SECTION ONE

Chronic Leukemias and Related Disorders
A History of the Chronic Leukemias

John M. Goldman and Myrtle Y. Gordon

Although chronic myeloid leukemia (CML) and chronic lymphocytic leukemia (CLL) can be grouped together for some purposes, they differ in many ways, CML being a disease with well-defined progressive stages (chronic phase; acceleration; transformation) occurring in middle life, whereas CLL is a relatively indolent disease involving mainly the elderly. Whereas CML has well-characterized molecular features, which can reasonably be assumed to be related to its pathogenesis, the cause of CLL is virtually unknown. The observations that have led to our current state of knowledge and ability to treat patients are the subject of this chapter (Table 1–1). Recent reviews on the history of CML have also been provided by Piller in 1997 and Geary in 2000.

DEFINITIONS, CLASSIFICATION, AND CHARACTERIZATION

The recognition that the leukemias are an extremely heterogeneous group of diseases has developed progressively since the condition was first described and owes much to technological development over the past 150 years or so. Thus, the distinctions between the chronic and acute and between the myeloid and lymphoid leukemias did not emerge for some time. The postmortem characteristics of the blood first attracted the attention of the early observers of leukemia. According to Gunz and Henderson, the first accurate description of leukemia was the observation of Donne and of Craigie. Nevertheless, the recognition of leukemia as a distinct entity is attributed to the observations of Donne6 and of Craigie.7 The observations that have led to the diagnosis of leukemia involved a remark of young age, abnormal white cells, fever, and death. CML-like disease in mice. The next contribution to the description of the leukemias was provided by Ehrlich in Germany, who developed methods for staining blood cells in 1881. The disease was considered to be a chronic one. CML has well characterized molecular features, which can reasonably be assumed to be related to its pathogenesis, the cause of CML is virtually unknown. ABO-ABL tyrosine kinase inhibitor into clinical practice as treatment for CML.
The first person to appreciate the role of the bone marrow may possibly have been William Shakespeare, when he wrote “Thy bone is marrowless, thy blood is cold.” In 1878 Neumann realized that the leukemias originated in the bone marrow and added myelogenous leukemias described by Virchow. Ehrlich identified a primitive cell type that he thought was ancestral to the lymphoid and myeloid cell lineages, and thereby probably made the first reference to the concept of a hemopoietic stem cell. The view that there are distinct hemopoietic cell lineages was later supported by Naegeli in 1900, when he distinguished between myeloblasts and lymphoblasts.

During the late nineteenth and early twentieth centuries, many new terms were conjured up to describe a variety of leukemias, and there was some confusion over the relationship between different types of lymphoid neoplasm. However, Turk in 1903 recognized that there was a close connection between lymphoid leukemias and lymphomas (lymphosarcomata) and grouped together the chronic and acute leukemias and the lymphomas as the “lymphomatoses,” a term that is roughly equivalent in meaning to the modern “lymphoproliferative disorders.” Until the 1930s, however, there was controversy over the relationship between leukemia in particular and cancer in general. The malignant nature of the leukemias was only established when the disease was induced in rodents by the intramedullary injection of tar and other chemical carcinogens. Descriptions of leukemic cells increased in sophistication with the development of special stains and phenotypic markers. The development of these tools led to the detailed definition of the chronic myeloid and lymphoid leukemias and to the description of the various types of transformation or “blast crisis” that ensue in myeloid and lymphoid leukemias and to the description of the “lymphomatoses,” a term that is roughly equivalent in meaning to the modern “lymphoproliferative disorders.”

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The study of cytogenetics developed during the 1950s, and in 1956 the number of human chromosomes in each normal cell was established as 46. The discovery of the Philadelphia (Ph) chromosome in 1960 by Nowell and Hungerford provided a marker that proved to be pathognomonic for the disease and heralded a new era. With this marker, it was possible to demonstrate that CML is a clonal disorder originating in a hematopoietic stem cell. Moreover, the development of clonal genic assays for hematopoietic progenitor cells in the 1970s enabled Fialkow and colleagues to demonstrate the clonal origin of leukemic progenitor cells from different lineages by study of individuals who were heterozygous for the isoenzymes of glucose-6-phosphate dehydrogenase (G6PD).

During the 1970s much attention was paid to the kinetics of leukemic cells, and it was generally concluded that the proliferating granulocytic compartment divides less actively in CML bone marrow than in normal bone marrow. A variety of indices was established to describe granulopoiesis in CML, and the likelihood that there was an element of residual regulation of granulopoiesis became appreciated. De Klein et al. found that the Ph translocation involved the movement of the normal human counterpart of the murine v- abl oncogene from chromosome 9 to chromosome 22, and one year later the reciprocal translocation of genetic material from chromosome 22 to chromosome 9 was identified. The translocation results in the formation of a fusion gene, BCR/ABL, on chromosome 22. Because of variability in the breakpoints in the BCR gene and the relative constancy of the ABL breakpoint, exon 2 of the ABL gene can be linked upstream to exon 2 of BCR (b2a2 junction) or to exon 3 of BCR (b3a2 junction). Both rearrangements result in the production of a hybrid messenger RNA and a hybrid BCR/ABL p210 protein tyrosine kinase. With today’s molecular technology, it is possible to detect very small numbers of cells expressing the BCR/ABL gene using the polymerase chain reaction (PCR), and this has obvious implications for the monitoring of disease and the management of patients. However, the biological effects of p210 expression in CML remain an enigma and a major challenge to cell and molecular biologists.

Chronic lymphocytic leukemia is an acquired B-cell disorder whose clonal origin can now be demonstrated by detecting unique rearrangements of immunoglobulin genes by Southern blot hybridization. The recognition of CML as a distinct clinical entity can be dated back to the turn of the century. Several authors provided case reports and clinical data that distinguished CLL from lymphoma. Osler in his text The Principles and Practice of Medicine recounted his experience of the disease at the Johns Hopkins Hospital in Baltimore, where CLL accounted for 22 percent of all leukemias and survival times of 3 to 11 years were noted. In 1924, Minot and Isaaac published the first comprehensive clinical report on a series of 80 patients, which according to one author, marked the formal emergence of CLL as a distinct and well described clinical entity.

There followed 50 years of definition and clinical description of CLL, which assisted clinical hematologists in their diagnosis, understanding, and treatment of the disease. Some of the most important contributions of this era were made by Galton in 1966 and Dameshek in 1967, who realized that CLL is a disease of cell accumulation as a result of a reduced cell death rate, rather than a proliferative disease. This reduction in cell death rate is thought to be due to suppression of apoptotic mechanisms and may be associated with dysfunction of the p53 gene. The tumor suppressor gene Bcl-2 also is known to inhibit apoptosis, and small lymphocytic malignancies, including CLL, express moderately high levels of the corresponding bcl-2 protein.

It was not until 1972 that the presence of immunoglobulins on the surface of CLL cells was first demonstrated, thus confirming CLL as a disease of B lymphocytes. Thereafter the development of methods for detailed immunological phenotyping led to an accurate description of the phenotype of CLL cells, which are arrested at an intermediate stage of B-cell differentiation. Cytogenetic studies revealed that there is no ‘marker’ abnormality in CLL equivalent to the Ph chromosome in CML, but several structural chromosome abnormalities occur consistently in varying proportions of cases. It is now widely recognized that there is an inverse correlation between the extent of chromosome aberrations and survival in CLL.

The precise etiology of CLL remains uncertain but studies identifying a tendency for CLL to occur in families suggest that...
there is a genetic disposition, which is expressed only under certain environmental conditions but which is not associated with any discernible pattern of inheritance. It is interesting to note parenthetically that CLL, although relatively common in the Western world, is rare in the Orient.

**TREATMENT**

**Chronic Myeloid Leukemia**

Fowler’s solution, a 1 percent solution of arsenic trioxide, was probably the first agent to show any beneficial effect in the treatment of CML. It had been introduced in 1786 as a general tonic for people and their animals and had been noted for its beneficial effect on the general health of horses. Lissauer’s patient apparently was moribund before receiving Fowler’s solution but subsequently became well and remained so for some months. Arsenic was used in the treatment of CML for some 30 years, and appropriate doses were found to control fever, reduce the white cell count, reduce the size of the spleen, relieve pruritis, and considerably improve anemia.

Roentgen’s discovery of X-rays in 1895 led to their enthusiastic use in the treatment of leukemias and lymphomas. Detection of X-rays against large spleens in CML resulted in a reduction in splenomegaly, with associated improvements in the blood picture and the patient’s general state of health. It soon became apparent that X-irradiation was toxic to normal cells as well as to leukemic cells and that fibrosis could be induced by overtreatment. More optimistically, it was realized that sublethal doses of X-irradiation resulted in reversible marrow hypocellularity, with a return to normal counts within a few weeks.

With the advent of cytotoxic drugs, the role of ionizing radiation in the treatment of CML diminished in the 1960s, before which time it had been the treatment of choice. It became restricted to the treatment of splenomegaly in patients with special features, such as women who are pregnant at the time of diagnosis. The major place for ionizing radiation in the modern treatment of CML consists of myeloablation and immunosuppression prior to autologous or allogeneic transplantation.

The role of surgery in the management of CML is also limited. At one time it was suggested as treatment for distressing priapism. The first splenectomy was carried out in 1866 with fatal results — the patient died as a result of postoperative hemorrhage. Later attempts at splenectomy were also complicated by high rates of mortality, and this situation persisted at least until 1966. Today, the mortality of the procedure in CML is much lower, but the indications for splenectomy remain controversial.

Modern chemotherapy has its origins in secret research on agents for use in chemical warfare. Thus, the first chemotherapeutic agent to be used in the treatment of leukemia was mustard gas or nitrogen mustard (HN2). The fact that it caused profound myelosuppression provided the rationale for its use in the treatment of leukemia. Importantly, it was found that patients who were or who became resistant to X-ray therapy could still respond to nitrogen mustard. Blood transfusion was performed without success in the 19th century and did not become a safe procedure until after the discovery of the human blood groups by Landsteiner in 1900. Antibiotics other than the sulfonamides were not available until the late 1940s, and bone marrow examination became more widespread around this time. Consequentially, more patients with nonspecific febrile disorders survived, and the number of cases diagnosed as leukemia increased rapidly.

The early experience with chemotherapy led to a search for new agents with increased specificity and lower toxicity. Urethane was used in the treatment of CML and in the maintenance of X-ray-induced remission in the 1940s, but by 1953 busulfan had been introduced and rapidly became the treatment of choice for CML. Dibromomannitol, first investigated in 1961, became an alternative for patients in chronic phase who ceased to respond to busulfan. Hydroxyurea was first used in the 1960s and replaced busulfan as the first-line cytotoxic drug for newly diagnosed patients. Hydroxyurea was succeeded by interferon alpha. The latest development in the systemic treatment of CML has been contributed by the results obtained from treating patients with imatinib mesylate (previously STI571), a selective inhibitor of ABL tyrosine kinases, which is currently in clinical trials.

The feasibility of leukapheresis as a method of tumor debulking in CML was established in the 1960s and was dependent on the development of continuous-flow blood cell separators. Today, there is probably little benefit in the long-term repeated leukapheresis of patients with CML, but the procedure is valuable for producing a rapid initial reduction in the white cell count and as a means for collecting large numbers of cells for use in autografting (see below).

Conventional doses of chemotherapy did not produce substantial increases in patient survival or delay the onset of acute transformation. Buckner et al. and Goldman et al. developed the concept that chronic-phase cells could be harvested at diagnosis, cryopreserved and stored in liquid nitrogen, and used as an autograft when the patient began to show signs of transformation. This was based on the hope that infusion of cells harvested at diagnosis would reinstate chronic-phase hematopoiesis for a period equivalent to the length of the first chronic phase. The Hammersmith experience of autografting chronic-phase CML patients with unmanipulated peripheral blood cells was updated in 1994 by Hoyle et al. This report summarizes a nonrandomized study but does indicate that blood cell autografting may prolong life for many patients and may be the treatment of choice for younger patients who do not have a suitable donor for allogeneic transplantation. It may be possible further to improve the results of peripheral blood autografting by using the strategy first reported by Carella et al. who demonstrated that recovery from...
chemotherapy was associated with the preferential release of Ph-negative, presumably normal, cells into the bloodstream and that these cells could be collected in sufficient numbers for reinfusion into the patient at a later date. In the light of the knowledge that normal stem cells coexist with leukemic stem cells in the marrow of CML patients and that CML stem cells survive poorly in culture, Barnett et al.75 cultured patient’s marrow in vitro prior to autografting in the hope that the normal cells would become relatively enriched. Other potential approaches to purging marrow for autografting include the use of antisense reagents designed to suppress the expression of p210 protein tyrosine kinase.76

At present, allogeneic transplantation is the only curative treatment for CML. According to Piller,7 administration of bone marrow to patients was first advocated by Thomas Fraser in 1894,77 who recommended that they eat bone marrow in sandwiches or in glycine flavored with port wine to improve the taste, but it is likely that sporadic attempts at bone marrow transplantation were made earlier. It was not until the understanding of human histocompatibility systems developed further and tissue matching became feasible that allogeneic bone marrow transplantation became a practical option for the treatment of any hematological or nonhematological disease. In this regard, the use of T-cell depletion as a means of reducing graft-versus-host disease (GvHD) confirmed that allogeneic T cells also have graft-versus-leukemia (GvL) activity.78 This has renewed enthusiasm for the immunotherapy of CML, which is marked by a poor use of donor lymphocyte infusions79 and in efforts to raise cytotoxic T-cell clones restricted to killing cells expressing particular leukemia-associated antigens.80

Chronic Lymphocytic Leukemia

The early histories of treating CML and CLL have much in common owing to the limited therapy available and the inability to distinguish the diseases with any degree of accuracy. In the 1940s and 1950s, Osgood77–79 tested the hypothesis that whole-body external irradiation or administration of radioactive phosphorus could be used in a titratable manner to control the leukocyte count at a level below 30 × 10⁹/L. He claimed that this strategy was effective in patients with slowly progressing disease and that it could increase the chance of survival to 20 years. However, his results were not confirmed in later randomized trials comparing irradiation with chlorambucil and other alkylating agents.80,81

Progress in the clinical management of patients with CLL has relied on improved understanding of the different types of disease and improved prognosis. In the past, diseases diagnosed as CLL would have included a mixture of T- and B-cell leukemias, hairy-cell leukemia, and a variety of other conditions associated with lymphocytosis. In contrast, the cells can now be identified accurately by cellular morphology, immunophenotype, and other features,82 so that subtypes of disease can be grouped together and clinical trials can be designed. In the future, expression profiling may allow further subgrouping of CLL, as it has done for non-Hodgkin’s lymphoma.

It has been recognized for many years that cases of CLL have variable clinical courses.83 This wide range in survival times for patients with CLL, from a few years to more than a decade, made therapeutic decisions difficult, particularly because some patients remained well even if they were not treated. This led to the development of staging systems, based on prognostic indicators and other criteria, to facilitate the choice of therapy for individual patients. The long list of prognostic indicators in CLL now includes age, sex, lymphocytosis doubling time, cell morphology, bone marrow involvement, immunophenotype, and cytogenetic abnormalities.84

Long-term low-dose treatment with chlorambucil has been a mainstay of CLL therapy and regulates the size of the malignant B-cell clone without major fluctuations in the blood count. The slowly progressive nature of the disease and its occurrence in the elderly has meant that experimental approaches to improve disease control and attempt to achieve a cure are attempted only in the rare cases of patients less than 50 years old or those with progressive disease who become cytopenic.

Progress has been due to several large studies85–88 and to the introduction of more specific drugs. It is now clear that treatment of stage 0 nonprogressing disease is not indicated and can be harmful. Patients who are resistant to chlorambucil may benefit from the cyclophosphamide-doxorubicin vincristine-prednisone (CHOP) drug regimen, and fludarabine and 2’-deoxycoformycin seem to have better selectivity of action than other drugs.89,90 Fludarabine has become acceptable as first-line therapy for symptomatic untreated CLL patients following the results of phase III trials.91 Monoclonal antibodies such as Campath 1-H (anti-CD52) and rituximab (a chimeric IDEC-CD20) monoclonal antibody, which binds to CD20 expressed on B lymphocytes, have also been used to treat CLL.92,93 Bone marrow transplantation can be curative,94 but most patients are above the upper age limit for this procedure. However, research is now being carried out into nonmyeloablative conditioning regimens for transplantation, although evidence of efficacy remains confined to small series or case reports.

ACKNOWLEDGMENT

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Epidemiology of the Chronic Leukemias

Ray Cartwright

CHRONIC LYMPHOCYTIC LEUKEMIA

The epidemiology of chronic lymphocytic leukemia (CLL) is hampered by two features of the condition. First, it is often found as a chance diagnosis and this in turn can be a reflection of medical care in a particular area, rather than a true representation of the totality of the disease. Second, in both descriptive and analytic epidemiological studies little attention is given to the quality of diagnostic definitions. Most epidemiological studies do not attempt to distinguish B-cell disease and most will include prolymphocytic leukemias and possibly lymphocytic lymphomas as part of what they term “CLL.”

There have been no large-scale comprehensive and diagnostically sound epidemiological studies of CLL published in the past decade.

Descriptive Epidemiology

Table 2–1 gives comparable age-standardized incidence rates from cancer registries covering registration periods around 1990.1 Even bearing in mind the caveats in the introduction, it seems clear that the condition is roughly twice as common in men and that rates vary considerably throughout the world.

The only reported exception to the male preponderance is from West Africa, where CLL in women aged 35 to 50 appears to be more common and that may be, in fact, prolymphocytic leukemia (PLL).2 The highest rates of CLL occur in Europe and in European populations in North America and Australasia. Lower rates occur in Polynesia, sub-Saharan Africa, and South and East Asia. The lowest recorded rates come from Japan. The Japanese data are likely to be accurate, being based on sound recording protocols. This 30-fold variation in national rates has led to many investigations as to the genetic basis of risk (see later).

Table 2–1. Age-Standardized World Incidence Rates of Chronic Lymphocytic Leukemia (CLL) and Chronic Myeloid Leukemia (CML)a

<table>
<thead>
<tr>
<th>Country</th>
<th>Male</th>
<th>Female</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harare, Zimbabwe, Africa</td>
<td>1.7</td>
<td>1.3</td>
<td>1.5</td>
<td>1.3</td>
</tr>
<tr>
<td>Cali, Colombia</td>
<td>0.5</td>
<td>0.2</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>Canada</td>
<td>3.7</td>
<td>1.8</td>
<td>1.4</td>
<td>0.8</td>
</tr>
<tr>
<td>U.S. SEER Whites</td>
<td>3.4</td>
<td>1.6</td>
<td>1.4</td>
<td>0.9</td>
</tr>
<tr>
<td>U.S. SEER Blacks</td>
<td>2.7</td>
<td>1.6</td>
<td>1.6</td>
<td>1.0</td>
</tr>
<tr>
<td>Shanghai, China</td>
<td>0.2</td>
<td>0.1</td>
<td>0.7</td>
<td>0.4</td>
</tr>
<tr>
<td>Bombay, India</td>
<td>0.6</td>
<td>0.3</td>
<td>0.9</td>
<td>0.6</td>
</tr>
<tr>
<td>Osaka, Japan</td>
<td>0.1</td>
<td>0.0</td>
<td>0.9</td>
<td>0.4</td>
</tr>
<tr>
<td>Israeli Jews</td>
<td>2.1</td>
<td>1.1</td>
<td>0.8</td>
<td>0.5</td>
</tr>
<tr>
<td>Denmark</td>
<td>3.6</td>
<td>1.5</td>
<td>1.1</td>
<td>0.6</td>
</tr>
<tr>
<td>Turin, Italy</td>
<td>2.2</td>
<td>0.9</td>
<td>1.5</td>
<td>0.6</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>2.2</td>
<td>1.0</td>
<td>0.9</td>
<td>0.5</td>
</tr>
<tr>
<td>Tarragona, Spain</td>
<td>2.4</td>
<td>0.9</td>
<td>1.1</td>
<td>0.7</td>
</tr>
<tr>
<td>England and Wales, U.K.</td>
<td>2.3</td>
<td>1.1</td>
<td>1.1</td>
<td>0.7</td>
</tr>
<tr>
<td>New South Wales, Australia</td>
<td>2.8</td>
<td>1.4</td>
<td>1.7</td>
<td>0.8</td>
</tr>
<tr>
<td>New Zealand</td>
<td>2.8</td>
<td>1.4</td>
<td>1.7</td>
<td>0.8</td>
</tr>
<tr>
<td>New Zealand</td>
<td>3.0</td>
<td>1.5</td>
<td>1.4</td>
<td>0.9</td>
</tr>
<tr>
<td>Total</td>
<td>1.6</td>
<td>0.8</td>
<td>2.2</td>
<td>0.7</td>
</tr>
</tbody>
</table>

The concept of a genetic basis of risk is reinforced by the observation that Japanese migrants to the United States and their descendants retain low rates.2 Studies of CLL subtypes in Japan suggest relatively few have the “typical” disease (with 90 percent small lymphocytes), only 7 in a series of 41, the rest being a variety of conditions, particularly large and prolymphocytic cell types.3

There is some evidence that CLL declined in incidence in the United States in both White and Black populations4 between 1973 and 1990. The decline is modest and may reflect diagnostic changes rather than any fundamental change. A similar study in the United Kingdom shows very little change in incidence from 1984 to 1989.5

CLL has not shown any evidence of close case aggregation or clustering,6 but some evidence of heterogeneity of geographic distribution was uncovered in a study of U.K. cases from 1984 to 1988.7 This observation may well reflect the difficulties in achieving a uniform standard of case ascertainment even in developed countries.

Analytic Epidemiology

Studies have concentrated on genetic and immune dysfunctional aspects of risk, with some attention given to lifestyles and occupations as other possible causes. However, in certain ways the most remarkable issues surrounding CLL concern the lack of...
clear associations with exposures that commonly cause many other different types of cancer. These include exposures to ionizing irradiation, for example, from the Life Span Study of Japanese A-bomb survivors and from radiotherapy survivor cohorts. Also, but slightly less clearly, there is little support for a link with CLL. doll and Peto, in the U.K. cohort that follows medical practitioners, show no risk. Similarly, although benzene is a well-accepted leukaemogen there is little evidence of a link with CLL. There is no compelling evidence linking CLL with HTLV-I or II infection or with human immunodeficiency virus (HIV) or in those people who are immunosuppressed after organ transplantation. There is weak evidence in a Swedish study to suggest pregnancy confers a protective effect on CLL. A variety of prior medical conditions have been reported to be in excess in CLL patients. These include scarlet fever, chronic ear infection, and bronchitis; psoriasis; rheumatoid arthritis, appendectomy, and chronic infections other than TB. However, there is little consistency among these studies; much of the results are based on small case numbers and all these results must be regarded as unreliable. Sunlight has strong immunosuppressive properties to lymphocytes circulating in the capillaries and a link has been established in Sweden between malignant melanoma and squamous cell cancer of the skin and CLL. Melanoma patients in Denmark have a twofold risk of subsequent CLL. Two Swedish studies suggest a risk of CLL from occupational (not residential) exposure to magnetic fields. A third study of Swedish railway workers also found a risk. However, there is little support from other studies apart from one small study from New Zealand, and these results cannot be thought of as conclusive. Most studies in this area fail to distinguish CLL as a specific subtype of leukemia and when they do so, they are negative (see, e.g., Ref. 39). Other occupational groups considered as potential risk sources for CLL include farming and agriculture, and chemical industry exposure especially the petrochemical industry. There are many studies showing weak links between various farming activities and lymphomas (usually non-Hodgkin’s lymphoma [NHL]); some of these studies include CLL as a separate subtype. Suspicions have been centered on pesticide exposure but no conclusive etiologic links exist. Certain studies have shown an association between CLL and chemical industries generally, with some suspicion directed toward the petro refinery industry. This suggestion is undoubtedly due to the known links between certain other leukemia types and benzene exposure. However, a large combined analysis of 19 studies shows no relation between CLL mortality and occupational risk in the petrochemical industry in the United States and United Kingdom. The same result holds true for a study of incident cases in the United Kingdom. Other occupational studies have examined large registers by record linkage to reveal possible risk exposures. These studies find occasional matches, for example, in the furniture and printing industries. Likewise some case control studies find unexpected results such as dust exposure and coal mining. Such observations are very likely to be chance findings.

### Table 2–2. Chronic Lymphocytic Leukemia (CLL) and Chronic Myeloid Leukemia (CML): Age-Specific Incidence Rates

<table>
<thead>
<tr>
<th>Age Band</th>
<th>CLL Male</th>
<th>CLL Female</th>
<th>CML Male</th>
<th>CML Female</th>
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<tr>
<td>0–4</td>
<td>0.04</td>
<td>0.29</td>
<td>0.09</td>
<td>0.15</td>
</tr>
<tr>
<td>5–9</td>
<td>0.04</td>
<td>0.04</td>
<td>0.04</td>
<td>0.15</td>
</tr>
<tr>
<td>10–14</td>
<td>0.12</td>
<td>0.08</td>
<td>0.08</td>
<td>0.08</td>
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<tr>
<td>15–19</td>
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<td>0.16</td>
<td>0.21</td>
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<tr>
<td>20–24</td>
<td>0.10</td>
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<td>45–49</td>
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<td>50–54</td>
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<td>70–74</td>
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<td>75–79</td>
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<td>4.69</td>
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<tr>
<td>Total case numbers</td>
<td>2040</td>
<td>387</td>
<td>291</td>
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*Cases per 100,000 per year. 1984–1989, parts of U.K. Based on special registration collections. (From Cartwright et al.)*
Other Risks
Past hair dye use was not associated with CLL risk in one small study and a cohort study. Conclusions
The most likely risk factors for CLL revolve around genetic effects and possibly related immune dysfunction. There is far less evidence for any significant environmental contribution from either traditional sources of cancer risk such as radiation, benzene, and cigarette smoking or indeed any other source.

CHRONIC MYELOID LEUKEMIA
The epidemiology of chronic myeloid leukemia (CML) could not present more contrast with that of CLL. The study of CML suffers less from problems of case ascertainment and diagnostic; its descriptive epidemiology is quite different and it shares little in common with the etiology of CLL.

Descriptive Epidemiology
CML is a rare disease, roughly half more common in males than females. It remarkably shows little variation worldwide. Table 2–1 shows that for most countries male standardized rates are around 1 per 100,000 per year and females roughly 0.6/0.7. There is a suggestion that African and U.S. Blacks have slightly higher rates. New Zealand Maoris show the highest rates but based on small case numbers. This might be in line with the parallel observation that they also have the highest rates worldwide of acute myeloid leukemia. The descriptive epidemiology affords little by way of clues to help understand the etiology of the condition.

Analytic Epidemiology
The main problem in determining the epidemiology of CML lies in its rarity; thus many published studies have inadequate case numbers to allow true confidence in the power of the observations reported. Nevertheless, due to consistency between studies more is probably known of the causes of CML than CLL.

Ionizing Irradiation and Chemotherapy
There is substantial evidence that high doses of ionizing irradiation lead to increased risk of CML (and certain other leukemias). The best evidence arises from the Japanese A-bomb survivor cohorts. CML (with acute myelocytic leukemia [AML] and acute lymphocytic leukemia [ALL]) were the earliest malignancies to appear, with CML rates peaking 5 years after the explosion in the younger exposed age groups and some years later in older (over 15) exposed persons. Most of the leukemic excess was over by 1980 and no risk was seen in those exposed in utero or their children. No risk was seen in exposures under 0.4 Gy and thereafter there is a dose-response in risk up to about 4 Gy.

Slightly lower risks of CML were seen in patients treated for ankylosing spondylitis either by external beam therapy or radium-224. Other case series treated with radiation also occasionally show excess of CML, for example, those treated for cervix cancer or for benign uterine bleeding. Most other therapy-related cohorts are too small to be likely to reveal a risk of CML after follow-up. Similarly CML is very rarely reported as a secondary outcome of chemotherapy for primary cancers. This does not preclude CML as a possible outcome, but if it is the risk is very low.

There is controversy regarding the effects of ionizing irradiation at lower doses, but generally speaking there is little firm and repeatable data. CML appears along with other leukemias in numerous case reports and studies of low-dose exposure either medically or environmentally, but never dominates any study nor is it alone responsible for any statistically significant excesses in such studies.

Nonionizing Irradiation
The numerous studies on leukemia risks associated with magnetic fields occasionally note CML. Most domestic exposure studies are generally negative for a CML risk with a few exceptions (e.g., Ref. 58). This is generally also true of occupational exposure to electromagnetic fields. Like CLL, CML is often pooled as “leukemia” in many exposure group studies of nonionizing irradiation.

Cigarette Smoking
Myeloid leukemias generally are associated with a risk of cigarette smoking; this is seen in several cohorts including the U.S. veteran study. In some studies CML has been separately identified as having an associated risk. Smoking also appears to be associated with a shortened time to blast crisis.

Occupations
CML is regularly reported among those heavily exposed to benzene, together with the acute leukemias. The majority of studies in this area have pooled CML with various AML types as “myeloid” leukemias and have assumed the risks are equal. For the heavily exposed cohorts this could well be true, with risks varying from threefold to 25-fold and showing a crude dose-response relationship with little statistically significant risk being seen in those exposed to less than 10 parts per million for less than 5 years.