Chapter

Introductory Chapter: A Brief History of Acute Leukemias Treatment

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1. The early history

The first case of leukemia had been probably described by Velpeau in 1827 [1]. Literally, he described his patient as '*A florist and seller of lemonade who had abandoned himself to the abuse of spirituous liquor and of women, without, however, becoming syphilitic*' [1, 2] that presented with abdomen distention, fatigue, fever, and side effects of urinary stones. At physical examination, severe hepatosplenomegaly was described, while the blood appeared "like gruel" [1, 2]. The patients actually died as soon as hospitalized [1, 2]. Despite probably depicting an acute leukemia (AL) case, a formal diagnosis was not made. Indeed, the first description of AL was dated in 1845, when two young pathologists, the German Rudolf Virchow and the British John Bennett, described it at the same time. Virchow suggested to name it "*leukämie*" (ie leukemia), a disease originating in the tissue producing blood cells; conversely, Bennett described it as "*leukocypenia*", being a type of pyemia, a suppuration of the blood [2]. The real nature of leukemia was then recognized in about 20 years, confirming Virchows theory (**Table 1**). Since then, attempts to cure it were made with scares success. At that time, the most widely used approach radiation, arsenic, and mesothorium (thorium-X).

Year	Development
1600 BC	First written description of cancer in ancient Egypt
1670*	Examination of the blood with the compound microscope
1827	First clinical description of leukemia by *Alfred-Armand-Luois-Marie Velpeau*
1847	Term "leukemia" coined by *Rudolph Virchow*
1872	*Franz-Ern-Christian Neumann* suggested that leukemia is a disease of the bone marrow
1877	*Paul Ehrlich* introduced histochemical staining
1913	Distinction of acute and chronic, lymphoid and myeloid leukemias
1914	*Theodor Boveri* proposed that leukemia arises from a single cell through chromosomal changes
1974	FAB classification of leukemias based on cytology
2008	WHO classification of leukemia including molecular subtypes

Table 1.
Evolution in leukemia diagnosis.

In 1930, Dr. Gloor from the Naegeli's clinic in Zurich [3], described "*the case of an American businessman*" whose white blood cell count reached $100x10^9$/L, with fever and anemia, a classical presentation of AL [2, 3]. He received radiation, arsenic, and mesothorium, and blood transfusion, achieving complete remission. Curiously (and possibly dramatically), when Dr. Gloor tried to publish this first successfully treated AL case, he lost his job and was outcasted in a small clinic in a peripheral canton, only a "fool or a knave" [2] possibly believing to cure AL. The patient, Eugene Metzger, died fifty years later, at the age of 102, in New York. Noteworthy, arsenic is nowadays a pillar of acute promyelocytic leukemia treatment, as established by Francesco Lo Coco and Colleagues [4]. A grapping hypothesis suggests that the curative effect might be due to the blood transfusion, acting as the first stem cell transplant, rather than on anti-leukemic agents only.

2. The advent of chemotherapy

In 1948, based on the evidence that AL children receiving folic acid did worsen, Dr. Farber proposed the first rational treatment for AL [2, 5]. He correctly guessed

Year	Development
1865	*Heinrich Lissauer* administered potassium arsenite to a woman with chronic myelogenous leukemia
1895	Radiation therapy was administered with transient benefit
1930	*Walther Gloor* cured the first leukemic patient with arsenic trioxide, irradiation, mesothorium and transfusion
1943	Isolation of folic acid
1948	Nitrogen mustard for Hodgkin disease; Antifols: aminopterin then amethopterin (methotrexate) for acute lymphoblastic leukemia
1951	Adrenocorticotropic hormone then prednisone for acute lymphoblastic leukemia
1953	Mercaptopurine, methotrexate licensed by the FDA
1955	Prednisone licensed by FDA
1958	Dexamethasone licensed by FDA
1958	Cyclophosphamide licensed by FDA
1963	Vincristine licensed by FDA
1969	Cytarabine licensed by FDA
1978	Native L-asparaginase licensed by FDA
1979	Daunorubicin licensed by FDA
1983	Etoposide licensed by FDA
1987	Mitoxantrone licensed by FDA
1994	Pegylated L-asparaginase licensed by FDA
1995	All-trans-retinoic acid approved for acute promyelocytic leukemia
2000	Arsenic trioxide licensed for acute promyelocytic leukemia by FDA
2001	Imatinib licensed for chronic myelogenous leukemia by FDA*

**During XXI century, several novel targeted agents were then approved.*

Table 2.
Development of anti-leukemia treatments (adapted from Paul S. Gaynon, Toska J. Zomorodian, and Donald Pinkel. History of leukemia: Historical perspectives. In childhood Leukemias: Third edition, by Ching-hon Pui, Ed. Cambridge university press 978–0–521-19661-1).

Date	Development
1873	Blood transfusion first applied to leukemic patients (*Callender*)
1901	First description of human blood groups (*Landsteiner*)
1937	First hospital blood bank
1954	Introduction of platelet transfusion
1957	First successful syngeneic bone marrow transplantation
1968	First successful sibling donor bone marrow transplant (immunodeficiency)
1972	First successful matched sibling donor marrow transplantation (aplastic anemia)
1974	Anthony Nolan Bone Marrow Donor Registry (UK)
1977	Evidence of survivals >1 for 18/110 patients with advanced leukemia transplanted from matched donors
1979	Report of Success >50% for matched sibling donor marrow transplantation for acute myeloid leukemia in first remission
1986	National Marrow Donor Registry Program (USA)
1983	First successful haploidentical T-cell depleted bone marrow transplant
1989	First successful transplant using umbilical cord blood
1997	First reduced-intensity bone marrow transplantation
2002	First generation CAR-T cells
2017	The FDA approves CD19-directed CAR T cells for the treatment of relapsed, refractory acute lymphoblastic leukemia in children and young adults.

Table 3.
Evolution of transfusion services and stem cell transplantation.

that blocking folic acid metabolism could on the contrary avoid leukemic cells growth. Based on that, he wrote "we may now with some justice hope that aminopterin, or some as yet unsynthesized substance related to it, will afford a substantial basis for real hope in this now hopeless disease" [5].

Despite Farber intuition, the prognosis of AL patients remained very poor throughout the 1950s and the 1960s. When Boggs, Wintrobe, and Cartwright examined the overall outcome of AL patients treated with 6- mercaptopurine (6-MP) and methotrexate, they were discouraged, and concluded that, "*the possibility of spontaneous remission must be entertained whenever a patient with acute leukemia becomes apparently well yet, so far as known, practically all such patients subsequently died in relapse. Of the extremely rare case in which the patient did not die, it may be said that the original diagnosis was incorrect*" [2, 6].

Conversely, in the pediatric setting, progressive and impressive improvements were seen starting in the 1960s, especially due to the big efforts of Don Pinkel and Colleagues at St. Jude Institute [7, 8]. Particularly, they systematically changed and improved their chemotherapy regimens, documenting a terrific improvement in a few decades in the prognosis of children affected by AL, an almost invariably fatal disease till then [7, 8].

By contrast, the prognosis remained dismal in adults. However, largely following pediatric studies, the treatment of lymphoid (ALL) and non-lymphoid (myeloid, AML) leukemias became progressively distinct. Eventually, in 1973, the combination of daunorubicin and cytarabine, administered according to the 3 + 7 scheme was documented to be effective in acute myeloid leukemia [9], while post-induction intensification was further developed for ALL (see a schematic timeline of anti-leukemia treatments development in **Table 2**).

In the 1950s, pre-clinical experiments led to the evidences that bone marrow engraftment after sub-lethal irradiation was associated to leukemia disappearance

in mice [10]. This prompted further clinical research in humans and in 1957 Donald Thomas described the first intravenous infusion of bone marrow in humans [11]. In the following decades, tremendous progresses were made and successful bone marrow transplantations were recorded in acute leukemia patients, wither with relapsed/refractory disease and in complete remission [12–14]. By time, bone marrow transplantation evolved to stem cell transplantation, with different sources being available such as marrow, peripheral blood, and umbilical cord blood. At the same time, donation was not limited to siblings but extended to voluntary matched donors, the first registry being funded in UK in 1974, and even only partially compatible ones, in the so called haploidentical transplant (**Table 3**).

Overall, however, the success of anti-leukemic treatments was achieved not only by developing new drugs and schemes (**Table 2**) [15] but also by dramatically improving supportive cares (**Table 3**) [15], especially as far as blood and derivates transfusion as well as anti-microbe drugs were concerned. Particularly, after the first blood transfusion in a leukemic patient in 1873, the most significant advancement was represented by blood groups description in 1901 by Landsteiner et al. Eventually, in 1937 the first hospital blood bank was established and blood products such as platelets were successfully administered in 1954 [15].

3. From chemotherapy to targeted drugs

The most recent advances, spanned across the last 3 decades, can be largely attributed to a terrific improvement in technology and a definitely better knowledge of leukemia biology (**Table 4**) [15]. Specifically, after the first recognition of recurrent genomic imbalances in the 1970s, patients' risk of recurrence, and therefore the most appropriate treatment (more or less intensified), were defined by cytogenetic analyses [16–17]. Subsequently, quantitative polymerase chain reaction (PCR) based techniques allowed an accurate and reliable quantitation of the residual

Year	Development
1670*	Examination of the blood with the compound microscope
1877	*Paul Ehrlich* introduced histochemical staining
1934	Flow cytometry
1960*	Metaphase cytogenetics; *Peter Nowell* and *David Hungerford* describe the Philadelphia chromosome
1975	Production of monoclonal antibodies
1978	Thiopurine methyltransferase polymorphisms related to response and toxicity
1980	Fluorescent in situ hybridization
1985	Polymerase chain reaction
1996	Gene expression arrays
1998	Minimal residual disease by the polymerase chain reaction
2001	Classification of AML risk based on cytogenetic features
2008	First whole genome sequencing in AML
2016	Genomic Classification and Prognosis in Acute Myeloid Leukemia
2017	Integration of Next-Generation Sequencing to Treat Acute Lymphoblastic Leukemia

**Approximately.*

Table 4.
Evolution of technologies that re-defined leukemia diagnosis and prognostication.

disease, this becoming a major factor in determining the choice of treatment (more or less intensified chemotherapy, stem cell transplantation, and targeted drugs) especially in ALL [18]. Finally, next generation sequencing, the first AML genome studied in 2008 [19], quickly led to a refined molecular classification of both AML and ALL [20–21], unveiling new therapeutic targets and hopefully nearing the new era of personalized medicine. Indeed, in the current century, a series of amazing new drugs have been licensed for acute leukemia treatment, including tyrosine kinase inhibitors, BCL2 inhibitors, IDH2 inhibitors, demethylating agents, and monoclonal antibodies including the novel bispecific T-cell engagers (**Table 3**). On the other hand, the latest frontier of cellular therapy relies on the chimeric antigen receptor T-cell therapies (CAR-T), firstly demonstrated to be effective in younger ALL patients [22].

We may certainly expect that further improvements in our understanding of leukemogenesis will lead to later significant success in curing these still terrible diseases.

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