Adult Leukemias 1

edited by

CLARA D. BLOOMFIELD

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Cancer Treatment and Research

Foreword

Where do you begin to look for a recent, authoritative article on the diagnosis or management of a particular malignancy? The few general oncology textbooks are generally out of date. Single papers in specialized journals are informative but seldom comprehensive; these are more often preliminary reports on a very limited number of patients. Certain general journals frequently publish good indepth reviews of cancer topics, and published symposium lectures are often the best overviews available. Unfortunately, these reviews and supplements appear sporadically, and the reader can never be sure when a topic of special interest will be covered.

Cancer Treatment and Research is a series of authoritative volumes which aim to meet this need. It is an attempt to establish a critical mass of oncology literature covering virtually all oncology topics, revised frequently to keep the coverage up to date, easily available on a single library shelf or by a single personal subscription.

We have approached the problem in the following fashion. First, by dividing the oncology literature into specific subdivisions such as lung cancer, genitourinary cancer, pediatric oncology, etc. Second, by asking eminent authorities in each of these areas to edit a volume on the specific topic on an annual or biannual basis. Each topic and tumor type is covered in a volume appearing frequently and predictably, discussing current diagnosis, staging, markers, all forms of treatment modalities, basic biology, and more.

In Cancer Treatment and Research, we have an outstanding group of editors, each having made a major commitment to bring to this new series the very best literature in his or her field. Martinus Nijhoff Publishers has made an equally major commitment to the rapid publication of high quality books, and world-wide distribution.

Where can you go to find quickly a recent authoritative article on any major oncology problem? We hope that Cancer Treatment and Research provides an answer.

WILLIAM L. MCGUIRE
Series Editor

Preface

Rapid advances have been made recently in our understanding of adult leukemia. These advances have resulted in our progressing in less than 15 years from an era where fewer than 25% of adults with acute myelogenous leukemia achieved remission and almost all were dead within a year to a time where we now expect 70 to 90% of patients to achieve remission and 15 to 20% to be cured.

With these rapid advances even the specialist has difficulty remaining current. Oncology textbooks are generally out of date by the time they are published. Timely in-depth reviews periodically appear but they can not be found in a single volume and the date and times of their publication are unpredictable. The purpose of the present series is to provide a regularly published single volume where recent advances in adult leukemia are authoritatively and comprehensively summarized and interpreted. These volumes will review current basic and clinical research in leukemia with an emphasis on application to the control of leukemia in adults. They will hopefully help bridge the gap between basic and clinical science and treatment of the patient.

Although the series will cover adult leukemia in general, this first volume considers only acute leukemia. Twelve different topics ranging from the viral induction of leukemia to its cure by intensive combination chemotherapy are lucidly discussed by internationally recognized experts in their respective fields. Most of the chapters consist of comprehensive state-of-the-art reviews which are accompanied by extensive up-to-date bibliographies and often useful detailed tabulations of previously published data. Several articles also include large amounts of previously unpublished data. Brief outlines at the front of each chapter should provide the reader with a rapid review of each chapter's contents and assist in locating specific information.

The scope of this volume is indicated by scanning the table of contents.

The first three chapters consider various aspects of leukemogenesis. Gallo and his colleagues lucidly summarize for the nonvirologist some of the exciting new data supporting a role for viruses in the etiology of human leukemia. Smith expands on a provocative area, briefly introduced by Gallo,—the potential role of the newly recognized growth factors (in particular T-cell growth factor) in leukemogenesis. Coltman provides a detailed survey and tabulation of the literature on chemotherapy- and radiotherapy-induced leukemia.

Chapters four through eight focus on various aspects of adult acute myeloid leukemia (AML). Bennett and Golomb review, respectively, morphologic and cytogenetic characteristics of the malignant cell from the viewpoint of clinical significance. Preisler, in a most provocative chapter, discusses new approaches to the treatment of AML based primarily on *in vitro* growth characteristics and drug sensitivities of the leukemic cell. Peterson presents the first in-depth consideration of leukemia in the elderly since the routine use of intensive chemotherapy. The data suggesting cure in a substantial fraction of adults with AML are analyzed by Keating with an emphasis on risk factors which predict for responsiveness to treatment.

Chapters nine and ten focus on adult acute lymphoblastic leukemia (ALL). Bloomfield provides the first comprehensive synthesis of studies of biologic characteristics of the malignant cell in adult, as distinct from childhood, ALL with an emphasis on the clinical utility of immunologic phenotype. Esterhay and Wiernik summarize the results of therapy for adult ALL.

The last two chapters consider aspects of therapy that apply to both adult AML and ALL. Strauss and Connett survey and critically analyze recent data regarding the role of granulocyte transfusions during induction chemotherapy. Kay discusses the current status and future potential of bone marrow transplantation as therapy for adults with acute leukemia.

Overall, these 12 chapters, although written by 16 authors from 11 different institutions, provide a comprehensive and remarkably consistent picture of what we now know about, and what we need to learn to better understand and treat, adult leukemia. It is hoped that this volume will be a valuable reference for all who study and treat acute leukemia and provocative and exciting reading for the generalist in medicine and science.

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ROBERT C. GALLO, FLOSSIE WONG-STAAL and FRANCIS RUSCETTI

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1. INTRODUCTION

RNA tumor viruses (or 'retroviruses') are the causative agents of leukemogenesis in several animal species. There is strong evidence that this group of viruses produces leukemias, lymphomas, and other hematopoietic neoplasias in chickens, wild mice, cows, cats, and gibbon apes. In these well-studied animal model systems, infectious retroviruses can usually, but not always, be isolated from tumor material. Isolates of infectious retroviral particles clearly of human origin have not been reproducibly obtained from human tumors. The questions then are, do viruses in the conventional sense or viral genetic information in the more recently understood sense (see later section) have a role in human leukemogenesis, and if so, how do they partake in these events, and why has it been so difficult to elucidate? In attempting to answer these questions, one should look at the accumulated data derived from studying human leukemia as well as the rapidly expanding information available on viral structure, 'transforming proteins' and cellular transformation from animal model systems.

Like most diseases the development of leukemia and lymphoma are multifactorial and, as a result, epidemiologists have looked for different risk factors. Epidemiological studies related to human leukemia have not proven that leukemias are *commonly* caused by radiation, environmental chemical carcinogens, or inherited abnormalities although they clearly can increase risk. In contrast, they tend to emphasize the rather diffuse geographic distribution of these diseases, their general failure to show cluster patterns, and a lack of clear genetic susceptibility. Similarly, such studies clearly show that the leukemias of man are not an *acute* infectious disease transmitted directly from patients [1]. On the other hand, and as emphasized before [2], these studies do not rule out a transmissible agent in the cause of the disease. Epidemiological patterns can be obscured by several circumstances. For example, if a virus is transmitted vertically, e.g., by congenital infection of the developing embryo or even of the egg or sperm, no infectious pattern may be discernible, especially if there is a long latency period. Long latency may even obscure detection of classical horizontal infections. Also, such

patterns may be difficult to discern if factors other than the transmissible agent are etiologically required. In fact, all these epidemiological complications do occur in one or another leukemia of animals. RNA tumor viruses are sometimes transmitted vertically. Sometimes they infect the germ cell (egg or sperm) or the developing embryo. In other instances they can be transmitted in the DNA of the germ line from generation to generation without visible evidence of virus in a manner identical to cellular genes (true endogenous retroviruses).

The latency of leukemia induction by retroviruses is variable and depends on the virus and the host. However, as in the case with most carcinogens, latency is usually relatively long. For instance, infection of a gibbon ape with gibbon ape leukemia virus may not induce leukemia until a few years later [3]. Clearly, there must be requirements other than virus for disease induction in many instances of animal leukemia. These factors may primarily be host factors, e.g., newborn animals are generally more susceptible to virus than adults and many animals may carry virus without getting disease. Risk to virus may be increased by specific genetic changes. Those genetic factors presently known to affect the incidence of animal leukemia tend to be those which relate to the control of virus replication. Host chromosomal changes can be associated with the risk of leukemia, e.g., the congenital syndromes like Fanconi's anemia and Down's syndrome are associated with an increase in the risk of developing leukemia. A striking example of the role of congenital and/or hereditory factors being involved in human leukemia is the high concordance of childhood leukemia in an identical twin of a child who already developed leukemia [4]. Whether or not any genetic factors cause an increased risk of leukemia by way of affecting the expression, replication, or susceptibility to virus in humans is unknown. Finally, it should be noted that a virus which is ubiquitous may still be pathogenic, but in that situation there can be problems in epidemiological inferences. EBV involvement in Burkitt's lymphoma is an excellent example. Is the reason for disease in some infected people and not in others due to strain variation in virus, genetics of the host, or environmental factors? In this case, it may be all three since various strains of EBV are now known to be variable in their transforming capacity, the geographic limits of the disease strongly imply other environmental factors are needed, and genetic susceptibility is suggested by the very high prevalence of specific chromosomal translocations which may be required for final stages of cell transformation [5].

Our objectives here will be to summarize some of the evidence that specific kinds of viruses are involved in the cause of naturally occurring animal leukemias, to discuss some of the basic features of these viruses and to consider the evidence that such viruses are also present in the human pop-

ulation, to consider whether the data imply etiological relevance and which (if any) results may be clinically useful. Although it has been suggested that infection of mothers by some common non-transforming viruses is associated with an increased risk of childhood leukemia, we will consider only classes of viruses which are known to be true tumor viruses, i.e., for which there is evidence for either *in vitro* cell transformation or *in vivo* experimental tumor production, and naturally occurring animal models.

2. EPSTEIN-BARR VIRUS

We will not consider EBV in detail here because it has been recently and extensively reviewed in a series of excellent articles by workers in the field [6]. However, it is important to emphasize that this complex member of the herpes DNA virus group induces a mitogenic effect on human B-lymphocytes *in vitro*, sometimes can produce malignant lymphomas after inoculation into some primates, causes infectious mononucleosis, and appears to be involved in at least the early phase of African Burkitt's lymphoma as well as some nasopharyngeal carcinomas. Recent reports also suggest that EBV causes some rare acute and fatal lymphoproliferative diseases in a genetically susceptible group of children who may have a defect in their immune response to EBV [7]. The molecular mechanisms by which EBV induces cell growth is poorly understood, but there is evidence that its effect in Burkitt's lymphoma may chiefly be as an initiating event in the mitogenic stimulation of B-cells, whereas other factors are required for frank malignant conversion. These other factors may be genetic susceptibility, malaria, or chromosomal changes developing for unknown reasons. On the other hand the fatal acute lymphoproliferative diseases in an immunologically compromised child may be directly and solely caused by EBV [7]. There have also been intermittent suggestions that EBV is involved in the cause of Hodgkin's disease. This speculation is based on the following considerations: 1) Some epidemiological considerations led to the suggestion that Hodgkin's disease is due to a common human virus causing an uncommon event. EBV, of course, fits that description. 2) The incidence of Hodgkin's disease is higher after infectious mononucleosis and sometimes it appears that infectious mononucleosis leads into Hodgkin's disease. 3) Sometimes high EBV antibody titers are found in the sera of patients with Hodgkin's disease. 4) Some epidemiological results suggest that Hodgkin's disease follows an epidemiological pattern similar to infectious mononucleosis (higher socioeconomic groups) [8]. However, all these arguments are equally consistent with alternative interpretations, as for example, that infectious mononucleosis and Hodgkin's disease are caused by different agents which follow

similar modes of transmission, and infectious mononucleosis can lead to an increased risk for Hodgkin's disease by reducing host defenses [9]. In fact, direct examination of the neoplastic cells of Hodgkin's disease (Reed-Sternberg cells) has failed to reveal any evidence for EBV [10]. There is no evidence whatsoever for a role for EBV in the more common human leukemias and lymphomas, and there is much direct evidence against it. For these diseases we must consider causes other than viruses or in some cases the possibility of causes by viruses other than EBV. The most important group of viruses in this regard are the type-C retroviruses because they cause leukemia in many species, and there is some recent evidence for their association with certain forms of leukemia and lymphoma of man. Moreover, and as we will discuss in this report, they may be important tools for unravelling the pathogenesis of human leukemias and lymphomas even when they are not the cause.

3. RETROVIRUSES AND LEUKEMOGENESIS: BASIC CONSIDERATIONS

3.1. Modes of Transmission

Retroviruses are either endogenous or exogenous to a species with which they are naturally associated. Endogenous viruses are carried in the germ line of their hosts, usually as a multigene family, and are vertically transmitted from parent to progeny. They are usually xenotropic, i.e., they have lost the capacity to infect their hosts. Furthermore, endogenous retroviruses are rarely associated with pathogenicity. Many species, including higher primates, harbor endogenous virus genomes. It was calculated that a tenth percent of the mouse genome was comprised of endogenous viral genes. Their ubiquity had prompted speculations that these genes may play an essential role in normal cellular functions. However, the concept of endogenous viruses has been greatly modified in recent years. First, analysis of the genetic loci containing these genomes showed that these are multiple and variable from individual to individual, in contrast to loci of cellular genes which are invariant [11]. This observation is indicative of random integration of the virus genomes after relatively recent exogenous infection, i.e., after speciation. Their acquisition after speciation seems to be generally applicable to endogenous virus genomes [12, 13], including those of the baboon endogenous virus [14] in contrast to earlier speculation that they were introduced into primates at least thirty million years ago [15]. Second, a rare but completely normal and healthy chicken was found to be devoid of the endogenous virus RAV-O. This argues against any essential role for RAV-O, the only known endogenous virus of chickens in development and growth of the animal.

Besides germ line transmission, retroviruses can also be spread by infection *in utero,* or horizontally among individuals. All of the retroviruses that cause leukemias and sarcomas are exogenous, i.e., the population at large does not carry complete genetic information that codes for these viruses. Infection with the exogenous viruses sometimes, but not always, leads to virus production and/or disease. Genetic and immunological factors of the hosts may play a role in determining the course of these events.

3.2. Structures and Replication of the Genomes of Non-defective Viruses

All retroviruses share a similar genetic structure. The retrovirus genomes contain two identical subunits of 30–35 S RNA bound together at the 5′ end by a 'dimer-linkage structure' to form a 60–70 S RNA complex [16]. The genomic RNA resembles cellular messenger RNA in that it has a cap structure of 5′–M^7GpppG^m at its 5′ end [17] and a stretch of poly(A) of approximately 200 residues at its 3′ end [18]. Immediately before the poly(A), there is a short region that is repeated at the 5′ terminus. All non-defective viruses have coding capacity for at least three gene products: *gag* (for group specific antigens), a precursor protein which is cleaved into four core proteins of the virion; *pol,* the virion RNA directed DNA polymerase (reverse transcriptase); and *env,* the virion envelope glycoproteins. These gene products are necessary, and probably sufficient for virus replication. A fourth region, *C* (for 'common'), is present near the 3′ end, and it is probably not codogenic. The order of these genes has been determined to be *5′-gag-pol-env-C-3′.*

The mechanism of retrovirus replication has been the subject of many recent reviews [19, 20] and will only be briefly dealt with here (see above reviews for references). Shortly after infection, a DNA copy (called the provirus) of the retrovirus RNA genome is synthesized. For this synthesis to occur the catalytic role of the virion DNA polymerase, reverse transcriptase, is needed. Like all DNA polymerases, reverse transcriptase can not initiate without a 'primer' molecule. Primers are nucleic acids (RNA or DNA) which are hydrogen bonded to the template nucleic acid at regions of base complementarity. The polymerase extends the primer by adding deoxyribonucleotides to its 3′ end (see Figure 1 for schematic illustration). The natural 'primer' for the reverse transcriptase reaction is a tRNA molecule, which binds at a defined distance from the 5′ end. The first DNA product then is a piece of DNA extending from the 3′-OH end of the tRNA to the 5′ terminus of the viral RNA. The length of this DNA (often called strong-stop DNA) is specific for a given family of viruses [21], e.g., 100–105 nucleotides for avian viruses and 135–145 nucleotides for murine viruses. The strong stop DNA terminates in a sequence that is repeated at the 3′ end of the genome. To synthesize the rest of the virus genome, the enzyme reverse transcriptase

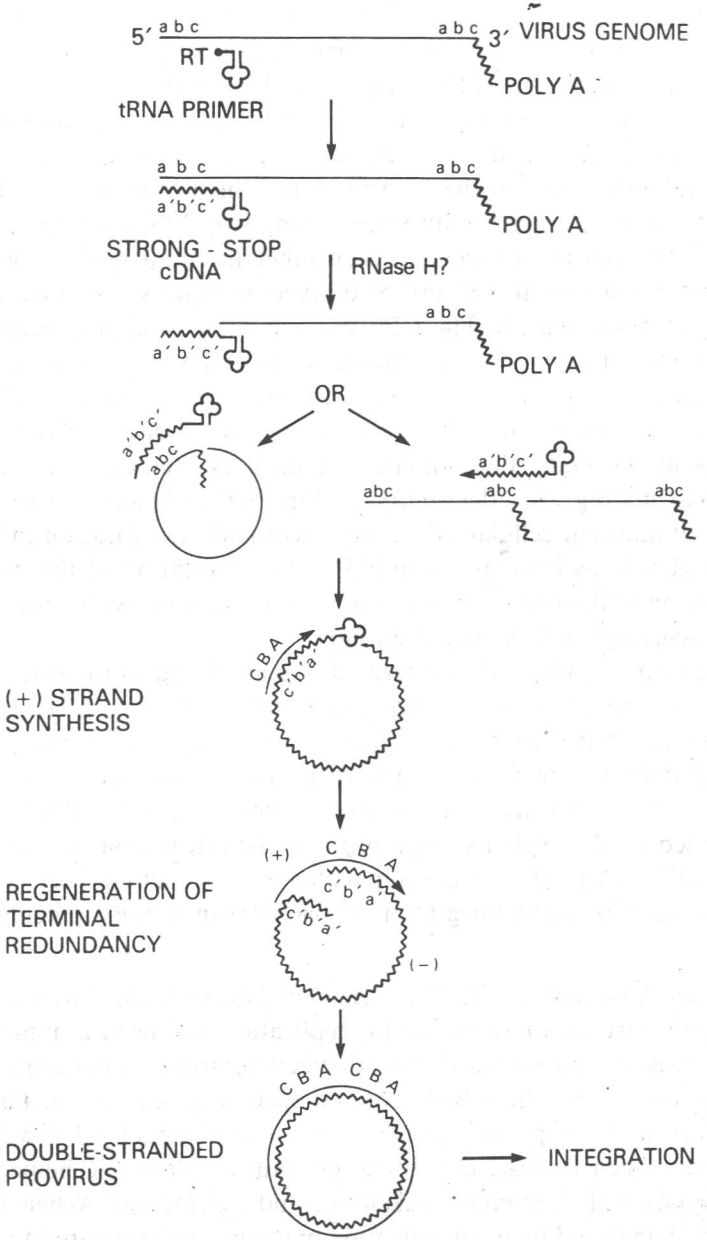

Figure 1. Synthesis of double-stranded provirus. Possible sequence of events for synthesis of double-stranded viral DNA intermediates. See text for description. A tRNA primer molecule binds to the viral RNA genome at a site 100–150 nucleotides from the 5′-end. The enzyme reverse transcriptase then extends 3′-OH of this molecule and copies up to the 5′-terminus of the template RNA. The resultant DNA (strong stop DNA) terminates in a sequence that is repeated at the 3′-end of the genome. The redundancy may provide means for circularization or dimer formation so that the rest of the RNA fenome may be copied. Plus strand synthesis commences before completion of the negative strand.