**Acute Lymphoblastic Leukemia**

**Mignon Loh**

1. A newly diagnosed patient with acute lymphoblastic leukemia (ALL) has a twin. Which of the following circumstances are associated with the highest risk for ALL development in that twin?

A. A 3-year-old boy with ALL and *ETV6*-*RUNX1* (*TEL*-*AML1*) fusion who has an identical twin brother

B. A 6-month-old boy with ALL and *MLL*-*AFF1* (*MLL*-*AF4*) fusion who has a twin sister

C. A 6-year-old boy with ALL and *MLL*-*AFF1* (*MLL*-*AF4*) fusion who has an identical twin brother

D. A 6-month-old boy with ALL and *MLL*-*AFF1* (*MLL*-*AF4*) fusion who has an identical twin brother

E. A 2-year-old boy with ALL and *TCF3-PBX1* (*E2A*-*PBX1*) fusion who has an identical twin brother

**Explanation**

Answer D is correct; the concordance rate for leukemia is highest for identical twins diagnosed in the first year of life. The concordance rate is about 50% in the first year of life and drops to a very low percentage by age 5 years. Concordance occurs because of *in* *utero* twin-to-twin transfer of either overt leukemia cells or cells with an initiating leukemia event (typically a translocation), with new secondary events acquired independently in each twin. Because 75% to 80% of infants with ALL have *MLL* translocations, most but not all cases of concordant ALL in twins are associated with *MLL* translocations. *ETV6*-*RUNX1* and *MLL* translocations typically occur *in utero* in patients diagnosed with leukemia in the first few years of life; the identical twins of the patients in answers A and C are at some risk at 3 (A) and 6 (C) years, but probably only 5% to 10% for A and a very low risk for C. The twin of the patient in answer B is fraternal and at much lower risk than the identical twin in answer D. *TCF3*-*PBX1* is much less likely to occur *in utero* than *ETV6*-*RUNX1* and *MLL* translocations, so the twin of the patient in answer E is at low but not zero risk.

2. Which of the following patients should *not* be treated with therapy used commonly for pediatric acute lymphoblastic leukemia (ALL)?

A. A 10-year-old boy with a large mediastinal mass, pleural and pericardial effusions, normal peripheral blood cell counts, and 3% T-lymphoblasts in the bone marrow

B. A 4-year-old girl with L2 morphology ALL with lymphoblasts expressing cytoplasmic mu heavy chains

C. A 3-year-old boy with ALL that expresses CD10, CD19, CD13, and CD33

D. A 20-year-old woman with B-precursor ALL and a white blood cell count of 40,000/mcL

E. A 4-year-old boy with WBC count 45,000/mcL, hepatosplenomegaly, and 50% lymphoblasts with deeply basophilic cytoplasm and cytoplasmic vacuoles and a t(2; 8)(p12;q24)

**Explanation**

Answer E is correct. Burkitt leukemia is defined by L3 morphology, with deeply basophilic cytoplasm and cytoplasmic vacuoles and the presence of translocations that join the c-Myc locus at 8q24 to an immunoglobulin heavy or light chain gene. The immunoglobulin kappa gene is located at 2p12. These patients require different therapy than other patients with ALL and typically are treated in the same way as patients with advanced stage Burkitt lymphoma using therapy that is intensive but short in duration and not including ALL maintenance chemotherapy. The patient described in answer A has stage III T-cell lymphoma, which is typically treated the same as is T-cell ALL. The patient described in answer B has pre-B cell ALL, and the patient described in answer C has ALL with expression of myeloid markers. The latter is not unusual and not associated with an adverse prognosis, so he should be treated like any other patient with ALL. The young woman described in answer D will fare much better if treated on a pediatric rather than adult ALL protocol.

3. What is the single strongest prognostic factor in acute lymphoblastic leukemia (ALL)?

A. Age

B. Initial WBC count

C. Sex

D. Early treatment response as assessed by minimal residual disease (MRD) at end of induction therapy

E. Presence of CNS leukemia (CNS3)

**Explanation**

Answer D is correct. Multivariate analyses consistently show that end induction MRD is the strongest prognostic factor in ALL. Age (answer A) and initial WBC count (answer B) remain prognostic but are not as powerful as MRD in multivariate analyses. Sex (answer C) remains prognostic of outcome in very large trials, with boys having inferior outcome to girls; however, sex is of only limited prognostic significance, with relative risks of 1.1 to 1.2 (which cannot be detected unless a very large number of patients is analyzed). CNS involvement (answer E) is prognostic of outcome in some but not all contemporary trials. It is more important as an indicator of a need for more CNS-directed therapy than as a prognostic factor.

4. The National Cancer Institute (NCI)/Rome risk factors are used to group patients with acute lymphoblastic leukemia (ALL) into standard- and high-risk groups. Which of the following patients has standard-risk ALL?

A. A 9-year-old boy with WBC count 45,000/mcL and B-lineage ALL

B. An 11-and-a-half-month-old girl with WBC count 5,000/mcL and B-lineage ALL

C. An 11-year-old girl with WBC count 5,000/mcL and B-lineage ALL

D. A 3-year-old boy with WBC count 5,000/mcL and T-cell ALL

E. A 3-year-old boy with WBC count 55,000/mcL and B-lineage ALL

**Explanation**

Answer A is correct. Standard-risk patients are those with age 1.01 to 9.99 years, initial WBC count less than 50,000/mcL, and B-lineage ALL. Patient B is an infant youger than 1 year. Patient C has high-risk ALL due to age greater than 10 years. The NCI criteria apply only to B-lineage ALL, and patient D has T-ALL. Patient E has high-risk ALL based on a WBC count greater than 50,000/mcL.

5. Which of the following factors is most prognostic for the highest-risk subgroup of infants younger than 1 year with acute lymphoblastic leukemia (ALL)?

A. CNS involvement

B. Initial WBC count 50,000/mcL or greater

C. *MLL* translocations

D. Age less than 3 months

E. *MLL* translocations and age less than 3 months

**Explanation:** Answer E is correct. The strongest prognostic factors in infants with ALL are age (younger than 3 months is worse than 3 months to younger than 6 months, which is worse than 6 to 12 months) and the presence of an *MLL* translocation. Infants with both age younger than 3 months and *MLL* translocations have an extremely poor outcome. CNS involvement (answer A) is much more common in infants with ALL than in older children, does not have prognostic significance, and is not usually considered an indication to alter therapy. The average WBC count is much higher in infants than in older children with ALL, and most have a WBC count of 50,000/mcL or greater (answer B). This (answer B) is of some prognostic importance but is nowhere near as strong as age less than 3 months and *MLL* translocations. Some studies (Interfant-99) have found that WBC 300,000/mcL or higher is a particularly poor prognostic marker.

6. Which of the following chromosome translocations is most likely to be seen in pediatric T-cell acute lymphoblastic leukemia (T-ALL)?

A. t(9;22)(q34;q11)

B. t(8;22)(q24;q11)

C. t(1;19)(q23;p13)

D. t(9;11)(q34; q23)

E. t(11;14)(p13;q11.2)

**Explanation**

Answer E is correct. The t(11;14)(p13;q11.2) fuses the T-cell receptor alpha/delta (*TCRA/D*) locus with *LMO2,* which occurs in about 7% of pediatric T-ALL cases and does not appear to have prognostic significance. The t(9;22)(q34;q11) or Philadelphia chromosome (answer A) occurs in about 4% of pediatric B-cell precursor ALL. The Philadelphia chromosome is also seen rarely in T-ALL, but with a frequency less than 1%. The t(8;22)(q24;q11) fuses c-MYC to the immunoglobulin lambda gene on chromosome 22 (answer B) and is a rare recurrent translocation in Burkitt leukemia and lymphoma, not T-ALL. The t(1;19)(q23;p13) (answer C) creates *TCF3*-*PBX1* (*E2A*-*PBX1*) fusion and is seen in about 5% of B-cell precursor ALL cases. The t(9;11)(q34;q23) (answer D) creates *MLL*-*AF9* fusion and is seen commonly in acute myeloid leukemia and less commonly in B-lineage ALL (especially infants).

7. Which of the following characteristics excludes a diagnosis of B-cell precursor acute lymphoblastic leukemia (ALL)?

A. Presence of T-cell receptor gene rearrangements

B. Expression of cytoplasmic CD3

C. Expression of surface CD13/33

D. Mediastinal mass

E. WBC count greater than 500,000/mcL

**Explanation**

Answer B is correct. Cytoplasmic CD3 expression is a diagnostic criterion for T-cell acute lymphoblastic leukemia (T-ALL) and cannot be present in B-cell precursor ALL. T-cell receptor gene rearrangements (answer A) occur in B-precursor ALL and are often used to monitor minimal residual disease. CD33 expression (answer C) is common in B-cell precursor ALL. Both a mediastinal mass (answer D) and hyperleukocytosis (answer E) are much more common in T-ALL than in B-cell precursor ALL, but neither precludes a diagnosis of B-cell precursor ALL.

8. A mother brings her 3-year-old son to the emergency department for excessive bruising. She gave him a bath before bedtime on Sunday night, and he was fine. On Monday morning, when she dressed him, she noticed tiny red spots on his skin. During the day, he developed extensive bruising without known trauma. He is otherwise well, has no fever, and has been playing happily. He is described as being very active and always climbing on things. He has a prior history of a humerus fracture at 18 months and a femur fracture at 30 months.

What is the most likely explanation for this history?

A. Acute lymphoblastic leukemia (ALL)

B. Acute myeloid leukemia (AML)

C. Nonaccidental trauma

D. Idiopathic thrombocytopenic purpura (ITP)

E. Viral infection

Explanation

Answer D is correct. In cases of ITP, the parents often can describe exactly when the onset of petechiae and bruising occurred, and children typically are otherwise well. ALL and AML (answers A and B) are possible, but the acute onset of petechiae and bruising is evidence against these diagnoses. In addition, most children with newly diagnosed acute leukemia have other complaints such as bone pain, lethargy, irritability, and fever. Although the prior history of fractures raises concern about nonaccidental trauma (answer C), the factors above argue against this diagnosis, and a CBC should reveal isolated thrombocytopenia. Viral infections (answer E) can be associated with cytopenias, but one would not expect the child to be otherwise well.

9. A 12-year-old boy has T-cell acute lymphoblastic leukemia (ALL) with an initial WBC count of 500,000/mcL and CNS3 status with CSF WBC 200/mcL (100% blasts) and RBC 10/mcL. The treatment regimen specifies that CNS radiation should be given.

What would the proper radiation regimen consist of?

A. 2,400 cGy to whole brain, excluding the globes of the eyes, and 1,200 cGy to spine

B. 1,800 cGy to whole brain, excluding the globes of the eyes, and 1,200 cGy to spine

C. 1,800 cGy to whole brain, excluding the globes of the eyes

D. 1,800 cGy to whole brain, including the entire globes of the eyes

E. 1,800 cGy to whole brain, including the posterior halves of the globes of the eyes

Explanation

Answer E is correct. Radiation therapy for ALL no longer routinely includes spinal radiation, which eliminates answers A and B. The standard dosage for patients with clear CNS involvement (as present in this case) generally is considered to be 1,800 cGy, with the target volume including the entire brain and meninges, including the frontal lobe and posterior halves of the globes of eyes, with optic disc and nerve, extending superior to vertex and posterior to occiput. Caudal border will be below skull base at C2 vertebral level. Some groups (St. Jude, UKALL, and DCOG) now believe that even patients with CNS3 involvement do not need CNS irradiation, but this is not the majority opinion at this time.

10. Which of the following patients is expected to have the best prognosis?

A. A 3-year-old boy with an initial WBC count of 2,000/mcL, ETV6-RUNX1 (TEL-AML1) fusion, and minimal residual disease (MRD) 0.14% at end induction

B. A 3-year-old girl with an initial WBC count of 2,000/mcL, TCF3-PBX1 (E2A-PBX1) fusion, and MRD 0.04% at end induction

C. A 3-year-old girl with an initial WBC count of 9,000/mcL, ETV6-RUNX1 (TEL-AML1) fusion, and MRD 0.07% at end induction

D. A 3-year-old girl with an initial WBC count of 2,000/mcL, hyperdiploidy with trisomies of chromosomes 4 and 10, and MRD 0.04% at end induction

E. A 3-year-old girl with an initial WBC count of 9,000/mcL, hyperdiploidy with trisomies of chromosomes 4 and 10, and MRD less than 0.01% at end induction

Explanation

Answer E is correct. Age, gender, initial WBC count, blast cell genetics, and day 29 MRD response all are prognostic of outcome. Patients aged 2 to 6 years with a WBC count less than 10,000 have the best prognosis. All of the patients in this example fall into this category. Initial WBC is a continuous variable, but it is hard to parse out the difference between 2,000/mcL and 9,000/mcL. The most favorable genetic features are ETV6-RUNX1 (TEL-AML1) fusion (present in answers A and C) and hyperdiploidy with favorable chromosomes trisomies (with 4 and 10 being most important; present in answers D and E). However, MRD response is the strongest prognostic factor, with patients with MRD less than 0.01% clearly doing best (present only in answer E).

11. A 16-year-old Hispanic boy presents with fever, fatigue, and swollen glands. A CBC demonstrates a WBC count of 89,000/mcL and cytogenetics revealed a t(Y;14)(p11;q32).

Which of the following fusion genes is most likely to be present?

A. *MLL-AF9*

B. *BCR-ABL1*

C. *IGH-CRLF2*

D. *TCF3-PBX1*

E. *EWS-FLI1*

Explanation

Answer C is correct. The presence of a chromosome translocation in most or all cells generally is indicative of a malignancy, although balanced translocations (Robertsonian translocations) can be seen in individuals without malignancies. The IGH/CRLF2 rearrangement indicative of Ph-like acute lymphoblastic leukemia (ALL) is more common in Hispanic adolescents and is associated with high expression of *CRLF2*. The locations of the other fusion genes are not on chromosome 14 or chromosome Y. *EWS-FLI1* (answer E) is a fusion gene found in Ewing sarcoma.

12.A 13-year-old girl with relapsed acute lymphoblastic leukemia (ALL) is undergoing reinduction chemotherapy. She develops high fevers with neutropenia approximately 3 weeks into her course, and a CT scan of her chest demonstrates four isolated pulmonary nodules that are about 1 cm in dimension. Her galactomannan is positive.

What is the most appropriate antimicrobial coverage for her?

A. Caspofungin

B. Voriconazole

C. Fluconazole

D. Nystatin

E. Zosyn

Explanation

Answer B is correct. The empiric therapy of pulmonary nodules during febrile neutropenic episodes has been revolutionized by the availability of voriconazole, a triazole antifungal medication. Caspofungin is second-line for aspergillosis, fluconazole has no activity against aspergillus, and Zosyn or another antibiotic would have already been in use in this patient.

13. Novel immunotherapeutics currently are being used in acute lymphoblastic leukemia (ALL) therapy, including bispecific T-cell engaging therapies. Cytokine release syndrome is a known complication of this therapy. What cytokine is associated with the acute onset of the inflammatory response seen in this acute complication?

A. IL-7

B. C3

C. IL-6

D. IL-4

E. IL-3

**Explanation**

Answer C is correct. Abnormal macrophage activation can occur in the context of blinatumomab therapy, particularly in the setting of high disease burden. Cytokine release syndrome (CRS) is best managed with supportive care. Laboratory values consistent with hemophagocytic lymphohistiocytosis include elevated ferritin, cytopenias, and hypofibrinogenemia. Elevated levels of IL-6 are associated with CRS and the use of tocilizumab, an IL-6 receptor antibody, can ameliorate the symptoms. IL-7 (answer A) is a signaling molecule involved in B-cell differentiation. C3 (answer B) is not generally assessed in CRS. IL-4 (answer D) induces differentiation of naive helper T cells to Th2 cells. IL-3 (answer E) promotes development of myeloid progenitor cells through binding of the IL-3 receptor.

14. Which chromosomal abnormality is associated with the worst prognosis?

A. *BCR-ABL1*

B. *ETV6-RUNX1*

C. *P2RY8-CRLF2*

D. Trisomy 4 and 10

E. Modal chromosome number less than 32

Explanation

The correct answer is E, modal chromosome number less than 32 (or hypodiploid) acute lymphoblastic leukemia (ALL). In the current era with tyrosine kinase inhibitor therapy, BCR-ABL1 no longer carries a dismal prognosis. ETV6-RUNX1 and trisomy 4 and 10 are known favorable cytogenetic risk factors and are common among children with ALL. *P2RY8-CRLF2* can be associated with a poorer prognosis in National Cancer Institute (NCI) high-risk patients but not in patients with NCI standard-risk disease. Hypodiploidy remains one of the most difficult subtypes of leukemia to cure.

15. What is a known side effect of inotuzumab?

A. Pulmonary fibrosis

B. Osteonecrosis

C. Kidney stones

D. Sinusoidal obstructive syndrome

E. Hypertension

Explanation

The correct answer is D, sinusoidal obstructive syndrome. Inotuzumab is a calicheamicin conjugated monoclonal antibody to CD22. It has an impressive response rate in adults with relapsed, refractory leukemia. In the INOVATE trial, the clinical response rate to single-agent inotuzumab was 80%, compared with 30% for patients who received standard chemotherapy. Sinusoidal obstructive syndrome occurred in 13% of enrolled patients, in contrast to less than 1% for those treated on chemotherapy. However, most of the cases developed in patients undergoing hematopoietic stem cell transplantation (HSCT). In a retrospective study of children with relapsed, refractory acute lymphoblastic leukemia who were treated on the compassionate use program, the incidence of sinusoidal obstructive syndrome was as high as 50% in patients who pursued HSCT after inotuzumab.

16. Blinatumomab, a bispecific T-cell engaging molecule, is active against which CD antigen that is expressed on B-lymphoblasts?

A. CD10

B. CD15

C. CD19

D. CD20

E. CD22

The correct answer is C. There are currently no targeted agents available for CD10 or CD15. Rituximab is a monoclonal antibody against CD20. Inotuzumab is a calicheamicin-conjugated monoclonal antibody against CD22. Blinatumomab is a bispecific T-cell engaging molecule that brings together a patient’s CD3-positive cells to the patient’s CD19-positive lymphoblasts.

17. Of the variables listed below, what is the most important factor for survival after relapse of acute lymphoblastic leukemia?

A. Time to marrow relapse since initial diagnosis

B. Sex

C. Central nervous system involvement at relapse

D. Response to induction therapy during initial diagnosis

E. Percent of marrow blasts at the time of relapse

The correct answer is A. The most important prognostic factor for survival after relapse is the time to relapse after initial diagnosis, especially for those with marrow involvement. Although outcomes after relapse may be shifting with new therapies that have become available for children and adolescents and young adults who experience relapse, historic outcomes for relapse prior to the introduction of these newer therapies (blinatumomab, inotuzumab, and CAR-T cells) were remarkably constant across multiple consortia. For example, survival for patients who relapse less than 18 months from initial diagnosis is the worst, with most 3-year survival rates less than 20%. Neither sex nor central nervous system involvement worsen the prognosis for marrow relapse. In addition, percent marrow blasts at the time of relapse has no significance, nor does the response rate of the patient at initial diagnosis, although measurable residual disease at end induction for B-acute lymphoblastic leukemia (ALL) and end consolidation for T-ALL is generally considered to be the most important prognostic variable for ultimate relapse.

18. An 8-year-old girl presents with National Cancer Institute (NCI) Standard Risk acute pre-B-cell acute lymphoblastic leukemia. Her family history is significant for her mother having been diagnosed with breast cancer at age 34 years and a maternal uncle who developed osteosarcoma as a teenager. What cytogenetic abnormality is most likely to be detected in this patient?

A. t(1;19)

B. *CRLF2* rearrangement with a *JAK2* mutation

C. *KMT2A* rearrangement

D. Hypodiploidy with a modal chromosome number of 34

E. Hypodiploidy with a modal chromosome number of 24

The correct answer is D. For this patient, her strong family history is notable for a number of solid tumors that are present in the Li-Fraumeni cancer predisposition syndrome. Defined by germline mutations in *TP53*, this particular cancer predisposition syndrome has data to support regular screening for early cancer detection through regular blood tests and MRI/ultrasound screening, so it will be important to institute cancer screening for this patient and any siblings. Next generation sequencing has revealed that hypodiploid acute lymphoblastic leukemia (ALL) with a modal chromosome number of 32-29 demonstrates a high percentage of *TP53* mutations; up to 90% of such patients have *TP53* mutations with 40% to 50% of these being germline mutations. Haploid ALL, which is a subtype of hypodiploid ALL and displays fewer than 32 chromosomes, does not usually harbor *TP53* mutations.

19. A 17-year-old boy presents with a 1-week history of cough and increasing shortness of breath. His pediatrician notes decreased breath sounds bilaterally and obtains a chest x-ray, which shows an anterior mediastinal fullness. He is transported to your hospital and has a CBC showing a white blood cell count of 180,000/dL with less than 50% circulating blasts. His coagulation parameters are also abnormal, with an international normalized ratio (INR) of 1.8 and a partial thromboplastin time (PTT) of 40 seconds. Immunophenotyping demonstrates an early T-cell precursor subtype. Which of the following characteristics portends the worse prognosis for this patient?

A. High presenting white blood cell count

B. Age at presentation

C. The presence of an anterior mediastinal mass

D. Persistent disease at the end of consolidation therapy

E. Early thymic precursor (ETP) immunophenotype

The correct answer is D. There is no prognostic significance to age or presenting white blood cell count for patients with T-cell acute lymphoblastic leukemia (ALL). It is common to see anterior mediastinal masses in T-cell ALL, and coagulopathies are common and can sometimes cause delays in diagnostic lumbar punctures. When first reported, the early thymic precursor (ETP) phenotype was considered a poor prognostic factor in retrospective studies, but more recently presented data do not support that ETP ALL represents a subtype of T ALL with a worse prognosis. However, as with other ALL subtypes, response to therapy is one of the most important predictors of future relapse. For T-cell ALL, end induction (also known as time point 1 in some European studies) minimal residual disease is not as prognostic as end consolidation (also known as time point 2 in some European studies).

20. A 19-year-old girl presents with acute leukemia. Flow cytometric studies that would be consistent with a diagnosis of mixed phenotype acute leukemia (MPAL) would include which of the following constellation of markers?

A. CD10+/CD19/dimCD45/CD22+/weak CD13/33

B. CD2+/CD3+/CD4+/TdT+/CD1a/CD34

C. weak CD33+/CD34+/weak CD38+/variable HLA-DR/weak MPO

D. CD10+/CD20+/bright CD45+/TdT neg/kappa-restricted

E. CD7+/CD13+/ variable CD19/CD117+/CD22+/CD79a+/TdT/weak CD33+/CD34+/CD38+/weak CD123+

The correct answer is E. Classic pre-B acute lymphoblastic leukemia (ALL) would be consistent with the flow in option A—frequently there is weak staining for CD13/33 in B-ALL. Option B demonstrates a classic T-cell ALL phenotype, while option C is classic for an acute myeloid leukemia. Option D is consistent with a mature B-cell phenotype, given the TdT negativity and the kappa restriction. Finally, option E displays markers consistent with a myeloid phenotype as well as B-cell phenotype, supporting the diagnosis of MPAL.