MEDICAL ONCOLOGY

An Advanced Course

A Self-Assessment Guide for
Subspecialty Board Examinations and Practice

JOSEPH G. SINKOVICS

PREFACE

The main purpose of this volume is to aid the fellows and residents in advanced training to prepare for the subspecialty board examination in medical oncology, hematology, and infectious diseases. Second, but not less important, this volume is intended to be of practical service to those physicians who treat patients with malignant diseases within their subspecialty (medical, surgical, gynecological, radiological, and pediatric oncology).

The large and rapidly expanding material has been carefully organized and condensed in a relatively small volume. Instead of reciting elementary features of the malignant diseases (which can be found in many textbooks of medicine, hematology, and oncology), newer advances in the pathology, etiology, immunology, natural history, diagnosis, and treatment of the most common malignant diseases are discussed.

The text is based on material from more than 8000 original publications. Original articles were preferred over previous textbooks. Inexperienced physicians should not apply any of the treatment regimens described in this volume without thoroughly studying the appropriate original articles and obtaining expert consultations.

For the sake of brevity, the style is often almost telegraphic. Contradictory data have been pointed out. In dealing with an entity, efforts were made to include all important points, but it was not possible to be complete within a volume of this size. The references cited should serve as a guide to further reading. Some very popular recent medical texts cite references by simply listing the journal, volume, page, and year of publication. This method would be inadequate in monographs or textbooks but appears to serve the purpose of this volume. In deviation from standard textbooks, several citations were made from science writers' reports and interviews, many of which are very valuable. Upon looking these up, the reader will find photographs of the authors, relatively uncensored text, and illustrations of better color and quality than those in most textbooks. Many of the interviews concern lectures given before the actual publication of a paper. Some show how medical history is made. Others collapse due to lack of supporting evidence. Thus these interviews, while interesting, should always be evaluated in expectation of further data and confirmation.

Practicing medical oncology for almost 20 years, observing my colleagues practice its many outbranchings, teaching it and being educated in it daily at our clinics, at the bedside, and in our research laboratories has enabled me to prepare this volume. I hope it will serve well patient and physician alike.

Joseph G. Sinkovics, M.D.

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Part One
HEMATOLOGICAL ONCOLOGY

1
ACUTE LEUKEMIAS

1.1 PRELEUKEMIC AND PREMALIGNANT CONDITIONS

Preleukemia

Characterized by hypercellular marrow not diagnostic of leukemia, insidious onset, onset usually after 50 years of age, and termination in acute nonlymphoblastic leukemia. Thus, preleukemia is diagnosed retrospectively. Presenting signs are weakness, pallor, splenomegaly, and ecchymoses. Preleukemia may last from 2 to 108 months (Sem Hemat 11:73, 1974). Preleukemic childhood acute lymphoblastic leukemia is very rare (J Ped 91:507, 1977). Neutropenia and anemia develop followed by thrombocytopenia; nucleated erythrocytes are common. Megaloblastoid erythrocyte precursors are frequent in the marrow, but ringed sideroblasts are rare (Arch Int Med 132:226, 1973). Abnormal granulocyte maturation is evident in vitro (Blood Cells 2:11, 1976) and bone marrow colony formation in gel culture is defective (NEJM 288:1083, 1973). Myeloperoxidase synthesis is arrested in preleukemic promyelocytes (Brit J Haemat 30:273, 1975) and these patients are susceptible to bacterial infections. Chromosomal abnormalities may be present, increasing the likelihood that acute leukemia will develop. Preleukemia carries a bad prognosis: Acute myelogenous leukemia (AML) occurring after preleukemia does not respond to chemotherapy. Chemotherapy is not indicated for preleukemia. Table 1.1 summarizes the preleukemic conditions (Am J Path 89: 459, 1977; Geriatrics p. 39, Jan 1978).

Smoldering leukemia yields diagnostic marrow aspirate, but it may last for months and years. In the marrow the percentage of blasts varies from 5 to heavy replacement. These patients all develop AML with a median survival of 16 months (JAMA 230:985, 1974). Indications for treatment are controversial. Pseudoleukemia may be observed in severe infections, during recovery from drug induced agranulocytosis, and in alcoholics with or without overwhelming infections (JAMA 236:1451, 1976).

Severe Combined Immunodeficiency

The Swiss type is inherited as autosomal recessive; others are sex-linked. Adenosine deaminase is defective. Both humoral and cell-mediated faculties are defective. Early death

TABLE 1.1 Preleukemic Conditions

Major types	Clinical features and subtypes
Cytopenic	Anemia (refractory, megaloblastoid, sideroblastic)
	Leukopenia
	Thrombocytopenia
	"Maturation block" in marrow
Myeloproliferative	Polycythemia vera (PV)
	Myelofibrosis
	Primary thrombocytosis
Chromosome breakage syndromes and congenital bone marrow aplasias	Bloom syndrome
	Fanconi anemia
	Ataxia telangiectasia

occurs with infectious complications: monilia, Pneumocystis carinii, gram-negative rods (Pseudomonas, Klebsiella, Escherichia coli), Staphylococcus aureus, and cytomegalovirus. Viral hepatitis runs fulminating course. Bacille Calmette Guerin (BCG) vaccination results in disseminated disease. Blood transfusions may cause severe graft-versus-host reaction. Adenosine deaminase restores lymphocyte responsiveness in vitro (Lancet 2:743, 1975). Bone marrow, fetal liver (NEJM 294:1076, 1976), or thymus transplants may correct immune defects at least in part. Thus longer survival is now possible. Major complications of transplants remain infections and graft-versus-host disease. Incidence of leukemia and lymphoma is increased (Ann Int Med 77:605, 1972).

DiGeorge Syndrome

Represents thymic and parathyroid defects: There are no delayed hypersensitivity reactions; there is no response to antigens that require T helper cells; and hypocalcemic tetany occurs. Classically congenital anomalies of face (hypertelorism) and great vessels are present. Nezelof syndrome is diagnosed when immune globulin levels are variable and specific antibody response does not occur. Some patients are defective for nucleotide phosphatase. Some patients improve after fetal thymus graft. Treatment with thymosin and transfer factor also provided benefit.

Ataxia Telangiectasia

Autosomal recessive. Features cerebellar ataxia (with degenerating Purkinje cells), oculocutaneous telangiectasia, and immunodeficiency resulting in recurrent upper respiratory tract infections. Thymus is hypoplastic, T lymphocytes are defective, serum IgA and IgE are reduced. Gonadal dys- or agenesis coexists. Nonketotic hyperglycemia without glycosuria occurs. Arrest of differentiation at various organs results in high persistent carcinoembryonic antigen and α-fetoprotein levels. Survivors show progeria (graying of hair, senile keratoses). Cause of death is either pneumonia or neoplasms (Ann Int Med 77:605, 1972). Most common neoplasms are leukemia and lymphoma (10%). Other neoplasms are carcinomas of skin, parotid gland, or stomach; glioma or medulloblastoma; dysgerminoma. Histocompatible bone marrow transplants occasionally correct immune defects; gamma globulin injections occasionally help.

X-Linked Agammaglobulinemia (Bruton)

Affected males lack differentiating B-lineage lymphoid cells. Lymph nodes lack follicles. Most patients synthesize some IgG and other globulins (IgM, IgA). Suppressor cells of B-lymphocyte differentiation are present in this entity but removal of these cells still does not bring about differentiation of B cells (J Clin Invest 58:109, 1976). Arthritis resembling rheumatoid disease develops (Ann Int Med 77:605, 1972). The incidence of leukemia and lymphoma is about 5%.

Isolated IgA Deficiency

The most common immune deficiency (1:600). Both recessive and dominant autosomal inheritance occur. HLA-A1 and HLA-B8 antigens are prevalent (Clin Imm Immunopath 7:311, 1977). Many patients develop antibodies to IgA. Transfusion thus may elicit anaphylactic shock. Only IgA-poor blood may be safely transfused. Respiratory and intestinal infections are common. Asthma and atopy are frequent. Rheumatoid arthritis and systemic lupus erythematosus (SLE) are severe complications. In addition to familial IgA deficiency, this condition may occur after some intrauterine infections (toxoplasma, rubella, cytomegalovirus). These patients possess potentially IgA-producing lymphoid cells but these fail to mature in vivo; pokeweed mitogen can induce maturation of these cells in vitro. Excess

suppressor T cells may be the cause of this maturation defect. Increased incidence of lymphoma ("reticulum cell sarcoma") and carcinomas of colon, lung, stomach, breast, esophagus, and skin occur.

IgM Deficiency

Severe recurrent episodes of bacteremia occur. Splenomegaly and increased incidence of lymphoreticular neoplasms and neuroblastoma follow.

Common Variable Immunodeficiency

Poorly defined heterogeneous group of various immune defects, most commonly those of immune globulins. B lymphocytes do not proliferate to plasma cell stage. B-lineage lymphocytes fail to respond to pokeweed mitogen or, if they do, fail to secrete immune globulins. Splenomegaly and enlarged Peyer plaques occur. Excessive T-suppressor lymphocyte activity contributes to pathogenesis (Lancet 2:609, 1974; NEJM 296:41, 1977). Increased incidence of not only malignant lymphoma and leukemia (Ann Int Med 77:605, 1972) but also of carcinomas of stomach, urinary bladder, breast occurs; medulloblastoma and liposarcoma also occurred.

Hypogammaglobulinemia and Thymoma

Adults are affected, females more often than males. The thymoma may be benign or malignant. Tracheal compression causes wheezing. Immune reactions that are T cell-mediated may be entirely normal or severely defective. B-lineage lymphocytes often respond poorly; IgG, IgA, and IgM are low. Severe infections (chronic hepatitis, diarrhea with Giardia lamblia, cytomegalovirus, P. carinii) occur. Myasthenia gravis and diabetes mellitus may coexist. Removal of thymic tumor does not correct hypoglobulinemia. Some patients circulate lymphoid cells that suppress immune globulin synthesis (J Clin Invest 58:109, 1976).

Pure Red Cell Aplasia

Granulocytic and megakaryocytic lines appear intact. Reticulocytopenia is severe. There are no erythrocyte precursors in otherwise normal-appearing marrow. About one-third of patients have benign, encapsulated spindle cell thymoma. Thymoma may predate anemia. Complement-dependent IgG antibody lytic to erythroblasts has been demonstrated (NEJM 291: 345, 1970; Arch Int Med 134:317, 1974). Antibody directed to erythropoietin receptors of young erythroid cells may be responsible for the maturation defect (Blood 49:155, 1977). Also, antibody to erythropoietin was found (Cancer Res 34:1325, 1974). Immunosuppressive therapy may reduce antibody levels. Acute leukemia can be a terminal event. Thymomas may be associated with collagen-autoimmune diseases. In one case of epithelial thymoma, Philadelphia (Ph^1) chromosome-positive CML (chronic myelogenous leukemia) and transitional cell carcinoma of the urinary bladder coexisted (Cancer 38:1414, 1976).

Suppressor lymphocytes play pathogenic role in aplastic anemia and pancytopenia: Some lymphocytes of these patients suppress erythropoiesis in normal marrow cultured in vitro (NEJM 296:10, 1977) or inhibit differentiation of granulocytes (NEJM 296:41, 1977). It is likely that suppressor cells are of T lineage because in vitro pretreatment of marrow from a patient with aplastic anemia with antihuman thymocyte horse immune globulin and complement resulted in colony growth of stem cells in soft agar that did not occur before treatment with antibody and complement (Lancet 1:669, 1976). Table 1.2 outlines a few selected systems with probable suppressor cell activity (NEJM 295:1489, 1976; Ann Int Med 88:226, 1978). A recent review on immune suppression of hematopoiesis is now available (Am J Med 64:301, 1978).

TABLE 1.2 Disorders of Suppressor Cell Systems

Suppressor cell activity	Clinical syndrome	Mechanism
Increased	Variable hypogammaglobulinemia	B cells defective; suppressor T cells aggravate defect
		B cells functional; suppressor T cells interfere with normal function
	Selective IgA deficiency	IgM, IgG production normal; IgA-producing B cells defective
		IgM, IgG production normal; IgA-producing cells functional but produce IgA only after removal of suppressor T cells from the system
	Multiple myeloma	Non-T (monocytic) suppressor cells interfere with polyclonal globulin production by suppressing nonneoplastic B cells
	Hodgkin disease	Suppressor cells interfere with effector cells (T lymphocytes) of delayed hypersensitivity and thus cause anergy
Decreased	SLE	Excessive antibody production (in particular to nucleoprotein antigens) occurs because of lack of regulatory suppressor cells
	Panleukopenia	Complement-dependent cytolytic antibody is formed against non-HL antigens of myeloid stem cells. Cyclophosphamide eliminates autoantibody-producing clone

HL = human leukocyte.

Wiskott-Aldrich Syndrome

Inheritance is X-linked recessive. Characteristic features are eczema, thromobocytopenia, and recurrent infections. Isohemagglutinins and IgM are decreased. When T-cell defects dominate, polysaccharide antigens fail to elicit antibody response (lack of helper T cells), but antibodies develop in response to protein antigens. Frequent complications other than infections are hemolytic anemia and nephrotic syndrome. Most frequent causes of death are infection, hemorrhage, malignant lymphoma, and leukemia (Ann Int Med 77:605, 1972). The incidence of malignancies is about 10%. Astrocytoma and leiomyosarcoma also occurred. Treatment with transfer factor brings about clinical improvement (no data on effect of malignant complications). Allogeneic bone marrow transplantation resulted in complete donor engraftment with improvement of clinical state and laboratory parameters; for allogeneic transplant adequate preparations (antithymocyte serum, total body irradiation, and procarbazine) are necessary (NEJM 298:921, 1978).

Trisomy 21 (Down Syndrome)

Related to increasing maternal age. Overall incidence is about 1:700 live births, but for young mothers it is 1:2000 births and for mothers in their forties 45:1000 births. Amniocentesis may be diagnostic for trisomy 21 (47 chromosomes). When a mongoloid child has 46 chromosomes, material from the 47th chromosome is translocated: The additional chromosome 21 is on chromosome 14 (D/G translocation) or occasionally on chromosome 22 (G/G translocation). Usually the phenotypically normal ("balanced translocation") mother has only 45 chromosomes with a 21-to-14 translocation, i.e., one large (fused) 14 and 21 chromosome and one normal 14 and 21 chromosome each. The chance for having a mongoloid child for these mothers is 1:10. If both 21 chromosomes were translocated, 100% of the offspring would be mongoloid. The extra chromosome occasionally may derive from the father with a chance for having a mongoloid child being 1:20.

Trisomy 21 may result from nondisjunction in the zygote. In this case the parents are of normal karyotype and the translocation occurred de novo during gametogenesis. Mosaicism may occur with cells having normal 46 chromosomes and with cells having trisomy 21 The offspring of parents with such mosaicism is at increased risk of being mongoloid. A triple dose of chromose 21 genes results in clinical mongoloidism; carriers of "balanced translocation" (normal double dose of chromosome 21 genes) are phenotypically normal.

Children with Down syndrome form one-third of those admitted to schools for the mentally retarded. Body size is small. Small oval head; sloping forehead; low-set ears; slanted eyes with medial epicanthal folds; open mouth; and large, fissured tongue are characteristic features. Depigmented (Brushfield) spots appear on iris; the lens may be opacified. Clinodactyly (inward-bent little fingers with small middle phalanx) and single palmar crease characterize the hands. Prints of fingers and toes have typical markings. Distinctive dermatoglyphics are the high axial triradius situated centrally in the palm with angles increased to 80° (normal 45°) (Arch Int Med 134:352, 1974); large hypothenar pattern; the "simian" crease; more loops and less whorls and arches in the fingerprints. Cardiac septal defects may occur.

Australia antigenemia is persistent, antibodies to Epstein-Barr virus (EBV) are high. IgG elevated, IgM low, IgA normal. Lymphocytosis is common but in vitro response to phytohemagglutinin (PHA) is low. Sensitization to dinitrochlorobenzene (DNCB) is defective. Levamisole (LMS) failed to restore T-cell defects (Lancet 1:163, 1977). Antibody response to flagellin (measure of B-cell response and helper T-cell function) is intact. The migration of peripheral blood leukocytes of children with Down syndrome was significantly more inhibited than that of normal children upon in vitro exposure to acute myeloblastic leukemia cells (Haematologia 10:23, 1976). Thymuses are often depleted of lymphocytes and have giant Hassal corpuscles. Fibroblasts show increased rate of malignant transformation upon exposure to simian vacuolating virus 40 (SV40).

Early mortality is due to infections, heart failure, or leukemia. Risk of leukemia is 20-fold increased (but for mongoloid children under 5 years of age it could be 100-fold increased). Both acute lymphocytic and myelocytic leukemias occur. Review of world literature suggests 58% acute myeloid and 42% acute lymphoid leukemia in patients with Down syndrome (Am J Med 53:203, 1972). Of 276 patients with Down syndrome and leukemia, 24 experienced clinical and hematologic remission spontaneously. It is possible that some of these patients may have had only a leukemoid reaction. An infant with Down syndrome developed acute myeloblastic leukemia, erythroleukemia, and had the Christchurch chromosome (NEJM 282:292, 1970). Possibly, incidence of retinoblastoma and testicular neoplasms is also increased.

Patients with Down syndrome age early but may survive over the sixth decade (JAMA 237:673, 1977). The brain of these patients shows calcifications, senility plaques, Alzheimer neurofibrillary degeneration, and Simchowitz granulovacuolar degeneration of nerve cells (Int Med News 11:9, 1978).

Trisomy 13 (Patau Syndrome)

These small infants are apneic, have microcephaly, myelomeningocele, microphthalmia, cleft lip and palate, and are deaf; anomalies of fingers, feet, heart are common. Midline anomalies are prominent (hemangiomas, bicornuate uterus, abnormal male genitals). Fetal Hgb persists. Polymorphonuclear leukocytes have nuclear projections. Survival beyond one year is rare. Incidence of leukemia is increased.

Bloom-German Syndrome

Autosomal recessive. These children are stunted with sunlight sensitivity and telangiectatic erythema of face resulting in scarring, depigmentation, and atrophy. Eyelashes are lost. Cafe au lait spots are frequent. Frequent chromosomal breaks and rearrangements are characteristic. Sensitivity of cultured fibroblasts to transformation by SV40 virus is increased. These patients suffer from multiple bacterial infections but handle viral infections normally. The lymphocytes respond to PHA but react poorly in the mixed leukocyte culture and do not react to pokeweed mitogen. Thus, B-lineage lymphocytes are affected seriously, T-lineage lymphocytes variably (J Clin Invest 56:1, 1975). These patients may reach adulthood. Incidence of leukemia and malignant lymphoma is high and a variety of other malignant tumors also occur.

Chediak-Higashi Syndrome

Autosomal recessive. Patients have partial oculocutaneous albinism, photophobia, and "silken sheen" hair. Peripheral neuropathy common. Susceptibility to pyogenic infections (S. aureus) is increased; but prophylactic treatment with oral cloxacillin was of no significant value. There is neutropenia; leukocytes have large lysosomes, fail to migrate or degranulate after phagocytosis, and are defective in their bactericidal capacity (Ann Int Med 76:293, 1972). Monocytes also fail to migrate. Serum muramidase levels are increased (due to increased granulocyte turnover). Serum globulins are normal. Mononuclear cells may infiltrate bone marrow, lymph nodes, and other organs. Death occurs with lymphadenopathy, hepatosplenomegaly, hypersplenism, hemorrhage, and infections. This clinical picture resembles malignant lymphoma. Similar disease occurs in cattle, mink, mouse, and whale.

Kostmann Infantile Genetic Agranulocytosis

Most patients die young with infections. Chromosome breaks and nonlymphocytic acute leukemia can occur (Sem Oncol 3:297, 1976).

Fanconi Aplastic Anemia

Autosomal recessive. Multiple anomalies (renal and splenic hypoplasia, hypoplastic thumbs and radii, patchy olive-brown melanin hyperpigmentation) occur. Fibroblasts exposed to SV40 virus undergo malignant transformation rapidly. Chromosome breaks are common. The incidence of acute myeloid and myelomonocytic leukemia is high (Sem Oncol 3:297, 1976; Cancer 39:1163, 1977). These patients often receive treatment with corticosteroids or with anabolic steroids (oxymetholone) and may develop primary hepatomas.

Sideroblastic Anemias

The hereditary X-linked form responds to pyridoxine. Some of the acquired forms terminate in AML. Acquired sideroblastic anemias develop in middle-aged or older patients. Iron-laden normoblasts are characteristic in the hyperplastic marrow. Ringed sideroblasts contain iron in perinuclear mitochondria. Anemia is hypochromic and microcytic, sometimes dimorphic. Bone marrow iron, serum iron, and transferrin are often increased ("ineffective

erythropoiesis"). There is striking contrast between erythroid hyperplasia in the marrow and poikilocytosis and lack of reticulocytes in the periphery. The following conditions may lead to sideroblastic anemia: rheumatoid arthritis, polyarteritis nodosa, multiple myeloma, Hodgkin disease, and myelofibrosis. Causes of sideroblastic anemia include: lead, ethanol, isoniazid, and cycloserine.

Paroxysmal Nocturnal Hemoglobinuria (PNH)

Hemolysis is augmented during sleep resulting in hemoglobin- and hemosiderinuria. The membrane of some erythrocytes becomes vulnerable to complement. This defect is diagnosed by acid hemolysis and sugar-water (sucrose lysis) tests. C3 is fixed and is activated by properdin pathway. It damages a common stem cell of erythropoietic and granulocytopoietic series. This stem cell is the progenitor of AML. Thus, some patients respond to the same bone marrow insult with the development of AML, others develop PNH. PNH may terminate in AML. Leukocyte alkaline phosphatase is low in PNH. Exposure to low concentrations of activated serum complement inhibits the chemotaxis of PNH (but not normal) granulocytes. This complement-mediated granulocyte dysfunction (Blood 47:931, 1976) may contribute to infectious complications. Young males are most often affected but not exclusively. Splenomegaly and severe normochromic, normocytic anemia follow. Marrow iron is depleted while kidneys accumulate hemosiderin. Life-threatening venous thrombi are formed but heparinization may increase hemolysis; warfarin may be used. Treatment consists of iron supplement and transfusions of washed RBC. One patient survived symptomless 2 years after bone marrow transplant from identical twin (Ann Int Med 84:692, 1976).

Acquired Bone Marrow Aplasia

May occur without known cause. Drug-induced stem cell damage is sometimes irreversible. Benzene and idiosyncratic (not dose-dependent) reaction to the nitrobenzene antibiotic chloramphenicol elicit marrow aplasia most frequently (Arch Int Med 132:440, 1973) (estimated incidence of marrow aplasia after chloramphenicol use is 1:30,000). Other compounds known to cause marrow aplasia are phenylbutazone, methylethyl hydantoin, gold salts, organic arsenicals, quinacrine, and some insecticides. One dramatic case of chronic lead poisoning leading to AML has been reported (JAMA 237:2627, 1977). Severe, sometimes protracted marrow aplasia occurs in patients treated for neoplasms with radiotherapy, alkylating agents, L-phenylalanine mustard, nitrosoureas, vinca alkaloids, and anthracycline antibiotics. Severe marrow aplasia is a preleukemic condition. Pallor, fatigue, weakness, petechiae, and ecchymoses occur first, infections follow much later. Lymphadenopathy and splenomegaly are conspicuously absent. Blood products (washed erythrocytes, platelets, leukocytes) should be administered only when indicated. Androgen hormones, various antigen preparations, etiocholanolone, corticosteroids are used for the stimulation of residual stem cells (or for the suppression of an as yet unidentified autoimmune reaction). Bone marrow transplantation is an investigational form of treatment which presently offers approximately 50% chance for long survival.

Leukemia After Chemotherapy

The three neoplastic conditions in which AML follows chemotherapy-induced remission are Hodgkin disease, multiple myeloma, and ovarian carcinoma. In Hodgkin disease, radiotherapy and combination chemotherapy (mechlorethamine, vincristine, procarbazine, prednisone) (Lancet 1:947, 1975), in multiple myeloma (Ann Int Med 86:440, 1977) and in ovarian carcinoma (NEJM 297:177, 1977) L-phenylalanin mustard (melphalan) were the therapeutic agents. Of 65 patients with treated Hodgkin disease in one series, and of 341 Hodgkin patients in another series, 4 and 7 patients, respectively, developed AML. The risk of treated patients with Hodgkin disease to develop second neoplasia is increased 21-fold. Of 5455 patients