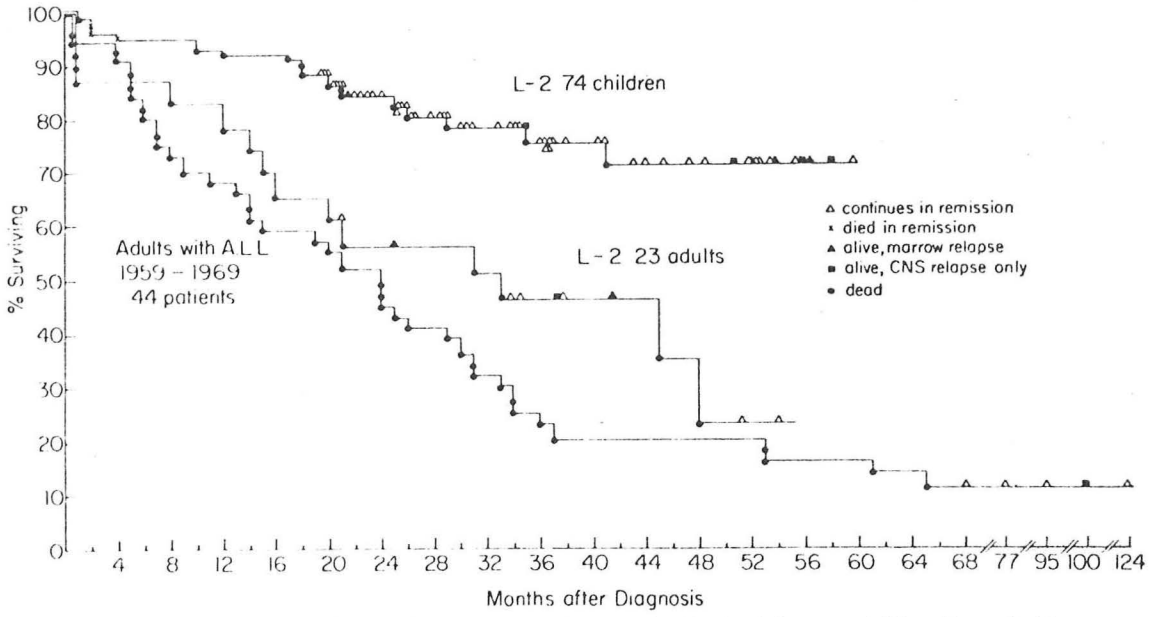


Fig. 1 Survival of children and adults with ALL treated with the L-2 protocol (life-table analysis).
(from ref. 47)

F. Problems

1. The major roadblock to further progress is relapse with subsequent development of resistance to available drugs.

2. Drug toxicity

   a. Usual side effects of cytotoxic drugs.

   b. Immunosuppression leading to interstitial pneumonia. The incidence of this complication varies widely in different clinics (53,55).

3. When to stop treatment is a problem arising from the success of modern management. Current information suggests maintenance therapy beyond 2-3 years does not prevent subsequent relapse, but this question is far from a satisfactory answer (56,57).

IX. ILLUSTRATIVE CASE REPORTS - similar therapy, different outcome.

A. J.T., CMC 138950, DOB 1-11-60, caucasian male. In August 1969, at age 9, J.T. complained of weight loss and fatigue. Physical examination showed a pale, thin white boy with shotty submandibular lymphadenopathy and a spleen down 9 cm. Chest film was normal. Hemoglobin was 8.6 g%, WBC 11,600, mostly lymphoblasts, and 84,000 platelets. A bone marrow aspirate revealed replacement with sheets of lymphoblasts and the diagnosis of ALL was made.

He achieved a remission after 4 weeks of vincristine and prednisone therapy, and was maintained on biweekly oral methotrexate. A bone marrow aspirate in October 1970 was normal. In July of 1971 he received prophylactic therapy to the CNS, including 2250 rads of radiotherapy to the brain and 5 weekly injections of intrathecal methotrexate. The CSF was normal at this time. Intensified maintenance therapy was then given, including vincristine and prednisone. From August 1971 to November 1973 maintenance therapy consisted of daily 6-mercaptopurine and weekly methotrexate and Cytoxan. In November of 1973, after over 4 years of continuous complete remission, all chemotherapy was stopped.

In July 1974 he developed headache, neck pain, sternal pain and tenderness, submandibular adenopathy, 4 fingerbreadth splenomegaly, and annular skin lesions. The WBC was 48,000 with 94% lymphoblasts. This first relapse, occurring nearly 5 years after diagnosis, was managed with vincristine and prednisone reinduction therapy. After remission was achieved, he was maintained on 6-MP, methotrexate, and Cytoxan as previously.

A rock hard left testicular mass was biopsied in August 1975, revealing a leukemic infiltrate (second relapse). A bone marrow aspirate was normal. He received 2400 rads to the testicles and regional nodes, with complete regression of the mass. Vincristine and prednisone were given, followed by 6-MP, methotrexate, and Cytoxan.

In December 1975 he complained of fatigue and headaches, and lumbar puncture revealed leukemic cells (third relapse). Intrathecal methotrexate and cytosine arabinoside were given. By January of 1976 bone marrow relapse was evident. He was given vincristine, prednisone, and Adriamycin, followed by cytosine arabinoside and methotrexate maintenance.

In March 1976 lymphoblasts were evident on peripheral smear, and lumbar puncture showed similar cells (fourth relapse). Therapy with vincristine, prednisone, Adriamycin, and intrathecal methotrexate plus cytosine did not induce a complete remission. A potential bone marrow transplant donor was sought, but none of his 4 siblings were histocompatible. His leukemia became progressively refractory to these medications, the WBC rising to 51,600 in June 1976. A course of L-asparaginase and 6-thioguanine was tried without success. He developed a staphylococcal abscess on the right arm. Paraparesis developed after an intrathecal injection of methotrexate. Otitis media with subsequent mastoiditis developed; a middle ear aspirate grew out E coli and aeromonas. Blood cultures grew pseudomonas and aeromonas. Terminally, pneumonia, and generalized bleeding occurred. He died on July 28, 1976, 6 years 10 months after diagnosis. Autopsy revealed widespread leukemia, leukemic bowel ulcerations colonized with candida organisms, candida pneumonia, and hemorrhagic infarction of the cauda equina.

B. K.T., CMC 158007, DOB 11-22-69, caucasian female. In October 1970 at age 11 months, K.T. became irritable, pale and bruised easily. Physical

examination revealed a fussy child with pallor, multiple ecchymoses, and bilateral femoral adenopathy. The spleen was not palpable. Chest film was normal. Hemoglobin was 3.5 g%, WBC 7,000 with an occasional lymphoblast present. The bone marrow aspirate consisted of a uniform population of lymphoblasts. A diagnosis of ALL was made, and a complete remission was obtained after 4 weeks of vincristine and prednisone therapy. She was maintained through June 1971 with biweekly oral methotrexate. Bone marrow aspiration in May 1971 revealed mildly megaloblastic changes and 5% lymphoblasts. Intensified maintenance therapy with vincristine and prednisone was then given for 4 weeks. In July 1971 a marrow aspirate revealed no pathologic diagnosis. She received whole brain radiotherapy and 5 injections of intrathecal methotrexate. Between July 1971 and December 1973 she received maintenance therapy, including daily 6-MP and weekly methotrexate/Cytoxan. All antileukemic therapy was then stopped, after 3 years of continuous complete remission. She has subsequently remained well and is now age 8, a healthy 2nd grader, 7½ years after the diagnosis of ALL.

These patients were treated comparably through the remission induction and maintenance phases of their disease. Therapy was stopped in both after 3-4 years of remission. Thereafter, one patient relapsed within 8 months, while the other remains in remission 4½ years later. One major difference between these 2 patients is the bulk of disease present at diagnosis. Age and sex also differ. What are the important prognostic factors in ALL?

X. PROGNOSTIC FACTORS IN ALL

A. A major conclusion of 15 years of clinical research was that ALL is clinically a heterogeneous disease: (58)

1. In 50% of children, disease can be eradicated.

2. In 40%, initial control is achieved but relapse occurs.

3. In 10%, the disease cannot be controlled initially.

B. If these groupings could reliably be made prospectively, alternate protocols for therapy of high-risk patients could designed and tested.

C. Current data suggest that the presence of T cell differentiation markers on the surface of leukemic cells is a major adverse prognostic factor (54,59). T cell ALL makes up about 20% of cases of ALL. (Table 6)

TABLE 6

T CELL ALL: ADVERSE PROGNOSIS

	T cell	Non T cell
Number of patients	20	75
Remission	18 (90%)	71 (95%)
Relapse first year	11 (61%)	19 (27%)
First relapse in CNS	7 (39%)	5 (7%)

(From ref. 59)

D. Overt CNS involvement at the time of diagnosis is a bad prognostic sign, primarily because disease in this site is easier to prevent than treat.

E. Certain other adverse prognostic factors are probably covariables with the T-cell phenotype (54):

1. Age over 8-10 years.

2. Presence of an anterior mediastinal mass.

3. Lymphoma-like presentation.

4. Extremely elevated white blood count.

F. Black children may have a worse outlook than caucasian children (60).

XI. THERAPY OF AGL (61)

A. Remission induction was achieved in less than 25% of patients until the introduction of 2 drugs:

1. Cytosine arabinoside, ("Ara-C"), a pyrimidine antimetabolite toxic to cells only in the DNA synthesis phase of the cell cycle.

2. Daunorubicin or its close congener, Adriamycin, anthracycline antibiotics that kill cells by binding to double-stranded DNA. These antibiotics are maximally toxic to cells in and immediately following the phase of DNA synthesis, but can kill cells in any phase of the cell cycle.

3. Current regimens vary widely but most hematologists agree that the production of complete marrow aplasia is mandatory to obtain a complete remission. Two general approaches have been moderately successful:

a. Intensive intermittent therapy with cytosine arabinoside and 6-thioguanine, yielding 56% remissions in one study (62). This program originated in animal studies where a synergistic effect of these 2 drugs was demonstrated (63,64).

b. Intermittent anthracycline and continuous cytosine arabinoside combination therapy, yielding 43-77% remissions in various studies (Table 7). Two tentative conclusions can be drawn from these studies:

(i) For rapid production of bone marrow aplasia, continuous IV administration of cytosine arabinoside is superior to intermittent bolus therapy. The difference is probably due to the rapid deamination of the drug in plasma (half life less than 30 minutes).

(ii) Three days of daunorubicin and 7 days of cytosine arabinoside yield more remissions than shorter periods of therapy (Table 7).

c. Rapid induction of marrow aplasia is advantageous because the period of greatest risk (and, therefore, hospitalization) is minimized. For this reason, many hematologists prefer vigorous anthracycline-ara C combinations over the ara C–6-thioguanine approach (61).

d. The role of additional drugs, such as vincristine, prednisone or cyclophosphamide in remission induction is unclear but probably minor.

4. Supportive therapy for the myelosuppressed patient.

a. Thrombocytopenia is clearly associated with fatal hemorrhage (65), but the exact indications for platelet transfusions remain a source of confusion. A recent small study suggested that prophylactic replacement (given whenever platelet count <20,000/μl) did not prevent any more hemorrhagic deaths then indicated replacement (given for bleeding episodes) (66). My advice is to "treat the number" (count <20,000) only if:

(i) There is a chance for remission; and

(ii) Significant bleeding occurs (not just petechiae); or

(iii) Fever or infection coexists; or

(iv) The WBC exceeds 100,000/μl.

This policy will avoid unnecessary alloimmunization, without exposing the patient to undue risk. Such a policy does require dose monitoring of the patient, and platelets should always be available. The Blood Bank would like to know when patients are at risk, i.e., when you anticipate needing platelets.

The dose is ordinarily 0.1 U/kg given often enough to keep the platelet count over 20,000/μl.

In the alloimmunized patient, single donor HL-A compatible platelets may be tried, since matching at the HL-A A and B loci is of overriding importance in obtaining compatible transfusion responses (67). The use of a cell separator, available at Wadley Blood Bank, facilitates the preparation of multiple platelet packs from single donors. Ordinarily, siblings will be the donors of matched platelet; lymphocyte cytotoxicity tests may be of help in selecting compatible donors (67).

b. Transfusions of granulocytes from red-cell compatible donors probably increase survival in the infected neutropenic patient. (68-70). Procurement of granulocytes is a formidable logistic problem at Parkland Hospital and elsewhere. Therefore, our current indications are restrictive:

(i) Neutropenia (<500/μl).

(ii) Documented infections (usually bacteremia), not just fever.

(iii) Failure to improve after 48 hours of appropriate antibiotic therapy.

(iv) Chance for a remission.

Obviously, a pool of potential donors must be identified in advance so that informed consent can be obtained and donors can be available within a few hours' notice. Requirements should be anticipated several days in advance so that Blood Bank personnel (Mary Jo Smith) can plan ahead. At least 4 daily transfusions were necessary in 1 study to make a statistically significant difference in survival (68-70). Collection of adequate numbers of granulocytes requires 3-6 hours of time to pump blood through filters of nylon fiber, which trap phagocytic cells. Therefore, this procedure is a major burden on a very busy blood bank.

c. Although most serious infections in neutropenic patients originate from endogenous flora, many of these pathogens are still hospital-acquired; that is, colonization with hospital bacteria can be demonstrated prior to overt infection (71). In the absence of protected environments such as laminar airflow rooms, granulocytopenic patients should be exposed to a minimum of potential pathogens. On entering the patient's room,

(i) Gowns and masks should be worn;

(ii) Hands should be washed;

(iii) Sitting in the room should be avoided.

(iv) Sterile disposable medical supplies should be used whenever possible.

Although the value of these measures has not been conclusively demonstrated, such commonsense procedures may reduce transfer of hospital-type resistant organisms to these patients (72). Obviously, personnel with skin, upper respiratory or other infections should avoid close contact with these patients.

5. Results

a. The results of several trials are shown in Table 7. About 50% of all patients achieve a remission. This figure drops to 30% in patients over 50, and may approach 80% in patients under 16.

b. Our own experience over the past 21 months is shown below

(i) Concurrent "Ad-OAP" therapy was used:

Adriamycin, 60 mg/m^2 IV day 1.

Oncovin (vincristine), 2 mg IV day 1.

Ara-C (cytosine arabinoside), 100 mg/m^2/day IV day 1-5.

Prednisone, 100 mg/day, day 1-5.

(ii) Four of 8 previously untreated patients achieved a complete remission.

(iii) Six of the 8 patients were under age 60. Three of the 4 remissions were in patients under 60.

(iv) Three of 4 patients achieving remission required 2 courses; one required 1 course.

(v) One of these patients died on the second day of therapy of sepsis and hemorrhage. She had acute promyelocytic leukemia, advanced rheumatoid arthritis, and a sacral decubitus ulcer.

TABLE 7

REMISSION INDUCTION IN AGL (ADULTS)

Regimen	Number of Patients	% Remission	Reference
Ara-C, 6-TG	88	56	62
Ara-C, 6-TG	66	36	73
Ara-C --- DNR/Adr			
5 day 1 day	72	54	74
5 day 2 day	74	43	73
7 day 3 day	28	64	75
7 day 3 day	43	77	76
7 day 3 day	22	73	77
10 day 3 day	12	75	77
Ad-OAP	46	83	78
Ara-C---DNR---6-TG	28	82	79

B. Remission maintenance therapy has not been shown unequivocally to prolong survival in AGL (80).

1. However, the median duration of unmaintained remissions is brief.

a. 1.2 months after cytosine arabinoside induction (81).

b. 2.2 months after daunorubicin or POMP drug induction (82).

2. Many different maintenance programs are being tried, with a trend towards more vigorous therapy. For example, based on a pilot study in Boston, our pediatric group now treats children in remission with courses of very intensive combination chemotherapy at 3 to 4 week intervals for a period of 12-16 months (83). Each course regularly produces marked pancytopenia, resulting in frequent hospitalizations. It is doubtful that many adults with AGL could tolerate such a regimen.

3. Our current protocol for maintenance is outlined below. Courses of therapy are given at monthly intervals. Drug dosages are lower than the doses used for remission induction therapy -- details can be obtained from protocols on file in the UTHSC Cancer Center (84). If possible, therapy is given on an outpatient basis.

   a. Ad-OAP (2 courses).

   b. Cytosine arabinoside - 6-thioguanine (2 courses).

   c. Cytoxan - Oncovin - Ara-C - Prednisone (COAP) (2 courses).

   d. Ad-OAP (1 course).

   e. Cytosine arabinoside - 6-thioguanine (2 courses).

   f. Ad-OAP (1 course).

   g. Repeat (c) through (f) in cyclic fashion, or administer "late intensification" therapy (See below).

   h. Results: One patient completed the sequence outlined as (a) through (f) above, then relapsed and died one month later. One patient returned to Mexico for further treatment and 2 patients have just begun maintenance cycles. This schedule is toxic and may require modification, particularly for older patients.

4. Duration of drug-maintained remissions varies widely. In most large series, median duration of remissions varies between 6 and 20 months (61).

5. Late intensification, introduced by the M.D. Anderson group, attempts to deal with the problems of relapse 6-24 months after successful induction therapy (85). Unfortunately, almost all patients with AGL who achieve remission relapse and die within this period (see below). In an attempt to prevent these relapses, the Anderson group gave intensive remission-induction style chemotherapy to patients who were in continuous remission for more than 1 year. They chose a combination of drugs that the patients had not previously received; this was usually the POMP regimen (85). Although the initial results suggested a prolongation of remission, subsequent followup has not shown an increase in survival in patients who received late intensification. Nevertheless, this concept deserves further trials with different drug combinations (POMP is not a particularly effective regimen in AGL (82)). The problem is that patients are exposed to the most active agents during the remission

induction and maintenance phases of therapy; no highly active agents are held in reserve.

C. Overall results of therapy in many trials can be briefly summarized.

1. Survival does not differ from untreated historical controls in patients who do not achieve remission (50% of these patients are dead in 2-5 months). Stated in another way, the beneficial effect of therapy on survival duration is measurable only in patients who obtain remission status.

2. Survival is clearly prolonged in patients who achieve remission (Median survival is 16-24 months).

3. After relapse, survival is the same as in patients who do not achieve remission (50% of patients are dead in 2-5 months).

4. The median survival of all patients with AGL is still less than 1 year (61). Survival of patients treated according to the Sloan-Kettering L-6 protocol (Figure 2) is shown in Figure 3.

D. Problems in therapy

1. Failure to achieve complete remission: 20-50% of patients, depending on age and possibly other factors do not achieve a remission with the best current regimens.

2. Relapse 6-24 months after remission induction:

a. This is the single most important problem in the therapy of AGL and eventually kills the vast majority of patients. Overall, only 25% of optimally treated patients survive beyond 2 years (61).

b. When patients are refractory to first-line drugs, we and others have tried 5-azacytidine, a pyrimidine antimetabolite. The mechanism of action of this investigational drug is not known. Twenty percent of patients refractory to the usual drugs are said to achieve a remission on 5-azacytidine (86). In 7 such patients, we have not seen a single remission.

3. Drug toxicity

a. Normal and leukemic myeloid precursors differ only slightly in sensitivity to the most effective antileukemic drugs. In ALL, the situation is different: the best drugs are not critically toxic to hematopoietic ALL precursors.

b. The cardiac toxicity of anthracycline antibiotics limits their total dose to about 500 mg/m^2 (87).

4. Treatment of the older patient: Patients over age 60 do not tolerate strongly myelosuppressive therapy well, and median survival in this age group is short (Section XIII). However, many patients in the 50-70 age range have achieved worthwhile remissions (88-90). Patients over age 70

FIGURE 2

INDUCTION + CONSOLIDATION

Drug	Dose
Arabinosylcytosine (Ara-C)	3.0mg/kg q 12hr. i.v.
Thioguanine (TG)	2.5mg/kg q 12hr. p.o.

MAINTENANCE

Drug	Dose
Vincristine (VCR)	0.03-0.04 mg/kg i.v.
Methotrexate (MTX)	10 mg x 4 p.o.
BCNU (1,3-Bis(2-chloroethyl)-1-nitrosourea	1.0-2.0 mg/kg i.v.
Thioguanine (TG)	10 mg/kg x 4 p.o.
Cytoxan (CTX)	10-20 mg/kg i.v.
Hydroxyurea (HU)	60-80 mg/kg x 4 p.o.
Daunorubicin (Daun)	1.0 mg/kg i.v.

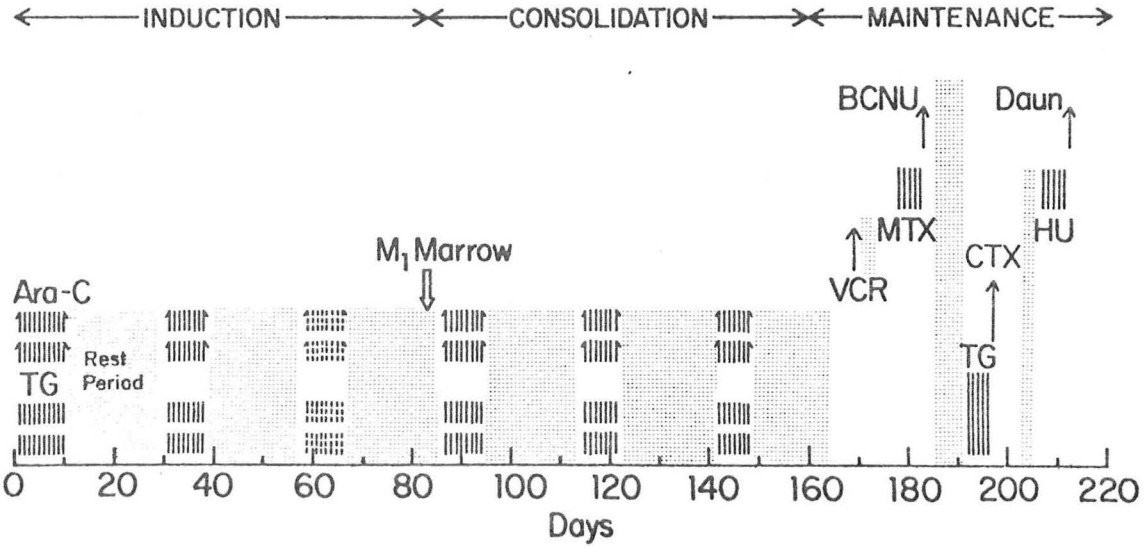
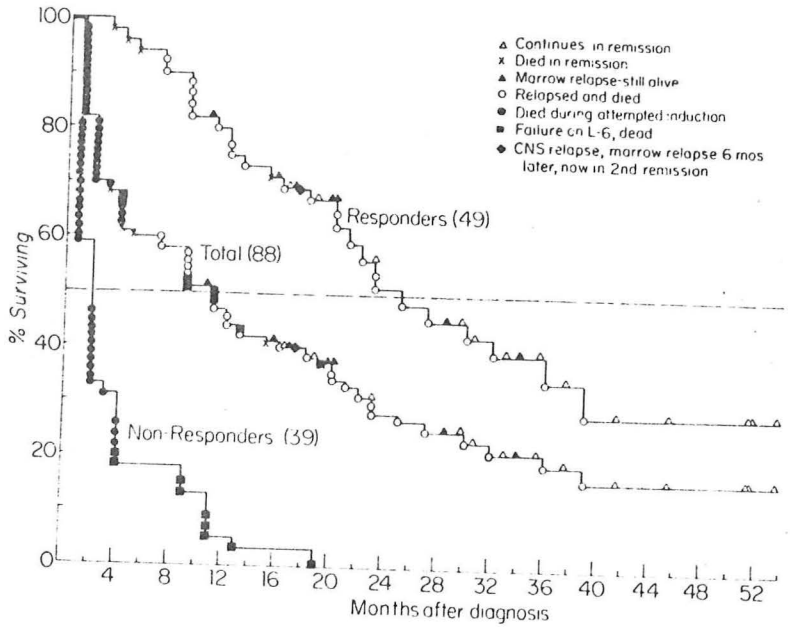


Fig. 2. Modified L-6 protocol

(from ref. 62)

FIGURE 3

Fig. 3. Survival of 88 evaluable previously untreated adults with AML treated with the L-6 protocol (life-table analysis).



(from ref. 62)

have not responded to therapy (88-90). The decision for therapy must be based on individual risk assessment. The final decision should be made by a patient who is well-informed of the risks as well as the benefits of therapy.

XII. ILLUSTRATIVE CASES, AGL: resistance and sensitivity to therapy.

A. B.G., PMH 15-97-74, DOB 8-31-57, Negro female. B.G., age 18, entered PMH in March 1976 complaining of severe sore throat. Physical exam revealed temperature of 103°, beefy red edematous pharynx, and tonsils covered with a white exudate, tender cervical lymph nodes, as well as shotty generalized lymphadenopathy. The WBC was 129,000 with 75% myeloblasts. Bone marrow aspirate was replaced with a monotonous population of myeloblasts. After 3 courses of Ad-OAP combination chemotherapy, she entered complete remission. She received one course of Ad-OAP maintenance therapy. In August 1976, she relapsed, presenting with pharyngitis and a WBC of 120,000, 90% blasts. Therapy with cytosine arabinoside plus 6-thioguanine was ineffective. Administration of 5-azacytidine lowered her WBC from 70,000 to 2,000, but myeloblasts persisted on the peripheral smear. By October 1976 the blast count had risen to 80,000. Another course of 5-azacytidine lowered her WBC to 17,000. A combination of 6-MP, methotrexate, vincristine, and prednisone (POMP) was then given, lowering her WBC to 1400. She quickly became refractory to additional courses of POMP and azacytidine. In December 1976, attempts to obtain a remission were stopped, and she received palliative Cytoxan and hydroxyurea in an attempt to avoid leukostasis. Nonetheless, her WBC rose to 223,000 and in the face of thrombocytopenia she developed bilateral macular and vitreous hemorrhages, leading to blindness. She became progressively more somnolent and died in January 1977, apparently of intracerebral leukostasis. No autopsy was performed.

B. S.D.K., PMH 523726, DOB 9-28-58, caucasian female. In December 1975, S.D.K. came to PMH complaining of fatigue, weight loss, and bleeding gums. Physical examination revealed a temperature of 101.4°, pallor, gingival bleeding, and the absence of lymphadenopathy or hepatosplenomegaly. The hemoglobin was 7.3 g%, WBC 1300, including 20% granulocytes, 72% lymphocytes, and a rare promyelocyte. The platelet count was 6500. Bone marrow aspirate contained sheets of promyelocytes, many containing Auer rods. Remission induction required 2 courses of Ad-OAP. The induction period was stormy; she developed DIC with hemorrhage, interstitial pneumonia responsive to pentamidine, and jaundice of obscure origin. A bone marrow aspirate in February 1976 showed mild hypocellularity and megaloblastosis, but no evidence of leukemia. During her fourth course of Ad-OAP maintenance therapy in June 1976, she developed headache, nausea, and an elevation of SGOT to 2200, all of which quickly resolved. Other liver function tests remained within normal limits. She then received 2 courses of cytosine arabinoside plus 6-thioguanine, followed by two courses of Cytoxan, vincristine, cytosine arabinoside and prednisone (COAP) combination chemotherapy. In January 1977 she was given late intensification therapy with POMP. This was complicated by jaundice and an SGOT rise to 540. In March 1977, she underwent liver biopsy to evaluate persistently elevated transaminases. The biopsy showed "continuing hepatitis". Between March 1977 and the present she has received monthly maintenance courses of vincristine, cytosine arabinoside and prednisone (OAP). A bone marrow aspirate in August 1977 was normal. Her CBC in May 1978 was normal. She currently is well and employed full-time at UTHSCD, $2\frac{1}{2}$ years after diagnosis.

These two patients received comparable remission induction therapy. One had a 2 month remission and survived 8 months. The other patient is still in her first remission, 30 months after diagnosis. An inherent difference in sensitivity of the leukemic cell lines to therapy is a reasonable hypothesis, but is there any way to recognize such differences prospectively?

XIII. PROGNOSTIC FACTORS IN AGL

A. The response to therapy even within morphologically similar subgroups of AGL is extremely variable. The basis for this is probably variations in the differential sensitivity of normal and leukemic hemopoietic cells to available drugs. Reliable methods to estimate differential sensitivity prior to treatment are not available.

B. Many attempts have been made to identify factors that predict prognosis in AGL (91). Unfortunately, no laboratory measurements have been found to predict likelihood of remission with any reliability, in spite of many studies of the morphology, biochemistry, growth patterns in vitro, and kinetic parameters of leukemic cells. Three clinical variables are correlated with survival time:

1. Age: A representative study is shown below:

Age	Number of Patients	Median Survival Days
15-19	22	210
20-29	28	250
30-39	37	150
40-49	43	175
50-59	51	175
60-69	55	120
70-79	44	50
80+	6	25

(From Ref. 91)

2. Pretreatment performance status (91)

Minimally symptomatic patients survive longer than patients with incapacitating symptoms at diagnosis.

3. Achievement of a complete remission:

As noted in Section XI, the median duration of survival of patients who achieve remission is approximately 3-4 times that of patients who do not respond to initial therapy (91).

XIV. PROSPECTS FOR IMPROVEMENTS IN THERAPY

A. Potential improvements in remission induction therapy for AGL

1. Refinements in morphologic diagnosis may lead to better selection of therapy.

   a. An example is the peculiar sensitivity of acute promyelocytic leukemia to anthracycline antibiotics (92).

   b. The morphologic process of recognizing subtypes of acute leukemias that might have clinical relevance is mostly a matter of recognizing different states of differentiation. The development of assays for biochemical and immunologic differentiation markers may extend morphologic studies.

      For example, in the blastic phase of CGL, the presence of the enzyme terminal deoxynucleotidyl transferase (TdT) in the leukemic cells may predict responsiveness to vincristine and prednisone (Table 8). This enzyme normally found only in thymocytes and a minor subpopulation of bone marrow lymphoid cells. TdT can be detected both biochemically and immunologically. In several ways, the TdT-containing blast cells in certain cases of CGL (blast crisis) resemble the common non-T type of lymphoblast seen in childhood ALL (115).

TABLE 8

REMISSION INDUCTION IN CGL
(BLAST CRISIS)
WITH VINCRISTINE AND PREDNISONE

	Blast cells TdT +	Blast cells Tdt -
# Patients	13	9
# Remissions	8	0

(From ref. 38)

   c. The ultrastructure and cytochemical reactions of granules in leukemic marrow cells are often abnormal, but a few cells with normal granule morphology can usually be identified (93). The absence of granulocyte precursors with normal granule morphology may be a poor prognostic sign, as regeneration of normal precursors may be extremely slow in such cases. Patients without detectable normal granulocyte precursors might become candidates for early bone marrow transplantation (Section XIV.C.) (93).

   d. The karyotypes of acute leukemias may have prognostic significance.

(i) The occasional Philadelphia chromosome positive acute leukemia may connote a poor prognosis, similar to the terminal phase of CGL (37).

(ii) Acute promyelocytic leukemia is associated with a specific translocation of a fragment of chromosome 17, usually to chromosome 15 (94,95). As previously noted, this disease is associated with DIC and is sensitive to anthracycline therapy.

(iii) Hypodiploidy, when found either in spontaneous AGL (96) or AGL arising after therapy with alkylating agents (97), is associated with a poor prognosis.

2. In vitro growth patterns of leukemic cells in semisolid media may correlate with prognosis, but methodology is now so variable that a consensus among the numerous investigators in this field has not emerged. In two studies, the formation of large colonies correlated with a poor response to treatment (98,99).

3. Tailoring therapy to the growth kinetics of leukemic cells has long been a goal of chemotherapists. The detection of quiescent populations of leukemic cells that are able to return to an actively proliferating state has emphasized the need for cell-cycle nonspecific therapy (100). Modern rapid methods of flow microfluorometry should assist serial evaluation of human leukemia cell kinetics (101).

4. Uncovering mechanisms of resistance to drugs is an active field of research and may lead to in vitro methods of measuring the sensitivity of leukemic cells to therapy (102). For example, the failure of AGL blasts to bind cytosine arabinoside has been correlated with clinical resistance to this drug (103).

5. New drug development absorbs a tremendous budget (104). Potential recent improvements in this process include:

   a. Better animal models; e.g., rat AGL instead of murine L1210 ALL (105).

   b. Less empiricism in the screening process (106). None of the most active antileukemic drugs in use today were discovered by random screening of synthetic or natural products.

   c. Better coordination of clinical resources to diminish lag time from preclinical studies to open market availability. Currently, this interval is 7-10 years.

6. Improved support of the myelosuppressed patient during remission induction. The use of barrier protection systems such as laminar airflow rooms, usually in conjunction with gut prophylaxis with oral nonabsorbable antibiotics, has been shown to reduce morbidity and mortality from severe infections such as pneumonias and septicemias (107-109). Unfortunately, the studies do not agree on which of these 2 measures is responsible for these effects. Moreover, an increase in remission or survival rates was not consistently demonstrated in these studies.

Therefore, the use of these very costly measures currently remains experimental.

B. Potential improvements in remission maintenance therapy for ALL and AGL.

1. Patients with T cell ALL respond to initial therapy, but relapse and die more often than patients with non-T cell ALL. The T cell patients are now receiving intensive, prolonged maintenance therapy in an attempt to increase survival times.

2. Detection of residual leukemic cells during remission is a high priority aim. This is not ordinarily possible by routine morphologic methods, but the recognition of a series of markers specific for certain types of leukemias may increase the sensitivity of detection of abnormal cells. If small increases in leukemic cell numbers can be reproducibly detected during remission (e.g., 0.1% to 1% of total marrow cells), intensification or modification of therapy might prevent clinically evident relapse. This result would be predicted from the observation that chemotherapy is often curative in animal models when the burden of tumor is small (110). In ALL, assays for minimal residual disease would also provide better guidelines for stopping therapy.

   Some of these newer markers are shown in Table 9. Some of the markers are differentiation antigens, while others appear specific to leukemic cells. Obviously, the latter sort of marker will ultimately be more useful for detection of minimal disease. However, an abnormal combination of differentiation antigens may provide a relatively specific fingerprint of the leukemic cell phenotype.

3. Immunotherapy is attractive because for any given "dose" it may kill a fixed number of tumor cells. On the other hand, a given dose of chemotherapy kills a constant fraction of the total cells. This means that the therapeutic index of chemotherapy decreases as the tumor cell burden decreases; the ratio of destruction of tumor cells to normal cells grows progressively smaller. Therefore, to eradicate small numbers of tumor cells, unacceptable toxicity may be the price. Immunotherapy might offer a way around this problem. Moreover, drug-resistant tumor cell variants might be eliminated in this way. From animal studies, immunotherapy is most effective when disease burden is small, as during remission. Thus, the suggestion has repeatedly been made that immunotherapy may provide the best hope of killing the last few leukemic cells remaining after chemotherapy. Immunotherapy has prolonged remissions in AGL but has not improved survival (116) (Figure 2). The mechanism of this effect is not clear and may represent a stimulation of normal hematopoiesis rather than augmentation of a specific immunologic response (116).

   As Klein has argued, spontaneous hematopoietic tumors may have arisen through selection for variants that escape immunologically specific rejection. Two incompletely understood non-specific mechanisms of rejection may be exploitable for purposes of anti-leukemia cell surveillance and should be further studied:

TABLE 9

MARKERS FOR DETECTION AND CLASSIFICATION OF ACUTE LEUKEMIAS

Marker	ALL		AGL	CGL (blast crisis)		Reference
	T	Non-T		Lymphoblastic	Myeloblastic	
Ia proteins*	Neg	Pos	Pos	Pos	Pos	111, 112
Thymocyte heteroantigens*	Pos	Neg	Neg	Neg	Neg	111
ALL antigens*	Neg	Pos	Neg	Pos	Neg	113
Terminal transferase (TdT)	Pos	Pos	Neg	Pos	Neg	38, 114
Granulocyte antigens*	Neg	Neg	Pos	Neg	Pos	115

Pos, positive
Neg, negative
*Markers found on the cell membrane

FIGURE 4

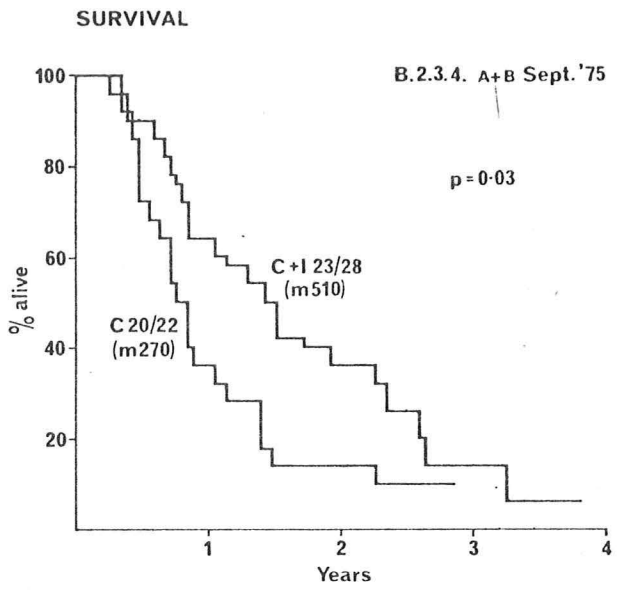


Fig. 4. Survival following remission of two groups of patients with AML (Bart's 2, 3, 4A, and 4B) allocated at presentation, one group receiving maintenance chemotherapy alone (C), the other group chemotherapy plus immunotherapy (C + I). The percentage surviving at different times has been calculated by standard actuarial methods. The vertical drops show the times at which individual patients died. Twenty of the 22 chemotherapy-alone patients and 23 of the 28 chemotherapy-plus-immunotherapy patients have died. Analysis of follow-up to August 7, 1975.
(from ref. 116)

a. Non-specific killer cell activity (117). Prior to specific sensitization, rodents and humans possess a class of lymphoid cells that can kill tumor cells in vitro and probably in vivo as well.

b. Hybrid resistance. F1 hybrid mice of appropriate strains reject grafts of normal or leukemic bone marrow from either parental strain (118). This result is not predicted by the classical rules of transplantation. The phenomenon suggests that a mechanism normally exists for rejecting hematopoietic cells that do not bear all the histocompatibility antigens of the host. A possibly related phenomenon is the increased resistance of F1 hybrids to syngeneic tumor grafts, as compared to the homozygous host (117). Whether these poorly understood rejection mechanisms could be brought to bear against syngeneic leukemic cells is not clear but deserves more study.

C. Bone marrow transplantation has long been an attractive concept for salvage of patients with acute leukemia refractory to other means of management. Recent results suggest that this therapy may be more effectively applied during remission of AGL, when the general condition of the patient is good enough to tolerate the major myelosuppression and graft versus host disease that accompanies this procedure (119).

1. The general protocol for transplantation of the patient with acute leukemia includes:

   a. Identification of a sibling donor matched at the major HL-A loci.

   b. Eradication of leukemia in the recipient with combination chemotherapy and total body irradiation. Such preparation is sufficiently intensive to be lethal if not followed by bone marrow reconstitution.

   c. Transplantation of donor marrow into the aplastic recipient.

   d. Methotrexate and/or antithymocyte globulin for the amelioration of graft versus host (GVH) disease.

   e. Maximal hematopoietic support during the period of bone marrow regeneration.

2. The major problems currently are:

   a. Recurrent leukemia, usually in the recipient cell line;

   b. GVH disease, often complicated by fatal interstitial pneumonia.

3. In a recent series of 100 patients who received marrow transplants for refractory acute leukemia (120):

   a. 54 had AGL; 46 ALL.

   b. 8 patients died in the first 17 days after transplantation of infection without evidence of a functioning graft.

   c. 94 patients had documented evidence of engraftment.

   d. Only 1 of these 94 patients subsequently rejected a graft. By contrast, rejection of bone marrow grafts after transplantation for aplastic anemia is a common problem (31% in one series) (119).

   e. 31 patients had a relapse of leukemia, leading to death in 26.

   f. 74 patients developed GVH disease.

      (i) 24 of these had mild GVHD.

      (ii) 50 had moderate to severe GVHD.

      (iii) 54 developed interstitial pneumonia, leading to death in 34.

      (iv) 10 patients died of other consequences of GVHD.

   g. 13 patients were alive with a graft, with no evidence of leukemia and off antileukemic therapy 1-4½ years after transplantation.

      The probability of survival in the entire group of 100 patients is constant after 2 years, suggesting that at least some of these patients have been cured.

4. In summary, this procedure, encompassing a major investment of medical resources, may salvage some patients with acute leukemia who could not be cured by any other available means.

XV. CONCLUSIONS

Factors known to cause leukemia in animals may also contribute to human acute leukemia. Unfortunately, in the vast majority of human cases, no etiologic factors can be recognized. At the present time, therefore, control must rely on eradication of malignant leukemic clones, mainly with chemotherapy. Effective therapy relies on a morphologic distinction between ALL and AGL. In childhood ALL, with optimal therapy, up to 50% of children survive five years and perhaps ultimately will be cured. The major problem in therapy of childhood and adult ALL is relapse of leukemia, with progressive development of drug resistance. In AGL, remission induction remains an uncertain venture, obtainable in perhaps 50-60% of all patients with optimal therapy. Disappointingly, almost all patients who achieve remission will relapse and die within three years. Lack of drugs with selective toxicity for AGL tumor cells is the major obstacle to better control of this disease.

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