ARTÍCULO DE REVISIÓN

Clinical and epidemiological aspects of leukemias

Aspectos clínicos y epidemiológicos de las leucemias

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ABSTRACT

Leukemia is a group of clonal diseases derived from a single cell with a genetic alteration in bone marrow or peripheral lymphoid tissue, and each type is determined by the specificity of the source cell. The objective of this research was to synthesize studies that characterize the clinical and epidemiological profile of patients with leukemia, the types of treatments used, duration and outcomes for the cases. This study is an integrative review of literature through databases Medical Literature Analysis and Retrieval System Online (MEDLINE), SCOPUS, Cumulative Index to Nursing & Allied Health Literature (CINAHL) and Science Direct. There were 4,274 articles rescued in the initial search, 188 were selected to compose the review sample after applying all the criteria for inclusion and exclusion adopted. Full articles were grouped into four categories, according to the variables of research: (a) more frequent subtypes of leukemia; (b) most widely used treatment; (c) duration of treatment; and (d) endpoint of the cases. It is concluded a prevalence of leukemia in pediatric patients, with a predominance of the subtype Acute Lymphoblastic Leukemia (ALL). In general, the male population is more affected by hematological malignancies. As the therapy is used, each leukemia subtype had its peculiarities regarding the treatment, especially the introduction of imatinib for chronic myeloid leukemia (CML) and prophylactic cranial irradiation for cases of ALL.

Chronic leukemia showed higher treatment duration. There was a significant improvement in survival of Acute Myeloid Leukemia, Chronic Lymphoid leukemia, CML and ALL, the latter approximately with 90% cure rate in children.

Keywords: leukemia; lymphoma; epidemiology; hematologic neoplasms; multiple myeloma; prognosis; drug therapy.

RESUMEN

La leucemia es un grupo de enfermedades clonales derivadas de una única célula con una alteración genética en la médula ósea o tejido linfoide periférico, y cada tipo se determina por la especificidad de la célula de origen. El objetivo de esta investigación fue sintetizar los estudios que caracterizan el perfil clínico y epidemiológico de los pacientes con leucemia, los tipos de tratamientos usados, la duración y los resultados para los casos. Este estudio es una revisión integradora de la literatura a través de bases de datos de análisis médicos, literatura y recuperación de sistema en línea (MEDLINE), SCOPUS, Cumulative Index de Enfermería y Salud Aliada Literatura (CINAHL) y Science Direct. Había 4 274 artículos rescatados en la búsqueda inicial, se seleccionaron 188 para componer la muestra de revisión después de aplicar todos los criterios de inclusión y exclusión adoptada. Los artículos completos se agruparon en cuatro categorías, según las variables de investigación: (a) los subtipos más frecuentes de leucemia; (b) el tratamiento más utilizado; (c) la duración del tratamiento; y (d) el punto final de los casos. Se concluye una prevalencia de leucemia en pacientes pediátricos, con predominio del subtipo de leucemia linfoblástica aguda (LLA). En general, la población masculina se ve más afectada por neoplasias hematológicas. Como se utiliza la terapia, cada subtipo de leucemia tenía sus peculiaridades con respecto al tratamiento, especialmente la introducción de imatinib para la leucemia mieloide crónica (CML) y la irradiación craneal profiláctica para los casos de ALL. La leucemia crónica mostró una mayor duración del tratamiento. Hubo una mejora significativa en la supervivencia de la leucemia mieloide aguda, leucemia linfoide crónica, LMC y LLA, aproximadamente, este último con la tasa de curación del 90% en los niños.

Palabras clave: leucemia; linfoma; epidemiología; neoplasias hematológicas; mieloma múltiple; pronóstico; quimioterapia.

INTRODUCTION

The World Health Organization (WHO), through the World Cancer Report 2014 characterizes cancer as a public health problem, especially among developing countries, expecting that the impact of cancer in the population in coming decades corresponds to 80% on more than 20 million new cases estimated for 2025[1].

For Brazil, there is an estimated of 600 000 new cases of cancer in 2016 [2]. Among the cancers that affect the general population, leukemia has events from childhood to the elderly stages. There were 352 000 new cases of leukemia estimated worldwide in

2012, corresponding to 2.5% of all new cancer cases and 265 000 deaths in the same period worldwide[1]. Leukemia is responsible for approximately 3% of all cancer cases in Brazil and worldwide[3].

Leukemia is a group of clonal diseases derived from a single cell with a genetic alteration in bone marrow or peripheral lymphoid tissue, with their types determined by the source cell specification, by cytologic examination, immunohistochemistry and cytogenetic classified as acute myeloid leukemia (AML), chronic myeloid leukemia (CML), acute lymphoblastic leukemia (ALL) and chronic lymphoid leukemia (CLL)[4].

The AML diagnosis is determined by the uncontrolled growth of differentiated cells of the myeloid type in the blood or bone marrow characterized by the presence of more than 20% blasts and represents 90% of cases of leukemia in adults. CML is a clonal disorder of a pluripotent stem cell, called as Philadelphia chromosome (Ph) when translocation occurs from the long arm of chromosome 22 to 9 and 9 to 22. This translocation brings most of the ABL to gene BCR region of chromosome 22, responsible for 15% of diagnoses of leukemia[5].

The ALL is characterized by immature lymphoid cells accumulate in bone marrow and is the most prevalent hematologic malignant neoplasm of childhood, with a higher incidence of two and five years old, and it is 25% of all cancers in this age group. CLL is diagnosed from the accumulation of mature lymphocytes of type B and T blood. However, it does not interfere with the production of normal cells, as in the previous type[6].

Given the importance of this issue and the social impact generated by the diagnosis and treatment of this disease, this study aims to summarize the studies that characterize the clinical and epidemiological profile of patients with leukemia, the type of treatment used, duration and outcomes for the cases.

METHOD

This study is an integrative literature review, to conferring scientific criticality followed the following steps: a) identifying the problem or research question, b) search the databases, c) evaluation of the data, d) data analysis, e) presentation of the results[7].

For the execution of searches of electronic databases, the following research question has been defined among the leukemia subtypes, which is the most common, the most common treatment, duration and outcomes found?

The literature search took place between December 2015 and January 2016, using the proxy licensed by the Federal University of Rio Grande do Norte (www.capes.ufrn.br/porta3128) by the following databases: Medical Literature Analysis and Retrieval System Online (MEDLINE), SCOPUS, Cumulative Index to Nursing & Allied Health Literature (CINAHL) and Science Direct.

The crosses were used by the indexed descriptors of Medical Subject Headings (MeSH): 1# "leukemia", 2# "epidemiology', 3# "hematologic neoplasms" and 4# "prognosis". The crosses were performed using the Boolean AND operator: 1# AND 2#, 1# AND 2# AND 3#, 1# AND 2# AND 4# and 1# AND 2# AND 3# AND 4#. Uncontrolled search was performed only in Science Direct base to obtain a representative sample of published articles that met the inclusion criteria. It was not used time frame, thus all the items available were analyzed.

The selected studies met the following inclusion criteria: studies addressing the clinical and epidemiological characteristics of patients with leukemia by the prevalence of characteristics, treatment, and outcome. Articles that were not available in full on the selected databases, studies of literature review type, reflective articles, previous notes, letters to the editor, pilot studies and qualitative research were excluded, as well as those who did not answer the main question of this study.

The first selection of studies was carried out by reading the titles and abstracts, with emphasis on objectives and results. Data were separated by the database and relevant topics. For data extraction, the classification of items according to the information presented was carried out: prevalence, treatment, outcome, incidence and treatment, incidence and outcomes, treatment and outcome and incidence/treatment/outcome.

In an initial search, there were 4 274 articles rescued, 188 of them were selected for the sample of this review after application of the inclusion criteria. Of the 4 086 studies excluded, 3 970 addressed the topic, but not on the topics of interest to this review, 28 articles were duplicated, 61 were literature review articles, and 27 had scientific events.

RESULTS AND DISCUSSION

Table 1 shows the 188 selected articles, organized by a database that was recovered and approached themes. There were 62 studies on the prevalence of the disease, 7 addressing kinds of treatments, 53 addressing the outcomes, seven on the prevalence/treatment/outcomes, three prevalence/treatment, 33 on the prevalence and outcomes and 23 addressing the treatments and their outcomes.

Table 1. Distribution of articles by topic and database. Natal/RN, 2016 (N=188)

Topic approach	DATABASE				
	SCOPUS	CINAHL	*Science Direct*	MEDLINE	TOTAL
Prevalence	46	04	11	01	**62**
Treatment	03	03	01	00	**07**
Outcome	32	17	04	00	**53**
Prevalence/Treatment/Outcome	03	01	03	00	**07**
Prevalence / Treatment	01	00	02	00	**03**
Prevalence / Outcome	20	02	09	02	**33**
Treatment / Outcome	10	12	01	00	**23**
TOTAL	**115**	**39**	**31**	**03**	**188**

Table 2 is the distribution of the final sample articles per database and performed by crossing, with a majority of SCOPUS articles and by #1 combinations (leukemia AND epidemiology).

Table 2. Distribution of articles per database and used crossings. Natal/RN, 2016 (n=188)

Databases	Crossings				
	#1	#2	#3	#4	TOTAL
SCOPUS	83	05	25	02	**115**
CINAHL	28	01	09	01	**39**
Science Direct	25	00	06	00	**31**
MEDLINE	02	00	01	00	**03**
TOTAL	**138**	**06**	**41**	**03**	**188**

Key: 1# = leukemia; 2# = epidemiology; 3# = hematologic neoplasms; 4# = prognosis. Crossings: **#1** = 1# AND 2#; **#2** = 1# AND 2# AND 3#, **#3** = 1# AND 2# AND 4#, **#4** = 1# AND 2# AND 3# AND 4#.

Because it was not a time frame determined, there was a significant distribution of studies by year of publication, giving an extensive analysis of the productions on leukemia over time. Studies published between 1964 and 2015 were rescued, of which 135 articles were published in the last ten years. Therefore, it is clear an important increase of publications in the last decade.

After systematic reading, the complete articles were grouped into four categories according to the variables of research: (a) more frequent subtypes of leukemia; (b) most widely used treatment; (c) duration of treatment; and (d) outcomes of the cases.

More frequent subtypes of leukemias

Most studies on this topic reported childhood leukemia, and the most incident subtype is the ALL[8]. Leukemia is approximately one-third of cancer cases in children aged 0 to 14 years old and 10% of adolescents aged 15 to 19 years old. In Europe, the overall incidence rate for leukemia in children was 44 per million people per year between 1988 and 1997. Among the types of leukemia, the lymphoid is found in 81% of cases, non-lymphocytic acute leukemia in 15%, CML in 1.5% and unspecified leukemia in 1,3% of cases[9].

In Brazil, it is estimated the occurrence of 10 070 new cases of leukemia in 2016, with male prevalence (5 540 cases) compared to women (4 530 cases). This type of cancer is the sixth most common in men in the northern region of the country, with an incidence of 3,81 cases per 100 thousand inhabitants[2].

In a survey conducted in a city in Brazil´s southeastern region in the 1990s, it was found an overall incidence of ALL of 12,5 cases per million people per year[10]. In three state capitals, two of them located in the northeast and one in the southeast, the estimated incidence was 5,76; 6,32 and 5,48 cases per 100,000 inhabitants, respectively. Despite the high underreporting of childhood cancer, ALL incidence rates in children are similar to those of developed countries[11].

Between 1979 and 1989 in Kuwait, the ALL was the most frequent among 723 cases (44.2%), with prevalence in the group aged between 0-4 years old, and the most common leukemia was in the children (90,5%). The AML represented 32,4% of leukemia and showed a progressive increase in incidence with age. On the other hand, CML constituted 14,8%, and CLL was 8,6% of all cases [12].

In Cape Province, South Africa, of the 460 cases acute leukaemia diagnosed, 223 (48,5%) occurred in white patients and 237 (51,5%) in those of mixed ancestry. The relationship between the incidence of acute leukemia and ethnicity was 2,12, 1,37 and 0,58 per 100 000 people white, brown and black, respectively. The average age of white people was 30 years old and for brown people, it was 15 years old, comparable data to black patients being 16 years old[13].

Another point of the overall analysis of the incidence of hematological malignancies found that with increasing age there was a decrease of lymphoid neoplasms[12,14]. Nevertheless, some studies have highlighted the increasing number of cases of CLL among women 50-64 years old and attributed the phenomenon to the introduction of breast cancer screening, which resulted in a large group of women under greater surveillance that possibly has led to increased detection of this type of leukemia[15].

In Canada, age-specific prevalence rates showed a steady increase with advancing years for this disease, being more common in men than in women (1,80:1)[16]. In the United States, CLL is the most common form of leukemia in adults. Among 1992 and 2007, there were 30 622 cases, of which men stood out with a higher incidence than women[17].

In France, the incidence rate of AML remained stable over time, ranging from 2,5 to 3,5 cases per 100 000 people per year. The average age at diagnosis was 63 years old. The ALL had an incidence of 1.5 cases per 100 000 in habitants/year, and it was more frequent in children aged four to six years old. The B-cell ALL were more common than T-cell ALL but showed better prognosis[18].

Biphenotypic leukemia, a rare condition, also had its impact on the US database of the Surveillance, Epidemiology, and End Results Program (SEER), between 2001 and 2011, which identified 313 patients with mixed phenotype acute leukemia. It presented an incidence of 0,35 cases per million people per year, with the worst result of prognosis among all subtypes of leukemia, and a direct relationship with age, extremely unfavorable for elderly patients[19].

The hairy cell leukemia (HCL) is also an unusual and barely frequent hematologic tumor subtype. In Mexico, the disease is about 1,12% of all cases of leukemia[20]. In Israel, the national database recorded 147 cases of HCL among men and 34 for women in the period 1991-2001, with incidence rates adjusted for age of 1,62 cases per million women and 7,97 per million people per year[21].

Globally, for AML and ALL subtypes, according to the French-American-British (FAB) classification, it was found that the incidence of AML-M2 was higher than the AML-M1. For ALL, there was a predominance of ALL-L2 subtype[22]. According to the Health World Organization classification criteria (WHO) B cell ALL consisted of the most common subtype[10].

Most used treatment

Each leukemia subtype showed their peculiarities relating to treatment. For AML, a minority of patients held the Hematopoietic Stem Cell Transplantation (HSCT). However, this procedure consists of a treatment modality used more frequently for oncology-hematological diseases genetically inherited or acquired[23].

The HSCT can occur through autologous transplantation, when the progenitor hematopoietic cells (PHC) are from the patient; allogeneic when PHC are from donors with compatible Human Leukocyte Antigen (HLA), related when they are from the same family and not unrelated without a consanguineous donor; or syngeneic

transplant, when PHC are identical twins[24]. After the graft, cyclosporine and mycophenolate mofetil are commonly found, preceded by total body radiation in D0 with or without the use of fludarabine[25].

The intravenous busulfan consisted of another drug used for autologous HSCT process in patients with AML. It has low toxicity compared with the version administered orally, easy to administer and associated with lower rates of the sinusoidal obstructive syndrome[26].

In the acute promyelocytic leukemia, characterized by the gene rearrangement involving the alpha retinoic acid receptor on chromosome 15, the treatment was through the administration of all-trans retinoic acid (ATRA) combined with based chemotherapy in anthracycline[27]. The arsenic trioxide (ATO) is also an antineoplastic chemotherapeutic agent approved for the treatment of relapsed or refractory acute promyelocytic leukemia[28, 29]. The ATO was used in preclinical studies for treating multiple myeloma, and the results showed a reduction in disease progression and induction of apoptosis in many cell lines that can be achieved safely in patients with this disease diagnóstido [30-32].

For CML, the first-line treatment was continuously carried out using the kinase inhibitor mesylate tyrosine imatinib or in the second line, dasatinib, and nilotinib[33]. Chronic lymphocytic leukemia (CLL) presented treatment centered on the use of fludarabine and cyclophosphamide and associated or not and with the cycle of one to five days, repeated every 28 days for up to six cycles. Its combined use was associated with a higher complete remission rate[34]. Besides fludarabine, the chlorambucil was also used as a first line treatment[35].

In Germany, the most commonly used first-line regimens adopted bendamustine in combination with rituximab, fludarabine-associated with cyclophosphamide and rituximab and bendamustine alone. In the second-line treatment, they were very similar to the first and their choice was due to the pathophysiologic characteristics of each patient. Chlorambucil has been used in the treatment of two lines, but in a limited number of patients [36].

In the cases of hairy cell leukemia, the pentostatin, and cladribine represented antineoplastic agents of choice for treatment, when pentostatin demonstrated an association between improving the health status of patients treated with minimal cost increase[37].

In ALL, the type of treatment varies between the combination of intrathecal methotrexate and adriamycin, and between radiation and cranial radiotherapy extended field for radiation[38]. In a study conducted in Poland, patients received prednisone, vincristine, adriamycin and cyclophosphamide as a treatment for induction of remission.

For consolidation, cytarabine and 6-thioguanine were administered and prophylaxis for Central Nervous System (CNS), patients, received cranial irradiation, intrathecal methotrexate, cytarabine and hydrocortisone[39]. Prophylactic cranial irradiation composed the standard treatment in children who were at high risk of relapse into the CNS by residual leukemic cells[40]. In the UK, the antineoplastic agent of choice for the ALL found was daunorubicin administered by peripheral venous access because of their high risk of venous thromboembolism[41].

Duration of treatment

The duration of antineoplastic treatment ranged according to the therapy used and leukemia subtype. In CML, the median duration of therapy using the tyrosine kinase inhibitor of the first line (imatinib) was 39,8 months and the use of tyrosine kinase inhibitors in the second line (Dasatinib or Nilotinib) was 22,4 months[33].

CLL showed decreasing numbers of patients within six months after diagnosis with the early-stage disease since international guidelines have a stronger tendency to discourage the treatment of indolent patients without active disease[15]. The cycles of chemotherapy fludarabine and cyclophosphamide, associated or not, were repeated every 28 days for a maximum of six cycles[34]. According to the National Cancer Institute Working Group, the average treatment duration was 9,2 years compared to 6,5 years updated by the International Workshop criteria and guidelines, which varies according to the monocyte count[42,43].

In the treatment of AML by chemotherapy, patients who achieved complete remission received a single course of Cytarabine 1,5 g/m^2 every one hour for 12 hours, which resulted in a total of 12 doses, for about four weeks after the record of complete remission. In some cases, intravenous mitoxantrone 12 mg/m^2 was used as a rescue therapy on days 7, 8 and 9, respectively[44].

For the cases of ALL, the treatment of remission induction, consolidation therapy phase, and maintenance, plus prophylaxis of central nervous system, showed an average total duration of 2,5 years[39].

Outcomes of cases

In general, the survival rate of patients with AML showed an increase significantly in recent years[9,45]. This better prognosis can be associated with increased investments of hospitalization and chemotherapy. In a study from data collected in the SEER, it was found that a total of 34 subjects diagnosed with ALL, the median survival, was 2,4 months with less than 7% of patients alive at two years, and it was still observed that the higher, the younger were the chances of survival[46]. In childhood, patients diagnosed between 10 and 19 years old are at increased risk of death compared to those diagnosed before 10 years, when the subtypes of AML with t (9;11) (p22;q23) MLLT3-MLL, AML without maturation and acute myelomonocytic leukemia showed indicative of poor prognosis [47].

The same was observed for the survival rate in CML, mainly associated with the implementation of imatinib mesylate as first-line therapy [33,48]. In the period 1993-2008, in the United States and Japan, it was found that the age-standardized mortality rates declined significantly in both countries after the availability of imatinib [48]. The increase in spending on anticancer treatment was also associated with increased survival of patients with CML[49].

The combination of fludarabine with cyclophosphamide led to a significant increase in complete remission for CLL, a higher overall response and overall progression-free survival[34]. Nevertheless, the B cells CLL has highly heterogeneous clinical course, and the prognosis is difficult to predict. In Gijón, Spain, in the 1997-2007 period, survival rates for intervals of five to ten years accounted for 87% and 73% for low risk, 75% and 49% for intermediate risk and 29% and 16% for high-risk, respectively[50]. Survival expectations for long-term patients with CLL showed substantial improvements in the last two decades, except for patients 80 years old or older at diagnosis[51, 52]. The main cause of mortality in patients suffering from this particular illness were infectious complications associated with low absolute monocyte count[43].

The more frequent ALL in childhood showed the relative five-year survival of approximately 90% of children with this diagnosis, and between 35 and 40% in adults in the same condition[18]. Despite treatment protocols include the prophylaxis of the central nervous system cranial irradiation, a relatively high incidence of relapse was observed in the CNS [39]. Thus, even if the ALL has high survival, this has evolved in such a way to present a risk of late effects in treated survivors, especially the risk of subsequent malignancy[53], such as the non-lymphoblastic leukemia, of myelodysplastic syndrome, osteoarthritis, fibroblast sarcoma, B cell ALL, lymphoma, thyroid carcinoma, basal cell carcinoma, adenocarcinoma, squamous cell carcinoma, meningioma, malignant histiocytosis anaplastic astrocytoma and glioblastoma. HSCT and high cumulative doses of cranial irradiation, etoposide, and cyclophosphamide are risk factors for this event[54].

Between 1943 and 2000, a total of 133 secondary malignancies were observed in 16 540 patients in a multicenter study in the American countries, Europe, Asia, and Oceania. Among them, 12 731 cases of leukemia, 1 246 Hodgkin's and 2 563 non-Hodgkin lymphomas, after a median follow-up period of 6,5 years. The most common secondary cancer after leukemia was brain cancer (19 cases), non-Hodgkin's lymphoma (nine cases) and thyroid cancer (nine cases)[55]. In the Pediatric Research Hospital St. Jude in Memphis in the US, between 1962 and 1998 from 2 169 of ALL patients treated who achieved complete remission and had a median follow-up of 18,7 years, 123 of them developed secondary malignancies as the first event after acute lymphoid leukemia, 46 myeloid malignancies, three lymphomas, 14 basal cell carcinomas, 16 carcinomas, six sarcomas, 16 meningiomas and 22 brain tumors [56].

For hairy cell leukemia (HCL), in the US, the median overall survival based on diagnostic period was five, six, four and 12 months for those diagnosed during 1973-1995, 1996-2000, 2001-2005 and 2006-2009, respectively. Thus, it was observed a recent sharp improvement in the survival of HCL, which can be associated with the use of improved therapeutic strategies [55].

The results show a higher prevalence of leukemia in pediatric patients, especially the ALL subtype. However, this population is the highest percentage of healing, which can reach up to 90% of cases, which declines with advancing age. There was also that its impact is more pronounced in the white population. The AML is the second most common subtype of leukemia, and in general, the male population is more affected by hematological malignancies.

Regarding the therapy used, each leukemia subtype presented its particularities, highlighting the success of imatinib mesylate use for the treatment of CML. The prophylactic cranial irradiation is a complementary therapeutic method for the treatment of ALL, to prevent recurrence of the tumor in the central nervous system.

The anticancer treatment period varied according to the treatment employed and leukemia subtype. For chronic leukemias (CML and CLL) has been verified the longest period of treatment ranged from 22,4 months to 9,2 years, respectively.

In recent years, the mortality rates standardized by age decreased significantly for the cases of AML and CML. This prognosis improvement may be associated with increased investments with hospitalization and chemotherapy. For CLL, there was also an increased survival, but for patients over 80 years old. The main cause of mortality in patients suffering from this cancer is infectious complications associated with a low count of absolute monocyte. The ALL shows the relative survival of approximately 90% in children, but between 35 and 40% in adults. It is observed a recent sharp improvement in survival of HCL, which may be associated with the use of improved therapeutic strategies.

Even it has seen the intensification of studies related to the theme, this is a subject that needs to be constantly studied and updated its revised data and processed to generate information to encourage epidemiological data. Therefore, when tracing the epidemiological cancer profile, the reality of this disease in the society is exposed to which the study is directed, as is possible, from the results, the increased knowledge by the professionals regarding this disease and of the population affected by it.

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