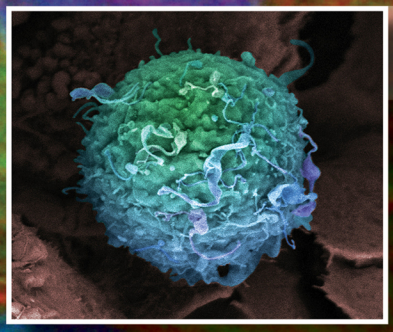
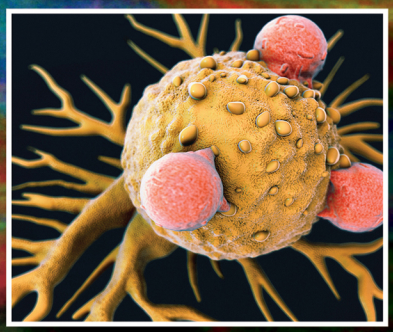
The MD Anderson Manual of Medical Oncology

THIRD EDITION





HAGOP M. KANTARJIAN
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The MD Anderson Manual of Medical Oncology

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Third Edition

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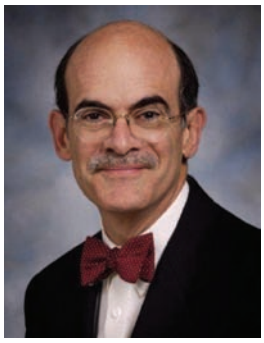

Charles A. Koller, MD
1948-2013

This third edition of *The MD Anderson Manual of Medical Oncology* is dedicated to Charles A. Koller, a valued member of MD Anderson's Leukemia Department for nearly three decades, a committed physician, and an editor of the first and second editions of *The MD Anderson Manual of Medical Oncology*.

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A Brief History of MD Anderson Cancer Center

Houston's evolution into the fourth largest city in the United States was propelled by four seminal events. First was the Great Galveston Hurricane of 1900, which destroyed the city port of Galveston and led to the realization that Houston could become a viable and safer deep-water port; this led to the widening of the Ship Channel to offer direct access to Houston. Second was the discovery of oil at Spindletop in Beaumont, Texas in 1901. This prompted the development of the oil industry in Texas and transformed Houston from a small town into a large city. Third was (of course) the commercialization of air conditioning in 1950's, which made Houston (and many Southern cities of the United States) more livable. And lastly, the allocation of land for the Texas Medical Center created the largest medical center in the world with one of the highest densities of clinical facilities for patient care, basic science, and translational research. The Texas Medical Center is a major contributor to Houston's economy and growth.

Several additional factors contributed to the creation of The University of Texas MD Anderson Cancer Center in Houston and its development into one of the most important cancer centers in the world. First was the generous philanthropy of visionary Texans such as Monroe Dunaway Anderson (Fig. 1) (his nephew died of leukemia in 1936) and his partner Will Clayton, who founded the charitable MD Anderson Foundation, which helped create the Texas Medical Center in 1945. The charter of the Anderson Foundation did not specify how the money should be used, but Mr. Anderson's trustees and close friends—Colonel William Bates, John Freeman and Horace Williams—leaned strongly in favor of health care. Soon after taking possession of the estate from its executors, the trustees turned to Dr. Ernest Bertner (Fig. 2) for advice. Dr. Bertner was a prominent Houston surgeon and gynecologist who was well known to the trustees because of his care for cancer patients, despite inadequate facilities and treatment options (he was later called the "father of the Texas Medical Center").

FIGURE 1.

FIGURE 2.

The trustees and Dr. Bertner noted that the 1941 Texas legislature authorized the University of Texas to create a hospital for cancer research and treatment, allocating $500,000 for the purpose. Today, that figure would be approximately $8 million. The Anderson trustees, with Dr. Bertner's guidance, seized the opportunity and offered to match the $500,000 legislative appropriation, if the hospital was to be named for Monroe Dunaway Anderson and located in Houston. The legislature accepted their offer. The trustees then purchased 134 acres of mosquito-infested land to create the Texas Medical Center, stating that the new cancer hospital would be located there. They made it known that the new state hospital should be an academic institution. In fact, MD Anderson was the first comprehensive cancer hospital to be associated with a major university as an independent free-standing unit.

In 1942, The University of Texas Board of Regents appointed Dr. Bertner as the director of the new hospital. A 6-acre property near downtown was purchased from the estate of Captain James A. Baker, grandfather of former Secretary of State James Baker III, and became the first campus of the hospital. An empty carriage house became the office and stables were the research laboratories. Twelve surplus army barracks were procured for patient clinics (Figs. 3A-C). With the addition of 22 leased beds at Hermann Hospital, the dream became reality, and the "MD Anderson Hospital and Tumor Institute" was created. A small

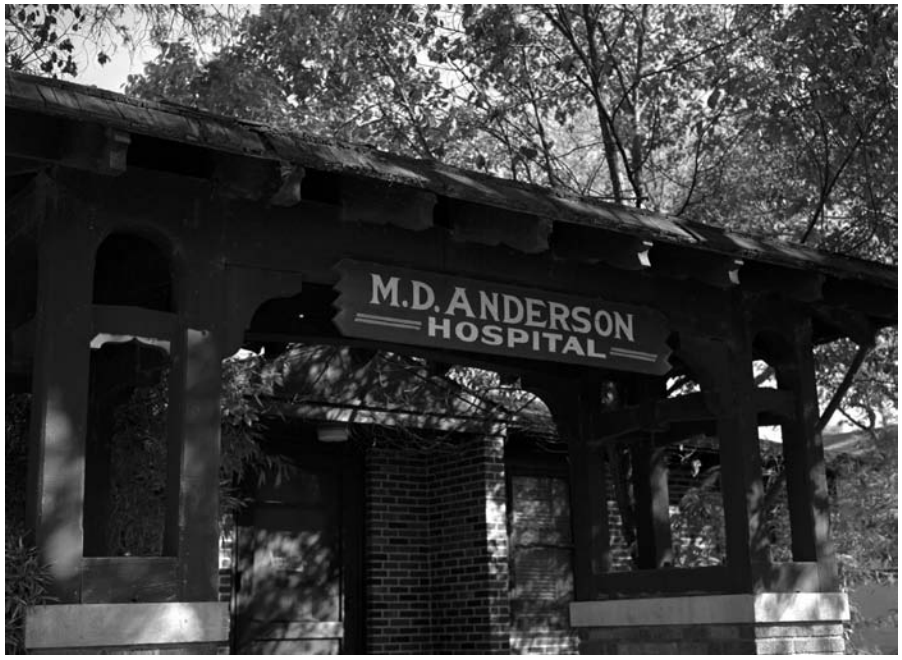

FIGURE 3A.

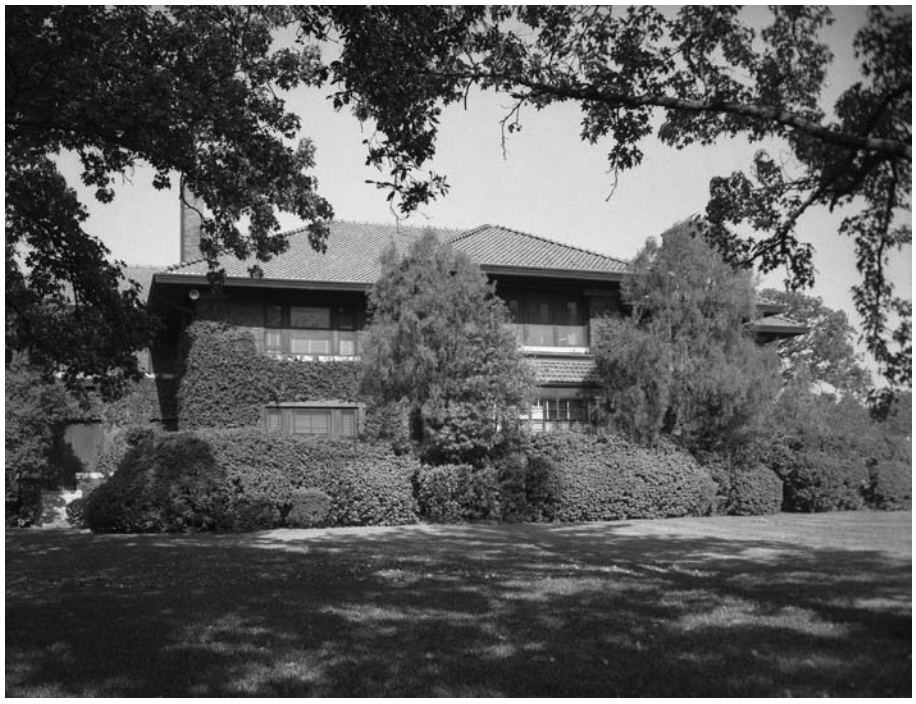

FIGURE 3B.

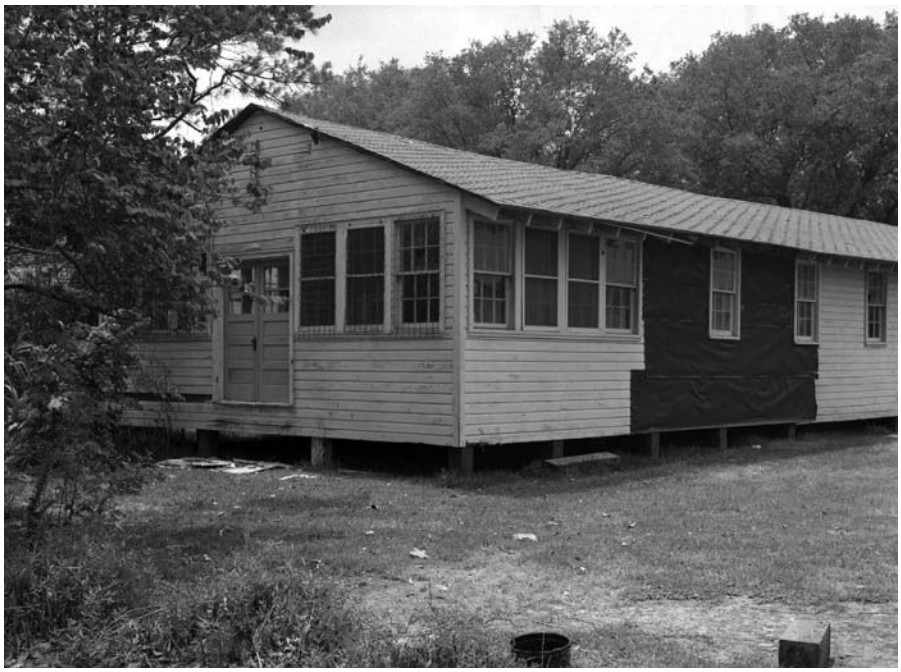

FIGURE 3C.

faculty of physicians and scientists was recruited from the University of Texas Medical Branch in Galveston, and cancer patients finally had a home. It was renamed "MD Anderson Hospital for Cancer Research" in 1942.

In 1946, Dr. Bertner persuaded Dr. Randolph Lee Clark, a native Texan, to become president of what was to become The University of Texas MD Anderson Cancer Center. Dr. Clark, a widely recognized surgeon, concentrated on recruiting an excellent surgical faculty and then set upon acquiring all the basic and clinical scientists and clinicians. From the outset, all efforts, whether administrative, clinical or research, were focused on developing excellence in research-driven cancer care. Forty-six patients were receiving treatment in these early quarters when the hospital moved to its current site in March 1954 (Figs. 4A and B).

FIGURE 4A.

FIGURE 4B.

FIGURE 5.

FIGURE 6A.

FIGURE 6B.

Additional resources to expand the MD Anderson infrastructure (Fig. 5) and research capacities came from several venues: (1) generous donations from the oil industry; (2) the visionary research and administrative leadership under its four presidents, Drs. Randolph Lee Clark (1946–1978) (Fig. 6A), Charles A. LeMaistre (1978–1996) (Fig. 6B), John Mendelsohn (1996–2011) (Fig. 6C), and Ronald DePinho (2011–present) (Fig. 6D); (3) the recruitment of world-renowned cancer research pioneers (some of the early legends included Drs. Emil J. Freireich, Emil Frei, Gilbert Fletcher, James Butler, Felix Rutledge, Gerald Dodd, and Sidney Wallace); and (4) the relentless research efforts of the cancer experts on the MD Anderson's faculty.

Today, MD Anderson is one of the largest cancer centers in the world, with more than 21,000 employees and 1800 faculty; serving more than 150,000 patients with cancer in Houston every year; operating a 700-bed cancer hospital; and being ranked as the No. 1 hospital for cancer care by the *U.S. News and World Report* in 11 of the past 14 years. The MD Anderson Cancer Center research has resulted in numerous discoveries that became standards of care across many types of cancers, and that have saved the lives and/or improved survivals and outcomes of millions of patients with cancer around the world.

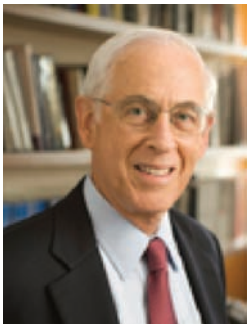

FIGURE 6C.

FIGURE 6D.

One component of MD Anderson's mission is to spread its knowledge about cancer research and discoveries across the globe. This educational mission is furthered by the hematology/oncology fellowship that currently trains more than 40 medical hematology-oncology cancer specialists on its premises. *The MD Anderson Manual of Medical Oncology*, created as part of our educational mission, is written by our fellows as first authors and supported in depth by senior tumor specialty faculty as co-authors. We envision this third edition expanding into a continuously updated electronic version that educates and spreads knowledge and discoveries in cancer research and therapy rapidly and widely.

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Foreword

The MD Anderson Manual of Medical Oncology, third edition, articulates the personalized, multidisciplinary approach to cancer management pioneered by the University of Texas MD Anderson Cancer Center. This approach has contributed to our ranking as number one in cancer care in 11 of the past 14 years in the *US News & World Report's* "America's Best Hospitals" survey. Our unique perspective has evolved from decades of clinical practice and research with more than a million patients treated. The book is designed to bring a pragmatic approach to cancer management that may serve as a guide for oncologists around the world. The text reflects how MD Anderson currently operates, including many patient care practices that would not have been recognized by practitioners just a decade ago. In a single year, 96,500 people with cancer—33,200 of them new patients—seek care at MD Anderson. Since the first edition, we have improved our ability to identify biomarkers that are predictive for survival, a major triumph in medical oncology that is demonstrated throughout the text.

The current edition emphasizes and discusses recent developments in precision medicine and immunotherapies.

Reflecting new advances in our approach to cancer management, the third edition of *The MD Anderson Manual of Medical Oncology* features several new chapters. For example, there are new chapters on important aspects of stem cell transplantation: cord blood transplant, haploidentical stem cell transplantation, and cellular therapy in allogeneic hematopoietic cell transplantation. In addition, new chapters on pediatric cancers, molecular biomarkers and cancer, immuno-oncology, targeted therapies in cancer, applied biostatistics, oncocardiology, pulmonary complications of cancer therapy, and cancer-associated thrombosis have been added.

To help clinicians quickly assess cancer management options, every chapter includes abundant tables, diagrams, and imaging photos. These include, for example, treatment algorithms and decision trees developed at MD Anderson for specific cancers or disease subtypes; promising novel therapy targets and the latest clinical trial phase of drugs targeting them; and new molecular therapies recommended to overcome resistance to previously effective therapies.

The new era of novel personalized, targeted therapeutics has also sparked the recent evolution of another crucial advancement in management of metastatic disease: the transition from sequential care culminating in the sole delivery of palliative care, to integration of ongoing active disease treatment with simultaneous interdisciplinary symptom control, palliative care, and rehabilitation to improve quality of life. Clinicians at MD Anderson no longer approach advanced metastatic disease management with palliative care goals alone; now, these patients are often offered frontline cancer treatment and the opportunity to participate in clinical trials for investigational drugs.

In recognition of the growing pool of patients who are surviving their cancer, MD Anderson has greatly expanded programs for cancer survivors since the publication of the first edition.

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Preface

When we first envisioned *The MD Anderson Manual of Medical Oncology*, we hoped that it would fill an important void in oncology reference material by serving as a hands-on resource for the practicing oncologist. The first edition, published in 2006, was written exclusively by our faculty and fellows with the idea of giving a bird's-eye view of how multidisciplinary care was practiced at our institution. We were proud of that initial effort and pleased that the book received positive reviews from several high-impact journals, including *JAMA*, *The Lancet*, and *The New England Journal of Medicine*.

The second edition, published in 2011, moved closer to the aims of providing more illustrations, figures, tables, and algorithms. In addition, the second edition included new chapters on myelodysplastic syndromes, Philadelphia chromosome-negative myeloproliferative neoplasms, T-cell lymphomas, small bowel cancer and appendiceal tumors, inflammatory breast cancer, and penile cancer.

In the third edition, we have continued the tradition of including evidence-based management algorithms in the form of flowcharts and diagrams, shaped by the clinical experience of our world-class faculty at MD Anderson. Readers are also provided with a practical guide to the diagnostic and therapeutic strategies used at MD Anderson.

The new edition of *The MD Anderson Manual of Medical Oncology* contains new chapters on cord blood transplant, haploidentical stem cell transplantation, cellular therapy in allogeneic hematopoietic cell transplantation, pediatric cancers, molecular biomarkers and cancer, immuno-oncology, targeted therapies in cancer, applied biostatistics, oncocardiology, pulmonary complications of cancer therapy, and cancer-associated thrombosis. In addition, there is expanded coverage of the rapidly growing areas of biological and immune therapies of cancer.

The new edition of *The MD Anderson Manual of Medical Oncology* will also be a continually updated version of the book, online, with the latest science and clinical recommendations from the world-renowned clinical investigators at MD Anderson.

We hope that this edition serves to help oncologists everywhere provide high-quality, state-of-the-art cancer care to their patients.

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1 Acute Lymphoblastic Leukemia

2 Adult Acute Myeloid Leukemia

3 Chronic Lymphocytic Leukemia and Associated Disorders

4 Chronic Myeloid Leukemia

5 Myelodysplastic Syndromes: The MD Anderson Cancer Center Approach

6 Philadelphia-Chromosome Negative Myeloproliferative Neoplasms

1 Acute Lymphoblastic Leukemia

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EPIDEMIOLOGY AND ETIOLOGY

Acute lymphoblastic leukemia (ALL) is characterized by the proliferation and accumulation of lymphoid progenitor cells in the blood, bone marrow, and other tissues. It has a bimodal distribution. The overall age-adjusted incidence is 1.7 per 100,000 persons, but ALL affects 4 to 5 per 100,000 persons during age 4 to 5 years and half that number around the fifth decade of life. Approximately 60% of cases are diagnosed in patients ≤20 years old, with a median age at diagnosis of 14 years. In 2014, the American Cancer Society estimated that approximately 6,000 individuals would be diagnosed with ALL that year ([1, 2]). Acute lymphoblastic leukemia represents 20% of adult leukemias but is the most common childhood acute leukemia, representing approximately 80% of cases ([1, 2]).

The etiology of ALL is unknown in most cases ([3-7]). Chromosomal translocations occurring in utero during fetal hematopoiesis have suggested genetic factors as the primary cause for pediatric ALL and postnatal genetic events as secondary contributors. Monozygotic and dizygotic twins of patients with ALL and individuals with genetic disorders, such as Klinefelter (XXY and variants) and Down (trisomy 21) syndromes, or inherited diseases with excessive chromosomal fragility, such as Bloom syndrome, Fanconi anemia, and ataxia telangiectasia, have all been found to have higher incidence of ALL, implicating a possible genetic predisposition. Additional studies have postulated infectious etiologies ([4]). Human T-cell lymphotropic virus type-1 is known to cause adult T-cell leukemia/lymphoma ([5]); Epstein-Barr virus has been associated with lymphoproliferative disorders, including Burkitt lymphoma and mature B-cell ALL ([6]); and varicella has been linked to childhood ALL ([7]).

CLINICAL PRESENTATION AND LABORATORY ABNORMALITIES

Presenting symptoms can be nonspecific, particularly in children. They largely reflect bone marrow failure and include malaise, fatigue, bleeding or bruising, and secondary infections. The B symptoms, such as fever, night sweats, and weight loss, are frequent. White blood cell (WBC) count at presentation varies widely, and circulating blasts are generally noted. Symptoms related to hyperleukocytosis are rare in ALL, given the lymphoblast morphology, even when WBC counts are high.

Leukemic involvement of the central nervous system (CNS) ranging from cranial neuropathies to meningeal infiltration occurs in <10% of patients at presentation. It is more common in mature B-cell ALL (Burkitt leukemia) ([8]). A history or findings of abdominal masses, significant spontaneous tumor lysis syndrome, and chin numbness (mental nerve) indicating cranial nerve involvement are also more common in this subtype of ALL ([9]). Lymphadenopathy and hepatosplenomegaly, although rarely symptomatic, are noted in approximately 20% of patients ([9]).

DIAGNOSIS

Immunophenotyping

The diagnosis of ALL is largely based on flow cytometric immunophenotyping, although identification of cytogenetic-molecular abnormalities plays a significant role (Fig. 1-1). The World Health Organization (WHO) proposed new guidelines for the diagnosis of neoplastic diseases of hematopoietic and lymphoid tissues ([10]). The French-American-British (FAB) Cooperative Group diagnostic approach, which recognizes L1 to L3 morphologic subtypes, has been essentially abandoned. A blast count of ≥20% was established as sufficient for diagnosis.

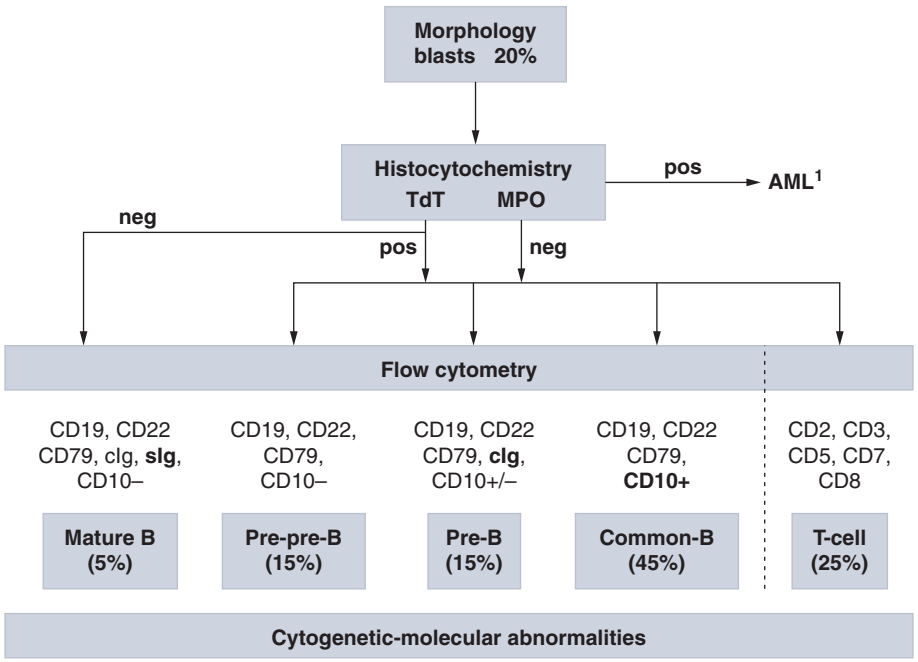
Flow cytometric analysis successfully assigns lineage in more than 95% of cases. True mixed phenotype acute leukemia is rare ([11]). Concomitant expression of markers from more than one lineage is seen in 15% to 50% of adult and 5% to 35% of pediatric ALL ([12-14]), but this is not prognostically relevant. Targeted genomic profiling may further define ALL subtypes with different response profiles to therapy and prognoses, which are only partially discriminated by current diagnostic tools.

Immunophenotypically, ALL blasts are negative for myeloperoxidase (MPO), although low-level MPO positivity (3%-5%) may occur in rare cases that otherwise lack expression of myeloid markers by flow cytometry ([15]). Terminal deoxynucleotidyl transferase (TdT), although not a specific marker of ALL, helps separate malignant lymphocytosis from reactive processes and distinguish L3 ALL (TdT negative) from other ALL subtypes ([16]).

Both the prior FAB and current WHO classification systems rely heavily on morphologic assessment ([17]), which accounts for cell size, cytoplasm, nucleoli, basophilia, and vacuolation. The former FAB L3 morphology, characterized by a high rate of cell turnover, is associated with mature B-cell ALL (Burkitt leukemia) and gives rise to the "starry sky" pattern on marrow biopsies.

Three broad immunophenotypic ALL groups can be distinguished: precursor B-cell, mature B-cell, and T-cell ALL (Table 1-1). Precursor B-cell ALL (B-ALL) stains positive for TdT, HLA-DR, CD19, and CD79a. According to the stages of maturation, further B-cell subgroups have been defined as pre-pre-B-ALL (pro–B-ALL), common ALL, and pre–B-ALL. Although they all stain positive for CD19, CD79a, or CD22, expression of CD10 (common ALL antigen [CALLA]) distinguishes common ALL (early pre–B-ALL), and cytoplasmic immunoglobulins with or without CD10 identify pre–B-ALL. Mature B-ALL (Burkitt leukemia) is TdT negative but expresses surface immunoglobulins (usually immunoglobulin M), as well as κ or λ light chains in a clonal fashion. It has almost ubiquitous expression of CD20, which has therapeutic implications ([18]).

T-cell ALL (T-ALL) further stratifies into subtypes based on different stages of thymic differentiation ([19]).



[1]Low-level myeloperoxidase (MPO) positivity (3%-5%) may occur in rare cases that otherwise lack expression of myeloid markers by flow cytometry.

FIGURE 1-1 Diagnosis of acute lymphoblastic leukemia. AML, acute myeloid leukemia.

Table 1-1 Immunophenotypic Classification of ALL

B Lineage		T Lineage	
CD19/CD79a/CD22		CD3 (Surface/Cytoplasmic)	
Pre-pre-B-ALL (pro–B-ALL)	—	Precursor T-ALL	CD1a, CD2, CD5, CD7, CD8, cCD3
Common ALL	CD10 (CALLA)	Mature T-ALL	Surface CD3 (plus any other T-cell markers)
Pre–B-ALL	Cytoplasmic IgM		
Mature B-ALL	Cytoplasmic or surface Ig κ or λ		

As the most lineage-specific marker for T-cell differentiation, surface CD3 (sCD3) is typically positive in mature T-ALL, which is also positive for either CD4 or CD8, but not both. However, pre–T-ALL is negative for CD4, CD8, and sCD3 but may still express cytoplasmic CD3. A more simplified classification divides T-ALL into early T-ALL ($sCD3^-$, $CD1a^-$), thymic T-ALL ($sCD3^{+/-}$, $CD1a^+$), and mature T-ALL ($sCD3^+$, $CD1a^+$). Only thymic T-ALL has excellent outcome with chemotherapy alone.

Cytogenetic-Molecular Profiling

Frequent cytogenetic and molecular abnormalities associated with adult ALL offer insight into the events leading to leukemic progression (Table 1-2) ([20]). They are of both prognostic and predictive significance and have varying frequencies in children and adults, which explains some of the differences in outcomes in these two groups. This is particularly true in the case of ALL harboring Philadelphia chromosome [t(9;22)] (Ph) or

Table 1-2 Cytogenetic and Molecular Abnormalities in ALL

Category	Cytogenetics	Involved Genes	Adults Frequency (%)	Children Frequency (%)
Hyperdiploid			2-15	10-26
Hypodiploid			5-10	5-10
Pseudodiploid	t(9;22)(q34;q11)	*BCR-ABL1*	15-25	2-6
	del(9)(q21-22)	*p15, p16*	6-30	20
	t(4;11);t(9;11);	*MLL*	5-10	<5
	t(11;19); t(3;11)			
	del(11)(q22-23)	*ATM*	25-30[a]	15[a]
	t(12;21)(p12;q22)	*TEL-AML1*	<1[b]	20-25[b]
	t(1;19)	*E2A-PBX1*	<5	<5
	t(17;19)	*E2A-HLF*	<5	<5
	t(1;14)(p32;q11)	*TAL1*	10-15	5-10
	t(7;9)(q34;q32)	*TAL2*	<1	<1
	t(10;14)(q24;q11)	*HOX11*	5-10	<5
	t(5;14)(q35;q32)	*HOX11L2*	1	2-3
	t(1;14)(p32;q11)	*TCR*	20-25[c]	20-25[c]
	del(13)(q14)	*miR15/miR16*	<5	<5
	t(8;14); t(8;22); t(2;8)	*C-MYC*	5	2-5
	+8	?	10-12	2
	del(7p)	?	5-10	<5
	del(5q)	?	<2	<2
	del(6q); t(6;12)	?	5	<5

[a]As determined by loss of heterozygosity.
[b]As determined by polymerase chain reaction.
[c]In T-cell ALL, overall incidence <10%.

other chromosomal changes with prognostic relevance such as Burkitt karyotypes [t(8;14), t(2;8), t(8;22)] or t(4;11). Next-generation sequencing, expression proteomics, and oligonucleotide microarrays have transformed our understanding of the genomic landscape of ALL and are yielding new molecular subgroups with actionable defects ([21-23]).

Recently, a Ph-like signature in 10% of children with standard-risk ALL and as many as 25% to 30% of young adults with ALL has been defined using genome-wide gene expression arrays. This subgroup lacks the expression of BCR-ABL1 fusion protein but does have a gene expression profile similar to BCR-ABL1 ALL ([24-26]). The vast majority of these patients have deletions in key transcription factors involved in B-cell signaling, such as IKZF1, TCF3, EBF1, PAX5, and VPREB1, as well as kinase-activating alterations involving ABL1, ABL2, CRLF2, CSF1R, EPOR, JAK2, NTRK3, PDGFRB, PTK2B, TSLP, or TYK2 and sequence mutations involving *FLT3*, *IL7R*, or *SH2B3*. The most common alterations (~50%) are rearrangements of CRLF2, which activate downstream signaling through JAK kinases, and approximately half of these cases have activating mutations in *JAK1* or *JAK2* (Fig. 1-2). Importantly, patients with ABL1, ABL2, CSF1R, and PDGFRB expression fusions were sensitive in in vitro and in vivo human xenograft models to ABL class tyrosine kinase inhibitors (TKIs; eg, dasatinib); rearrangements in *EPOR*, *IL-7R*, and *JAK2* mutations and fusions were sensitive to JAK kinase inhibitors (eg, ruxolitinib); and patients with ETV6-NTRK3 fusion were sensitive to ALK kinase inhibitors (eg, crizotinib) ([25]), further expanding therapeutic options in this subgroup with poor outcome.

Observations of epigenetic alterations regulating distinct molecular pathways that occur frequently at presentation and relapse have identified a "hypermethylator" phenotype of ALL ([27]). These patients may respond favorably to treatment with hypomethylating agents (azacitidine or decitabine). Identification of these and other molecular and cytogenetic changes in adult ALL drives the development of risk-adapted and targeted therapies, particularly in high-risk groups (Table 1-3) ([28]).

FRONTLINE THERAPY

Therapy for ALL consists of complex and comprehensive regimens consisting of several phases: induction, intensified consolidation, maintenance, and CNS prophylaxis ([9,29]). Each involves the use of a core group of agents considered the backbone of therapy in a time- and dose-dependent manner, with a goal of restoring normal hematopoiesis, eradicating resistant subclones, providing adequate prophylaxis of sanctuary sites (eg, CNS, testicles), and eliminating minimal residual disease (MRD) during the consolidation and maintenance phases ([9,30]). Combining anthracyclines (eg, daunorubicin or doxorubicin), vincristine, and dexamethasone (for better CNS penetration), often coupled with cyclophosphamide or asparaginase with growth factor support, represents the cornerstone of ALL induction regimens. This results in complete remission (CR) rates of 70% to 90% and median remission durations of 18 months ([30,31]). Patients who achieve CR subsequently transition to the consolidation phase, which, depending on the risk-oriented subtype, may consist of consolidation chemotherapy (cytarabine, methotrexate, cyclophosphamide, and 6-mercaptopurine) or allogeneic hematopoietic stem-cell transplantation (AHSCT). Consolidation is followed by prolonged maintenance therapy with daily 6-mercaptopurine, weekly methotrexate, and monthly pulses of vincristine and prednisone or dexamethasone, given over 2 to 3 years (POMP or DOMP, depending on corticosteroid used) ([30-32]). Maintenance, which is omitted in mature B-ALL due to high cure rates, may also involve the use of TKIs for patients with Ph-positive ALL. Primary CNS involvement at diagnosis is rare (<10%) but is as high as 50% to 75% at 1 year without prophylactic administration of intrathecal chemotherapy (IT) ([31]). Although high-dose cytarabine (1-7.5 mg/m^2) and methotrexate (5-8 g/m^2) successfully penetrate the blood-brain barrier, they are too toxic to serve as the sole CNS prophylaxis. The inclusion of IT prophylaxis (methotrexate, cytarabine, liposomal cytarabine, hydrocortisone, or thiotepa) reduces the incidence of CNS relapse to 4% by allowing sustained therapeutic concentration of the agents in the cerebrospinal fluid. The number of ITs varies according

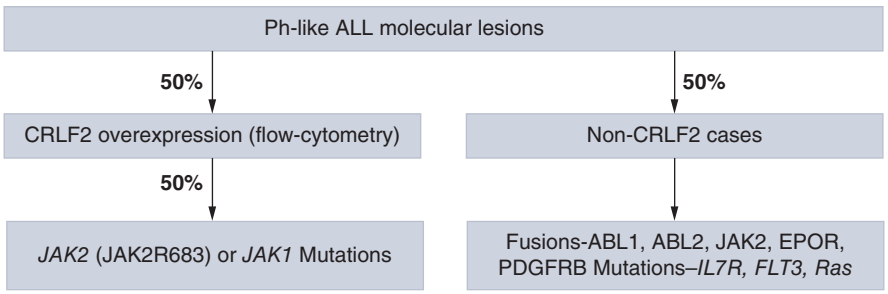


FIGURE 1-2 **Ph-like acute lymphoblastic leukemia (ALL) molecular lesions and associated molecular fusions or mutations.**

Table 1-3 Recent Genetic Determinants in ALL by Lineage

ALL Lineage	Cytogenetic Aberration	Involved Genes	Protein	Comments
B cell	BCR/ABL+ (Ph+)	*IKZF1*	Ikaros	Poor outcome. 80% of Ph+ cases.
		CRLF2 + the Ig heavy chain locus; or an interstitial *PAR1* deletion	CRLF2	5%-10% of cases with no molecular rearrangement. Poor outcome. 50% of children with Down syndrome.
	BCR/ABL-like	*IKZF1* deletions; rearrangements/ mutations in *CRLF2*, *IGH-CRLF2*, and *NUP214-ABL1*; in-frame fusions of *EBF1-PDGFRB*, *BCR-JAK2*, or *STRN3-JAK2*; cryptic *IGH-EPOR* rearrangements		15% of cases. Potential use of TKIs and/or mTOR and JAK2 inhibitors.
	Near hypodiploid	*NRAS*, *KRAS*, *FLT3*, and *NF1*		70% of cases.
	Low hypodiploid	*IKZF2*, and by *TP53* disruptions, *CDKN2A/B* locus deletion		91% of cases.
	Hyperdiploid	*CREBBP*		
		NT5C2 mutations	NT5C2	
		TP53 mutations		6% of cases.
T cell		*PICALM-MLLT10*, *NUP214-ABL1* fusion, *EML-ABL1*, *SET-NUP214* fusion, *MLL*, *NOTCH1*, *FBW7*, *BCL11B*, *JAK1*, *PTPN2*, *IL7R*, *PHF6*, *RAS/PTEN*		*NOTCH1* (>60%) and/or *FBW7* (~20%) mutations associated with a favorable outcome. *RAS/PTEN* and *JAK1* usually poor outcome.

mTOR, mammalian target of rapamycin; TKI, tyrosine kinase inhibitor.

to protocol (usually 8 for standard risk, 12 for Ph positive, and 16 for Burkitt), and in rare cases of extramedullary disease spread (eg, masses or chloromas), IT may even be supplemented by radiation therapy.

One extensively studied regimen used in treatment of adult ALL is the hyper-CVAD (HCVAD) regimen, where patients receive hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine for a total of eight alternating cycles approximately every 3 to 4 weeks (Table 1-4) ([30,31]). This is followed by 2 years of POMP maintenance therapy, interspersed with intensification courses during months 6, 7, 18, and 19. The number of IT injections (two per course) depends on the risk of CNS relapse, which has been identified as high for patients with mature B-ALL. Our current approach is giving 8 ITs for nonmature B-ALL and 16 ITs for mature B-ALL, resulting in a 5-year overall survival (OS) between 38% and 50% ([30]). Due the improved cure rates of Ph-positive ALL patients, an increase in the CNS relapse rate was observed, which is the reason the protocol was modified to include 12 ITs for Ph-positive ALL.

Mature B-Cell and Burkitt Acute Lymphoblastic Leukemia

The addition of rituximab to short intensive chemotherapy has also improved outcome in adult Burkitt and Burkitt-type lymphoma or ALL ([29, 33, 34]). Hoelzer and colleagues have recently reported the benefit of adding rituximab to short intensive chemotherapy in 363 patients with Burkitt lymphoma/leukemia; the addition of rituximab resulted in CR and 5-year survival rates of 88% and 80%, respectively ([33]). Higher rates of survival were reported in adolescents compared to adults and elderly patients (90% vs 84% vs 62%, respectively) ([33]). Low-intensity chemotherapy with infused etoposide, doxorubicin, and cyclophosphamide with vincristine, prednisone, and rituximab (EPOCH-R) was recently tested in 30 adult patients with Burkitt lymphoma ([35]). The progression-free survival (PFS) and OS rates were 90% and 100%, respectively. Of note, marrow involvement was present in only 13% of patients, and CNS involvement was present in only 3% of patients ([35]).

CD20-Positive Pre–B-Cell Acute Lymphoblastic Leukemia

There have been several alterations to traditional protocols with further refining of the disease. Expression of cell surface marker CD20 in adult ALL ranges from 35% to ubiquitous depending on the subtype and has been associated with an inferior prognosis ([18]). The addition of two doses of monoclonal CD20 antibody

Table 1-4 Doses and Schedule of the Hyper-CVAD Regimen

Therapy Segment	Dose and Schedule
Induction and intensified consolidation	Hyper-CVAD (courses 1, 3, 5, and 7)
	• Cyclophosphamide 300 mg/m^2 IV over 3 h every 12 h for 6 doses on days 1-3
	• Mesna 600 mg/m^2 as an IV continuous infusion over 24 h daily on days 1-3 (starting approximately 1 h prior to cyclophosphamide and finishing 12 h after the last dose)
	• Doxorubicin 50 mg/m^2 IV continuous infusion over 24 h on day 4
	• Vincristine 2 mg IV on days 4 and 11
	• Dexamethasone 40 mg daily on days 1-4 and 4-11
	Methotrexate (MTX) and high-dose cytarabine (courses 2, 4, 6, and 8)
	• MTX 200 mg/m^2 IV over 2 h followed by 800 mg/m^2 IV over 22 h on day 1
	• Leucovorin rescue 15 mg every 6 h for eight doses (starting 12 h after completion of MTX)
	• Cytarabine 3 g/m^2 IV over 2 h every 12 h for 4 doses on days 2 and 3
	• Methylprednisolone 50 mg IV twice daily on days 1-3
CNS prophylaxis	IT MTX 12 mg (6 mg if via Omaya reservoir) on day 2 and cytarabine 100 mg on day 7 of each course
	Low risk: 6 IT
	High risk: 8 IT
	Mature B cell: 16 IT
Maintenance therapy	POMP
	• 6-Mercaptopurine 50 mg orally three times per day
	• MTX 20 mg/m^2 orally weekly
	• Prednisone 200 mg orally days 1-5 every month
	• Vincristine 2 mg IV every month
	• Intensification with four additional courses of hyper-CVAD plus MTX/cytarabine
Supportive care	• Antibiotic prophylaxis (levofloxacin, fluconazole, valacyclovir)
	• Hematopoietic growth factor support during induction and consolidation
	• Laminar air flow rooms (for patients ≥60 years old)

CNS, central nervous system; IT, intrathecal; IV, intravenous.

(rituximab) administered with the first four cycles of chemotherapy and during maintenance intensification at months 6 and 18 resulted in improved OS in younger patients compared with similar chemotherapy historical controls (75% vs 47% at 3 years; P = .003) ([36]). Improvement in the 5-year remission duration and survival rates was also reported in patients <55 years old by the German Multicenter Study Group for ALL (GMALL) when rituximab was added to standard induction and consolidation therapy ([37]).

Ofatumumab is a more potent second-generation anti-CD20 monoclonal antibody that binds to a membrane proximal small-loop epitope on the CD20 protein. A phase II study in CD20-positive pre–B-ALL combined ofatumumab with HCVAD during induction, resulting in a 96% rate of both CR and MRD negativity. At a median follow-up of 14 months, the 1-year PFS and OS rates were 94% and 92%, respectively ([38]).

Philadelphia-Positive Acute Lymphoblastic Leukemia

Philadelphia-positive ALL used to have a very poor outcome in general. The incorporation of TKIs into treatment regimens has significantly improved patient outcomes, as supported by several reports ([39-42]). Incorporation of early, daily, and concurrent TKI with chemotherapy has proven more effective than intermittent pulses ([41, 42]).

Second-generation TKIs, such as the dual src and abl inhibitor dasatinib, which is more potent than imatinib and crosses the blood-brain barrier ([43]), have also been investigated in combination with chemotherapy. In an attempt to improve on the outcomes with imatinib, dasatinib was administered at 100 mg daily for 14 days with induction chemotherapy, followed by 70 mg continuous dosing with the consolidation cycles, and at

100 mg daily continuously during the maintenance phase ([44]). Overall, 94% of patients achieved CR, 96% achieved complete cytogenetic response (CCyR), and 65% achieved complete molecular response (CMR). Allogeneic hematopoietic stem-cell transplantation was performed in 22 patients (12 in first CR and 10 in second CR), with 3-year disease-free survival (DFS) and OS rates of 49% and 61%, respectively.

Attempting to reduce exposure to cytotoxic chemotherapy by intensifying chemotherapy with TKIs can be very effective but toxic ([45, 46]). Patients in the GRAAPH-2005 study were randomized to imatinib 800 mg daily for 4 weeks combined with weekly vincristine and dexamethasone versus imatinib 800 mg daily for 2 weeks combined with HCVAD chemotherapy ([45]). The CR rate was higher in the low-intensity group due to induction-related mortality in the HCVAD group (7% vs <1%; $P = .01$). An equal number of patients in each group proceeded to autologous stem cell transplantation and allogeneic stem cell transplantation, and at 3 years, OS was similar between the two arms (53% for low intensity vs 49% for HCVAD; $P = .61$).

Studies have also evaluated the use of dasatinib and nilotinib with low-intensity chemotherapy ([46-48]). In the EWALL-Ph-01 study, dasatinib with low-intensity chemotherapy was administered to 71 patients with newly diagnosed Ph-positive ALL age ≥55 years ([46]). Dasatinib was dosed at 140 mg once daily during induction and at 100 mg daily during consolidation, yielding a CR rate of 94%. The estimated 3-year OS was 45%.

Many Ph-positive ALL patients can relapse with threonine-to-isoleucine mutation at position 315 (T315I), which is refractory to imatinib and second-generation TKIs. A third-generation TKI, ponatinib, which has activity against T315I, was evaluated in phase I and II trials in patients with Ph-positive leukemias and was shown to have significant antileukemic activity ([49, 50]). More recently, 39 patients with newly diagnosed Ph-positive ALL were treated with HCVAD and ponatinib 45 mg daily for 14 days during induction and then continuously thereafter until CCyR and CMR were obtained, when decreases to 30 mg and 15 mg daily could be instituted, respectively. The CR, CCyR, and CMR rates were 100%, 100%, and 74%, respectively. After a median follow-up of 20 months, 1-year PFS and OS were 97% and 87%, respectively ([51]).

Although current standard of care still advocates AHSCT consolidation in first CR ([39]), new information regarding the status of MRD in Ph-positive ALL has raised a question as to who should be referred for it. The predictive value of MRD assessment by quantitative reverse transcriptase polymerase chain reaction (RT-PCR) and multiparameter flow cytometry (FCM) was recently assessed in patients with Ph-positive ALL treated with combination chemotherapy and TKIs who did not undergo AHSCT. Achieving major molecular response at 3, 6, 9, and 12 months ($P = .02$, .04, .05, and .01, respectively) and having negative FCM at 3 and 12 months were associated with improved survival ($P = .04$ and .001, respectively) ([52]). This information suggests that patients with early and sustained molecular response may not need consolidation with AHSCT.

T-Cell Acute Lymphoblastic Leukemia

Treatment of adult T-ALL and T-cell lymphoblastic lymphoma (T-LL) results in a long-term survival rate of 40% to 60%, and the outcome is strongly associated with T-cell phenotype ([53, 54]). Adding nelarabine, a selective anti–T-ALL agent may further improve the outcome. In a single-arm, phase II study, 48 patients with newly diagnosed T-ALL or T-LL were treated with HCVAD and neralabine ([55]). The CR rate was 93%; the 5-year survival rate was 66% after a median follow-up of 41 months. These rates were 38% and 70% for patients with early T-cell precursor (ETP) and mature T-ALL, respectively. Indeed, ETP-ALL is a distinct T-cell entity characterized by the absence of CD1a, sCD3, and CD8 expression; weak CD5 expression; and expression of one or more myeloid or stem cell–associated markers ([54]). It confers poor prognosis with the use of standard intensive chemotherapy, which results in high rates of remission failure and relapse compared to patients with typical T-ALL (72% at 10 years vs 10% at 10 years). This phenotype is in part a reflection of the higher degree of genomic instability (number and size of genetic defects) that ETP-ALL harbors, with over 60% of adult patients carrying mutations in *DNMT3A*, *FLT3*, or *NOTCH1*, which may allow for tailored induction regimens with targeted therapies ([56]). Following induction, AHSCT should be considered in first remission for all ETP-ALL patients.

Adolescent and Young Adult Acute Lymphoblastic Leukemia

Retrospective studies have shown that pediatric regimens resulted in better outcomes than adult regimens (which had deviated significantly from the established principles of ALL therapy in pediatric regimens). Pediatric-inspired regimens, such as the Berlin-Frankfurt-Münster (BFM) regimen (Table 1-5), deliver more intensive nonmyelosuppressive agents like vincristine, asparaginase, corticosteroids, and CNS therapy ([54, 55]).

The Group for Research on Adult Acute Lymphoblastic Leukemia (GRAALL) evaluated a pediatric-inspired regimen in patients up to age 60 years and compared the results to a historical control group treated with an adult regimen. In patients treated with the pediatric-inspired regimen, the CR rate was 93%, and at 42 months, event-free survival (EFS) and OS rates were 55% (95% CI, 48%-52%) and 60% (95% CI, 53%-66%), respectively ([57]).